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THE STRUCTURAL CHEMISTRY OF ADRENERGIC NEURAL TRANSMISSION SYSTEMS

by

Saraswathi Vishveshwara

A dissertation submitted to the Graduate Faculty in Biochemistry in partial fulfillment of the requiremants for the degree of Doctor of Philosophy, The City University of New York.

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Abstract

THE STRUCTURAL CHEMISTRY OF ADRENERGIC NEURAL TRANSMISSION SYSTEMS

by

Saraswathi Vishveshwara

Adviser: Professor David L. Beveridge

The results of INDO molecular orbital calculations on the geometries and electronic structures of R(-) norepinephrine, R(-) epinephrine, R(-) isoproterenol, dopamine, erythro-ephedrine, threo ephedrine, R(-) phenylethenolamine and phenyl-ethylamine are presented.[1,2] The conformations predicted to be preferred in the free space approximation are discussed in terms of intramolecular interactions, and the calculated potential energy surfaces and electronic charge distributions for each molecule are considered in terms of crystallographic, spectroscopic and bio-assay data. The effect of substituents on various parts of phenylethylamine molecule are studied in terms of potential energies and electronic distributions. A comparision of the similarities and differences in the calculated results of α and β adrenergic molecules, is carried out. A total consideration of the above results in a biological perspective, and a critical evaluation of the current theories of adrenergic action are presented.

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A. Introduction:

A.1 Objectives. It is the aim of this study to characterize as fully as possible the structural chemistry of norepinephrine and a series of its congeners through use of self consistent field (SCF) molecular orbital theory (MOT) at the intermediate neglect of differential overlap (INDO) level of approximation. This work involves the systematic calculation of expectation values for total energy and atomic charge densities as functions of atomic internal displacement coordinates. The potential energies calculated in the free space approximation are used to construct surfaces of conformational energy, and detailed considerations of charge density as a function of conformation are carried out in order that they might provide theoretical evidence for the nature of stabilizing intramolecular interactions. Consideration of theoretical evidence for such interactions is facilitated through the reduction of the expression for total energy into monoatomic and diatomic contributions, (energy breakup). Evaluation is made of the similarities and differences in the above results for selected adrenergic compounds, and the relationship between these results and results reported from x-ray crystallography, molecular spectroscopy and molecular pharmacology is fully developed. Current thought concerning the role of structure and conformation in adrenergic action is developed in the context of accumulated data.

A.2. Background. The transmission of information in neural systems involves the passage of impulses of electrical current throughout a net work of nerve cells (neurons)[3]. When the membrane potential of a neuron is decreased below a critical level, an action potential sweeps along the axonal fiber and invades the terminal regions of the neuron. This degenerates vesicle or granule structures in the terminus and permits the release of chemical neurotransmitter into the interneuronal (synaptic) region. The neurotransmitter diffuses across the synaptic gap and interacts with the postsynaptic membrane. This interaction brings about a structural change in the postsynaptic membrane, resulting in an increased ionic permeability, a lowering of the postsynaptic membrane potential and propogation of the neural impulse. Details of these events are still an area of active research[4,5].

Peripheral neural transmission systems are classified at several levels of organization[6]. Generally anatomical and physiological differences form the basis of classification. Afferent signals from the sensory receptor organs provide the input to the central nervous system. The motor nerves (efferent) carry impulses from the latter to the organs such as muscles and glands. Efferent nerves are further divided into somatic and autonomic systems. Somatic efferent nerves innervate voluntary (skeletal) muscles, and have neural transmission mediated by acetylcholine which promotes the impulses across the neuromuscular junction in a process thought to be analogous to synaptic transmission. Autonomic or vesceral efferent nervous system innervate all body structures(e.g. heart, liver, stomach) other

than voluntary muscles. Unlike somatic efferent nerves, autonomic efferents contain peripherially positioned ganglia and therefore neural transmission in this system has a natural classification of pre-ganglionic and post-ganglionic. All pre-ganglionic transmissions are mediated by acetylcholine. The postganglionic fibers sensitive to acetylcholine are called parasympathetic, while those activated by norepinephrine or epinephrine are called sympathetic. The activation of sympathetic nerves is known to prepare the animal for " fight or fright "[7]. The term " Adrenergic transmission " refers to the type of neural transmission which is mediated by norepinephrine or epinephrine mentioned above.

Adrenergic neural transmission is further divided into α and β categories based upon the different activities of sympathomimetics[8]. In general, the excitatory actions leading to the contraction of smooth muscle are mediated by α-adrenergic receptors, whereas inhibitory actions leading to the relaxation of smooth muscles and stimulation of cardiac muscles are mediated by β-receptors. Norepinephrine and isoproterenol have maximal activities respectively at α and β receptors. A major part of the adrenergic molecules is reabsorbed by presynaptic granules, thereby removing them from the site of action. A minor fraction of the active molecules is also metabolized by the enzyme monoamine oxidase (MAO), which is located intracellularly, as well as by the extracellular enzyme catechol hydroxy methyl transferase (COMT). Similarly the endogeneous stores of norepinephrine is depleted by rauwolfa alkaloids (e.g. reserpine).

In molecular pharmocology, the term " specific receptor " is used for the specific part of the effector cell or in particular, specific part of the postsynaptic membrane interacting with the neurotransmitters. The neurotransmitters and molecules which mimic their activities are called agonists. Inhibitors can act at various stages. For instance, they can (a) prevent the release of the transmitter from granular cells, (b) interfere with the passage of the transmitter from presynaptic membrane to the synaptic gap or (c) bind to the receptor thereby inhibiting the action of the agonist. The antagonists that block the transmission by binding with the receptor can provide valuable information on the agonist-receptor interactions. A number of phenylethylamine derivatives act as adrenergic agonists. The antagonists like phenoxybenzamine, tholazoline specifically block the α-receptors whereas compounds like dichloroisoproterenol and propranol block the β-adrenergic receptors[9].

It should be noted at this point that the classification of adrenergic receptors have arisen empirically, and detailed considerations reveal that the systems are considerably more complicated. There is evidence that the adrenergic α and β recepters are in some cases part of the same tissue area and evidence for further subclassification of the β-recepters[10] based on inhibitor studies[11-14]. The β-adrenergic action has been linked to metabolic steps as well as membrane interactions[15]. Further complications arise from the fact that the activities of the molecules vary widely depending on the biological source of the tissues. Thus the classification of adrenergic receptors

is of qualitative nature to a considerable extent.

Some of the adrenergic compounds are capable of only releasing norepinephrine from storage sites, which in turn interacts with the postsynaptic membrane. Whether a molecule releases norepinephrine from storage or interacts directly with the postsynaptic membrane can be determined by various methods[16,17]. A method used extensively involves the measurement of the activity of the tissue which is pretreated with reserpine[18]. Adrenergic molecules are said to have " direct activity " if they interact directly with the receptor. On the other hand, the molecule which release norepinephrine from its storage are known to have " indirect activity ". " Mixed activity " is exhibited by some of the amines which have some direct activity, though the maximum response is produced by the release of norepinephrine from the granules. Minor variations in the structure of norepinephrine seem to produce different types of adrenergic activities[19].

The relative specificity of adrenergic neural transmisssion processes signals a significant role for molecular geometry of the neurotransmitter in synaptic events. The spacial conformation and electronic structural characteristics of the neurotransmitter and receptor appear tp be specifically complementary or capable of a mutual structural adaptation. The exogenous neurochemically active substance appears to function by adopting a geometry resembling that of an endogenous transmitter and interacting with the corresponding receptor. The isolation and characterization of receptors have received major emphasis in several groups and recent progress has been encouraging. However as yet this work is not advanced enough to give information on receptors at a

molecular level.

The most readily accessible bases at present for the consideration of neural processes at a molecular level are the structural features and geometrical conformations of the neurotransmitters and structurally related active substances. The development of gross structure-sctivity correlations based on the relative agonists and antagonists of neural receptors has been the domain of molecular pharmacology and an account[7,19,20] of the state of massive research efforts in this area is available. At the conformational level, the physiochemical methods and a broad based efforts to synthesize agonists with specific orientation of functional groups have produced important results for the development and evaluation of current theories.

A study of the structure-activity relationship involves a knowledge of the biological activity of the agonists and its molecular and electronic structural properties. For future reference the molecular geometry of norepinephrine is given in Fig.1. The essential geometry of norepinephrine and other adrenergic molecules can be specified in terms of five dihedral angles: τ(C6-C7-C8-N), τ(C5-C6-C7-C8), τ(H-O3-C7-C6), τ(H-O1-C2-C1), τ(H-O2-C3-C4), which are defined with respect to the numbering system shown in Fig.1. The terms antiplanar, -synclinal and +synclinal are referred to the dihedral angle τ(C6-C7-C8-N) at 180°, -60°, and +60° respectively. The notation $\{\tau 1, \tau 2\}$ will be used to represent the values of dihedral angles τ(C6-C7-C8-N) and τ(C5-C6-C7-C8). Adrenergic agonists vary in their substituents on nitrogen and carbons C8, C7, C3 and C2.

The effect of varying substituents on biological activity and on structural aspects of adrenergic agonists as found in literature will be summarized in the following paragraphs.

Extensive gross structure-activity studies have substantiated a basic differentiation in α and β activities in terms of substitution on ammonium nitrogen, with increased size of the N-substituent leading to decreased α activity and increased β-activity. Thus, as mentioned before norepinephrine has maximum α effects. Further, substitution of the second and third amino hydrogens leads to a decrease in the activity in general[21]. Similarly a methyl substitution on carbon(C8) is found to decrease the adrenergic activity[22,23]. The D(-) isomers which have R configuration[24] are more active than their L(+) isomers[25,7]. The deoxy derivatives such as dopamine also exhibit a low level of adrenergic activity. The catechol moiety is important for activities at both α and β adrenergic receptors. Essential elements of this pattern of binding have been confirmed by NMR spin relaxation experiments on agonist-receptor interactions[26]. The catechol hydroxy groups are essential for direct activity, especially the presence of meta-hydroxy group seems to be important for direct activity[19]. Patil et al.[25] have also shown that the (R) stereospecificity is significant for direct activity.

Both experimental and theoretical methods are utilized in the conformational analysis of adrenergic neurotransmitters. Experimentally, structural information has been collected for solid state systems using x-ray and neutron diffraction techniques,

and for solution phase systems using nuclear magnetic resonance (NMR) and infrared(IR) vibrational spectroscopy. The crystallographic techniques give structures stable in the crystalline solid and spectroscopic techniques yield structural information only on specific internal coordinates amenable to analysis. In interpretation of results three dimentional molecular models have been useful in estimating sterically allowed and forbidden conformations, but the relative stability of conformers within sterically allowed regions requires a theoretical calculation of conformational energies. The theoretical methods are in principle capable of complete enumaration of energetically preferred structures, but in practice this approach is limited to approximations required to make calculations on many particle systems tractable. Theoretical studies of neurotransmitter structure have used methods ranging from semiempirical pairwise potential functions to a variety of approaches based on molecular quantum mechanics. The capabilities and limitations of some of the latter methods will be presented in the theory and method sections.

The conformational aspects of adrenergic problems are related to the orientation of the quaternary nitrogen with respect to the β-hydroxy oxygen and the catechol ring. The crystal structure of R(-) norepinephrine hydrochloride[27] has been reported by Carlstorm and Bergin and a reduction of their unit cell coordinates on the dihedral angles defined earlier shows τ(C6-C7-C8-N) =176°, τ(C5-C6-C7-C8) = -97°, τ(H-O3-C7-C8) = 46°, τ (H-O1-C2-C1) = -17° and τ(H-O2-C3-C4) = 123°. The hydroxy hydrogens are involved in intermolecular hydrogen bonding.

Spectroscopic studies of norepinephrine in solution have been reported by Reisch, Alfes and Mollman[28] using NMR and by Mesley and Evans[29] using IR methods. Both of these studies focus on analytical methods designed for identification rather than conformational analysis.

Theoretical calculations of the conformational stability of norepinephrine have been reported by Kier[30] using extended Huckel theory (EHT), by Pullman, Coubeils, Courriere and Gervois[31] using perturbative configuration interaction (PCILO) method and at SCF-INDO level by Pedersen, Hoskins and Cable[32]. All these results are in close qualitative accord in regard to the global minima at τ(C5-C6-C7-C8) = $\pm 90^{o}$ and τ(C6-C7-C8-N) = 180^{o}, which also correspond to those found in the crystal structure. Pedersen et al.[32] have also calculated the effect of $Li(H_2O)_2$ chelation and found that the -synclinal geometry about τ(C6-C7-C8-N) to be prefentially stabilized over antiplanar geometry.

The structure of phenylethylamine forms the skeleton of adrenergic molecules. Different adrenergic agonists vary in their substituents on different parts of the basic molecule. Often hydroxy groups are found on carbons C2, C3, and C7 and alkyl groups are found on C8 and nitrogen. Among the five dihedral angles mentioned before, τ(C6-C7-C8-N) specifies the relative orientation of the quarternary nitrogen with respect to the β-hydroxy oxygen and catechol ring and this coordinate has been the concern of a number of experimental and theoretical studies of adrenergic compounds, specifically with regard to whether

this dihedral angle is +synclinal, -synclinal, antiplanar or if several geometries are substantially populated in solution or in the biological fluid. The crystal structure of norepinephrine as described above, phenylethylamine[33], ephedrine[34], dopamine[35] and isoproterenol[36] all give τ(C6-C7-C8-N) in the antiplanar form. The catechol ring in all the above crystals is oriented perpendicular to the plane of the ethylamine side chain, so that τ(C5-C6-C7-C8) is around -90° in dopamine and R(-) ephedrine crystals and around $+90^{\circ}$ in phenylethylamine and isoproterenol crystals. Hydroxy hydrogens are often involved in intermolecular hydrogen bonding. τ(H-O3-C7-C6) takes the value of -63° in ephedrine and -100° in isoproterenol. The orientation of catechol hydroxy groups is known in norepinephrine and isoproterenol crystals, τ(H-O1-C2-C1) being -16° and τ(H-O2-C3-C4) being -13° in isoproterenol.

Many of the theoretical calculations have shown that τ(C6-C7-C8-N) is antiplanar. However, some of the synclinal conformers in a few cases have energies as low as those of their antiplanar forms. The EHT calculations by George et al.[37] show the antiplanar form as the global minimum in a series of N-substituted adrenergic molecules. The PCILO method by Pullman et al.[31] on a series of adrenergic molecules show the appearence of three equivalent stable conformations, one antiplanar and two synclinal, in compounds unsubstituted at the ethylamine side chain. Further their number reduces to two, one antiplanar and a -synclinal, in the derivatives containing the β-hydroxy group, the antiplanar form having a slightly greater stability. Smissman

and coworkers[38] have synthesyzed some of the rigid analogues of adrenergic molecules. Their conformational analysis using spectroscopic methods have produced interesting results but are not yet conclusive on the orientation of τ(C6-C7-C8-N).

Recent calculations by Katz, Heller and Jacobson[44] on norepinephrine using CNDO method has shown that the -synclinal and antiplanar conformations have minimum energies, the -synclinal conformer being slightly more stable. Their calculations on dopamine and on its anions reveal the existance of energy minima at -synclinal, antiplanar and +synclinal conformations. Further their CNDO studies on polyhydroxy phenylethylamines show that the conformational preferences are influenced to a great extent by the hydroxy groups on carbons 1 and 5. Interesting calculations have been carried out on methyl derivatives of phenylethylamines by Weintraub and Hopfinger[45], using empirical potential functions (EPF) method. For each molecule the calculations have been carried out on free base, on cation in vacuum and in aqueous solution. Both synclinal and antiplanar conformations were found to have low energies, the antiplanar conformation preferred over the synclinal conformation only in the case of cation in aqueous solution.

Extensive studies of ephedrine and pseudo ephedrine, the erythro and threo α-methyl derivatives of N-methyl phenylethenolamine have been directed towards accounting for interesting trends in the activities of these isomers at α-recepters[7]. Patil et al.[25] have shown that a significant amount of direct activity is exhibited only by R(-) ephedrine. The NMR studies

by Portughese[39] and by Hynes[40] support the above findings, since only in R(-) ephedrine the C-methyl group is oriented below the plane of phenylethenolamine moiety when it resides in its preferred conformation. The theoretical calculations of Kier[41] shows a preference for τ(C6-C7-C8-N) antiplanar in R(-) ephedrine and -synclinal in ψ-ephedrine, and an α adrenergic receptor model was proposed on this basis.

Although the antiplanar form of τ(C6-C7-C8-N) has been found to have the stablest conformation in a number of adrenergic molecules, NMR studies show that other conformations are also populated in solutions. A ratio of 43:57 antiplanar:synclinal for dopamine was obtained by Buster and Egan[42] using NMR spin coupling analysis. Portughese[39] estimated a ratio of (ap+ -sc):+sc as 90:10 for R(-) ephedrine whereas a ratio of 84:16 ap:(-sc+sc) was obtained for ψ-ephedrine. A support for the effect of N-substitution on the conformation as a function of τ(C6-C7-C8-N) was provided from NMR studies by Forrest, Heacock and Forrest[43]. They provisionally estimated the ratio of antiplanar:synclinal as 70:30 for epinephrine and 50:50 for isoproterenol. Thus, varying substituents on the nitrogen, α and β carbons of the phenylethylamine side chain seem to have subtle influences on the conformational preference of adrenergic molecules. Since theoretical methods can yield energies of the molecule in all possible conformations, they can be used to study the influence of substituents on various parts of the molecule, eventhough the calculated energies are not very accurate on an absolute basis.

Once the structural information for biologically active molecules has been gathered, the traditional approach to characterize the system has been to consider the structural variations alongside the relative biological activities, and hypothesize on the role of structure and conformation in the biological process. Patterns in primary structure and chirality emerge simply from the consideration of structural formulae and absolute configurations. Three dimensional conformational effects are considered in terms of structures which are at least sterically permitted and possibly energetically preferred, i.e. corresponding to a global or local minimum in conformational energy. The theoretical methods treat the molecule under consideration as an isolated entity, free from environmental effects, whereas the molecule in a biological fluid is likely to be significantly influenced by the solvent and proximity to a neural receptor. Some cognizance of this, qualitative or quantitative, is in order in theoretical structure activity relationships. The structural data derived from crystallography is also subject to considerations on this point. The characterizations of conformation in solution provide highly relavant information but are usually restricted to certain coordinated where NMR spin coupling analyses can be applied or where model compounds permit caliberation of conformational aspects of viberational freequencies in the IR spectra.

The most useful structure-activity information for characterizing the role of conformation in normal neurotransmission comes from data on the transmitter and the derivatives which

introduce minimal primary sturctural changes but influence secondary structure. There are several obvious mechanisms by which a change such as addition of a substituent methyl group to a neurotransmitter may infuence its biological activity. The substituents may sterically prevent the compound from accesing a biologically active conformation which properly orients the functional groups, or electronically influence the position of preferred conformations. Alternatively, the substituent group may conceivably cause a charge redistribution on functional groups leading to eiether enhancement or decrease in biological activity. Finally, it is possible for substituent group to have direct bonded or nonbonded interaction with the biological receptors. Such interactions might be steric, hydrophobic or electrostatic in nature and may enhance or diminish biological activity.

The study of structure-activity relationships in adrenergic receptors is mainly focused on correlating the effects of N-substitution with the α and β types of activities. The possible explainations for the increase of β-activity in passing from norepinephrine to isoproterenol and vice versa have centered upon (a) The effect of alkyl substituent on the quarternary nitrogen pK_a (which could be related to some mechanistic steps): (b) an influence of the alkyl group on preferred conformations of τ(C6-C7-C8-N), (c) direct hydrophobic interaction of the alkyl chain and the receptor, and (d) interference of the alkyl group in ammonoum hydrogen bonding with the α-adrenergic receptors. Sinistri and Villa[46] have studied the pK_a effect

and found the variation to be less than 1 pKa unit and the values support the protonation equillibrium of the ammonium function. Pratesi and Grana[21] have attempted to correlate these pK values with positive inductive effect of the alkyl group linked to the nitrogen. They favor the idea that the inductive effects of the groups influence the adrenergic activity. Larsen[47] suggested a hypothesis, according to which the alkyl group on the nitrogen influences the conformation, so that the molecule with and without N-substituents can exist in two different forms. George, Kier and Hoyland[37] investigated the effect of increasing N-alkyl substitution on conformation and charge distribution in adrenergic catecholamines using EHT calculations and concluded that N-alkyl influence was negligibally small. They suggest the possibility of hydrophobic bonding of the substituents at the β-receptors. George et al.[37] and Pratesi and Grana[21] suggest that a hydrogen bonding takes place between the amino hydrogens and the α-receptors. Thus different approaches have been used to explain α and β adrenergic activities, some of which will be examined in the light of our results obtained by INDO calculations, in the discussion section.

Before concluding this section, we may note in passing that the β-activity is linked to the metabolic effects such as stimulation of adenyl cyclase[48] and efforts are being made to study the interaction of catecholamines with ATP and adenyl cyclase[49,50,19].

A. 3. Rationale. As described in the previous section, the relationship for adrenergic agonists between structure, conformation and biological activity has been studied through x-ray crystallography, molecular spectroscopy, molecular quantum mechanics and bioassay techniques. At the outset of the thesis research described herein, however, a knowledge of the secondary minima and the effect of various substituents on the molecular conformation and electronic charge distribution on adrenergic compounds was not completely available. Thus a total energy minimization of norepinephrine as a function of conformation with respect to τ(C5-C6-C7-C8) and τ(C6-C7-C8-N) was in order. The aim here was to locate energy minima in the surface, develop an understanding of the minima in terms of structural forces and to consider the relationship between the calculated minima and molecular geometries considered in experimental studies.

Examination of Fig.1. shows that if bond lengths and angles are directly adopted from crystallographic data, and if hydrogen bond lengths and angles are assumed to be standard, conformational designation of norepinephrine reduces to a five parameter problem: τ(C6-C7-C8-N), τ(C5-C6-C7-C8), τ(H-O2-C3-C4), τ(H-O1-C2-C1) and τ(H-O3-C7-C6). The latter three dihedral angles represent the position of hydroxy hydrogens. The position of these hydrogens are mainly decided by the surrounding environment in the crystal, but should be positioned at a minimum energy conformation for the isolated molecule. Energy minimization was done by INDO calculation and the same dihedrals were used as input for the INDO calculations on other adrenergic

molecules. Thus with three parameters fixed, total energy minimization of norepinephrine reduces to a consideration of τ(C5-C6-C7-C8) and τ(C6-C7-C8-N). Accordingly the INDO potential energy surface of norepinephrine as a function of τ(C5-C6-C7-C8) and τ(C6-C7-C8-N) was generated. Further, characterization of the nature of intramolecular forces stabilizing the -synclinal and antiplanar conformations is developed through a study of norepinephrine with an energy breakup[51].

With the molecular electronic structure of norepinephrine well charicterized on a theoretical basis, the next logical step in an appraoch to a comprehensive theoretical treatment of adrenergic neural transmission systems involves a systamatic study of the potential energy surfaces and electronic structures of a number of adrenergic molecules such as epinephrine, isoproterenol, at a comparable level of approximation. Then a detailed study of the differences and similarities among energetically preferred conformations of adrenergic agonists can be made. By studying the similarities and differences in the preferred conformations and electronic structures, we should be able to consider the mechanisms of action between the agonists and adrenergic receptors at a molecular level. Since the direct and indirect types of action are related to the hydroxy groups and since the orientation of these groups affects the variation in dipole moments, a study of dipole moment values calculated from the INDO generated wave functions would be a profitable line of approach in our investigations. This also gives qualitative ideas on solvent effects. Overall, this study should provide additional insight into the nature of

direct and indirect types of adrenergic activities. Finally, theories currently offered on the structural chemistry of adrenergic action may be constructively criticized on the basis of foregoing considerations and reorganized to a more comprehensive form.

B. Specific Aims:

The specific aims of this study are as follows:

1. The quantum theoretical calculations of norepinephrine's τ(C5-C6-C7-C8) and τ(C6-C7-C8-N) potential energy surface and molecular electronic structure using approximate SCF-MOT including all valence electrons.

a. The orientation of hydroxy hydrogens, represented by the dihedral angles τ(H-O1-C2-C1), τ(H-O2-C3-C4) and τ(H-O3-C7-C6), are fixed by preliminary INDO calculation of the potential energy surfaces.

2. Consideration of the above results in terms of basic stereochemical principles, and specific evaluation of the intramolecular interactions, respondible for the stabilization of -synclinal and antiplanar conformations of τ(C6-C7-C8-N) (gauche orientation of the O-C-C-N group) in norepinephrine. The latter is accomplished through use of an energy breakup.

3. The calculation of the potential energy surfaces and profiles, and atomic charge densities analogous to those generated for norepinephrine for the compounds:

epinephrine
isoproterenol
dopamine
erythro ephedrine
threoephedrine
phenylethylamine
phenylethenolamine

4. The computerized plotting of the potential energy surfaces for accurate presentation and location of minima, and the computerized stereographic display of energetically preferred conformations of each molecule under consideration.

5. A detailed development of the relationship between the results of the quantum theoretical calculations and results reported from x-ray crystallography and molecular spectroscopy for each molecule.

6. A detailed comparision of the calculated potential energy surfaces and electronic charge distributions of adrenergic compounds.

7. Total consideration of the above results in a biological perspective and a critical evaluation and reconsideration of current theories of the structural chemistry of adrenergic action.

C. Methods and Theory:

The calculation of a potential energy surface for a molecule involves the calculation of the total energy of the system as a function of internal atomic displacement coordinates. In quantum mechanical systems, the energy is an expectation value of the Hamiltonian operator and molecular wavefunction, and thus a calculation of the wavefunction at a number of points in configuration space is required. For the Hamiltonian operator H and molecular wavefunction Ψ energy is given as

$$E = \int \Psi H \Psi \, d\tau \qquad (1)$$

Molecular wavefunctions computed in this research are based on spin-restricted molecular orbital theory, with the 2n-electron wavefunction Ψ considered as a Slater determinant of the molecular orbitals ψ_i

$$\Psi = |\psi_1(1)\bar{\psi}_1(2)\psi_2(3)\bar{\psi}_2(4)\ldots\psi_n(2n-1)\bar{\psi}_n(2n)| \qquad (2)$$

The molecular orbitals are individually expanded as linear combinations of atomic orbitals (LCAO) ϕ_μ centered on constituent atoms

$$\psi_i = \sum_\mu c_{\mu i}\phi_\mu \qquad (3)$$

where the $c_{\mu i}$ are linear expansion coefficients. The calculation of the molecular wavefunction reduces to the determination of the coefficients by matrix Hartree-Fock self-consistant field procedures[52]. The total energy of the system at a given geometry is given by the expression

$$E = \sum_{\mu\gamma}\sum P_{\mu\gamma}(H_{\mu\gamma} + G_{\mu\gamma}) + \sum_{A<B} \Sigma Z_A Z_B R_{AB}^{-1} \qquad (4)$$

where the summation over greek and latin letters refer to orbitals and atoms respectively. The first term on the right hand side of equation 4 is the electronic energy of the system and involves $H_{\mu\gamma}$, the one-electron matrix element between atomic orbitals ϕ_μ and ϕ_γ, and is representative of the kinetic and nuclear attraction operators. The $G_{\mu\gamma}$ are elements of the matrix representative of electron replusion operators. The density matrix elements $P_{\mu\gamma}$ are defined in terms of the LCAO coefficients as

$$P_{\mu\gamma} = 2\sum_{i}^{n} c_{\mu i} c_{\gamma i} \qquad (5)$$

and specify the distribution of electronic charge in the system. The second term on the right side of equation 4 accounts for internuclear repulsions, and involves the core charges Z_A, Z_B, and the internuclear seperation between atoms A and B, R_{AB}.

Theoretical studies of neurotransmitter structure have used methods ranging from empirical pairwise potential functions to a variety of approaches based on molecular quantum mechanics. The quantum mechanical methods currently being used treat σ and π electrons explicitly, and fall into four basic categories: approximate independent molecular orbital theory, approximate self consistant field molecular orbital theory, approximate configurational interaction(CI) methods and ab initio SCF-MO methods.

In calculating electronic wavefunctions, one considers simultaneously the attraction between electrons and atomic nuclei of a molecule and interelectron repulsions in the framework of molecular orbital theory. However, the size of the mathematical problem goes up as least as N^4, where N is the number of electrons. Thus for large bio-organic molecules the calculation of precise wavefunctions is beyond the time limitations of our present generation of computers. In view of this, considerable effort has been devoted to developing molecular orbital methods capable of treating large organic and bio-organic molecules with sufficient accuracy to provide the information necessary for the treatment of scientific problems in chemistry and molecular biology[53]. The quantum mechanical methods which are currently being used are mentioned above, and these methods as well as those used in early work are discussed in the following paragraphs.

Approximate molecular orbital theories began with methods limited to pi-electrons of unsaturated molecules such as in Huckel theory,[54] which has been extensively applied to problems in biochemistry by Pullman and collaborators[55]. Methods of this type have often been criticized on the grounds of giving too many approximations to be a basis for reliable theory, since inter-electron repulsions are neglected. A more refined approach to pi-electron theory including inter-electron repulsion in a self-consistant field manner was introduced by Pariser, Parr and Pople[56] and has been highly succesful in accounting especially for the wavelengths of electron absorption

bands in ultraviolet spectra. The consideration of all chemically effective electrons in a molecule in approximate molecular orbital theory was developed in the form of Extended Huckel Theory by Hoffman[57] but is subject to criticism with regard to inter-electron repulsions, just as was simple Huckel theory. EHT falls into the category of approximate independent electron molecular orbital theory and has been widely used by Hoffman[58] in innovative studies of organic reaction mechanisms. The quantitative application of this method to conformational problems has proved less succesful, with bond lengths sometimes unreliable and bond angles and dihedral angles giving some reasonable agreement with experiment in certain sysrems. The well known limitations of independent electron molecular orbital theory in treating heteroatomic systems is a special disadvantage for neurotransmitter structures, as evidenced in the molecular electronic charge distributions computed using EHT[59].

Self-consistant field molecular orbital theory has provided a framework for the development of a series of approximate methods for theoretical studies of polyatomic molecules. The principle approximations are the neglect of differential overlap in two-empirical parameterization of certain one electron integrals. Valence electron SCF theories involving complete neglect of differential overlap (CNDO) and intermediate neglect of differential overlap (INDO), where differential overlap is neglected only in polycentric electron repulsion integrals were developed by Pople, Segal, Santry, Beveridge and Dobosh,[60,61] and parametrized for elements of the first row of the periodic table. Generally these methods produce good electronic charge

distributions as evidenced by the agreement between theory and experiment for electric dipole moments,[53] and they are among the best approximate molecular orbital methods currently available for treating large organic and bio-organic molecules. Bond lengths and angles are reasonably well accomodated, with certain exceptions[53]. The agreement between theory and experiment to be expected for rotational barriers and dihedral angles has been well documented[62]. The methods have shown success tempered with significant inadquacies, such as failure to reproduce the planar geometry of unsaturated polyenic hydrocarbons[63]. Bond ionization excitation energies are poorly reproduced by INDO and CNDO[53], but a modification of INDO due to Dewar (MINDO)[64] has proved to accomodate bond energies and ionization energies. Jaffe and del Bene[65] have reworked the CNDO method for excitation energies. Extension of the methodology to second row elements and transition metals has proved to be quite complicated, although some progress has been recently acheived[66,67].

An alternative approach to the quantum mechanical calculation of conformational energy is the PCILO method[68], where the energy is developed using perturbative configuration interaction methods on a localized molecular orbital basis. A wide range of applications of the PCILO method to biological molecules has been reported by Pullman and coworkers[69], using atomic integrals evaluated in the CNDO approximation. This approach has some basic theoretical and technical advantages for conformational problems, since with the perturbation

expansion carried to third order some representation of electron correlation is introduced, and since there is no iterative matrix eigenvalue problem to solve, the calculations are relatively fast even for large molecules. Energy variation with respect to dihedral angles in PCILO/CNDO calculations is significantly less than that for SCF/CNDO calculations due to a natural tendency of configuration interaction to depress higher energy regions relatively more than lower energy regions, and rotational barriers may be too low. The PCILO localized orbital basis may be designed using basic chemical intution, and as chosen appears to correct for tendencies in the approximate SCF methods to overestimate intramolecular effects such as hydrogen bondings.

With modest amounts of computer time available, however, molecular orbital theory with atomic integrals evaluated at the INDO level of approximation does provide a quantum mechanical computational vantage point tractable for extensive calculation of conformational energy maps of molecules of the size considered herein.

Using the INDO method, the total energy of the system is calculated using equation 4 with the appropriate integral approximations included. The net electrical charges Δq_A associated with each of the atoms A in the molecule is given by

$$\Delta q_A = Z_A - \sum_{\mu}^{A} P_{\mu\mu} \qquad (6)$$

where the summation includes all $P_{\mu\mu}$ for orbitals centered on atom A. The electric dipole moment $\underset{\sim}{\mu}$ at the INDO level is given by the expression

$$\underset{\sim}{\mu} \quad \underset{\sim}{\mu}_{chg} + \underset{\sim}{\mu}_{hyb}$$

where

$$\underset{\sim}{\mu}_{chg} = 2.546 \sum_{A} \Delta P_{AA} R_A \tag{8}$$

and, e.g.

$$(\mu_{hyb})_x = -14.674 \sum_{A(\neq H)} \zeta_A^{-1} P_{2S_A 2P_{XA}} \tag{9}$$

where ζ is the orbital exponent of the orbitals centered on atom A.

In computing conformational stability, the total energy E is calculated as a function of the appropriate internal displacement coordinates, and the calculated energy E can be partitioned into monoatomic and diatomic contributions E_A and E_{AB} respectively such that [70b]

$$E = \sum_{A} E_A + \sum_{A<B} E_{AB} \tag{10}$$

and the variation of individual terms examined seperately. The expressions for E_A and E_{AB} are:

$$\begin{aligned} E_A = \sum_{\mu}^{A} P_{\mu\mu} \; [\; & 2U_{\mu\mu} + .25P_{SS}F^\circ + P_{SS}(P_{SX}+P_{SY}+P_{SZ})(F^\circ - .167G^1) \\ & + .5(P_{XX}^2+P_{YY}^2+P_{ZZ}^2)(.5F^\circ+(4/50)F^2)+2(P_{XX}P_{YY}+P_{XX}P_{ZZ}+P_{YY}P_{ZZ})(F^\circ-7F^2) \\ & + .5(P_{SX}^2+P_{SY}^2+P_{SZ}^2)(G^1-F^\circ)+(P_{XY}^2+P_{XZ}^2+P_{YZ}^2)((11/50)F^2-(1/2)F^\circ) \;] \end{aligned} \tag{11}$$

$$E_{AB} = \sum_{\mu}^{A}\sum_{\gamma}^{B} P_{\mu\gamma}[(\beta_A^\circ+\beta_B^\circ)S_{\mu\gamma}-(1/2)P_{\mu\gamma}\gamma_{AB}]$$

$$+(1/2)[P_{AA}(P_{BB}-2Z_B)+P_{BB}(P_{AA}-2Z_A)]\gamma_{AB} \qquad (12)$$

where $U_{\mu\mu}$ is a monoatomic core integral; F^0, F^2 and G^1 are Slater-Condon notation for one-center radial atomic integrals; γ_{AB} is a two center repulsion integral; β_A° and β_B° are bonding parameters; and $S_{\mu\gamma}$ is an overlap between atomic orbitals ϕ_μ and ϕ_γ. Values for these quantities are assigned as described in Ref. 53. Elucidation of the factors responsible for the conformational stability of the gauche O-C-C-N^+ grouping is approached by examinining the variation in E and individual E_A and E_{AB} for norepinephrine as a function of τ(O3-C7-C8-N). A significant variation in an E_A term may be ascribed to charge redistribution and rehybridization effects, while a variation in E_{AB} signals a change in bonding.

The fortran routines which have the capabilities of performing SCF-MO calculations at the INDO level of approximation require as input total molecular charge, an indication if the calculation is to be carried out in the ground state or an excited state (ground state for all calculations presented herein), and the atomic number and cartesian coordinates for each atom in the molecule. Once these data are provided, the INDO wavefunction and the properties calculatable therefrom are uniquely defined, and thus are obtainable through an automatic computational procedure. This system is conviently interfaced with the model builder system[71] (SUBROUTINE ZMAT) which accepts as input intramolecular bond lengths and angles, and four atoms torsions, and generates cartesian coordinates in an arbitrary

frame. Thus the completion of INDO calculations reduces to a problem of geometrical input. For the calculations presented herein, great value has been placed upon the results of crystal structure determinations for input. Although this approach has possible limitations, it has the advantage of keeping the input to the MO calculation well in contact with physical reality, and obviates the extensive preliminary setting of numerous geometrical parameters. A fortran routine XTAL[70a] which had been specifically developed by Radna for convenient workup of crystallographic data was used. A part of this program frequently employed in the work presented herein is SUBROUTINE UNZMAT which accepts cartesian coordinates (derived directly from the crystal unit cell) and generates input to model builder.

Intramolecular steric interactions have the capability of significantly influencing INDO calculated potential energy surfaces. Thus it is advantageous to have access to a computationally inexpensive method of evaluating intramolecular steric interactions before the relatively more expensive MO calculations are undertaken. Accordingly a routine SZMAT was utilized which accepts input to model builder, and also parameters for systamatic incrementing of crucial bond lengths or angles or more frequently, four atom torsions. The routine preserves on peripheral storage devices the interatomic distance arrays of all pairs of atoms which anywhere in the conformations considered have an interatomic distance of less than 3Å. Toward completion of the routine these arrays are

printed with a summary steric grid which clearly defines sterically permitted and forbidden regions in conformational space. These steric grids can have significant correlation with INDO calculated potential energy surfaces.

Data acquired in the course of quantum mechanical calculations as described above must be reduced to a form suitable for developing a detailed understanding of each individual system and for cross-comparison of each system with others. In this regard, extensive use is made of computer graphic for display of potential energy surfaces and conformations of molecules. Here reliance is placed on two programs: CONSURF and ORTEP.

CONSURF is a fortran program for graphic display of contour lines representative of a function of two variables. This routine is used to contour potential energy surfaces as functions of atomic internal displacement coordinates. An example of CONSURF output is presented in Fig. 2.

ORTEP is a modification of the fortran coded Oak Ridge Thermal Ellipsoid Plot program which was developed by C. K. Johnson[72]. This routine provides for automatic drawing of molecular geometries on an incremental plotter, Input of cartesian or crystallographic coordinates of a molecular system is accepted, and output like that presented in Fig.5. is produced. Accurate display of molecular geometry in this manner substantively aids in the elucidation of common structural features of sets of compounds.

D. Results:

As noted in the previous section, prior to the calculation of the potential energy surface of adrenergic molecules as a function of τ(C6-C7-C8-N) and τ(C5-C6-C7-C8), it is valuable to know the orientation of all the hydroxy groups with respect to the skeleton molecule. Though the position of hydroxy hydrogens in some cases are available from neutron diffraction experiments, it may not be suited for the calculations in free space approximations, since the experiments are carried out on crystalline molecules. Therefore the orientation of the hydroxy groups were fixed based on the results of INDO calculation on norepinephrine as functions of dihedral angles τ(H-O3-C7-C8), τ(H-O1-C2-C1) and τ(H-O2-C3-C4). The dihedral angles thus obtained are used to calculate the potential energy surface of τ(C6-C7-C8-N) and τ(C5-C6-C7-C8) in all the adrenergic molecules that are studied. This will be further discussed in subsequent paragraphs. All other molecular parameters used in the calculations on adrenergic substances described herein are given in Appendix. The potential energy surfaces that are presented were traced from a computer generated contour surface. The contour is based on 144 grid points that are calculated at 30^0 interval and they are spaced at an interval of 1 kcal/mole.

The energy surface of norepinephrine as function of τ(C6-C7-C8-N) and τ(H-O3-C7-C6) is given in Fig.2. The minima on the surface are labelled A, B and C in the order of increasing energy. The absolute minimum on the surface is located at

τ(H-03-C7-C6) = 300° and τ(C6-C7-C8-N) = 210°. The local minimum at τ(H-03-C7-C6) = 300° and τ(C6-C7-C8-N)= 300° point B is calaulated to be 4 kcals above the absolute minimum. Local minimum C is calculated to be 8 kcals above the global minimum and is located at τ(H-03-C7-C6) = 300° and τ(C6-C7-C8-N) = 60°. In all the three minima, A, B and C, the dihedral angle τ(H-03-C7-C6) = 300°. This agrees with the PCILO calculation carried out by Pullman, Coubeils, Courriere and Gervois[31]. However, τ(H-03-C7-C6) is 143° in the crystal of norepinephrine hydrochloride[27] and the difference is perhaps due to the fact that 03 is involved in intermolecular hydrogen bonding in the chloride crystal of norepinephrine.

The potential energy surface of norepinephrine as a function of τ(H-01-C2-C1) and τ(H-02-C3-C4) is presented in Fig.3. The minima are labelled as A, B and C where A and B are the absolute minima and the minimum C occurs at 0.6 kcals above the global minima. The dihedral angles corresponding to the point A are τ(H-01-C2-C1) = 180°, τ(H-02-C3-C4) = 0° and the angles at the minimum B are τ(H-01-C2-C1) = 0° and τ(H-02-C3-C4) = 180° and both these dihedral angles take the value of 180° in the case of the secondary minimum C. The minima A and B correspond to the conformation at which one of the catechol hydroxy hydrogen is directed towards an adjacent oxygen and this position is favorable for intramolecular hydrogen bonding. Experimental

or theoretical data are not available on the orientation of hydroxy groups of adrenergic molecules in solution in order to compare with the above results.

After setting the hydroxy groups to the minimum energy configuration, the potential energy surface of norepinephrine was calculated as a function of the dihedral angles τ(C6-C7-C8-N) and τ(C5-C6-C7-C8). The results of this calculation are presented in Fig.4. The minima are labelled A-F. The global minima corresponding to the points A and B are located at $\{210,90\}$ and $\{210,-90\}$. The secondary minima C and D are located at $\{300,-90\}$, $\{300,90\}$ respectively and the energies are about 3.5 kcals above the global minima. The minima E and F are about 7.5 kcals above the global minima and they occur at $\{60,90\}$ and $\{60,-90\}$.

The conformation associated with the calculated minimum $\{210,-90\}$ can be identified with the $\{176,-97\}$ geometry observed for norepinephrine in the chloride crystal. It is interesting to note that all the minima occur at τ(C5-C6-C7-C8) = $\pm 90^{\circ}$. The minima at the values $\pm 90^{\circ}$ in the coordinate τ(C5-C6-C7-C8) which positions the catechol ring are clearly developed in response to weak steric effects involving amino-hydrogens and phenyl hydrogens. When τ(C6-C7-C8-N) is between 60° and -60°, the rotation of τ(C5-C6-C7-C8) is hindered due to the possibility of steric interaction since the catechol ring lies near the amino group. Thus a large fraction of the energy surface in Fig.4 are of high energy region for τ(C6-C7-C8-N) between 60° and -60°.

When potential energy of norepinephrine is considered as a function of τ(C6-C7-C8-N), the global and the local minima appear at approximately 210° and ±60° respectively. With τ(C5-C6-C7-C8) held at -90°, the calculated minima in τ(C6-C7-C8-N) shown in Fig.4 correspond roughly to the minima in a potential energy profile for rotation of tetrahedrally hybridized atoms about an essential single bond, which are expected to occur at 60°, 180° and 300°. However, the negative synclinal conformer is more stable than positive synclinal conformer. This preferential stabilization is due to the interaction between the cationic head and the electronegative oxygen. A weak intramolecular hydrogen bonding is also possible. The hydrogen bonding is most commonly found in circumstances involving an A-H···X structure where A and X are both electronegative with respect to hydrogen. The structure is stabilized by a combination of coulomb, Vander waals and charge transfer forces[73]. In the ammonium cationic head, the electronegative nitrogen may effectively withdraw electrons from the hydrogens activating the hydrogens for hydrogen bonding. An accurate account of hydrogen bonding energies is somewhat beyond the capability of the level of calculations presented herein, since Vander Waals forces are not accomodated in the orbital approximation. The semiempirical nature of the INDO methodology also introduces uncertainty in the calculated energies. Nevertheless a contribution from coulomb forces should appear and calculated charge distributions should be recognizable. This is significant in that the coulomb energy is generally held to be the dominant attractive contribution to

weak hydrogen bonds[74].

The wave function generated in the SCF-INDO calculation was used to evaluate the dipole moment values of norepinephrine as a function of τ(C6-C7-C8-N) and τ(C5-C6-C7-C8). The estimated values range from 4.9 to 16 debyes. The conformation corresponding to the lowest dipole is $\{0,180\}$ and that corresponding to the highest value is $\{180,330\}$. The dipole moment of any molecule containing hydroxy groups depend on the direction of theO-H bonds. As discussed before, the orientation of the hydroxy groups in norepinephrine and in other adrenergic molecules are fixed on the basis of minimum energy conformation in free space as determined by SCF-INDO calculations. These positions may differ from those in solutions. Nevertheless, a comparision of the dipole moment values for different adrenergic molecules can be carried out, since the positions of the hydroxy groups are maintained the same in all the molecules.

The calculated net atomic charges for norepinephrine, in the conformations $\{210,-90\}$, $\{300,-90\}$ and $\{60,-90\}$ are shown in Figures 5-7. In the antiplanar conformation, the positive charge associated with the nitrogen is delocalized over the entire cationic head. The hydrogens attached to the nitrogen carry a net positive charge of approximately .2. The net charge on the nitrogen is .055. Total charge on $-NH_3^+$ adds up to .662. The charge density on the electronegative oxygen -03 is -.375. The phenyl ring carries a net positive charge 0.091.

The electronic charge distribution of norepinephrine in {300,-90} and {60,-90} conformations may be best understood in terms of perturbations on the distribution for {210,-90} conformation. In the {300,-90} conformer, net charge on the cationic head is still .664. The negative charge on the β-hydroxy oxygen is .363, indicating a slight electronic charge transfer out of the oxygen atom. This charge slightly decreases the coulombic attraction between the β-hydroxy oxygen and the proximal amino hydrogen and correlates with a slightly higher potential energy of the -synclinal conformation. The negative charge lost by the oxygen is partly gained by the ring, the net charge of which sums up to +.053.

In the {60,-90} conformer, the net positive charge on the nitrogen has decreased to .642 and the net negative charge on the β-hydroxy oxygen has decreased to .339. It considerably reduces the coulombic attraction between the β-hydroxy oxygen and the hydrogens on the nitrogen. Further, the distance between the β-hydroxy oxygen and none of the amino-hydrogens is less than 3.9 Å in the synclinal conformation where as the distance between the hydroxy oxygen and one of the amino-hydrogens is 2.56 Å in the -synclinal conformation and two of the amino hydrogens are at 2.29 Å and 2.75 Å distant from the β-hydroxy oxygen in the antiperiplanar conformation. The variation in the charge densities and the distances are in accordance with an increase in the energy of the synclinal conformer over the antiperiplanar or the -synclinal conformers. The net charge on the catechol ring in the {60,-90} conformer is +.055.

Though the net positive charge on the catechol ring is lower for {300,-90} and {60,-90} conformers than that of the {210,-90} conformer, there is no significant change in the net negative charge on the catechol hydroxy oxygens. Therefore the catechol hydroxy oxygens do not contribute to the potential energy minimum by direct coulombic interaction. However, the charge densities on the ring carbons and hydrogens that are close to the cationic head vary with conformation indicating the interaction of the cationic head with the ring. Carbon C1 and the hydrogens attached to C1 are closer to the cationic head in the -synclinal conformation with an N-C1 distance = 3.1 Å and an N-H on C1 distance being 2.94 Å. Carbon C5 and the hydrogen bonded to C5 are closer to the amino group in the +synclinal conformation with the distance between N-C5 = 3.06 Å and N-H on C5 = 2.94 Å. The electron density on C1 has reduced from -.051 in the -synclinal conformation to -.03 in the +synclinal conformation. Similarly the charge densities on the hydrogen bonded to C1 are -.009 and +.01 in the -synclinal and the +synclinal conformations respectively. In the negative synclinal conformation the charge density on C5 is +.019 and on the hydrogen attached to C5 is -.013. The charge densities are +.001 and -.034 on C5 and on hydrogen respectively in the positive synclinal conformation. The same trend i.e, the ring carbons and the hydrogens those are close to the cationic head acquiring more negative charge, is also seen when τ(C5-C6-C7-C8) = 90^0.

Thus the energy minima that are obtained seem to be due to the combined effects of the steric factors and electronic interactions. The occurrence of the absolute minima at $\{210,\pm90\}$ is due to steric factors, and is also enhanced by coulombic interaction between the cationic head and the β-hydroxy oxygen. In the secondary minima $\{300,\pm90\}$, the cationic head is placed in such a way that it can interact with β-hydroxy oxygen as well as with one of the ring carbons and hydrogens attached to it. The N-O3 distance is 3.64 Å in the $\{60,\pm90\}$ conformation; this rather large seperation reduces the interaction between the positively charged amino hydrogens and β-hydroxy oxygen. The variations of the charge density distributions with different energy minimum conformations suggest that the electrostatic interactions are partly responsible for the observed minima. Similar conclusions can be drawn from the studies that are mentioned below.

In order to determine quantitiatively the stabilizing forces that lead to the various minima as a function of τ(C6-C7-C8-N), a partitioning of the INDO total energy of norepinephrine into monoatomic and diatomic contributions was carried out. The variations in many individual contributions exceeded the variations in the calculated total energy, emphasizing the fact that the total energy is a subtle balance of widely varying terms, Each E_A and E_{AB} was individually examined as a function of τ(C6-C7-C8-N) and the significant results are displayed in Fig.8 to 10. All relevant contributions from the partitioned energies responsible for the stability of

the antiplanar, -synclinal and +synclinal regions of τ(C6-C6-C8-N) are represented in these figures, as are particularly interesting contributions that tend to increase the energy in the regions of minima.

Selected monoatomic contributions to the total energy of norepinephrine are plotted together with the total energy as a function of τ(C6-C7-C8-N) in Figure 8 and the analogous plots for selected diatomic contributions are given in Figure 9. The calculated net stabilization of the antiperiplanar and the -synclinal conformers are correlated with the contributions from the monoatomic O3 term, and the diatomic oxygen-hydrogen term, involving the amino-hydrogens proximal to the oxygen. The stability of the synclinal conformer depends on the monoatomic contributions from the proximal carbon and hydrogen of the ring, and the monoatomic contributions from the hydrogens bonded to the β-hydroxy oxygen, The diatomic O3-C7 contribution is also responsible for the stability of the synclinal conformation. Thus the calculated stabilization of the energetically preferred conformation in the antiplanar and -synclinal forms is directly associated with the interaction between the oxygen and C7 and the cationic head, with the interactions between the oxygen and the proximal amino hydrogens indicated as a significant factor.

Analogous calculations on norepinephrine have been reported by Pedersen, Hoskins and Cable[32] at the SCF-INDO level and by Katz, Heller and Jacobson[44] at the level of CNDO method. Pullman et al.[31] have reported the studies on norepinephrine

using PCILO method and Kier[30] has carried out EHT calculations. The EHT, PCILO-CNDO ans SCF-INDO results are in close accord with a low energy valley for τ(C6-C7-C8-N) = 180° and global minima at τ(C5-C6-C7-C8) = ±90°, the conformation which is also in accordance with the crystal geometry. The CNDO calculations by Katz et al. also give similar results except that τ(C6-C7-C8-N) = -60° is slightly more preferred over antiplanar conformation.

The INDO calculations of Pedersen et al.[32] show -sc and ap geometries about τ(C6-C7-C8-N) at about the same energy. We have found that the crystal geometry about τ(H-O3-C7-C6) is due to intermolecular forces in the crystal and the energetically preferred value is -60°. This latter value is more appropriate for calculations in the free space approximation and was adopted for the results represented in Fig. 4; this may be the cause of descrepancy. Pedersen et al have made some exploratory calculations on the effect of $Li(H_2O)_2$ chelation, and found the -sc geometry about τ(C6-C7-C8-N) to be prefentially stabilized over ap. Pullman et al.[31] have used τ(H-O3-C7-C6)=60° and their minima correspond to those obtained by us using SCF-INDO method. However, the energy difference between ap and -sc is about 3.5 kcals/mole as calculated by INDO method whereas the differences produced by PCILO calculations are of the order of 1-2 kcals/mole. EHT calculations, as calculated by Kier[37] could not distinguish between the -sc and the+sc conformations.

It is important that the results of the calculations should agree with the experimental observations. The absolute minimum energy conformation of norepinephrine obtained by us and by other authors using theoretical methods agree with that of the crystal geometry of norepinephrine hydrochloride. However, one can not get the secondary minima and their relative population by crystallographic methods. The population analysis of various conformations of norepinephrine in solution has not yet been carried out. Among the theoretical calculations, INDO and PCILO methods yield similar results with regard to the stability of -sc and +sc conformers. In the previous discussions it was attributed to the interaction between the β-hydroxy oxygen and the cationic head. Though there is a possibility that such an interaction is overestimated by INDO method, the results should be reliable at least on a qualitative basis.

With the structural chemistry of norepinephrine and the forces responsible for the stability of various minima well characterized by molecular quantum mechanics at the INDO level of approximation, a study at this level of approximation was carried out on important adrenergic agonists: dopamine, epinephrine, isoproterenol, erythro ephedrine, threo ephdrine, phenylethylamine and phenylethenolamine. The results of this work are presented in the following paragraphs.

Dopamine: The coordinates of heavy atoms in dopamine hydrochloride crystal have been given by Carlstorm and Bergin[35]. The crystal geometry with respect to the dihedral angles τ(C6-C7-C8-N) and τ(C5-C6-C7-C8) can be represented as $\{174,-99\}$. The crystal geometry was adopted for the SCF-INDO calculation except for the hydrogen bond lengths and distances which were assumed to have standard values. The potential energy surface as a function of τ(C6-C7-C8-N) and τ(C5-C6-C7-C8) is given in Fig.11. The minima are labelled from A-F. The energies of all the minima fall below 1 kcals/mole. The point A corresponds to the absolute minimum $\{180,90\}$. The minima B and C are about .1 kcals above the absolute minimum and the corresponding conformations are $\{180,-90\}$ and $\{300,-90\}$. The geometry of the local minimum E is $\{60,90\}$ and the energy at this conformation is .5 kcals above the global minimum. The local minima D and F are about .7-.8 kcals above the absolute minimum and are located at $\{300,90\}$ and $\{60,-90\}$. Since the energy differences calculated by SCF-INDO method are good only on a qualitative basis, it is not possible to estimate accurately the population of different conformers. Therefore an energy difference of 1 kcals/mole is arbitrarily taken as a unit and all the conformations which have an energy difference below 1 kcal/mole are represented to have the same energy.

The energy minima obtained at τ(C5-C6-C7-C8) = $\pm 90^{\circ}$ is due to the steric reasons discussed in the case of norepinephrine. With τ(C5-C6-C7-C8) = -90°, the calculated minima in τ(C6-C7-C8-N) shown in Fig.11 correspond to the potential

energy profile for rotation of tetrahedrally hybridized atoms about a single bond. Both the -sc and the +sc conformers have approximately same energies unlike as in the case of norepinephrine. This is due to the absence of β-hydroxy group on C7 which eliminates the interaction of oxygen with the cationic group, the interaction that is responsible for the higher stability of -sc conformation in norepinephrine.

The above results agree with both the experiment and computations by other theoretical methods. The energies calculated by Buster and Eggen[42] using EHT method show that the antiplanar conformation is of the lowest energy and the two gauche conformers are about 2.56 kcals above the global minima. The same authors also calculated the potential energies using pairwise potential method which placed the global minimum in the antiplanar conformation and the two synclinal conformations at about .36 kcals above the absolute minima. However, the EHT calculations by Kier[75] do not predict the minimum at the antiplanar geometry. The minima obtained by the PCILO method as computed by Pullman et al.[31] and by CNDO method as calculated by Katz et al[44] are also similar to those obtained by us. The NMR experiments[42] show that the antiplanar and the synclinal conformers of dopamine exist in the ratio of 49:51 at room temperature. The minimum B in Fig.11 is identifiable with the crystal geometry {174,-99}.

The net atomic charges for {60,-90}, {180,-90} and {300,-90} are shown in Fig 12 to 14. The ring carbon and hydrogens that are close to the amino group in the particular conformation

tend to accquire more negative charge. C5 and the hydrogen attached to C5 are more negative in {60,-90} conformation whereas C1 and the hydrogen bonded to C1 are more negative in the {300,-90} conformation. This indicates an electrostatic type of interaction between the amino group and the ring atoms that are close to the $-NH_3^+$ group. Though there is a slight change in the net charge on the meta-hydroxy oxygen, the interaction between meta oxygen and the $-NH_3^+$ group is not significant since the energy difference that is obtained between the +sc and the -sc conformations is negligible. The calculated dipole moments range from 6.9 to 18.3 debyes. And the conformations encountered at the lowest and the highest values are {0,180} and {180,0} respectively.

Epinephrine: The crystal geometry of norepinephrine was used as input for SCF-INDO calculation. The geometrical parameters of the methyl group on the nitrogen was assumed to be of standard dimensions. The potential energy surface of epinephrine given in Fig.15 resembles that of norepinephrine. The energy minima are labelled A-F as before. The global minima A and B correspond to {210,90} and {210,-90} respectively. The secondary minima C and D are located at {300,-90} and {300,90}, and the energies are 2.5 kcals above the absolute minima. The minima E and F, located at {60,90} and {60,-90} have energies about 5.2 kcals above the antiplanar conformers.

The occurrence of the various minima in the norepinephrine and epinephrine at the same configurations show that there are no drastic changes in the preferred conformations of adrenergic

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molecules on replacing an amino hydrogen with a methyl group. However, the relative energy differences have slightly decreased upon methylation of the amino nitrogen. The -sc conformers in norepinephrine have 3.5 kcals above the global minima and those in epinephrine have about 2.5 kcals above the global minima. Similarly the + sc conformations of norepinephrine and epinephrine have energies 7.8 and 5.2 kcals respectively above the global minima.

The calculated net atomic charges of epinephrine in the conformations {60,-90}, {210,-90} and {300,-90} are given in Fig 16 to 18. The change in the charge density distributions of epinephrine in synclinal,antiplanar and -synclinal conformations follow the same trend as that observed in the case of norepinephrine. The total charges on the cationic head in the conformations {60,-90}, {210,-90} and {300,-90} are +.693, +.703 and +.706 respectively. Though the total positive charge on the cationic head is slightly higher than that of norepinephrine in the particular conformation, the methyl group in epinephrine delocalizes some of the positive charge in the amino hydrogens. The other differences in the charge density distribution as compared to norepinephrine are as follows. There is an increase in the positive charge on C8 and a decrease in the positive charge on C7. There is no significant change in the net charge on the catechol ring. The calculated dipole moments range from 4.3 to 15.02 debyes, the lowest and the highest values encountered at {0,180} and {150,300} respectively.

The results obtained by George et al.[37] using EHT method do not distinguish between the +synclinal and the -synclinal conformations, both of which have an energy of 3.7 kcals above the antiplanar conformation. Pullman et al.[31] using PCILO method have presented results similar to the one computed by INDO method given in Fig.15. However, the relative energies between various minima are smaller than that computed by INDO method.

Isoproterenol: The crystal structrure of isoproterenol sulfate studied by Mathew and Palenik[36] resembles those of other adrenergic molecules and can be represented as {175,102}. The dihedral angle τ(H-O3-C7-C6) is -100° and the angles corresponding to the catechol hydroxy groups in the crystal structure are τ(H-O1-C2-C1) = -16° and τ(H-O2-C3-C4) = -14°. The hydroxy hydrogens are involved in hydrogen bonding with sulfate or water oxygens.

In the SCF-INDO calculations on isoproterenol, the crystal geometry was used as the input data except fot the dihedrals corresponding to the hydroxy hydrogens. The conformational energy map generated as a function of τ(C6-C7-C8-N) and τ(C5-C6-C7-C8) is shown in Fig.19. The absolute minimum B at {210,120} can be identified with the crystal geometry. Another absolute minimum A is located at {210,-90}. At τ(C5-C6-C7-C8) = $\pm 90^{\circ}$, the rotation of τ(C6-C7-C8-N) from 210° to 360° results in a steady increase of the energy in small amounts. In otherwords, although the energies around -sc conformation are of the order of 4-5 kcals/mole above the antiplanar

conformation, no minima are found in this region. The minimum C at {60,-90} is 3.2 kcals above the global minima and the point D at {30,240} has an energy 4.9 kcals higher than the absolute minima. The electrostatic attraction between the cationic head and the β-hydroxy oxygen which seemed to stabilize the -sc conformer over the +sc conformer in norepinephrine, fails to explain the relative stability of the secondary minima in isoproterenol. It is not clear as to how the presence of isopropyl group on nitrogen influences the stability of the local minima.

The calculated lowest and highest dipole values are 1.97 and 13.36 debyes and these values are obtained for the conformations {30,150} and {120,300} respectively. The conformations producing the extremal dipole values are approximately the same for norepinephrine, epinephrine, dopamine and isoproterenol. It is interesting to note that the common structural features in these molecules is the presence of 2,3 catechol hydroxy groups.

The net atomic charges calculated for isoproterenol in {60,-90}, {210,-90} and {300,-90} conformations are given in Fig.20 to 22. A comparision of the above charge densities with those of norepinephrine and epinephrine can be made at this stage. We note that the general nature of charge distribution has not changed. For example, the β-hydroxy oxygen accquires more negative charge in the conformation where the cationic amino group is closer to the oxygen-03. And the ring carbons C5, C9 and hydrogens attached to them also gain

more negative charge when located near the cationic group. The total positive charge on the cationic head are .706, .719 and .729 in the conformations {60,-90}, {210,-90} and {300,-90} respectively. Similarly the positive charge on the catechol ring are .66, .94 and .60 in the conformations as above. In passing from norepinephrine to epinephrine and then to isoproterenol, one can observe a gradual increase of positive charge on the cationic head, but a decrease in the negative charge on the amino hydrogens. At the same time the positive charge on C8 increases and on C7 decreases from norepinephrine to isoproterenol. The negative charge on the hydrogen bonded to O3 remain more or less unaltered in norepinephrine and epinephrine whereas they decrease in isoproterenol.

Thus the substitution on nitrogen in adrenergic molecules does not seem to produce pronounced effects on the preferred conformations especially on the absolute minima. However, subtle differences are observed due to the presence of alkyl group on the notrogen. There is no direct evidence for substitution effect. Nevertheless we do observe a decrease in the relative energies between the secondary minima from norepinephrine to epinephrine and then to isoproterenol. As discussed earlier, we also observe a noticable trend in the charge density distributions. These facts seem to indicate a possible influence of the alkyl substituent on the conformations and electronic charge distributions in adrenergic molecules.

George et al.[37] have compared a few of the adrenergic molecules to find out the effect of substitution on nitrogen. Based on the conformational analysis using EHT method and a

study of model compounds using CNDO method, George et al. arrive at the conclusion that the substitution on nitrogen has no effect whatsoever either on the preferred geometry or on the net atomic charges. However, the conformational analysis was based on the rotation of τ(C6-C7-C8-N) by 60^{o} increment and the results thus obtained on dopamine and norepinephrine differ from those of the other authors as mentioned before. The alkyl amine model compounds used to find out the charge density distributions are not very good representitives of adrenergic molecules, since the aromatic ring and the hydroxy groups can greatly influence the charge distributions. In fact the nitrogen in the model compounds have accquired fairly high negative charge whereas the charges on nitrogen in adrenergic molecules are slightly positive as represented in some of the figures previously described. The results of NMR spin coupling analysis of a number of adrenergic substances have been published by Forrest, Heacock and Forrest[43] and their provisional estimates of antiplanar:synclinal ratios range from 70:30 for epinephrine to 50:50 for isoproterenol. Even though their results are approximate, one can still assume that the ratios are not the same for both epinephrine and isoproterenol on the the basis of their work. In effect, the presence of alkyl group on nitrogen probably alters the population of various conformers. As we have already seen these differences are also born out by our calculations.

R(-) Ephedrine: The crystal geometry of R(-) ephedrine hydrochloride given by Carlstorm and Bergin[34] was used as the input data. The crystal geometry is represented by {164,-81}. The β-hydroxy group in the crystal is not involved in hydrogen bonding and the dihedral angle τ(H-O3-C7-C6) is -63°. The SCF-INDO calculated potential energy surface of R(-) ephedrine is given in Fig.23. The minima A and B are located at {180,120} and {180,300} respectively. The minima located at {270,90} and {270,270} represented on the Fig.23 as C and D are only about 0.2 kcals above A and B. The barrier between A and D as well as that between B and C is of the order of 0.97 kcals. Thus the rotation of τ(C6-C7-C8-N) between 180° and 270° does not alter the energy to a great extent when τ(C5-C6-C7-C8) is fixed at ± 90°. However the presence of methyl group on the α-carbon restricts the rotation of τ(C5-C6-C7-C8). In contrast to other adrenergic molecules without α-substitution, energetically forbidden area on the energy surface of ephedrine extends from -200° to +60° of τ(C6-C7-C8-N). In other adrenergic molecules, the forbidden region do not extend over such a large area as in the case of ephedrine. The enhancement of the forbidden region in the latter case is due to the restriction imposed on the rotation of τ(C5-C6-C7-C8) by the presence of methyl group on C7. Thus the weak steric effect produced by the interaction of phenyl hydrogens narrows down the energetically preferred regions of ephedrine.

The net atomic charge distributions of R(-) ephedrine in the conformations {60,270}, {180,300} and {270,270} are

given in Fig.24 to 26. The nature of charge distribution resembles that of other adrenergic molecules which contain β-hydroxy oxygen. The variations in the charge densities on oxygen and on the ring carbons C1, C5 and hydrogens attached to them, in different conformations indicate the role of electrostatic interaction between the cationic head and the oxygen and phenyl ring. The extremal dipole values are calculated to be 3.9 and 9.9 debyes and they are obtained at the conformations {0,0} and {150,90} respectively.

The conformational analysis of R(-) ephedrine has been studied by various authors with no substantial disagreement. Among the theoretical methods, the above mentioned results obtained by INDO method agree with those computed by PCILO method.[31] The absolute minima calculated by Kier[41] using EHT method corresponds approximately to {180,-90}. However, the minimum that is found at the -sc conformation by INDO and PCILO method does not appear in the calculations by Kier. Instead the minimum occurs at the +sc conformation, where the hydroxy and amino methyl groups are trans to each other. The results of NMR experiments[39,40] suggest that ephedrine resides chiefly in the antiplanar and negative synclinal conformations. Portoghese[39] suggest the possibility of intramolecular hydrogen bonding of the type $\overset{+}{N}$-H···O being responsible for the stabilization of the antiplanar and -sc conformers.

R(-) Pseudo Ephedrine: The SCF-INDO calculated conformational map for ψ-ephedrine is presented in Fig.27. A comparision of this energy surface with that of R(-) ephedrine in Fig.23 shows that the energetically forbidden regions appear as mirror images. Thus the change in the configuration on α-carbon of ephedrine affects only the high energy regions on the map in such a way that the forbidden region is produced when the α-methyl group approaches the phenyl ring. Therefore it can be safely concluded that the only effect brought about by the α-methyl group on the conformation of ephedrine is to restrict the rotation of τ(C5-C6-C7-C8). The minima on the surface are not affected by the α-methyl group. The absolute minima in Fig.27, represented by A and B are located at {210,90} and {210,-90} respectively. The minima C and D located at {270,±90} are calculated to be only about .6 kcals above the global minima. The local minima E, located at {60,90} is 3.0 kcals and the minima F, located at {60,-90} is 2.7 kcals above the global minima.

The sterically forbidden regions on the surface of pseudo-ephedrine appear in such a way that a free rotation of τ(C5-C6-C7-C8) is not possible when τ(C6-C7-C8-N) is positive synclinal. However, the energy barrier is not so high for τ(C5-C6-C7-C8) between 90° and 270° when τ(C6-C7-C8-N) is between 200° and 270°. Thus the position of the phenyl ring need not be so rigid when τ(C6-C7-C8-N) has a value corresponding to the absolute minima. In contrast, R(-) ephedrine presents an energy surface in which the rotation of τ(C5-C6-C7-C8)

has limited flexibility. In fact it is impossible to cross the barrier between 90^{o} and 270^{o} of τ(C5-C6-C7-C8) when τ(C6-C7-C8-N) is between antiplanar and -synclinal orientation. Whether the increased biological activity of R(-) ephedrine over R(-) pseudo ephedrine is due to fixed position of the phenyl ring with respect to the side chain in its preferred conformation or due to direct interaction with the receptor, can not be decided.

A comparision of the experimental results on ephedrine isomers with the above mentioned results should be of intrest. Infrared studies reported by Kanasawa[76] show that the difference in freequency between free and internally bonded -OH is greater for pseudo ephedrine and hence it forms stronger intramolecular hydrogen bonds than ephedrine. NMR studies by Hyne[40] and Portoghese[39] also provide evidence that the internal bonding is stronger for ψ-ephedrine than for ephedrine. Various conformations of ephedrine and ψ-ephedrine given in Fig.28 show that the +sc conformer of ephedrine poses fewer nonbonded interactions than those of ψ-ephedrine. As a consequence the ratio of (-sc+ap):+sc conformers can be expected to be slightly higher for ψ-ephedrine. In that case the N-H$\cdots$O distance will be within hydrogen bonding distance for a larger portion of ψ-ephedrine molecules. This could explain the stronger intramolecular hydrogen bond of ψ-ephedrine over its enentiomer. When the potential energy surface of ephedrine (Fig.23) and ψ-ephedrine (Fig.27) are compared for the region of τ(C6-C7-C8-N) between 180^{o} and 270^{o}, the energetically forbidden region is

larger in the case of ephedrine. This is the region where the cationic group comes closer to the β-oxygen thereby facilitating hydrogen bonding. Thus the results obtained by INDO calculations on ephedrine isomers can be qualitatively correlated with the percentage distributions of various conformers observed by the experiment. The results obtained by Kier[41] using EHT method on ψ-ephedrine do not agree with the above results. The absolute minimum is obtained for the -sc conformer and the antiplanar conformer has a higher energy than the +sc and -sc conformers.

The net atomic charges on ψ-ephedrine in {180,270} {300,270} and {60,270} conformations given in Fig.29 to 31 resemble those of R(-) ephedrine conformers. The computed lowest dipole moment is4.2debyes at {0,0} and the highest value of debyes is obtained at {150,90}.

Phenylethylamine: The potential energy surface of phenylethylamine calculated by SCF-INDO method is given in Fig.32. The absolute minima appears on the edges of the surface where the amino group is very close to the phenyl ring. Perhaps an overestimation of the electrostatic interaction between the phenyl ring and the amino group by the method employed is responsible for the appearence of these minima. If the minima on the edges are neglected, one can see six equivalent minima at {60,±90}, {180,±90} and {300,±90}. They correspond to the minima obtained in case of dopamine. {180,90} conformation corresponds to the crystal geometry. Pullman et al.[31] obtained

equivalent minima in antiplanar, +synclinal and -synclinal conformations by employing PCILO method. The dipole moment calculated from the INDO generated wave function range from 7.24 to 14.6 debyes. These values are encountered at {0.0} and {180,±90} respectively and the extremal dipole values of ephedrine isomers also occur around the same configuration.

Phenylethenolamine: The INDO calculation was carried out on crystal geometry of phenylethylamine[33] with a β-hydroxy group having standard geometrical dimensions. The potential energy surface is given in Fig.33. As in the case of phenylethylamine, the absolute minimum is obtaioned at {330,150}. Perhaps this is also an overestimation of electrostatic attraction by INDO method. Other minima are obtained around {180,±90} {300,90} and {300,240}. The minima obtained around the positive synclinal conformation are about 5-7 kcals above the antiplanar and -sc conformations. Thus the introduction of -OH group lowers the energies of ap and -sc conformers from the +sc conformer and the results can be compared with other adrenergic molecules with the β-hydroxy oxygen. The calculated dipole values range from 6.18 to 12.65 debyes. The lowest value is observed at {0,0} and the {150,90} conformation is found to produce the highest value. The same conformations are found to produce the extremal dipole values in adrenergic molecules lacking catechol hydroxy groups that have been studied so far by INDO method.

E. Discussion:

The results of the preceeding section can be combined with the biological data in order to gain deeper understanding of the nature of adrenergic agonists. This would in turn facilitate a critical analysis of the structural chemistry of adrenergic transmission. The biological activity depends on the nature of interaction between the agonist and the receptor. It would have been easier to study the agonist-receptor interaction, if a purified receptor could be isolated. Unfortunately at present, attempts to isolate adrenergic receptors have not met with significant success. Yet, considerable light can be shed on the nature of agonist-receptor interaction by studying the agonist alone. All adrenergic agonists have the basic structure of phenylethylamine and differ only in the substituents on various parts of this structure. As discussed in the introduction, the biological activity of adrenergic molecules vary widly depending on these substituents. The effect of changing the substituents on the agonist-receptor interaction, which in turn is responsible for the observed biological activity may be due to the following reasons: (a) The activity may depend on the preferred conformation of the molecule which could vary with the substituents. (b) The changes in the structure may alter the electronic distributions on various atoms of the molecule, thereby influencing the electronic interaction between the agonist and the receptor. (c) The substituents may interact directly with the receptor. In the following paragraphs we shall examine the above factors in light of the results we have

obtained by INDO calculations.

The conformational energies of the molecules studied as a function of τ(C5-C6-C7-C8) and τ(C6-C7-C8-N) are summarized in Table.1. The biological activities of these molecules are also presented in the table. A common feature in all the molecules is the occurence of the absolute minima around {180,±90}. So, if one assumes that the receptor interacts with the lowest energy conformer of the agonist, then one has to conclude that the substituents will not influence the activity by altering the prederred conformation of the adrenergic molecules. On the otherhand, the energy differences between the global and the local minima are quite low in many cases and the energy barriers are not too high. At physiological and room temperatures many conformations are thermally populated, in solid and in solutions environmental effects are certainly important. Consequently the agonist receptor interaction may very well take place in conformations other than those most preferred in the free space. In such cases, the information on the local minima and their relative populations would be valuable. The method employed may not give accurate energies and thus a quantitative analysis of the population of various conformers is not possible. However, a qualitative comparision of this factor can be made among a series of molecules of related structures.

A study of the adrenergic molecules with varying substitution on nitrogen has shown that the energy difference between the trans and the gauche conformers with respect to

τ(C6-C7-C8-N) have decreased from norepinephrine to isoproterenol. A slight decrease in the positive charge on amino hydrogens resulting in a decreased electrostatic attraction between the β-hydroxy oxygen and the cationic head also indicate that the stability of the negative synclinal over +synclinal conformer is greater in the case of norepinephrine than in the case of isoproterenol. Different ratios of trans:gauche conformers in epinephrine and isoproterenol found by NMR experiment[43] also indicate that the substituent on nitrogen can alter the ratio of the population of various conformers in solution, The biological activities of adrenergic molecules tend towards β activity as the size of the substituent on nitrogen increases. At the molecular level, the gradual decrease in the conformational ratio of trans to gauche with N-substitution may be connected to its biological activity.

Pratesi and Grana[21] suggested that the trend of activity observed in the series of N-substituted molecules may involve a varying electronic effect of the alkyl group on the onium nitrogen and hydrogens. The charge densities calculated by SCF-INDO method on norepinephrine, epinephrine and isoproterenol show that there is no significant change in the charge distribution on the nitrogen atom. However, the charge densities on the amino hydrogens have slightly decreased on N-substitution. Therefore the degree of ionic interaction between the amino-hydrogens and the anionic part of the receptor can vary with substitution on nitrogen. The fact that N,N dimethyl norepinephrine has a low level of activity and β-(3,4 dihydroxy phenyl) β-hydroxyethyltrimethyl ammonium ion is practically free of

adrenergic effect,[21] shows that the amino hydrogens may be important for adrenergic activity. It is possible that gradual decrease in the charge density distribution on amino hydrogens from norepinephrine to isoproterenol has a significant role in adrenergic activity.

The foregoing results appear to be relevant to some of the current theoretical considerations pertaining to α and β activities. For instance, George, Kier and Hoyland[37] have studied the effect of N-substituion on adrenergic molecules by EHT method. As mentioned before, they observe little change, either conformational or electronic, brought about by N-substitution. They suggest that α-adrenergic response is probably due to the formation of hydrogen bond between an onium proton and a negatively charged receptor moiety. And they further suggest that the reaction with β-receptor takes place by an interaction of the N-alkyl group and a receptor feature by long range forces, most notably dispersion binding. However, this model was proposed on the assumption that the N-alkyl group has no effect at all on the conformation or on the electronic charge distribution of the molecule. On the otherhand, variation in the energy of secondary minima and charge densities on amino hydrogens with N-substitution, which we have observed in our calculations, show that such a model is not of absolute necessity although it is a possibility.

Another model relating the effect of N-substitution to the biological activity at the molecular level was proposed by Larsen.[47] He postulates that the adrenergic molecules can

assume either an aziradine form or a quinone form depending on the N-substitution. The aziradine form is supposed to react with the α-receptor and similarly the quinone form with the β-receptor resulting in a covalent bond between the β-carbon and the receptor. Some of the drawbacks of this chemical model have been pointed out by other authors. For instance, since the model assumes an ultimate covalent bond formation with the receptor features, it can not explain the highly reversible nature of adrenergic action, as shown by complete extractability of catecholamines from tissues[77] and the ease with which the blocking agents reverse catecholamine effects as evidenced by NMR experiments.[26] The model also can not explain the activity of the molecules that lack catechol hydroxy groups. In addition to these criticisms, we may note that our own calculations do not support Larsen's hypothesis since the conformational stabilities of adrnergic molecules are not drastically different for different N-substituents.

Our discussions above indicate that all the three mechanisms discussed at the begining of this section can be affected by N-substitution. The energy calculations show that the conformational preference may play a role if the receptor interacts with the agonist in its secondary minimal conformations also. Similarly the variation in the calculated charge densities suggests that an ionic bond or hydrogen bond between the receptor and the aminohydrogens may be a signifiant factor depending on the ionic nature of the receptor. Finally hydrophobic bonding between the alkyl group and the receptor may

also be responsible for the β-activity, though our calculations and similar ones make no direct predictions about this possibility.

The β-hydroxy group in a few adrenergic molecules seem to play an important role in stabilizing the negative synclinal conformer over the positive synclinal conformer with respect to τ(C6-C7-C8-N). The β-oxygen may also interact directly with the receptor since the biological activity depends on the stereoisomer, the activity being greater for D(-) isomer.

A study of ephedrine isomers by INDO method shows that the α-methyl group restricts the rotation of the phenyl group which is indirectly supported by NMR experiments.[39] However, the absolute and the secondary minima do not change with different enantiomers of ephedrine as functions of τ(C5-C6-C7-C8) and τ(C6-C7-C8-N). Consequently the geometry of the nitrogen, oxygen and the phenyl ring will remain the same in all the four enantiomers and this geometry is also observed in other adrenergic molecules. Only the α-methyl group resides in different enantiomers. Therefore the varying activities of ephedrine isomers may be due to the interference of the α-methyl group with the reaction between the agonist and the receptor. In fact only R(-) ephedrine seems to have some direct activity whereas the adrenergic activity of other ephedrine enantiomers is only indirect.[25] Thus the α-methyl group perhaps presents the least hinderance to the interaction of ephedrines with receptors when it is in R(-) ephedrine form.

Kier[41] and Pullman et al.[31] have proposed models for α-receptor based on their conformational analyses. The basic

feature invoked in these models is the constancy of variuos distances among the nitrogen, the β-oxygen and the phenyl ring of all the α-adrenergic agonists in their preferred conformations. The values we have obtained for these distances are comparable to those obtained by the above authors. The reason for the constacy of distances is that the absolute energy minimum is obtained at the same conformation in all the molecules. We may point out that this is observed also in the case of molecules which are predominently β-active. Therefore the constacy of distances mentioned above may be a necessary condition for activity but definately not a sufficient one.

The role of catechol hydroxy groups is not well understood in terms of their activities. A major step in the metabolism of adrenergic molecules is the methylation of catechol hydroxy oxygen by the enzyme catechol O-methyl transferase. It is one of the ways of removing the active adrenergic molecules from the site of action. But it is known that the reuptake of adrenergic molecules by the presynaptic granules is the major mechanism of removing them from the site of action.[9] Therefore the presence or absence of catechol hydroxy group does not significantly contribute to the rate of disappearence of the active molecules. On the other hand, an interesting observation of a different nature can be made on the biological data concerning catechol hydroxy groups. In most of the cases adrenergic molecules exhibiting a direct activity contain catechol hydroxy groups especially the meta hydroxy group.[19] Using our results we can examine whether the hydroxy groups are essential for direct interaction with the receptor or they alter the conformational

preference or charge distributions.

As we have seen the conformation of agonists as functions of τ(C5-C6-C7-C8) and τ(C6-C7-C8-N) is not influenced by the catechol hydroxy groups. The charge densities are also not affected to a significant extent. Nevertheless, a noticable pattern can be observed in the variation of the dipole moments with the molecular conformation. An account of the calculated extremal dipole moments and the encountered conformations are given in Table.2, together with the biological activity. As we can see in the table all the molecules have the lowest dipole moment when τ(C6-C7-C8-N) is around 0^{o} and all of them have the highest dipole moments for τ(C6-C7-C8-N) around 180^{o}. With regard to τ(C5-C6-C7-C8), the lowest values are obtained around 0^{o} and 180^{o} for molecules with and without catechol hydroxy groups respectively. Similarly, the highest dipole moment as function of τ(C5-C6-C7-C8) is obtained around -60^{o} to 0^{o} in the case of molecules with catechol hydroxy group and at 90^{o} for molecules without catechol hydroxy group. Thus there is evidence that the nature of the variation of dipole moment depends on the catechol hydroxy groups. The dependence of the variation of the dipole mement on the presence of catechol hydroxy groups can be elucidated by comparing the highest dipole moment with that for the conformation obtained by changing τ(C5-C6-C7-C8) through 180^{o}. Such a rotation of τ(C5-C6-C7-C8) does not alter the steric relation of the phenyl ring with respect to the rest of the molecule. However, the orientation of the catechol hydroxy groups will be varied if

they are present. And the dipole values should not alter much for the molecules without catechol hydroxy groups owing to the symmetry of the benzene ring. In fact the results in Table.2. show that the dipole moments of molecules with catechol hydroxy groups changes considerably when τ(C5-C6-C7-C8) is rotated by 180^{o} whereas such a rotation has negligible effect on the dipole moments of melecules with catechol hydroxy groups. Furthermore in the case of molecules with catechol hydroxy groups, the rotation of τ(C5-C6-C7-C8) by 180^{o} produces a larger variation in the dipole values when τ(C6-C7-C8-N) has the value around 0^{o} than when it has a value around 180^{o}. Another difference that can be noticed between the molecules with and without catechol hydroxy groups is the magnitude of variation in dipole values. That is, the difference between the extremal values in molecules with catechol hydroxy groups is around 11 debyes and that in the molecules without those hydroxy groups is around 6.5 debyes as shown in Table.2.

The dipole moment as a function of molecular geometry plays an important role in deciding the preferred conformation in solution. Sinanoglu has developed the Solvent Effect Theory[78-81] in which the solcent effect is divided into various contributions. Beveridge[82] has modified it so that the theory can be applied when the solute is amenable to the treatment by molecular quantum mechanics. In this formalism the total energy of the molecule in solution is obtained by adding the solute energy calculated in free space and the solvation energy which is a sum of electrostatic and van der waal interaction enerties and the energy

required for the cavity formation. The above theory and the results obtained on acetylcholine[82] show that the total energy of the molecule depends to a great extent on the energy calculated in free space, the molecular volume and dipole mement, all of which are dependent on the conformation. Thus the observed differences in the dipole moment of adrenergic molecules with and without catechol hydroxy groups might influence the preferred conformations in solution. Particularly the position of the phenyl ring seems to be affected in this manner. Of course we must recognize the fact that the theory of solvent effect is incipient just as the experimental information available in this direction is far from extensive. For instance, at present the conformational analysis of some of the adrenergic molecules in solution have produced results pertaining only to τ(C6-C7-C8-N) and no experimental data is available on the orientation of the phenyl ring on any of the adrenergic molecules in solution.

Finally, in reference to structure-activity relationship we have noted that the adrenergic molecules in general exhibit direct activity if they contain the catechol hydroxy group and indirectly in its absence, the two categories which differ in their pattern in dipole moments. Whether the hydroxy groups are involved in direct interaction with the receptor or influence the conformational preference in solution to produce a specific type of biological activity is yet to be understood.

F. Summary and Conclusions:

The INDO molecular orbital calculations on norepinephrine and a series of adrenergic molecules reveal the occurrence of absolute minima with respect to the torsional angles τ(C5-C6-C7-C8) and τ(C6-C7-C8-N) around the same conformations in all the molecules. These conformations agree with their crystal geometries. It is concluded that the varying biological activities of adrenergic molecules is not a conformational effect, if these molecules interact with the receptors only in their absolute minimal conformations. On the other hand the relative population of various local minima, whose energy differences are in many cases fairly low in comparision with the absolute minima. are not the same in different adrenergic molecules, as evidenced by the energy calculations. This information allows us to consider possible conformational effects that may take place under physiological conditions in a series of N-substituted molecules.

The energy stabilization of the -synclinal conformation over +synclinal conformation with respect to τ(C6-C7-C8-N) in molecules containing β-hydroxy groups is attributed to the electrostatic attraction between the cationic group and the β-hydroxy oxygen as reflected by electronic charge distributions as well as the energy break up studies on norepinephrine. The observation that the molecules without β-hydroxy group (dopamine, phenylethylamine) show no prefential stabilization between the two synclinal conformation, also supports the above conclusion. However, the system becomes more complicated

for molecules such as isoproterenol.

In addition to conformational effects, a possible ionic bond is invoked between the amino hydrogens and an anionic part of the receptor, as one of the mechanisms of interaction, based on the variation of the charge density distribution with varying N-substituent.

Catechol hydroxy groups are found to influence the dipole moments significantly. In view of the fact that the solvent effect theory considers the dipole moment as a significant factor in conformational preference in solution, the catechol hydroxy groups possibly influences the orientation of the phenyl ring in solution. Such a conformational preference may be linked to the type of adrenergic activity which is classified as direct and indirect type. In addition, direct interaction of the catechol hydroxy groups in direct activity may be possible, just as the alkyl group may interact directly with the receptors.

Thus the INDO studies have enabled us to conclude that the varying adrenergic activities of a number of adrenergic molecules with a basic structure of phenylethylamine, is a subtle balance of various effects such as conformational, electronic and direct interaction.

Appendix:

The coordinates obtained by crystallographic data are used to get the interatomic diatances, bond angles and dihedral angles from the program XTAL. When the crystallographic data are not available or if the positions of hydrogens are not determined in the crystal, standard dimensions of bond lengths and angles are made use of. The dihedral angles corresponding to the orientation of hydroxy hydrogens are obtained by energy minimization procedure using INDO calculations on norepinephrine. The input for INDO calculation requires that each individual atoms in a molecule be represented by a bond length between that atom and a previously defined one, and two bond angles or one bond angle and a dihedral angle with reference to previously described atoms in a form called Z MATRIX. The energies are calculated as functions of τ(C5-C6-C7-C8) and τ(C6-C7-C8-N) which are set to zero at the begining of the program. The goemetrical parameters used as input for INDO calculations on adrenergic molecules, are given in the following pages. Along with the title of the molecule, a reference to particular figure, which shows the numbering system for that molecule, is given.

R(-) norepinephrine (Figure 1, crystal geometry[27])

Bond Length(Å)	Bond Angle (degree)	Dihedral Angle (degree)
C1-C2 = 1.403	C1-C2-C3 = 120.0	C1-C2-C3-C4 = 0.0
C2-C3 = 1.393	C2-C3-C4 = 119.7	C2-C3-C4-C5 = 0.0
C3-C4 = 1.386	C3-C4-C5 = 119.2	C3-C4-C5-C6 = 0.0
C4-C5 = 1.391	C4-C5-C6 = 122.3	C4-C5-C6-C7 = 180.0
C5-C6 = 1.363	C5-C6-C7 = 119.6	C5-C6-C7-C8 = 0.0
C6-C7 = 1.525	C6-C7-C8 = 107.8	C6-C7-C8-N = 0.0
C7-C8 = 1.523	C7-C8-N = 110.6	O1-C2-C1-H = 0.0
C8-N = 1.493	O1-C2-C1 = 119.1	O2-C3-C2-O1 = 0.0
C2-O1 = 1.37	O2-C3-C2 = 118.9	H-C1-C4-C7 = 0.0
C3-O2 = 1.388	O3-C7-C6 = 111.8	H-O1-C2-C1 = 180.0
C7-O3 = 1.37	O3-C7-C8 = 105.8	H-O2-C3-C4 = 0.0
C1-H = 1.07	H-C1-C6 = 123.0	H-C4-C3-C2 = 0.0
C4-H = 1.09	H-C4-C3 = 113.0	H-C5-C4-H = 0.0
C5-H = 1.06	H-C7-O3 = 111.0	H-O3-C7-C6 = 300.0
C7-H = 1.06	H-C7-C8 = 108.0	Ha-N-C8-C7 = 180.0
C8-Hd = 1.26	Hd-C8-C7 = 106.0	
C8-He = 0.96	Hd-C8-N = 101.0	
N-Ha = 0.96	He-C8-C7 = 106.0	
N-Hb = 0.85	Ha-N-C8 = 115.0	
N-Hc = 0.99	Hb-N-C8 = 110.0	
O1-H = 1.04	Hc-N-C8 = 107.0	
O2-H = 0.81	Hb-N-Ha = 98.0	
O3-H = 1.15	Hc-N-Ha = 102.0	
	H-O1-C2 = 132.0	
	H-O2-C3 = 100.0	
	H-O3-C7 = 137.0	
	H-C5-C4 = 110.0	
	He-C8-N = 119.0	

Dopamine (Figure 13): crystal geometry[35] is used for heavy atoms and standard geometry is used for hydrogens.

Bond Length(Å)	Bond Angle (degree)	Dihedral Angle (degree)
C1-C2 = 1.4249	C1-C2-C3 = 120.72518	C1-C2-C3-C4 = -.53179
C2-C3 = 1.3916	C2-C3-C4 = 120.17495	C2-C3-C4-C5 = 1.63193
C3-C4 = 1.3895	C3-C4-C5 = 119.06004	C3-C4-C5-C6 = -.8839
C4-C5 = 1.4086	C4-C5-C6 = 121.01149	C4-C5-C6-C7 = 176.9225
C5-C6 = 1.391	C5-C6-C7 = 120.19045	C5-C6-C7-C8 = 0.0
C6-C7 = 1.5279	C6-C7-C8 = 110.69173	C6-C7-C8-N = 0.0
C7-C8 = 1.509	C7-C8-N = 110.52561	O1-C2-C1-C6 = 178.75945
C8-N = 1.5091	O1-C2-C1 = 117.29565	O2-C3-C4-C5 = -177.32403
C2-O1 = 1.361	O2-C3-C4 = 122.64077	H-C1-C2-C3 = 180.0
C3-O2 = 1.3942	H-C1-C2 = 120.0	H-C4-C3-C2 = 180.0
C1-H = 1.08	H-C4-C3 = 120.0	H-C5-C4-C3 = 180.0
C4-H = 1.08	H-C5-C4 = 120.0	Ha-N-C8-C7 = 180.0
C5-H = 1.08	Hf-C7-C6 = 109.471221	H-O1-C2-C1 = 180.0
C7-Hf = 1.09	Hf-C7-C8 = 109.471221	H-O2-C3-C4 = 0.0
C7-Hg = 1.09	Hg-C7-C6 = 109.471221	
C8-Hd = 1.09	Hg-C7-C8 = 109.471221	
C8-He = 1.09	Hd-C8-C7 = 109.471221	
N-Ha = 1.01	Hd-C8-N = 109.471221	
N-Hb = 1.01	He-C8-C7 = 109.471221	
N-Hc = 1.01	He-C8-N = 109.471221	
O1-H = 0.96	Ha-N-C8 = 109.471221	
O2-H = 0.96	Hb-N-C8 = 109.471221	
	Hc-N-C8 = 109.471221	
	Hb-N-Ha = 109.471221	
	Hc-N-Ha = 109.471221	
	H-O1-C2 = 109.471221	
	H-O2-C3 = 109.471221	

R(-) epinephrine(Figure 17): crystal geometry is used for norepinephrine part and a standard geometry is used for N-methyl group.

Bond Length(Å)	Bond Angle (degree)	Dihedral Angle (degree)
C1-C2 = 1.4019	C1-C2-C3 = 120.08196	C1-C2-C3-C4 = -2.53064
C2-C3 = 1.3912	C2-C3-C4 = 119.67384	C2-C3-C4-C5 = 0.33441
C3-C4 = 1.3846	C3-C4-C5 = 119.15219	C3-C4-C5-C6 = 1.51672
C4-C5 = 1.39	C4-C5-C6 = 122.29079	C4-C5-C6-C7 = 177.1853
C5-C6 = 1.3615	C5-C6-C7 = 119.64659	C5-C6-C7-C8 = 0.0
C6-C7 = 1.5251	C6-C7-C8 = 107.7559	C6-C7-C8-N = 0.0
C8-N = 1.494	C7-C8-N = 110.63422	O1-C2-C1-C6 = -178.42599
N-C9 = 1.54	C8-N-C9 = 119.471221	O2-C3-C2-C1 = -179.80709
C2-O1 = 1.3698	O1-C2-C1 = 119.06698	H-C1-C6-C7 = -2.45908
C3-O2 = 1.3896	O2-C3-C2 = 118.87407	H-O1-C2-C1 = 180.0
C7-O3 = 1.4334	O3-C7-C6 = 111.83918	H-O2-C3-C4 = 0.0
O1-H = 1.0374	H-C1-C6 = 123.07389	H-C4-C3-C2 = -169.95148
O2-H = 0.8102	H-C4-C3 = 112.48947	H-C5-C4-C3 = -172.04419
O3-H = 1.1509	H-C5-C4 = 110.26749	H-O3-C7-C6 = 300.0
N-Hb = 0.9613	H-C7-C8 = 107.92854	Hb-N-C8-C7 = 80.55142
N-Hc = 0.9910	H-C7-C6 = 111.65393	Hf-C9-N-C8 = 180.0
C1-H = 1.0698	Hd-C8-C7 = 105.63317	
C4-H = 1.0912	Hd-C8-N = 100.83132	
C5-H = 1.0615	He-C8-C7 = 106.03434	
C7-H = 1.0592	He-C8-N = 118.35931	
C8-Hd = 1.2555	Hf-C9-N = 109.471221	
C8-He = 0.962	Hg-C9-N = 109.471221	
C9-Hf = 1.09	Hg-C9-Hf = 109.471221	
C9-Hg = 1.09	Hh-C9-N = 109.471221	
C9-Hh = 1.09	Hh-C9-Hf = 109.471221	
	Hb-N-C8 = 115.95253	
	Hc-N-C8 = 107.28813	
	Hb-N-Hc = 121.60574	
	H-O1-C2 = 131.85893	
	H-O2-C3 = 100.36379	
	H-O3-C7 = 137.13287	
	O3-C7-C8 = 105.80513	

R(-) isoproterenol(Figure 21, crystal geometry[36])

Bond Length(Å)	Bond Angle (degree)	Dihedral Angle (degree)
C1-C2 = 1.3761	C1-C2-C3 = 121.4895	C1-C2-C3-C4 = 0.6285
C2-C3 = 1.374	C2-C3-C4 = 118.6791	C2-C3-C4-C5 = -.9392
C3-C4 = 1.365	C3-C4-C5 = 120.3297	C3-C4-C5-C6 = 0.7651
C4-C5 = 1.3981	C4-C5-C6 = 120.5106	C4-C5-C6-C7 = -179.2883
C5-C6 = 1.3668	C5-C6-C7 = 124.2341	C5-C6-C7-C8 = 0.0
C6-C7 = 1.5266	C6-C7-C8 = 109.7136	C6-C7-C8-N = 0.0
C7-C8 = 1.5071	C7-C8-N = 110.0027	C9-N-C8-C7 = -156.2802
C8-N = 1.4991	C8-N-C9 = 114.7495	C10-C9-N-C8 = 176.7651
C9-N = 1.5119	C10-C9-N = 107.5397	H-C10-C9-N = 175.8834
C10-C9= 1.5342	C11-C9-N = 111.1116	H-C11-C9-N = -156.2612
C11-C9= 1.4941	C11-C9-C10=111.5188	H-C1-C2-C3 = -173.1468
C2-O1 = 1.376	O1-C2-C1 = 121.1638	H-O1-C2-C1 = 180.0
C3-O2 = 1.3703	O1-C2-C3 = 117.3289	H-O2-C3-C4 = 0.0
C7-O3 = 1.3922	O2-C3-C2 = 118.1304	H-O3-C7-C6 = 300.0
C1-H = 1.022	O2-C3-C4 = 123.1807	
C4-H = 0.9085	O3-C7-C6 = 113.2601	
C5-H = o.8823	O3-C7-C8 = 107.9603	
C7-H = 1.2057	H-C1-C2 = 121.7037	
C8-Hc = 0.9865	H-C4-C3 = 117.0166	
C8-Hd = 1.2582	H-C4-C5 = 122.6135	
C9-H = 1.2414	H-C5-C4 = 116.7545	
C10-He= 1.0477	H-C5-C6 = 122.6685	
C10-Hf= 1.118	H-C7-C6 = 112.108	
C10-Hg= 1.2217	H-C7-C8 = 123.6693	
C11-Hh= 1.0927	Hc-C8-C7 = 118.1272	
C12-Hi= 1.1479	Hc-C8-N = 110.2702	
C13-Hj= 1.0639	Hd-C8-C7 = 103.7116	
N-Ha = 0.9619	Hd-C8-N = 105.203	
N-Hb = 1.0374	H-C9-C10 = 118.2165	
O1-H = 0.9956	H-C9-N = 100.5436	
O2-H = 0.9198	He-C10-C9= 109.1491	
O3-H = 1.1712	Hf-C10-C9= 110.8617	

(Continued on next page)

R(-) isoproterenol(continued):

Bond Length(Å)	Bond Angle (degree)	Dihedral Angle (degree)
	Hf-C10-He= 115.6485	
	Hg-C10-C9= 101.4336	
	Hg-C10-He= 111.0769	
	Hh-C11-C9= 118.0007	
	Hi-C11-C9= 112.6402	
	Hi-C11-Hh= 80.3278	
	Hj-C11-C9= 95.8769	
	Hj-C11-Hh= 120.0627	
	Ha-N-C8 = 109.1966	
	Ha-N-C9 = 111.0899	
	Hb-N-C8 = 108.4057	
	Hb-N-C9 = 106.0099	
	H-O1-C2 = 89.7893	
	H-O2-C3 = 116.9911	
	H-O3-C7 = 105.5921	

Erythro and Threo Ephedrine (Figures 25 and 29): crystal geometry[34] of R(-) ephedrine is used for heavy atoms and standard geometry is used for hydrogens.

Bond Length(Å)		Bond Angle (degree)		Dihedral Angle (degree)	
C1-C2	= 1.396	C1-C2-C3	= 120.66851	C1-C2-C3-C4	= 0.33602
C2-C3	= 1.3832	C2-C3-C4	= 119.674	C2-C3-C4-C5	= -.27999
C3-C4	= 1.3899	C3-C4-C5	= 119.40823	C3-C4-C5-C6	= 0.11784
C4-C5	= 1.4015	C4-C5-C6	= 120.57086	C4-C5-C6-C7	= 178.78372
C5-C6	= 1.39	C5-C6-C7	= 117.96695	C5-C6-C7-C8	= 0.0
C6-C7	= 1.5201	C6-C7-C8	= 110.53762	C6-C7-C8-N	= 0.0
C7-C8	= 1.5374	C7-C8-C10	= 113.14949	C9-N-C8-C7	= -170.0795
C8-C10	= 1.5264	C7-C8-N	= 107.62217	H-O1-C7-C6	= 300.0
C8-N	= 1.5029	C10-C8-N	= 110.00391	H-C10-C8-C7	= 180.0
C9-N	= 1.4731	C8-N-C9	= 115.05864	H-C9-N-C8	= 180.0
O1-C7	= 1.4182	O1-C7-C6	= 115.00451		
C1-H	= 1.08	O1-C7-C8	= 105.67256		
C2-H	= 1.08	H-C1-C2	= 120.0		
C3-H	= 1.08	H-C2-C1	= 119.665745		
C4-H	= 1.08	H-C2-C3	= 119.665745		
C5-H	= 1.08	H-C3-C2	= 120.163		
C7-H	= 1.09	H-C3-C4	= 120.163		
C8-H	= 1.09	H-C4-C3	= 120.295885		
C9-Hc	= 1.09	H-C4-C5	= 120.295885		
C9-Hd	= 1.09	H-C5-C4	= 119.71457		
C9-He	= 1.09	H-C5-C6	= 119.71457		
C10-Hf	= 1.09	H-C7-C6	= 109.471221		
C10-Hg	= 1.09	H-C7-C8	= 109.471221		
C10-Hh	= 1.09	H-C8-C7	= 109.471221		
O1-H	= 0.98	H-C8-N	= 109.471221		
N-Ha	= 1.01	Hc-C9-N	= 109.471221		
N-Hb	= 1.01	Hd-C9-N	= 109.471221		

(Continued on next page)

Erythro and Threo Ephedrine(continued):

Bond Length(Å)	Bond Angle (degree)	Dihedral Angle (degree)
	He-C9-N = 109.471221	
	Hd-C9-Hc = 109.471221	
	He-C9-Hc = 109.471221	
	Hf-C10-C8= 109.471221	
	Hg-C10-C8= 109.471221	
	Hg-C10-Hf= 109.471221	
	Hh-C10-C8= 109.471221	
	Hh-C10-Hf= 109.471221	
	H-O1-C7 = 109.471221	
	Ha-N-C8 = 109.471221	
	Ha-N-C9 = 109.471221	
	Hb-N-C8 = 109.471221	
	Hb-N-C9 = 109.471221	

Phenylethylamine (Figure 34): crystal geometry[33] is used for heavy atoms and standard geometry is used for hydrogens.

Bond Length(Å)	Bond Angle (degree)	Dihedral Angle (degree)
C1-C2 = 1.43	C1-C2-C3 = 119.3	C1-C2-C3-C4 = 0.0
C2-C3 = 1.3604	C2-C3-C4 = 122.22034	C2-C3-C4-C5 = 0.0
C3-C4 = 1.4196	C3-C4-C5 = 118.0	C3-C4-C5-C6 = 0.0
C4-C5 = 1.43	C4-C5-C6 = 123.0	C4-C5-C6-C7 = 180.0
C5-C6 = 1.3549	C5-C6-C7 = 120.0174	C5-C6-C7-C8 = 0.0
C6-C7 = 1.4719	C6-C7-C8 = 110.55095	C6-C7-C8-N = 0.0
C7-C8 = 1.5558	C7-C8-N = 112.406	H-C1-C2-C3 = 180.0
C8-N = 1.4856	H-C1-C2 = 120.0	H-C2-C3-C4 = 180.0
C1-H = 1.08	H-C2-C3 = 120.0	H-C3-C4-C5 = 180.0
C2-H = 1.08	H-C3-C4 = 120.0	H-C4-C5-C6 = 180.0
C3-H = 1.08	H-C4-C5 = 120.0	H-C5-C6-C1 = 180.0
C4-H = 1.08	H-C5-C6 = 120.0	H-N-C8-C7 = 180.0
C5-H = 1.08	Hf-C7-C6 = 109.471221	
C7-Hf = 1.09	Hf-C7-C8 = 109.471221	
C7-Hg = 1.09	Hg-C7-C6 = 109.471221	
C8-Hd = 1.09	Hg-C7-C8 = 109.471221	
C8-He = 1.09	Hd-C8-C7 = 109.471221	
N-Ha = 1.09	Hd-C8-N = 109.471221	
N-Hb = 1.09	He-C8-C7 = 109.471221	
N-Hc = 1.09	He-C8-N = 109.471221	
	Ha-N-C8 = 109.471221	
	Hb-N-C8 = 109.471221	
	Hb-N-Ha = 109.471221	
	Hc-N-C8 = 109.471221	
	Hc-N-Ha = 109.471221	

Note : The above data is common to R(-) phenylethenolamine which carries a hydroxy group with standard geometry on C7 instead of Hg.

Table.1.

compound	biological activity* α-activity	β-activity	calculated conformational energies of minima
R(-)norepinephrine	99[a], 100[e]	12.5[b], 2[c]	{210,90}, {210,120}, {210,270}, {300,270}, {300,90}, {60,90}, {60,270} 0.0 0.0 0.0 3.39 3.7 7.03 7.66
R(-) epinephrine	84[a], 91[e]	50[b], 5-10[c] 40[d]	{210,270}, {210,90}, {300,270}, {300,90}, {60,90}, {60,270} 0.0 0.05 2.27 2.82 5.06 5.39
R(-)isoproterenol		100[b], 100[c] 100[d]	{210,120}, {210,270}, {60,90}, {300,270}, {300,90}, {30,240} 0.0 0,25 3.17 3.2 3.9 4.94
R(-)ephedrine	60[a]		{180,300}, {180,120}, {270,90}, {270,270}, {60,270}, {60,90} 0.0 0.07 0.22 0.23 3.99 4.46
R(-) pseudo ephedrine	-[a]		{210,270}, {210,90}, {270,270}, {270,90}, {60,270}, {60,90} 0.0 0.04 0.62 0.62 2,7 3.14
dopamine	67[e]		{180,90}, {180,270}, {300,270}, {60,90}, {300,90}, {60,270} 0.0 0.09 0.14 0.47 0.74 0.81
R(-)phenethenolamine	-[f]		{330,150}, {330,240}, {210,90}, {210,270}, {270,60}, {60,90}, {60,270} 0.0 1.22 2.53 2.55 2.69 7.66 7.75
phenylethylamine	-[f]		{330,150}, {30,210}, {300,240}, {60,120}, {300,60}, {60,300}, {180,120} 0.0 0.0 2.12 2.12 3.96 3.96 4.67 {180,240} 4.67

Key for Table 1:

a. Rat vas deferens, Ref. 25.

b. Bronchodilator activity in guinea pig, Ref. 21.

c. Blood lactic acid in rat, Ref. 21.

d. Bronchodilator activity, Ref. 19, p225.

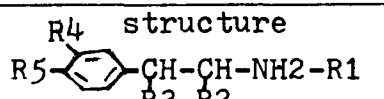
e. Rat vas deferens, Ref. 19, p222.

f. Exhibit mainly indirect activity, Ref. 19, p218.

*α-activities are given as percentages relative to R(-) norepinephrine.

β-activities are given as percentages relative to R(-) isoproterenol.

Table.2.

compound	structure  R1 R2 R3 R4 R5	type of activity[a]	dipole values and corresponding conformations					
			minimum	maximum	range	minimum'*	maximum'*	maximum''*
norepine-phrine	H H OH OH OH	direct	4.93 {0,180}	15.95 {180,330}	11.02	9.58 {0,0}	15.7 {180,30}	14.12 {180,150}
epineph-rine	CH3 H OH OH OH	direct	4.27 {0,180}	15.02 {150,300}	10.75	9.13 {0,0}	13.71 {150,60}	12.57 {150,120}
isoprote-renol	CH(CH3)2 H OH OH OH	direct	1.97 {30,150}	13.36 {120,300}	11.39	9.6 {30,330} 6.76 {30,210}	10.2 {120,60}	8.38 {120,120}
dopamine	H H H OH OH	direct	6.87 {0,180}	18.31 {180,0}	11.44	11.97 {0,0}	16.34 {180,180}	
phenethe-nolamine	H H OH H H	mixed and indirect	6.18 {0,0}	12.65 {150,90}	6.47	6.46 {0,180}	12.64 {150,270}	
phenethyl-amine	H H H H H	indirect	7.24 {0,0}	14.6 {180,90}	7.36	7.52 {0,180}	14.6 {180,270}	
R(-)ephed-drine	CH3 CH3 OH H H	mixed	3.87 {0,0}	9.93 {150,90}	6.06	4.28 {0,180}	9.84 {150,270}	
R(-) pseudo ephedrine	CH3 CH3 OH H H	indirect[b]	4.16 {0,0}					

a) Ref.19; b0 Ref.25:

*Denoting the conformation yielding the lowest dipole moment value as $\{\tau_{1min}, \tau_{2min}\}$, and the the conformation yielding the highest dipole value as $\{\tau_{1max}, \tau_{2max}\}$, the following terms are defined:

minimum' = dipole moment at the conformation $\{\tau_{1min}, (\tau_{2min} + 180^{o})\}$

maximum' = dipole moment at the conformation $\{\tau_{1max}, (360^{o} - \tau_{2max})\}$

maximum''= dipole mimant at the conformation $\{\tau_{1max}, (\tau_{2max} + 180^{o})\}$

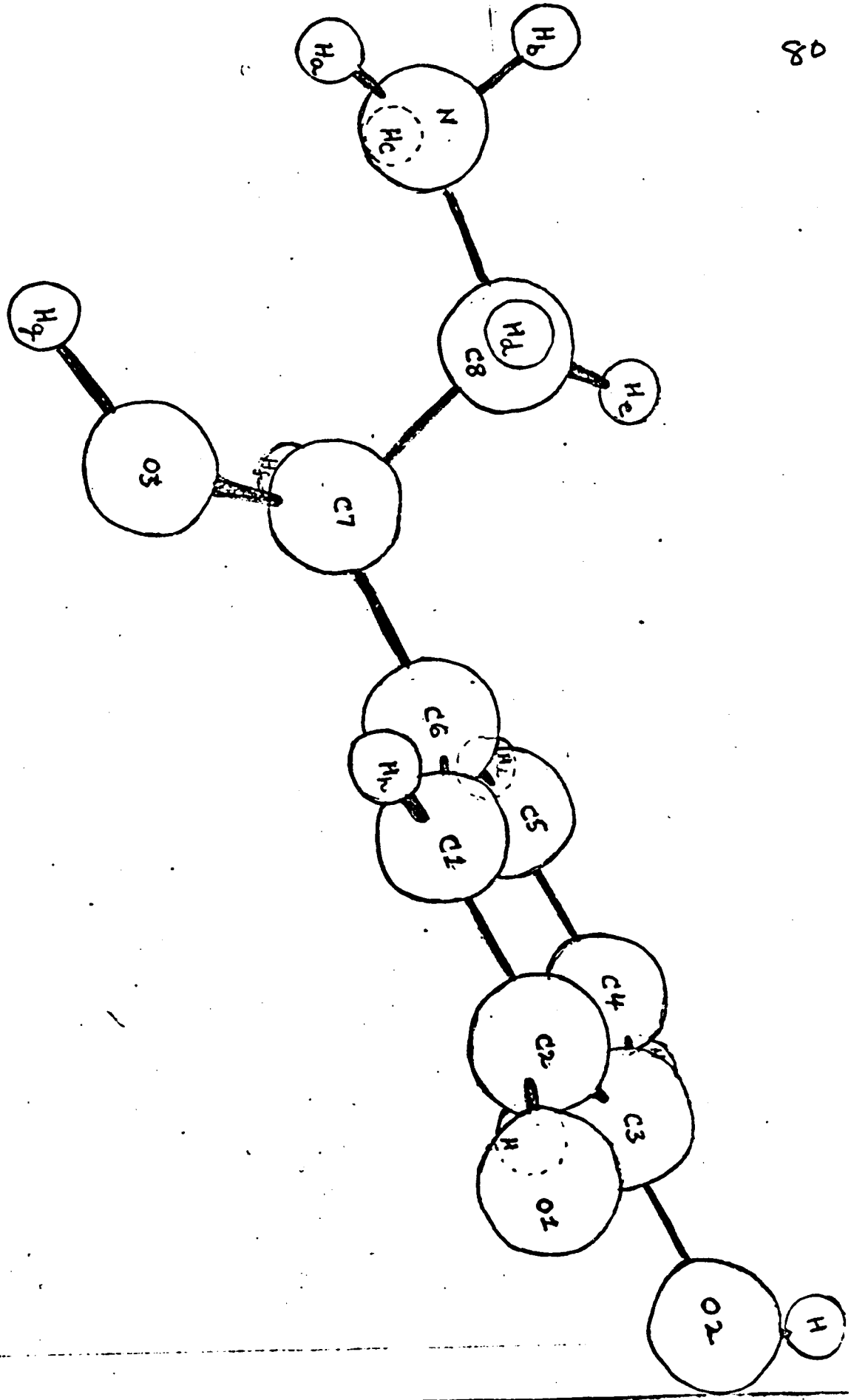


Figure 1.

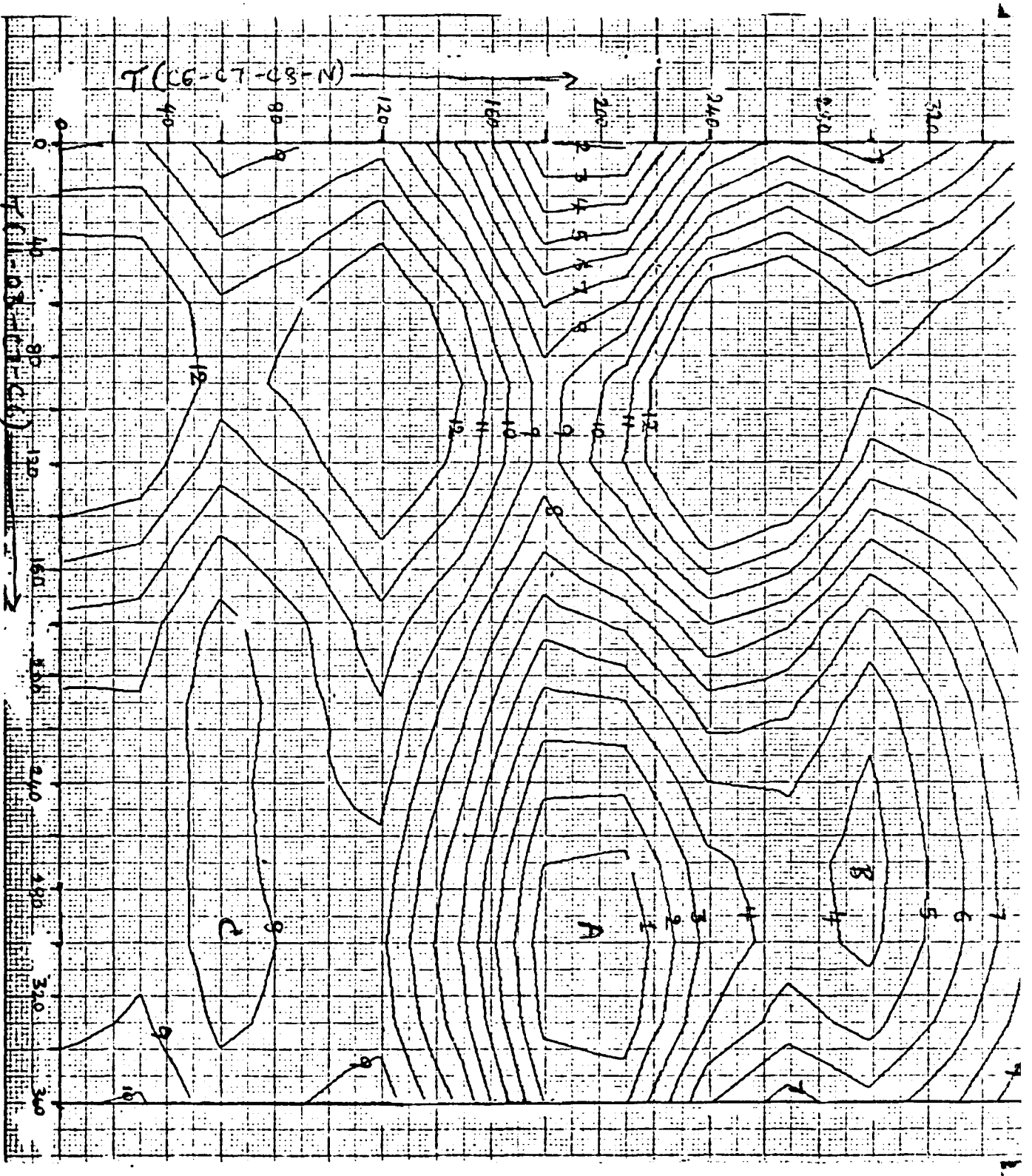


Figure 2.

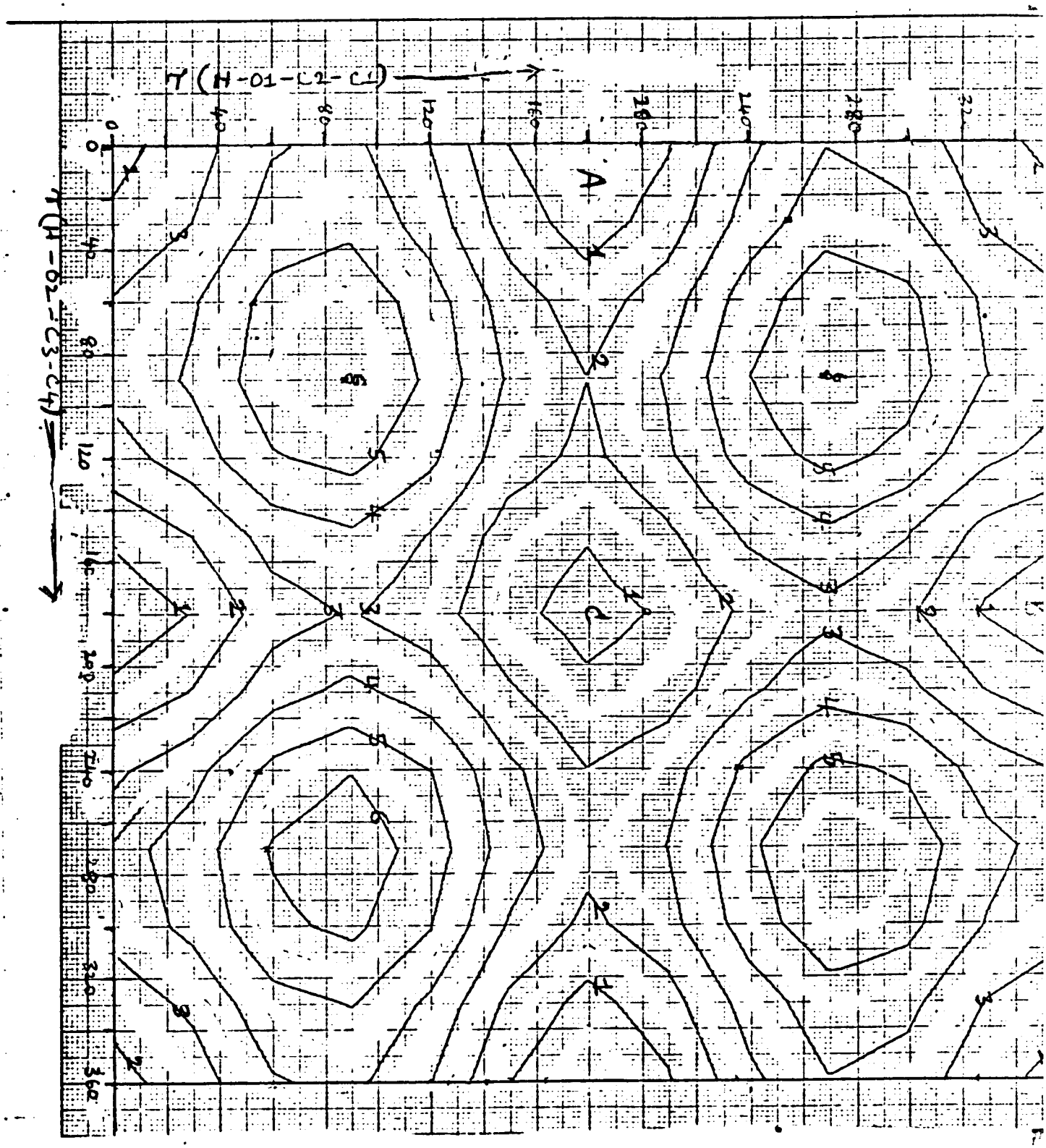


Figure 3.

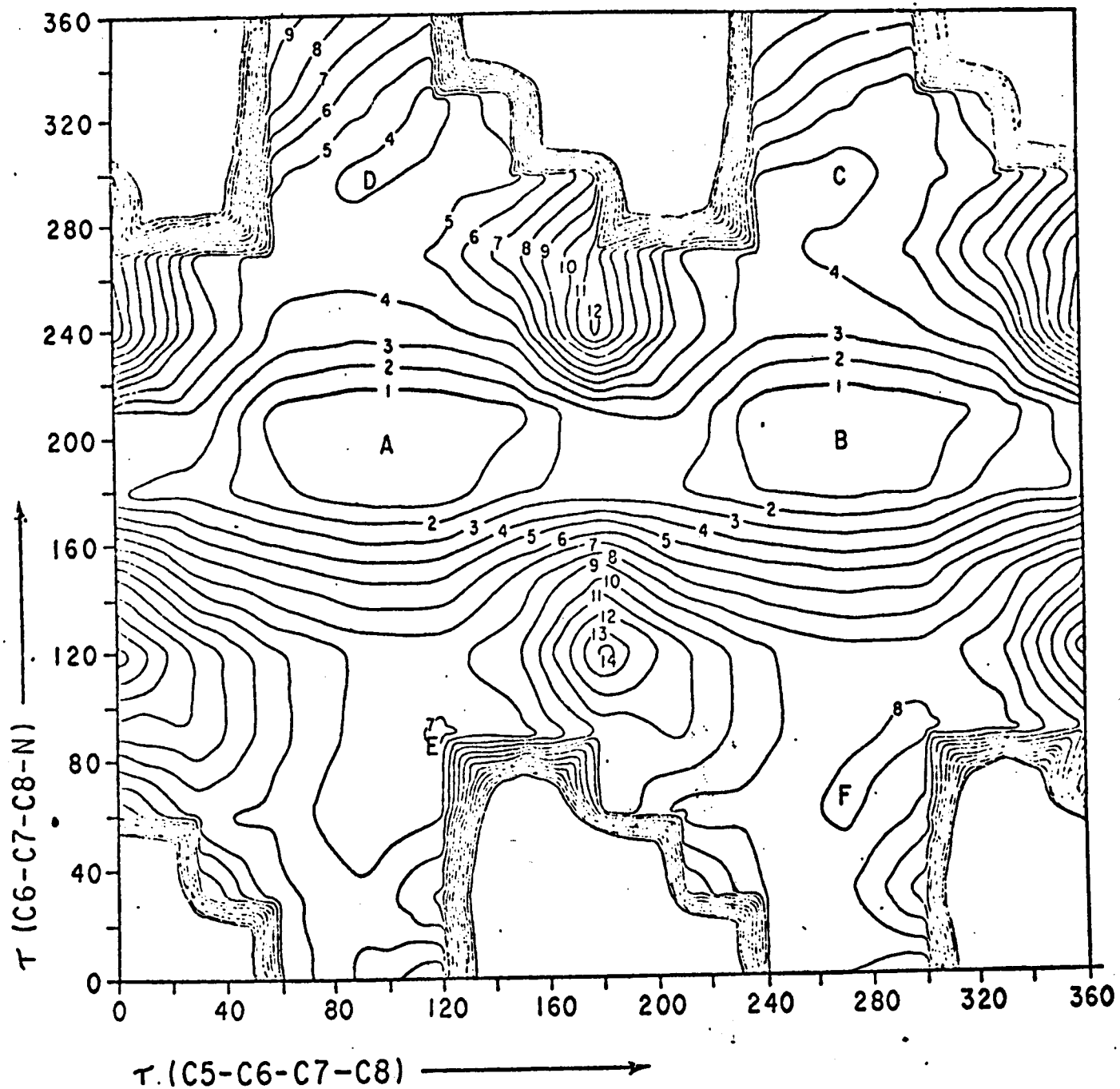
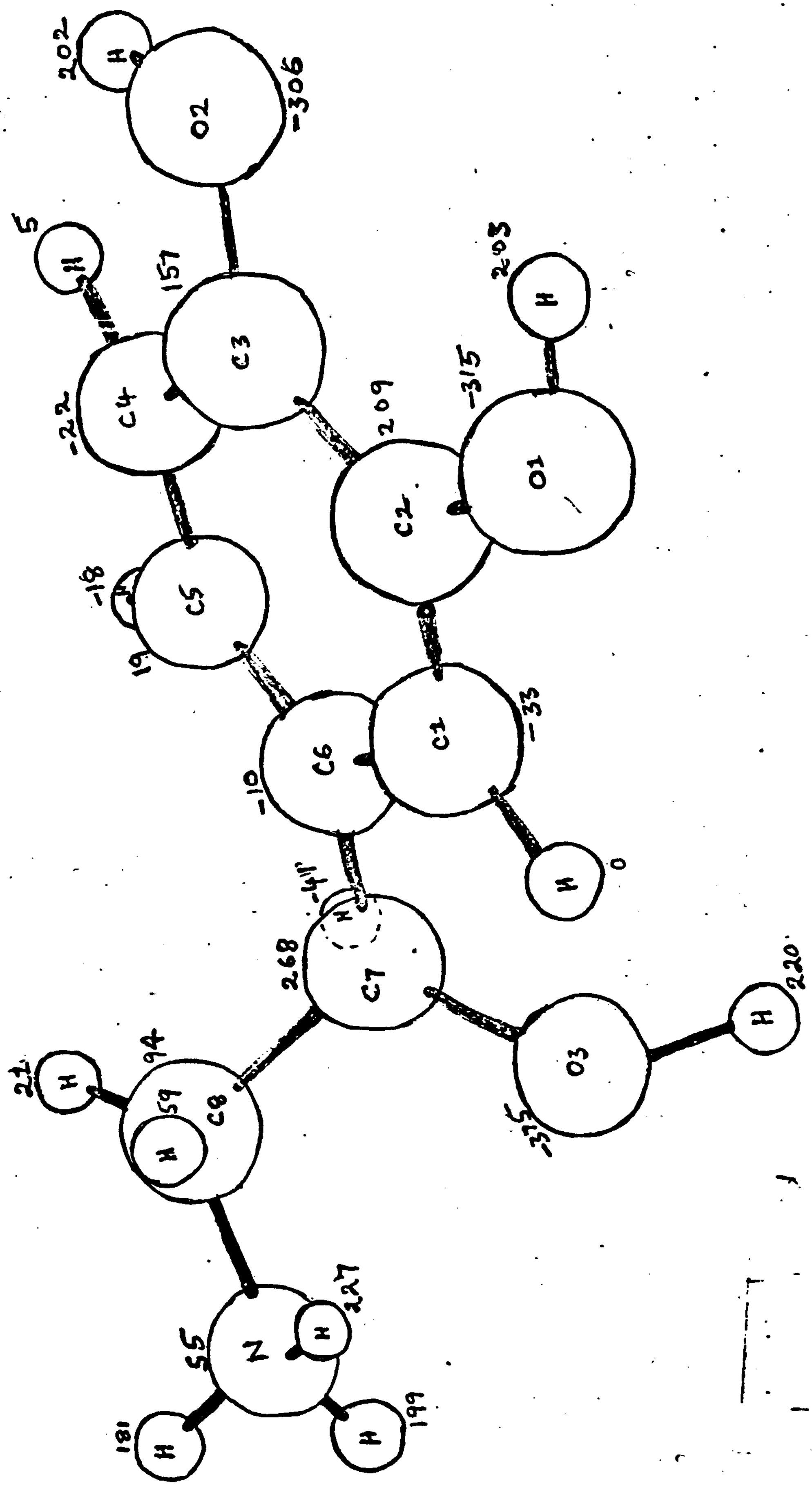

360
320
280
240
200
160
120
80
40
0
0
40
80
120
160
200
240
280
320
360
A
B
C
D
E
F
τ (C6-C7-C8-N)
τ.(C5-C6-C7-C8)

Figure 4.



O1
O2
O3
C1
C2
C3
C4
C5
C6
C7
C8
N
H
202
-306
157
5
-22
203
-315
209
-18
19
-33
-10
0
268
220
94
59
21
-325
55
227
181
199

Figure 5.

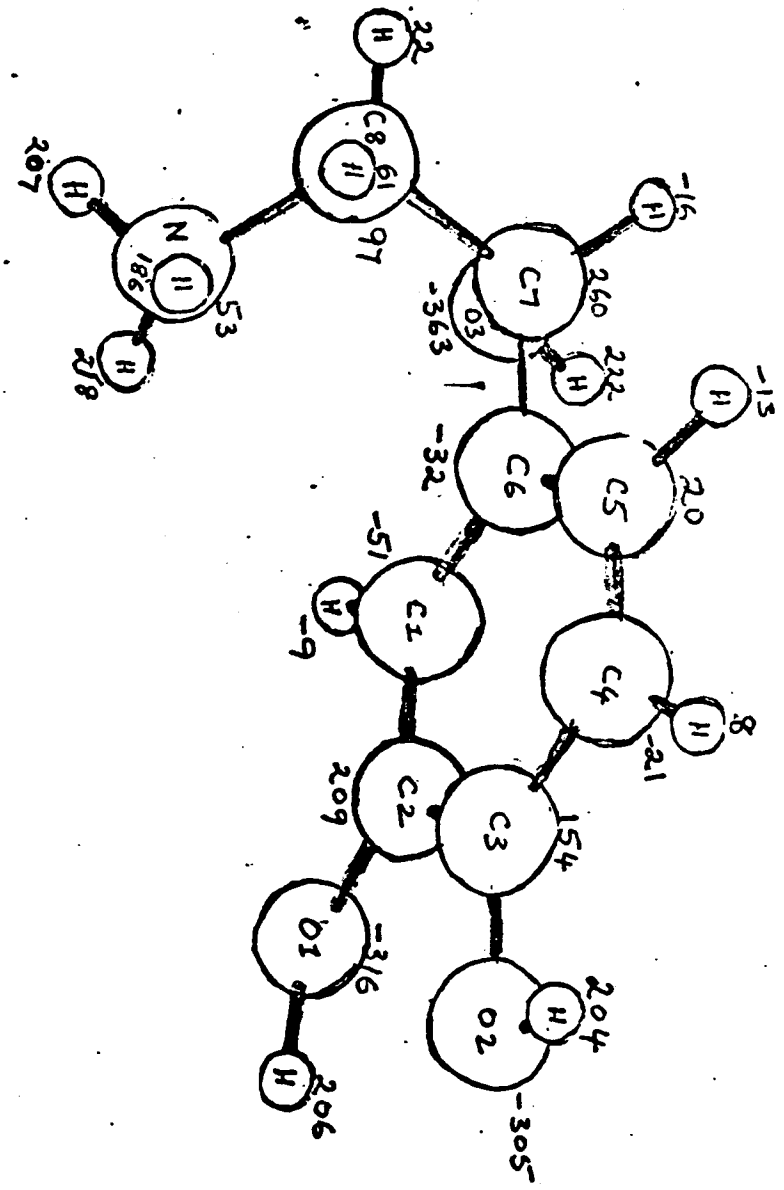

H
32
C8
61
H
207
N
181
H
208
11
53
97
C7
-363
O3
260
H
232
H
-16
-15
C6
-32
C5
20
C1
-51
H
-9
C4
H
-8
-21
C2
209
C3
154
O1
-316
O2
204
H
206
-305

Figure 6.

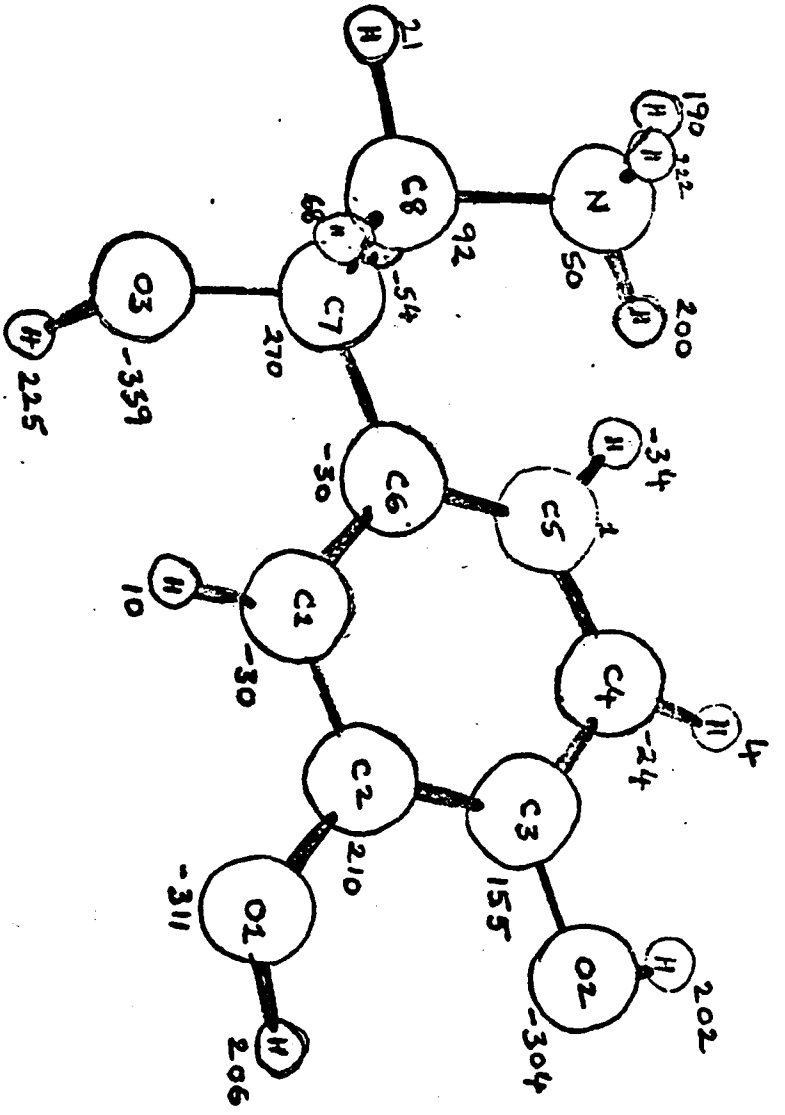
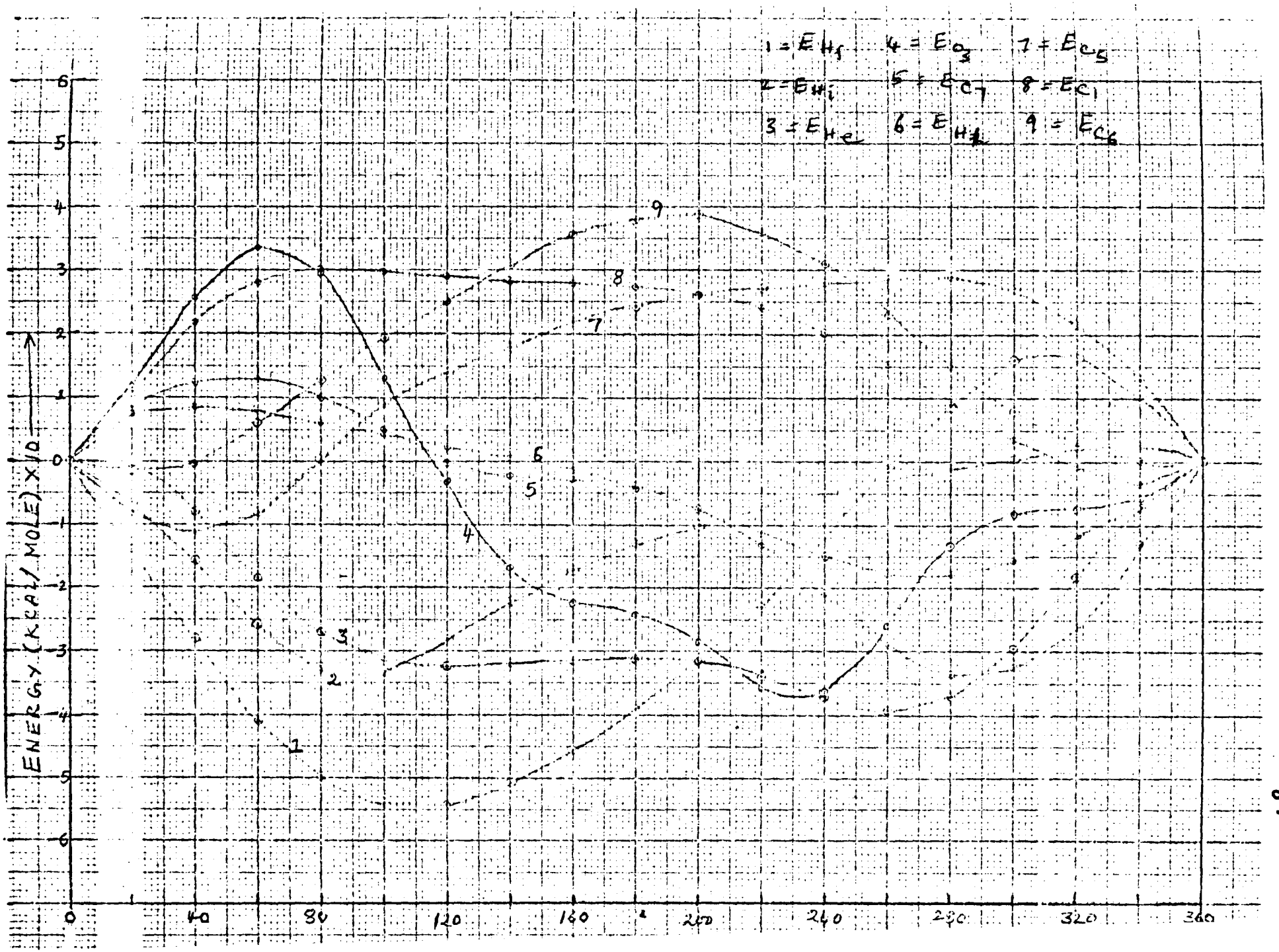
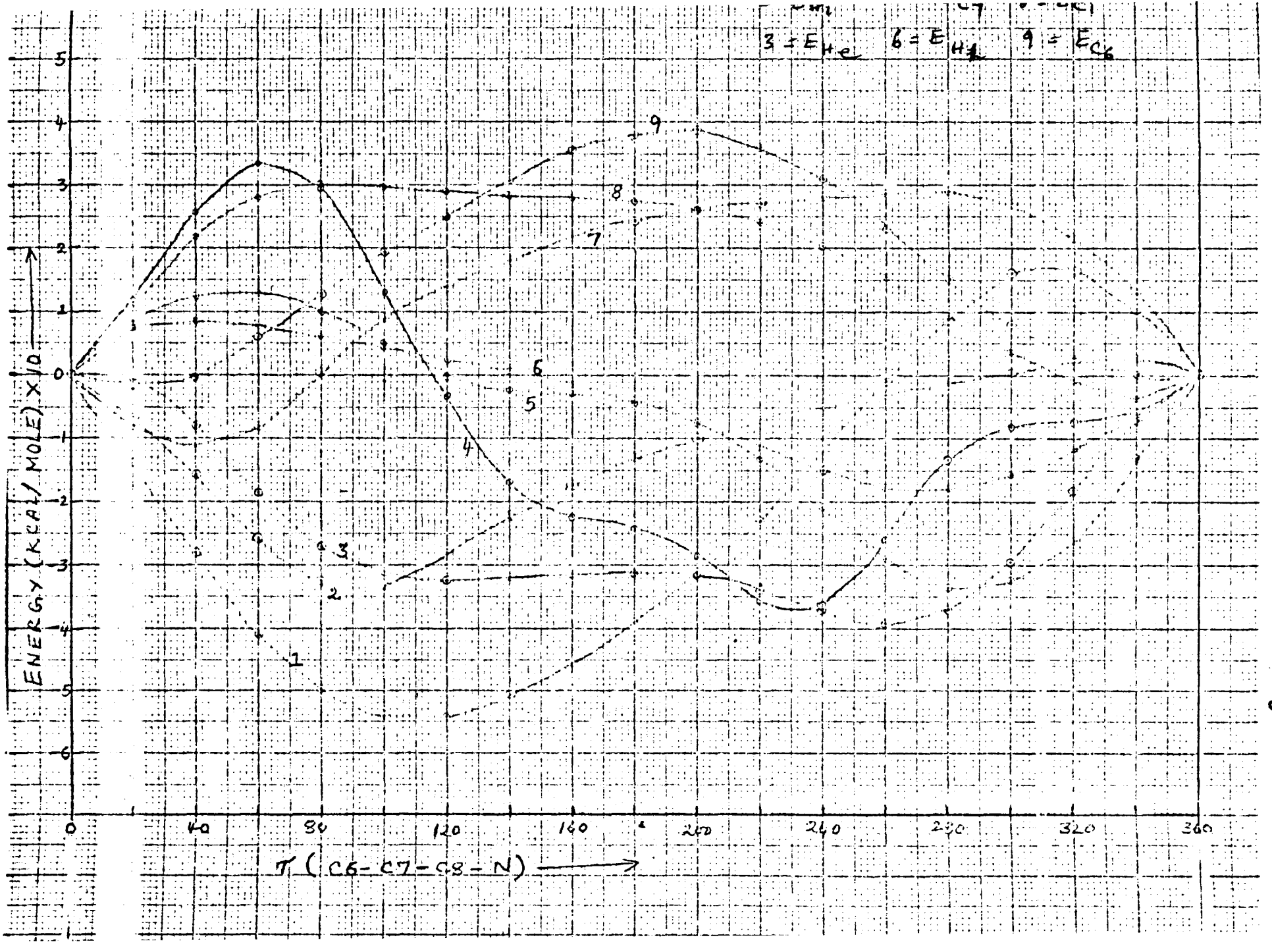

H
21
H
190
H
222
C8
N
46
92
50
-54
H
200
O3
C7
H
225
-359
270
C6
-30
H
-34
C5
H
10
C1
-30
C4
H
4
-24
C2
C3
210
155
-311
O1
O2
H
202
H
206
-304

Figure 7.


1 = E H1
2 = E H2
3 = E H3
4 = E O3
5 = E C7
6 = E H4
7 = E C5
8 = E C1
9 = E C6
ENERGY (KCAL / MOLE) X 10
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
0
40
80
120
160
200
240
280
320
360


3 = E_{He}
6 = E_{H_2}
9 = E_{C_6}
ENERGY (KCAL/MOLE) X 10
T (C6-C7-C8-N)
0
40
80
120
160
200
240
280
320
360

1 = E_N

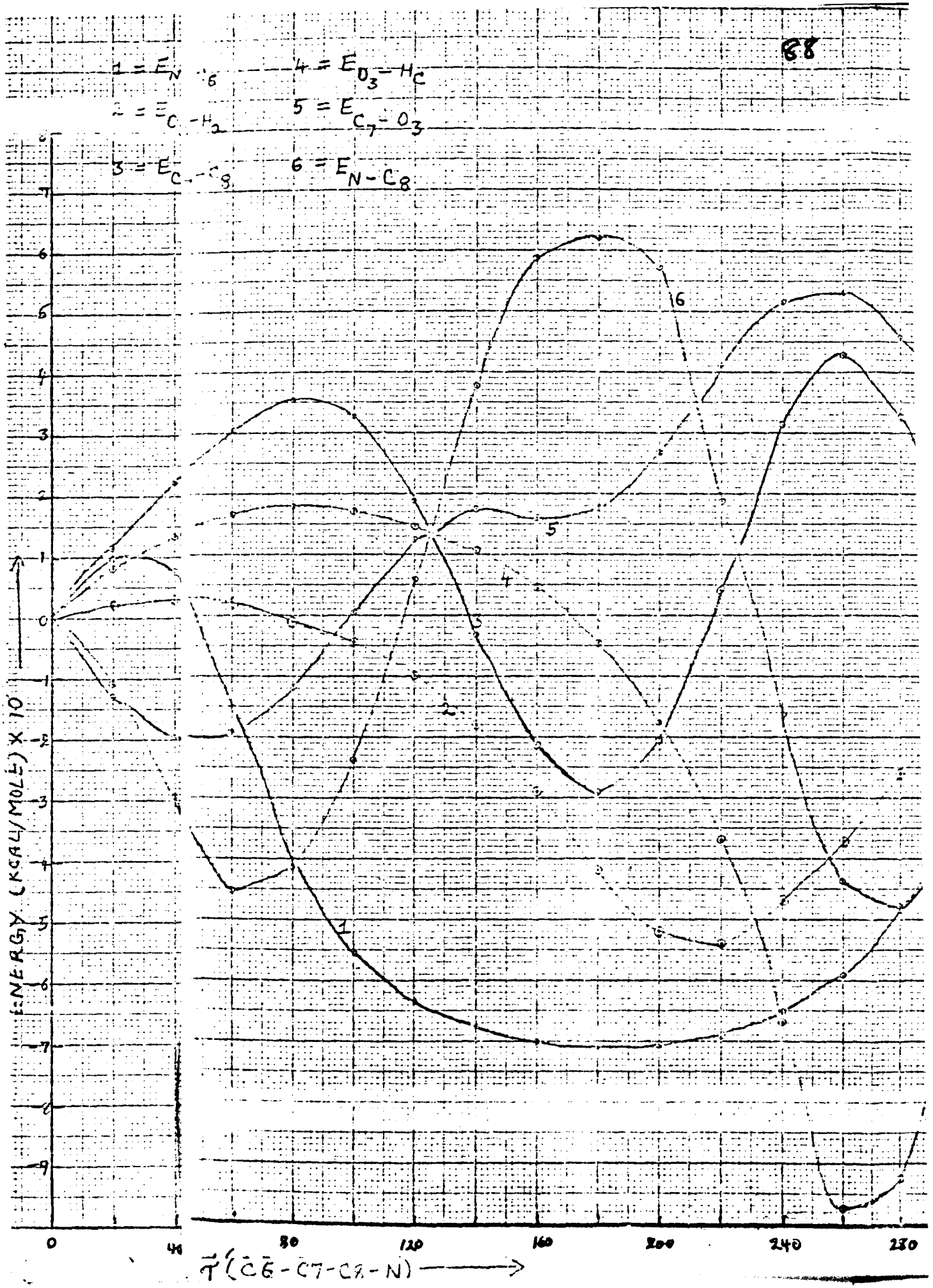
2 = $E_{C_1-H_2}$

3 = $E_{C_6-C_8}$

4 = $E_{O_3-H_C}$

5 = $E_{C_7-O_3}$

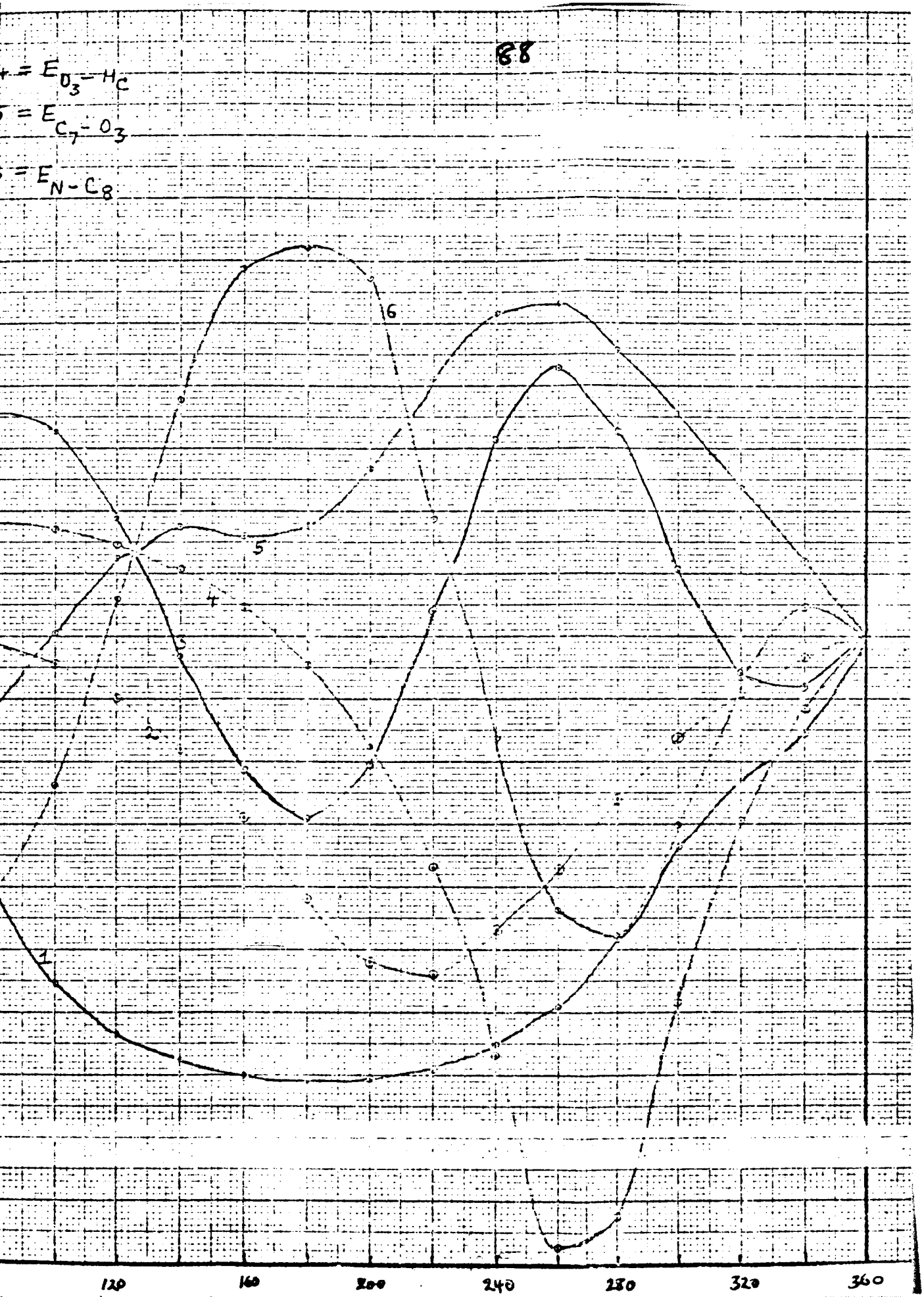
6 = E_{N-C_8}



$+ = E_{O_3 - H_C}$

$5 = E_{C_7 - O_3}$

$= E_{N - C_8}$



ENERGY (KCAL/MOLE)
τ (C6-C7-C8-N)
40
80
120
160
200
240
280
320
360
0
1
2
3
4
5
6
7
8
9
10

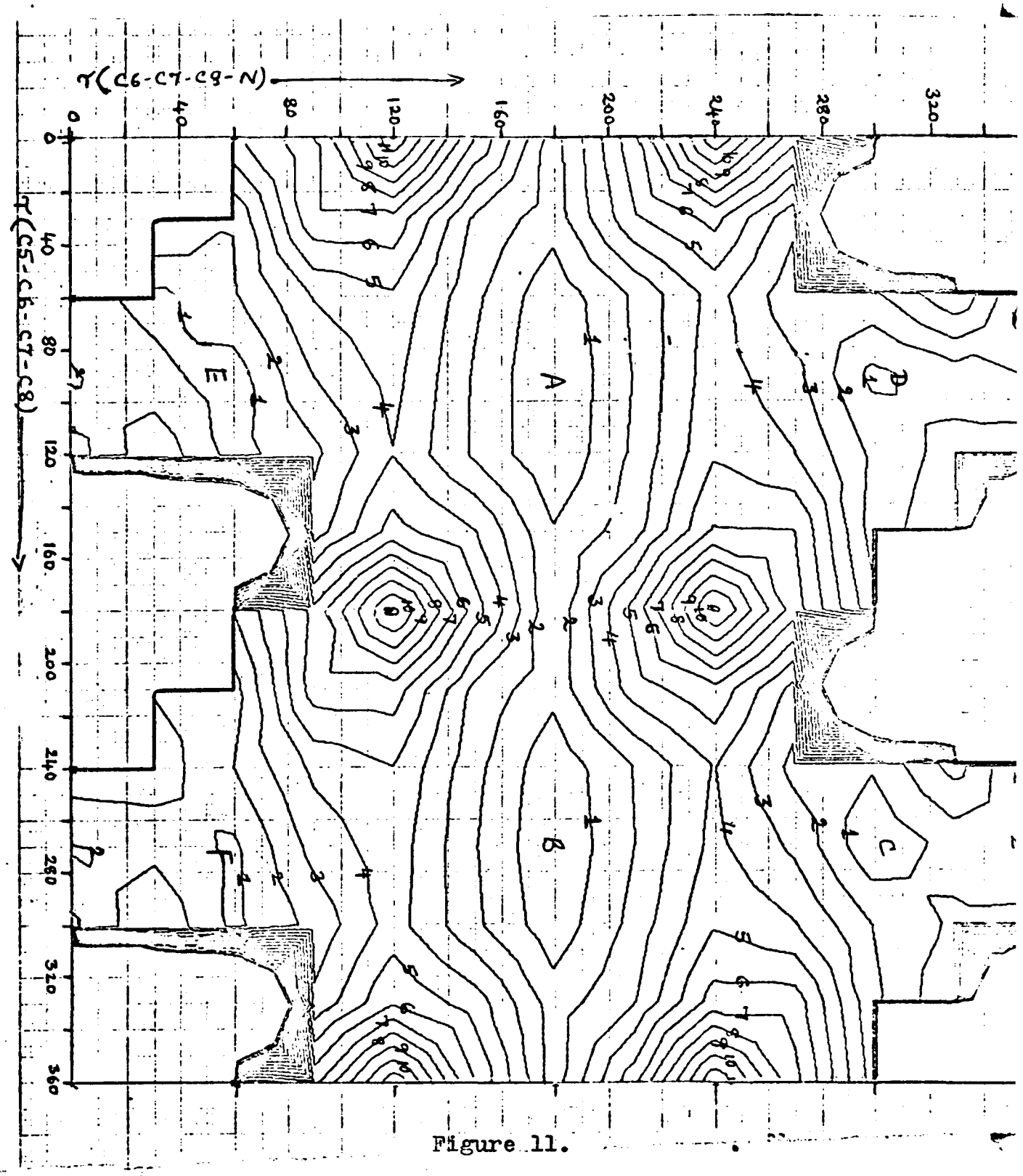


Figure 11.

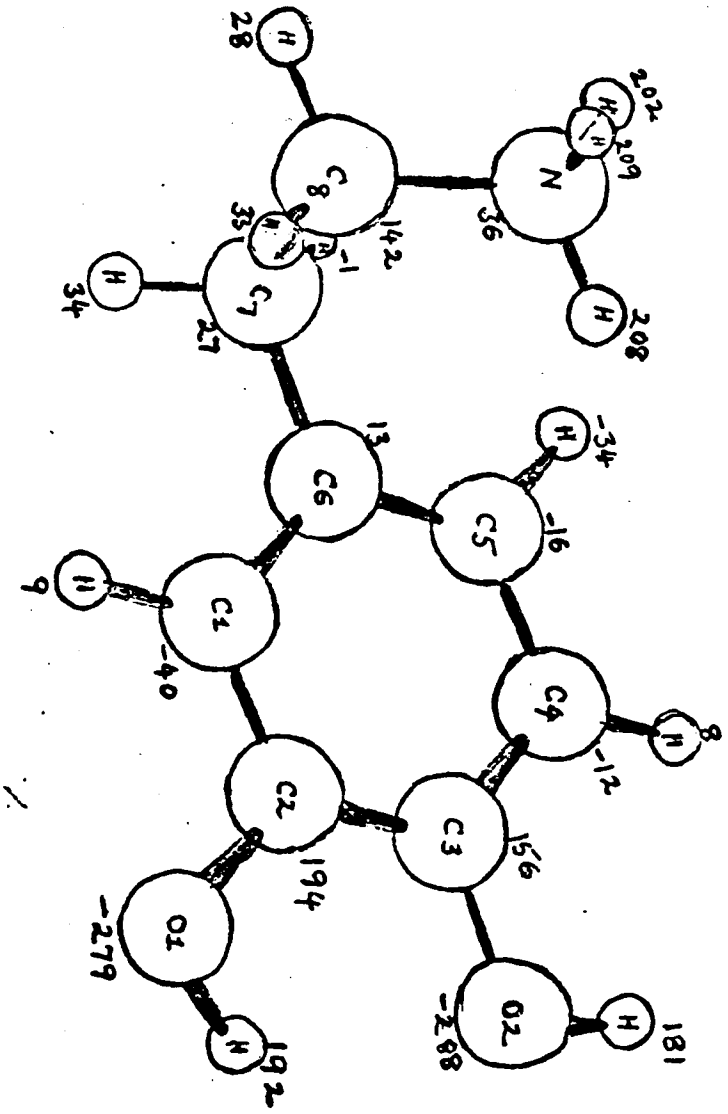

H
28
C8
142
N
36
202
H
209
H
208
H
33
-1
H
34
C7
27
13
C6
-34
C5
-16
H
9
C1
-40
C4
H
-12
C2
C3
156
194
O1
-279
O2
-288
H
181
H
192

Figure 12.

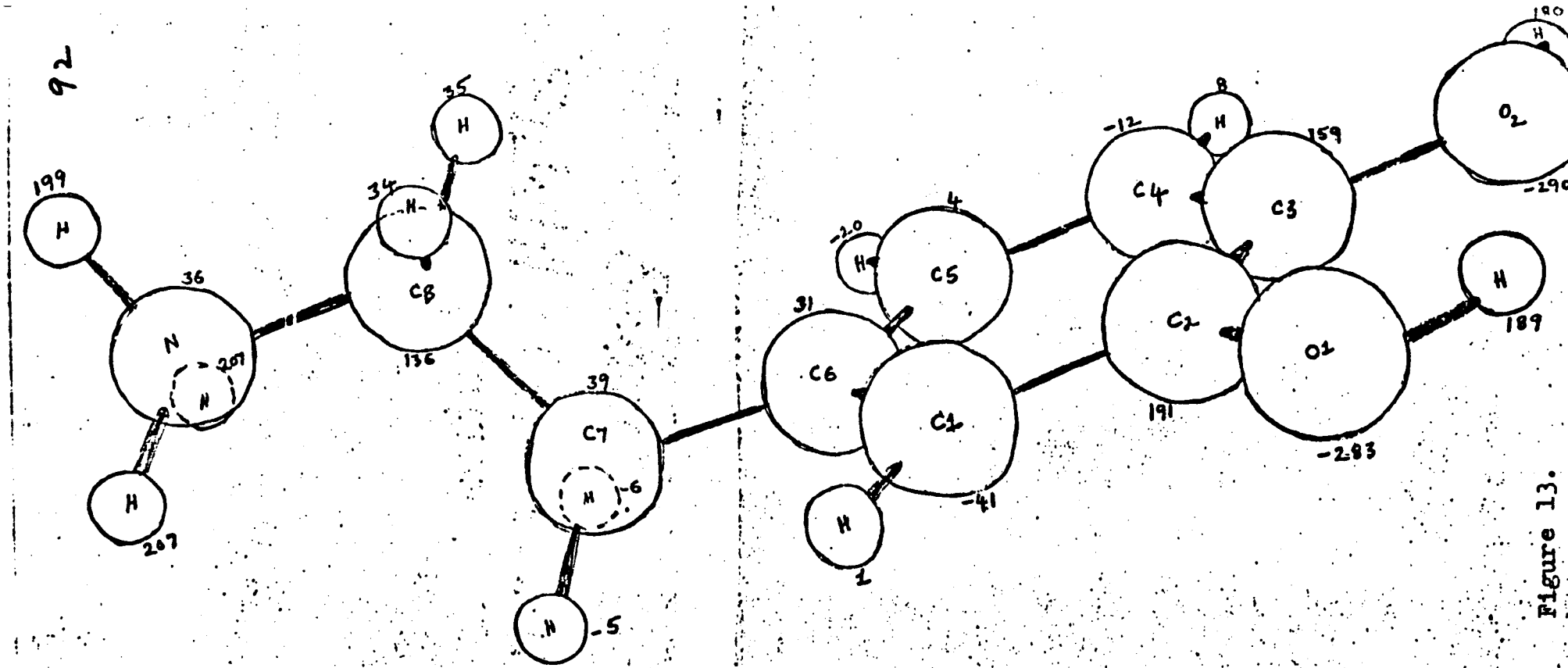

92
H
199
N
36
-207
H
207
CB
34
H
35
136
C7
39
H
-6
H
-5
C6
31
C5
4
H
-2.0
C1
H
1
-41
C4
-12
H
8
C3
159
C2
191
O1
-283
O2
H
189
-290

Figure 13.

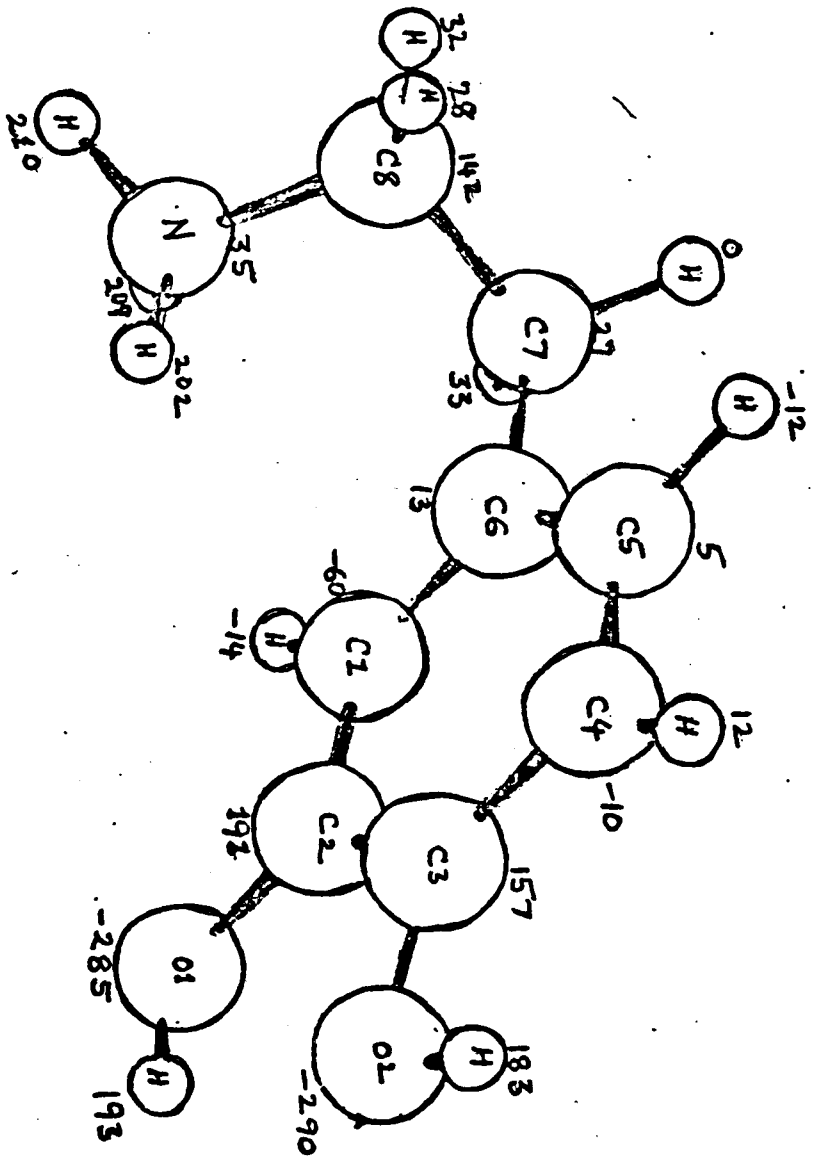

H
32
78
C8
142
H
240
N
35
0
H
209
202
C7
27
33
-12
H
C6
13
C5
5
-60
-14
H
C1
C4
12
H
-10
192
C2
C3
157
-285
O1
O2
183
H
-290
H
193

Figure 14.

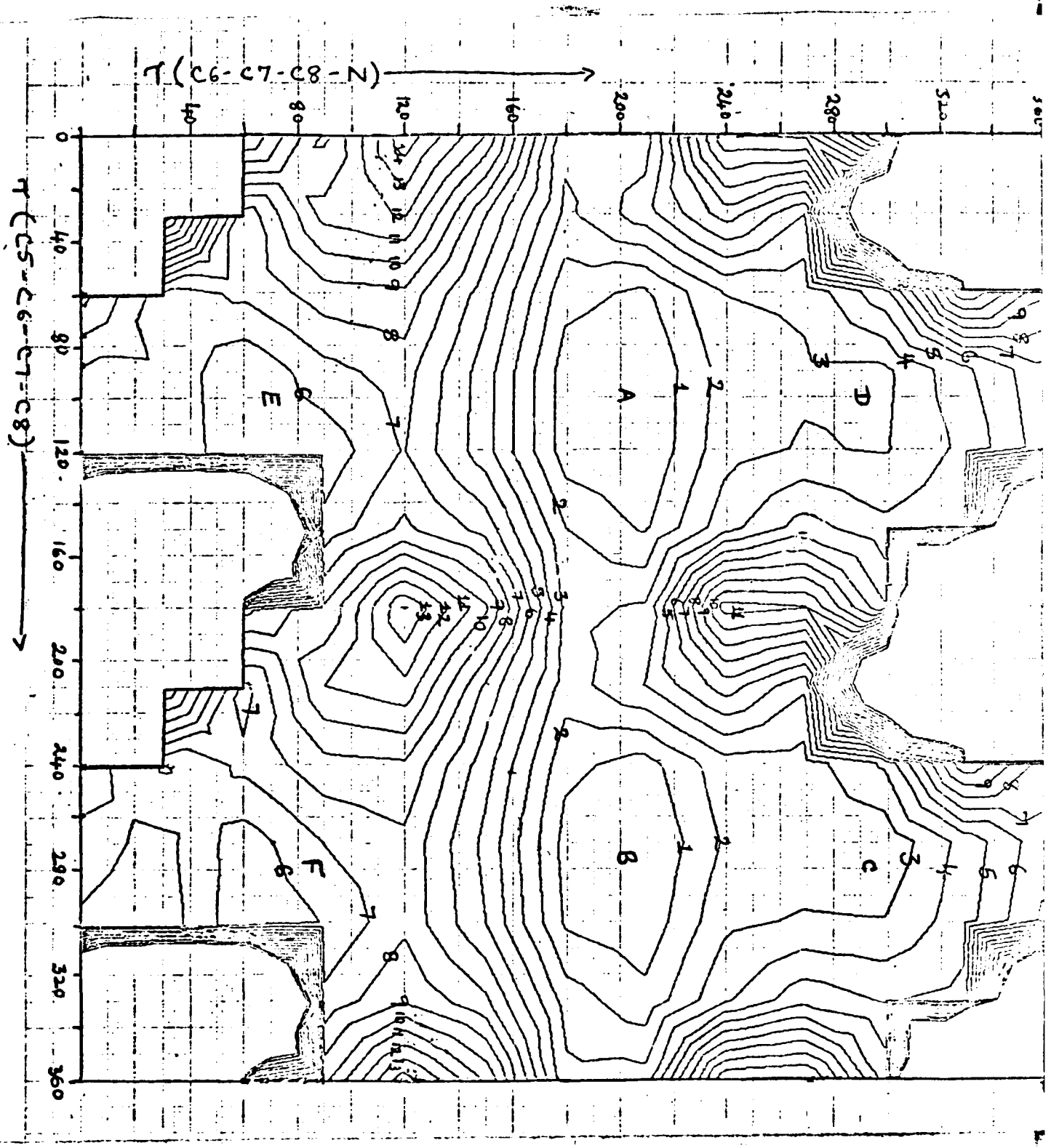


Figure 15.

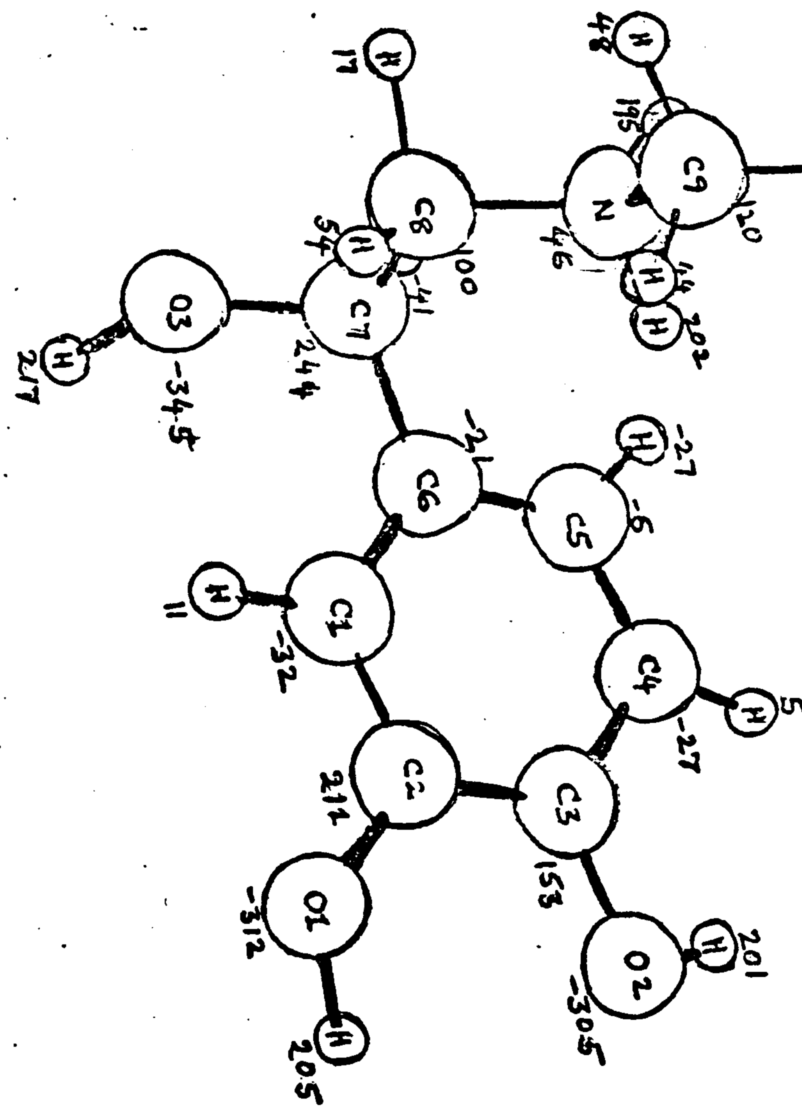


Figure 16.

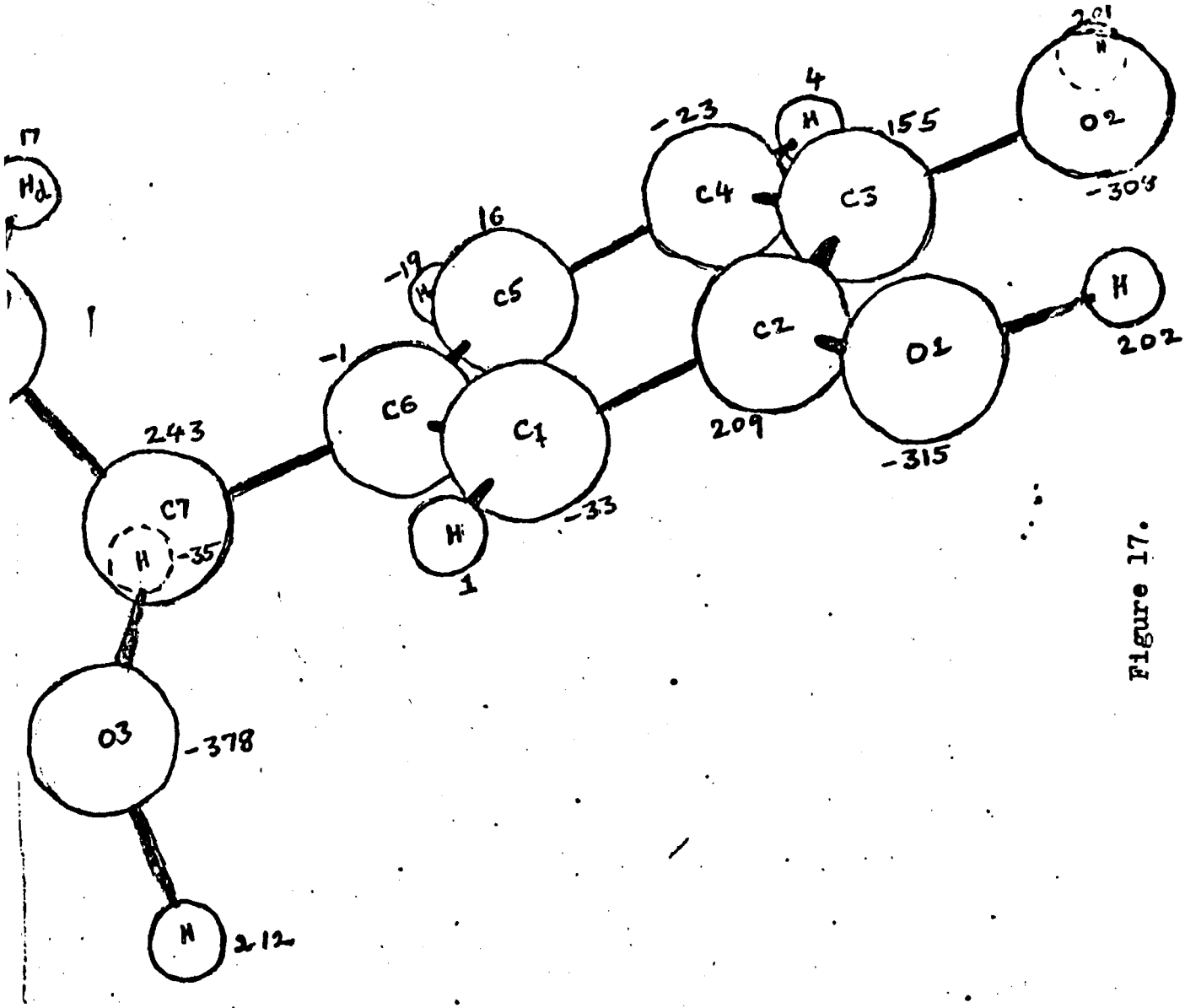
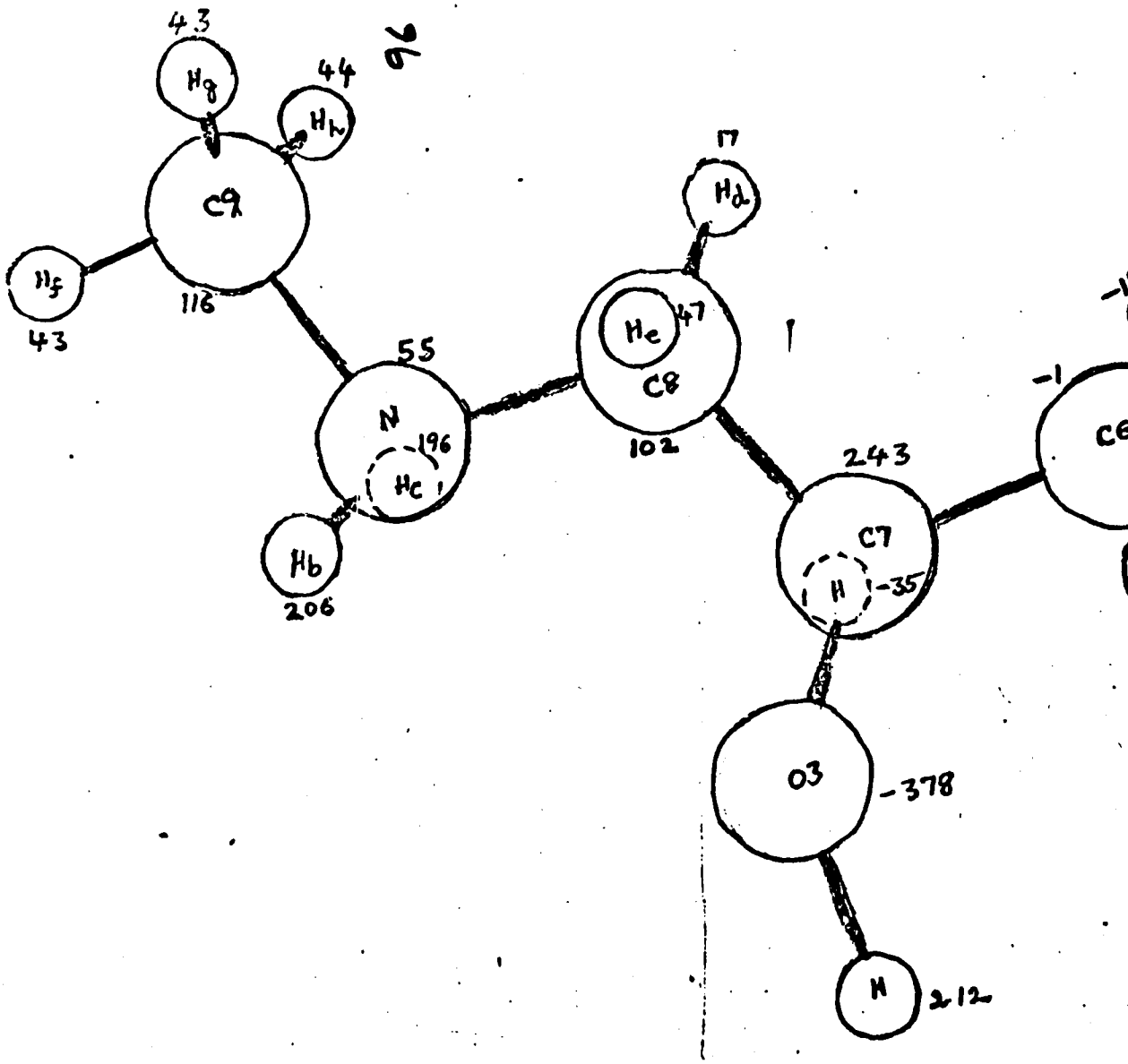

17
Hd
243
C7
H
-35
O3
-378
N
212
C6
-1
C5
16
H
-19
C1
H
1
-33
C4
-23
H
4
C3
155
C2
209
O1
-315
O2
-305
201
H
H
202

Figure 17.


43
Hg
44
Hh
C9
Hf
43
116
55
N
196
Hc
Hb
206
17
Hd
He
47
C8
102
243
C7
H
-35
-1
O3
-378
H
212

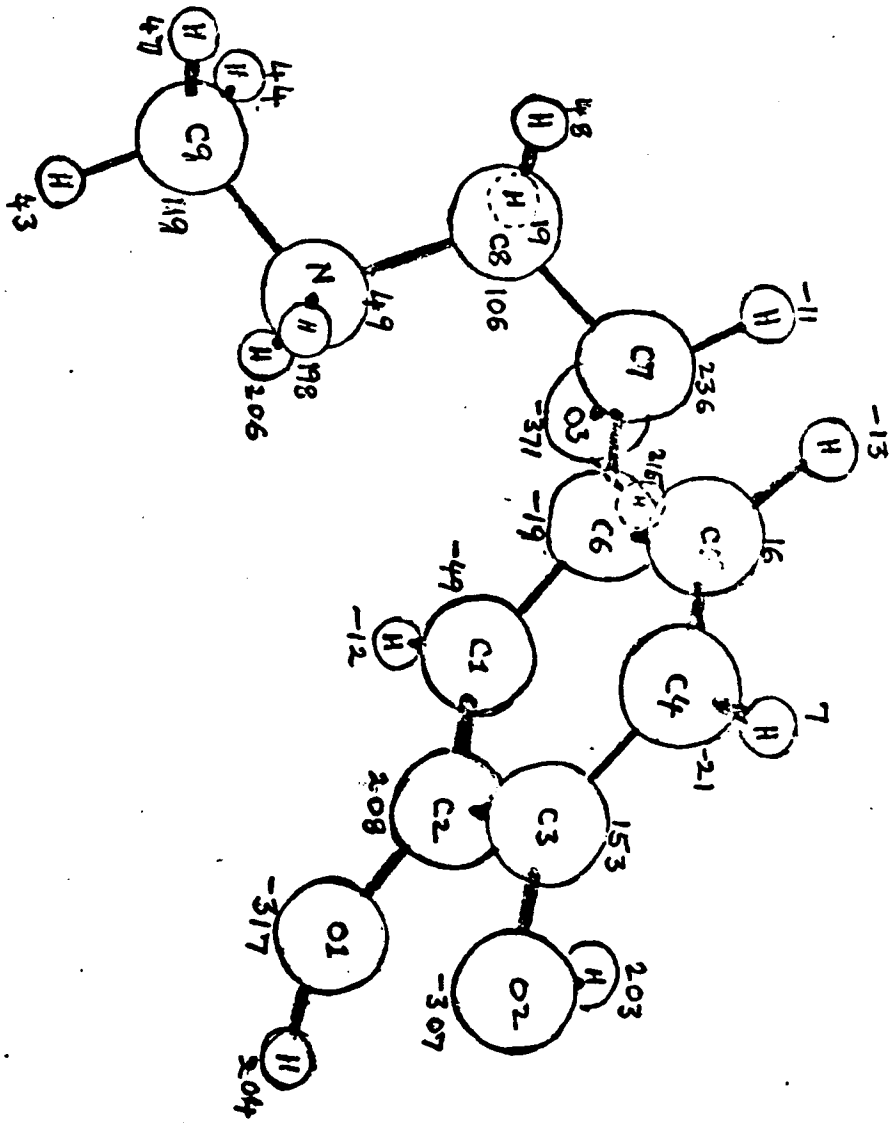
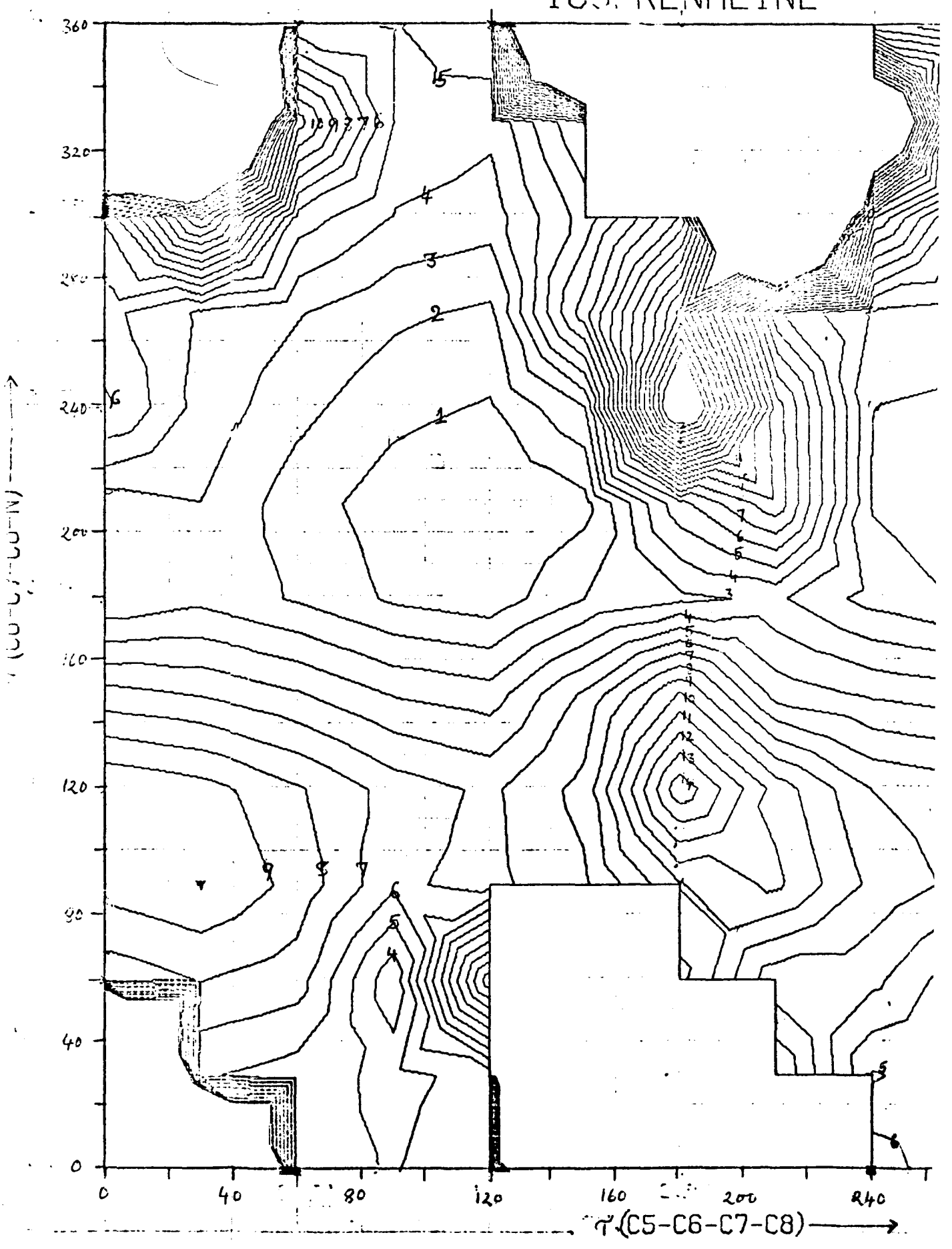
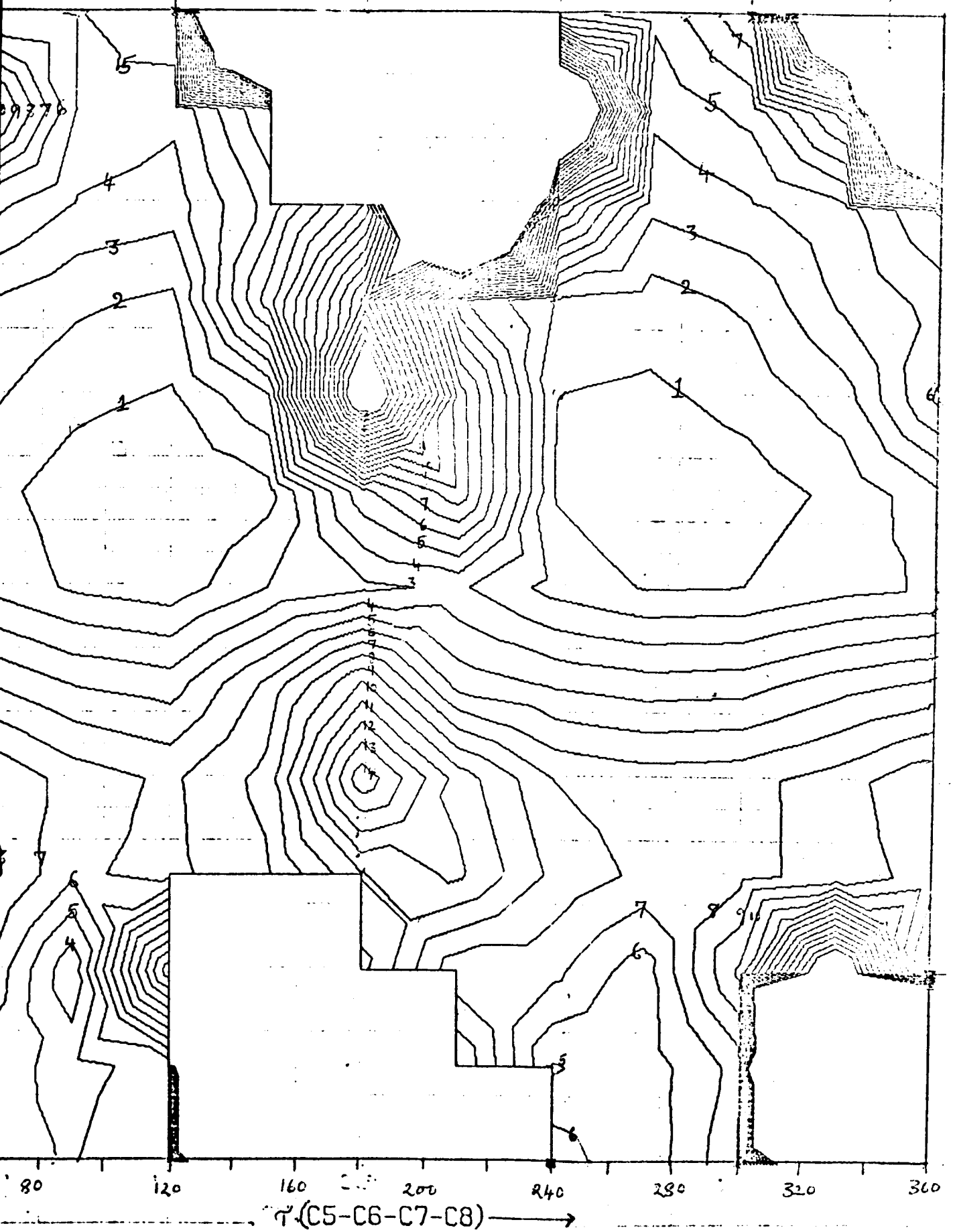

H
47
H
44
C9
H
43
119
H
48
H
C8
19
N
149
106
H
198
206
C7
236
H
-11
O3
-371
H
-13
C6
-19
C5
16
-44
H
-12
C1
C4
7
H
-21
208
C2
C3
153
-317
O1
O2
203
H
-307
H
304

Figure 18.


ISOPRENALINE
360
320
240
200
160
120
90
40
0
0
40
80
120
160
200
240
τ(C5-C6-C7-C8)

ISOPRENALINE



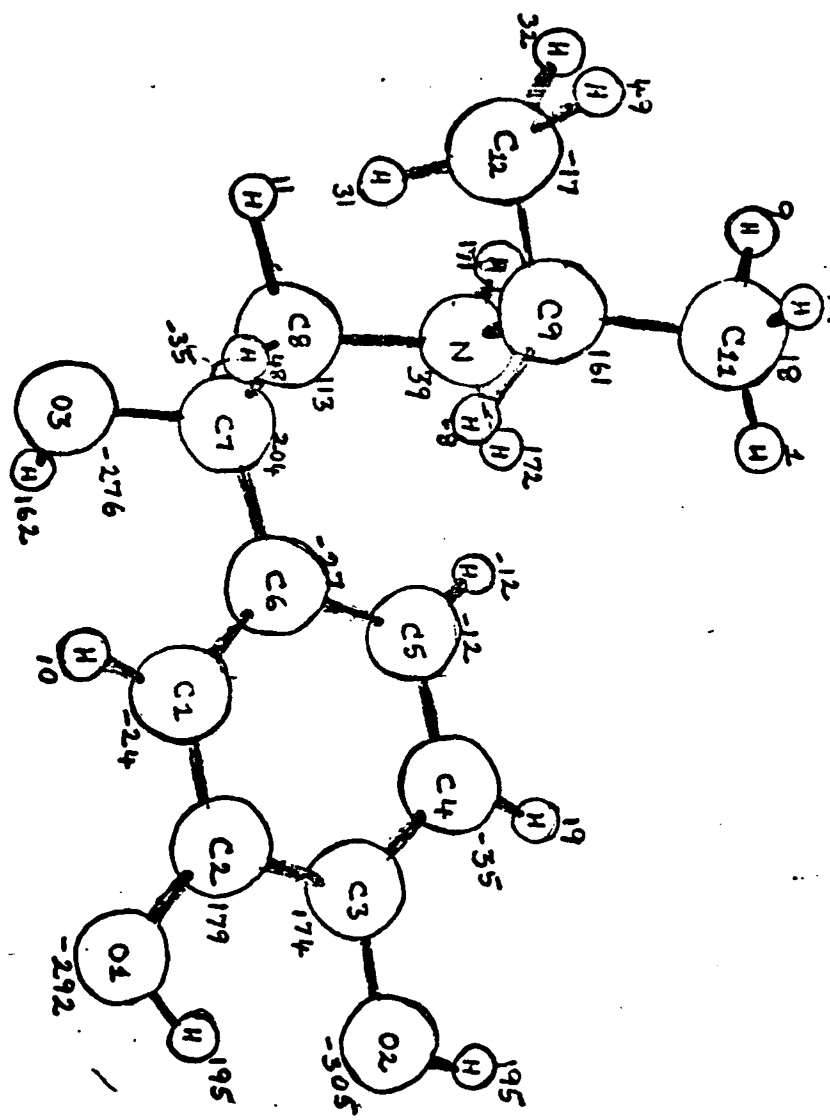


Figure 20.

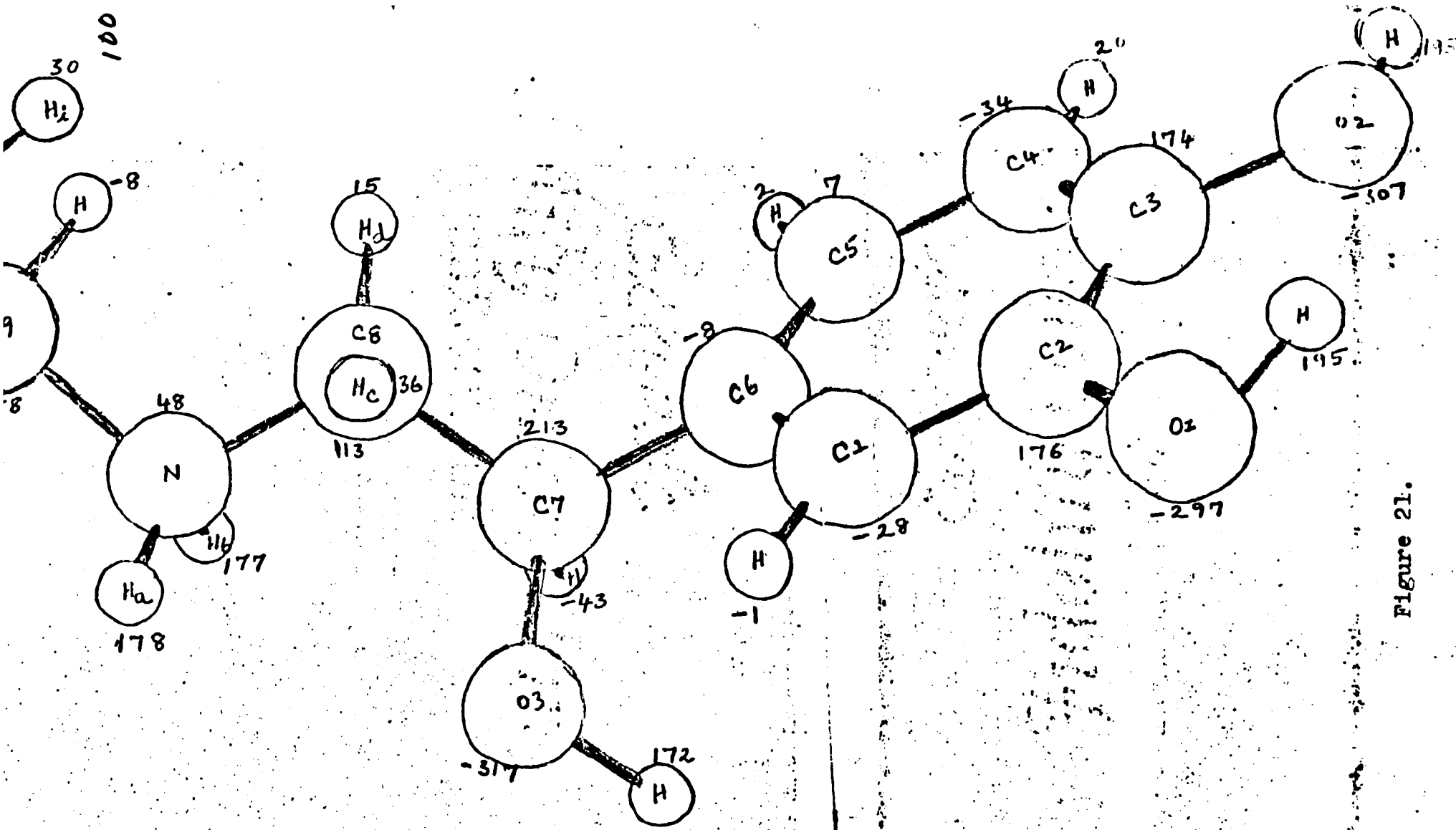

100
30
H_i
H
-8
9
8
48
N
H_a
178
H_b
177
C8
H_c
36
113
15
H_d
213
C7
H
-43
O3
-317
172
H
-8
C6
C5
2
7
H
-1
C1
-28
C4
-34
20
H
C3
174
C2
176
O1
-297
O2
-307
H
195
H
195

Figure 21.

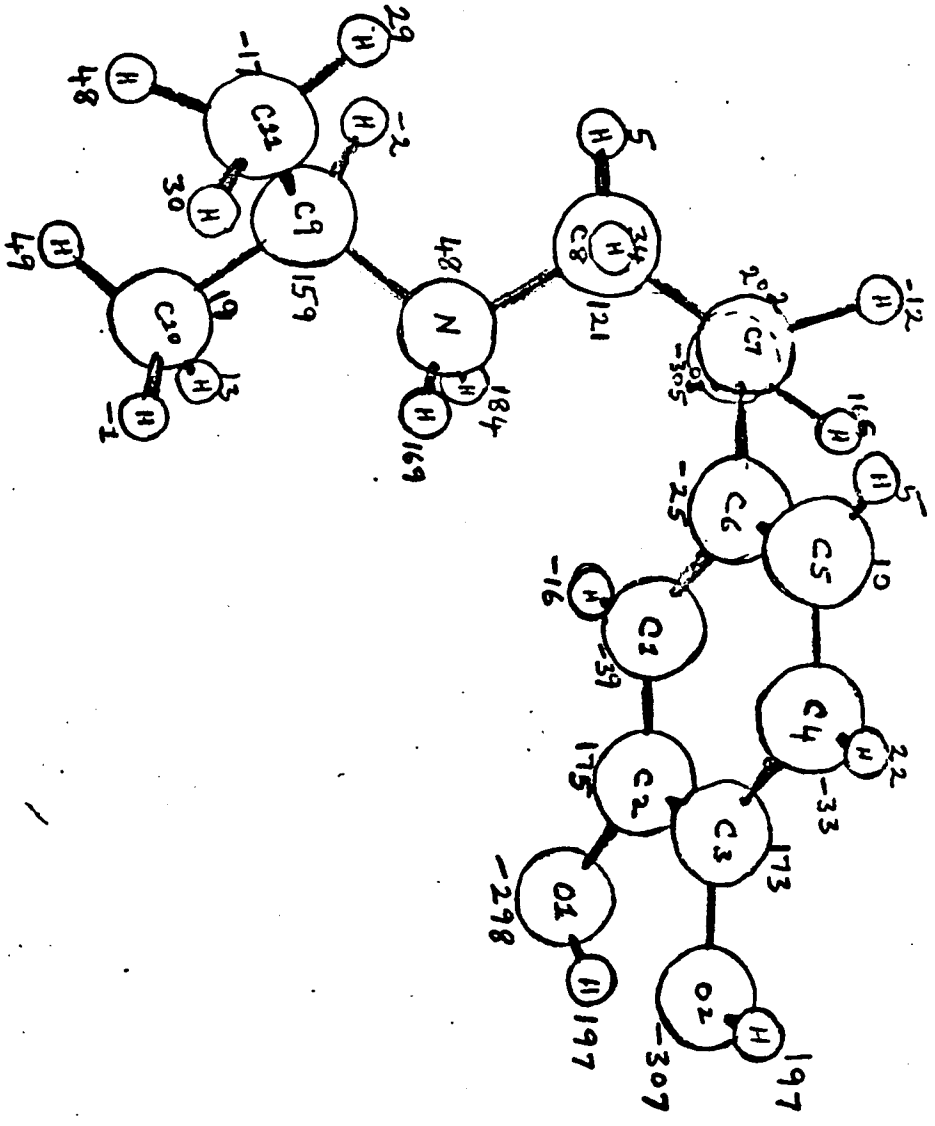

29
48
-17
-2
5
30
34
49
48
2°
-12
19
159
121
-305
184
169
146
5
-25
19
-16
-39
22
175
-33
173
-298
197
-307
197

Figure 22.

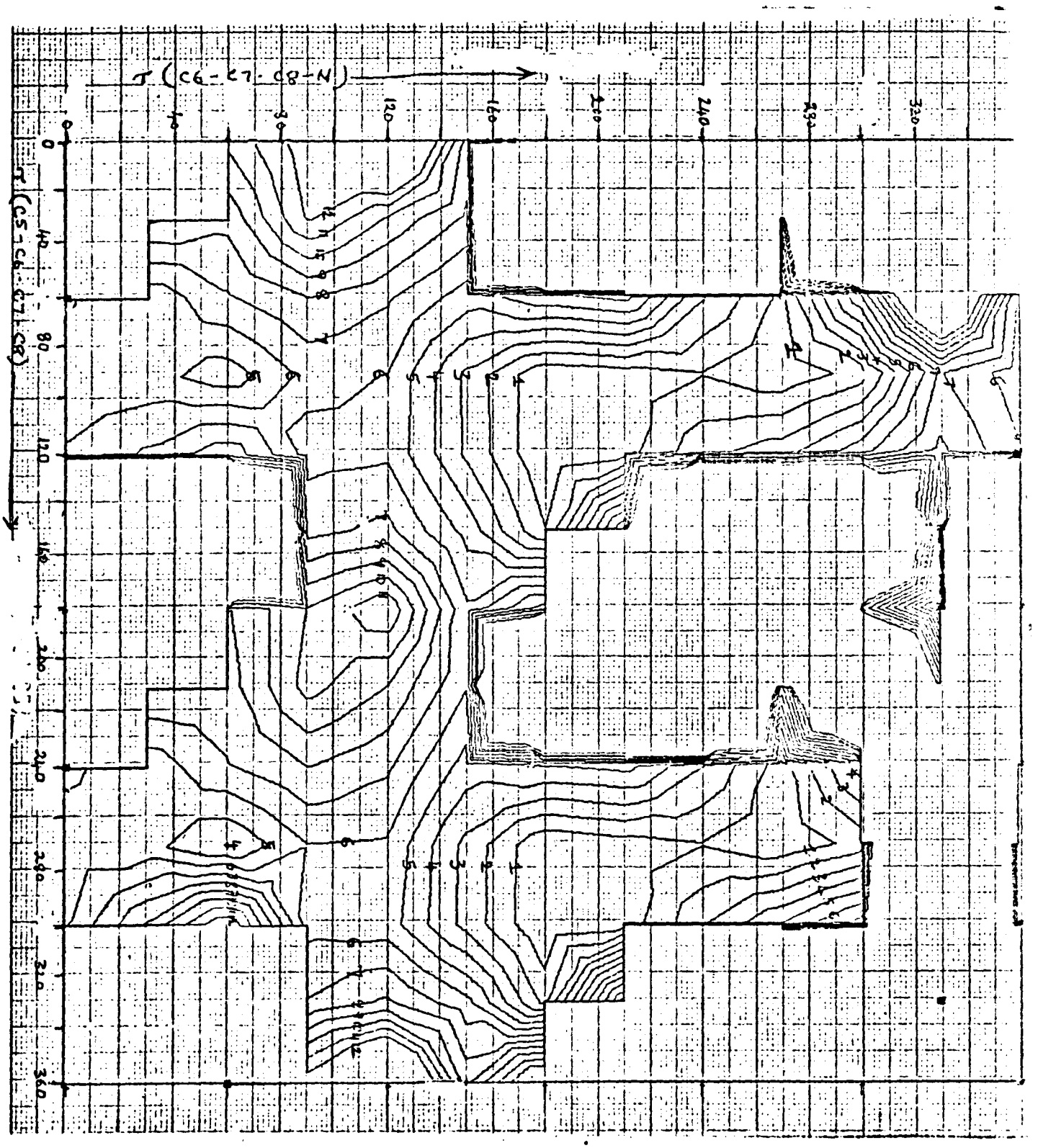


Figure 23.

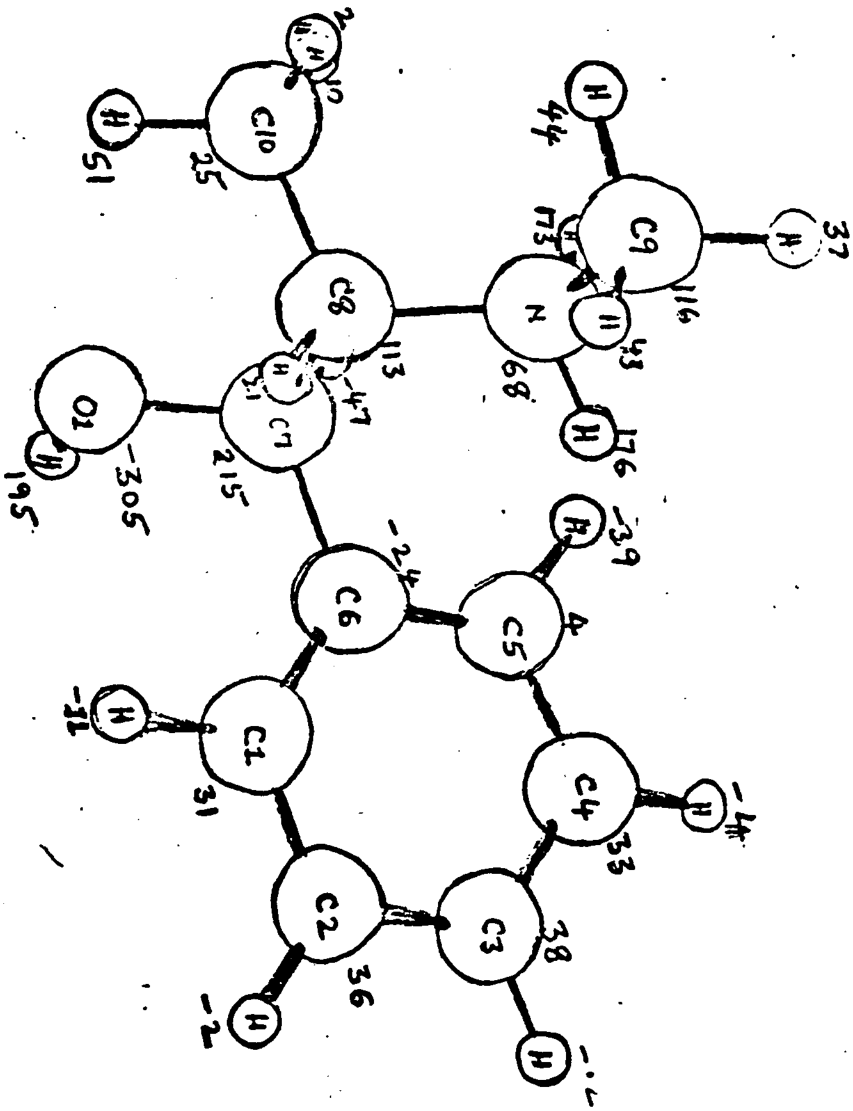
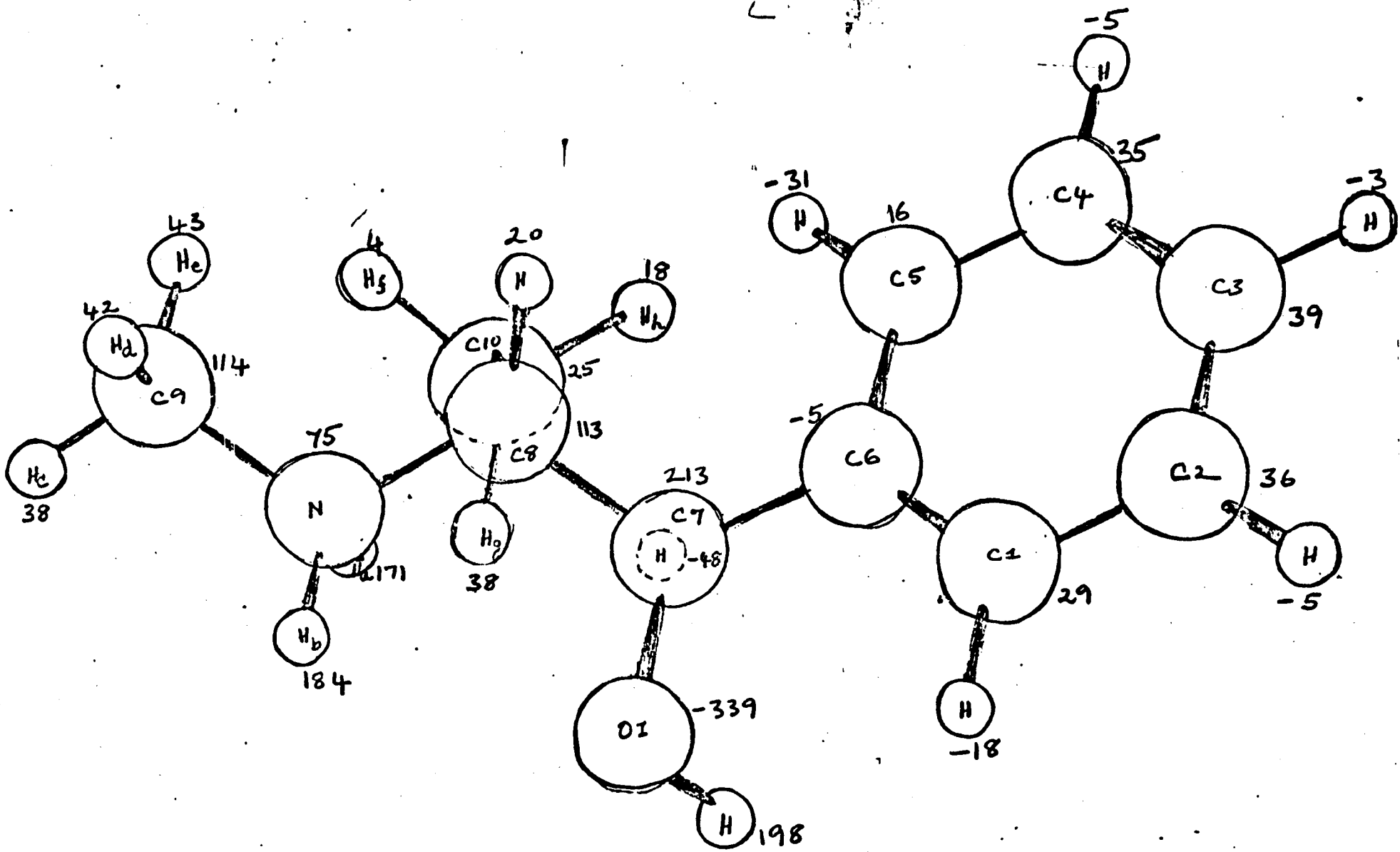


Figure 24.


-5
H
35
C4
-3
H
-31
H
16
C5
C3
39
43
He
4
Hf
20
H
18
Hh
42
Hd
C10
25
114
C9
113
75
C8
-5
C6
213
C7
C2
36
Hc
38
N
H
-48
C1
29
H
-5
Hg
38
171
Hb
184
O1
-339
H
-18
H
198

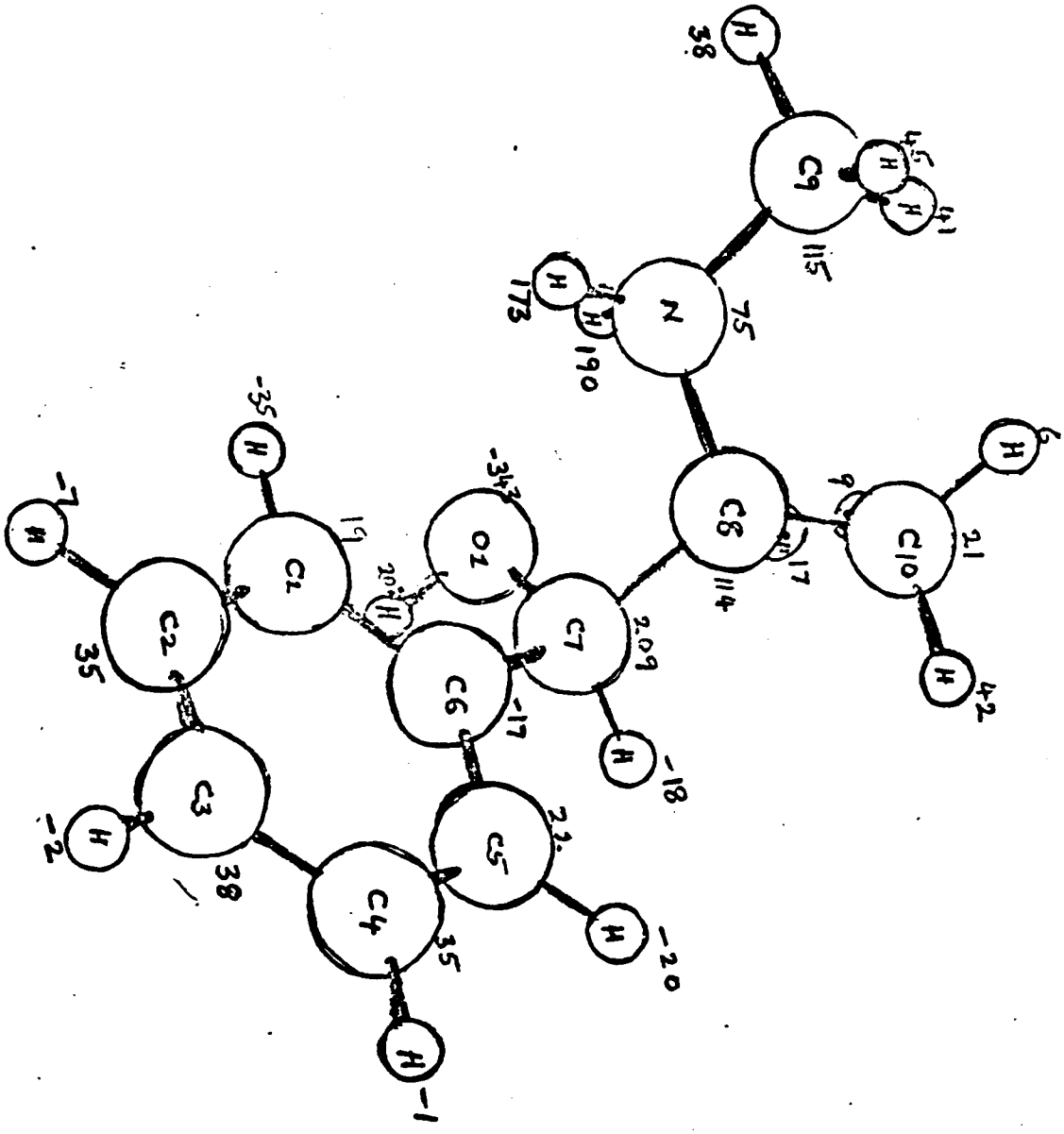

H
38
C9
45
41
115
N
75
H
173
H
190
C8
114
17
C10
21
6
H
42
H
O1
-34
C7
2.09
H
-18
C6
-17
C5
2.1
H
-20
C4
35
H
-1
C3
38
H
-2
C2
35
H
-7
C1
19
H
-35
20

Figure 26.

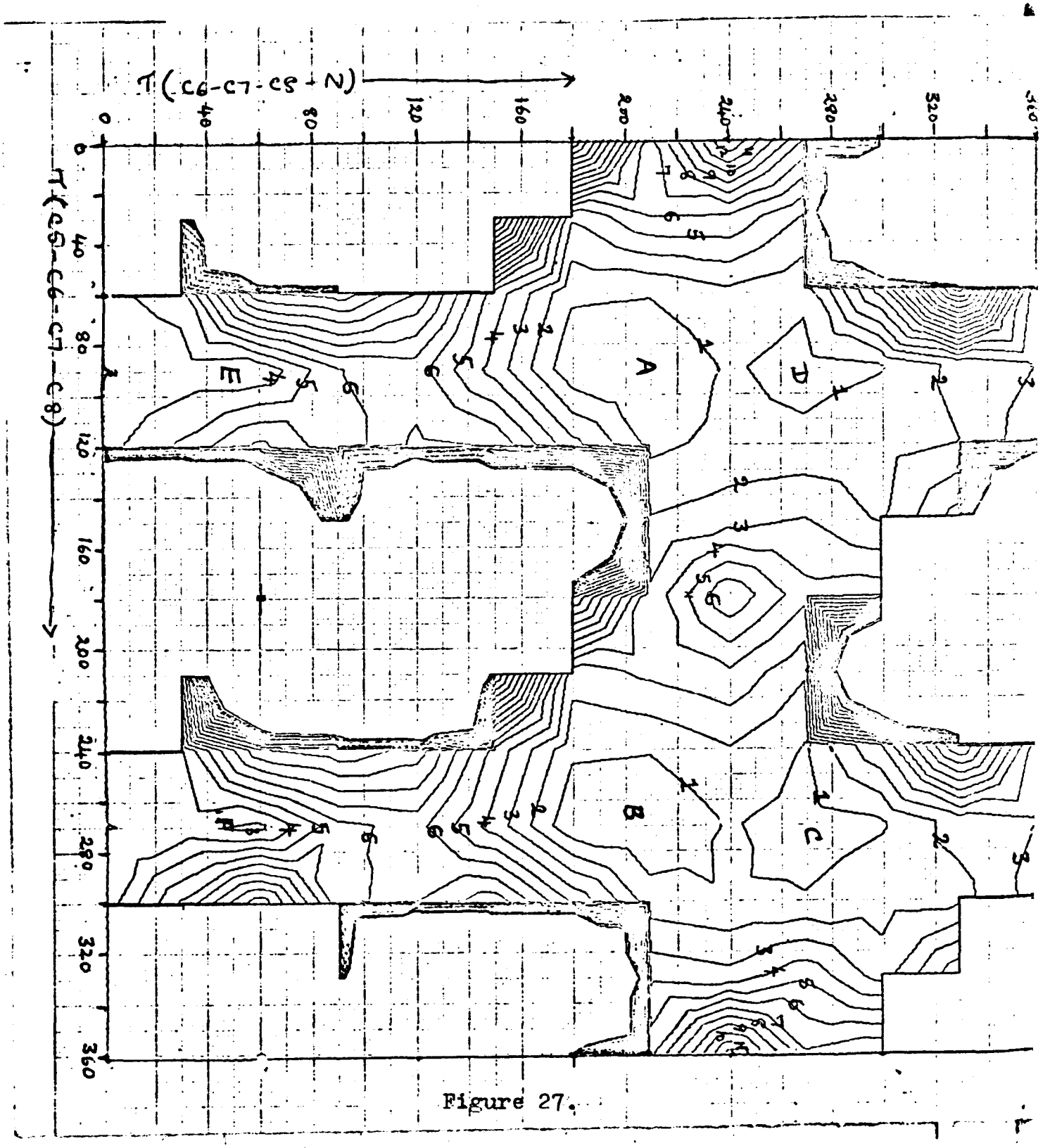
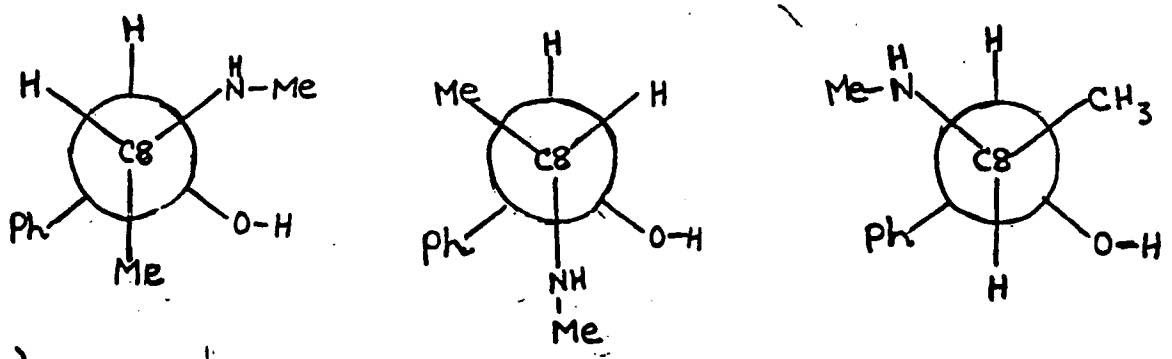
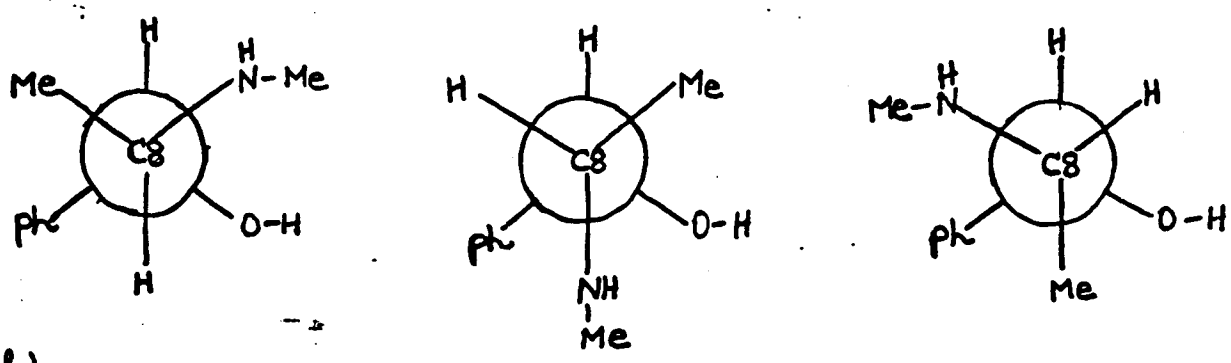


Figure 27.


H
H
N-Me
C8
Ph
O-H
Me
Me
H
C8
Ph
O-H
NH
Me
Me-N
H
H
CH3
C8
Ph
O-H
H

(a)


H
Me
N-Me
C8
Ph
O-H
H
H
Me
C8
Ph
O-H
NH
Me
Me-N
H
H
C8
Ph
O-H
Me

(b)

FIGURE 28

α·R, β·R ψ EPHEDRINE {210 / 270} ψ eph {

{210
270}

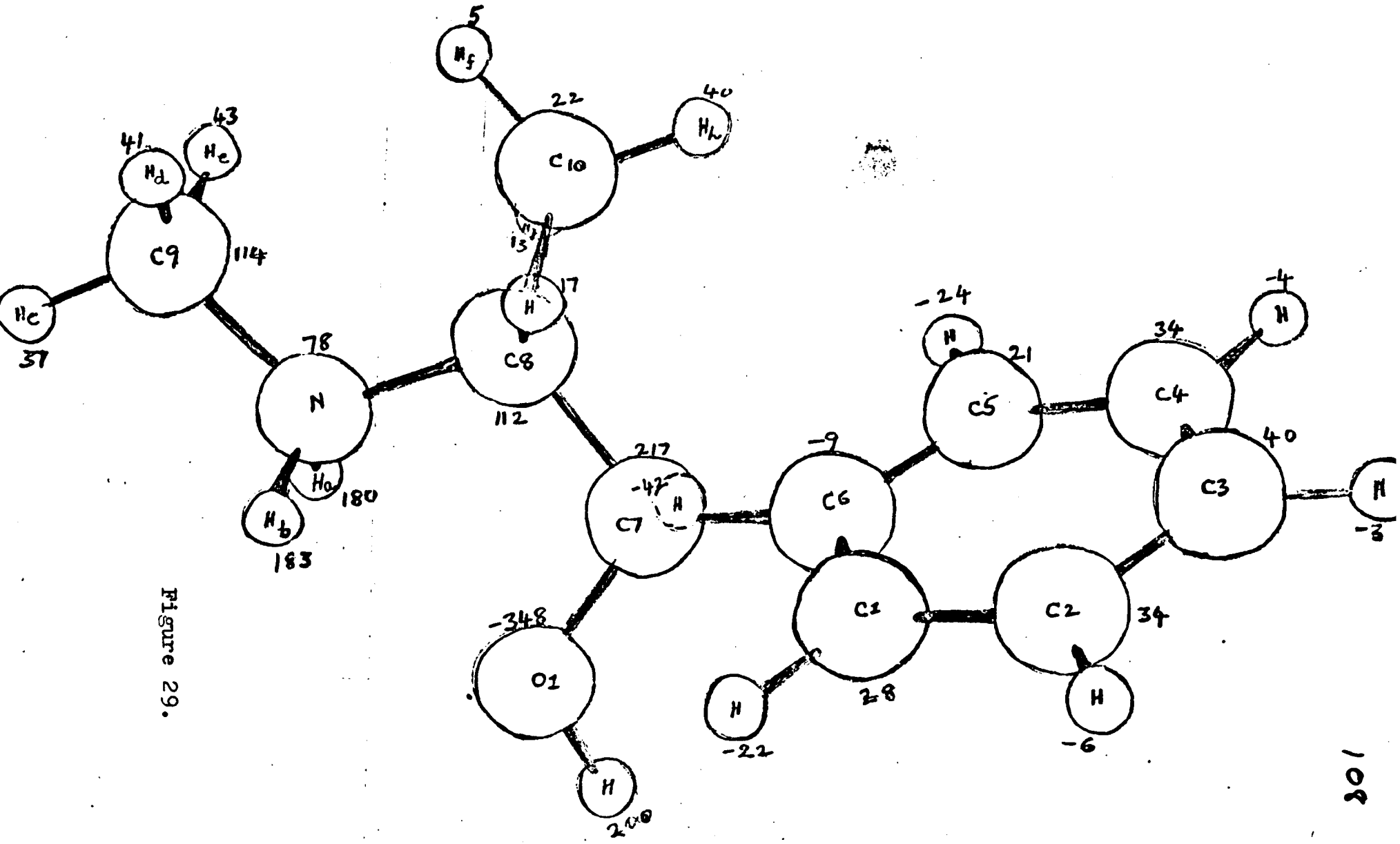


Figure 29.

901

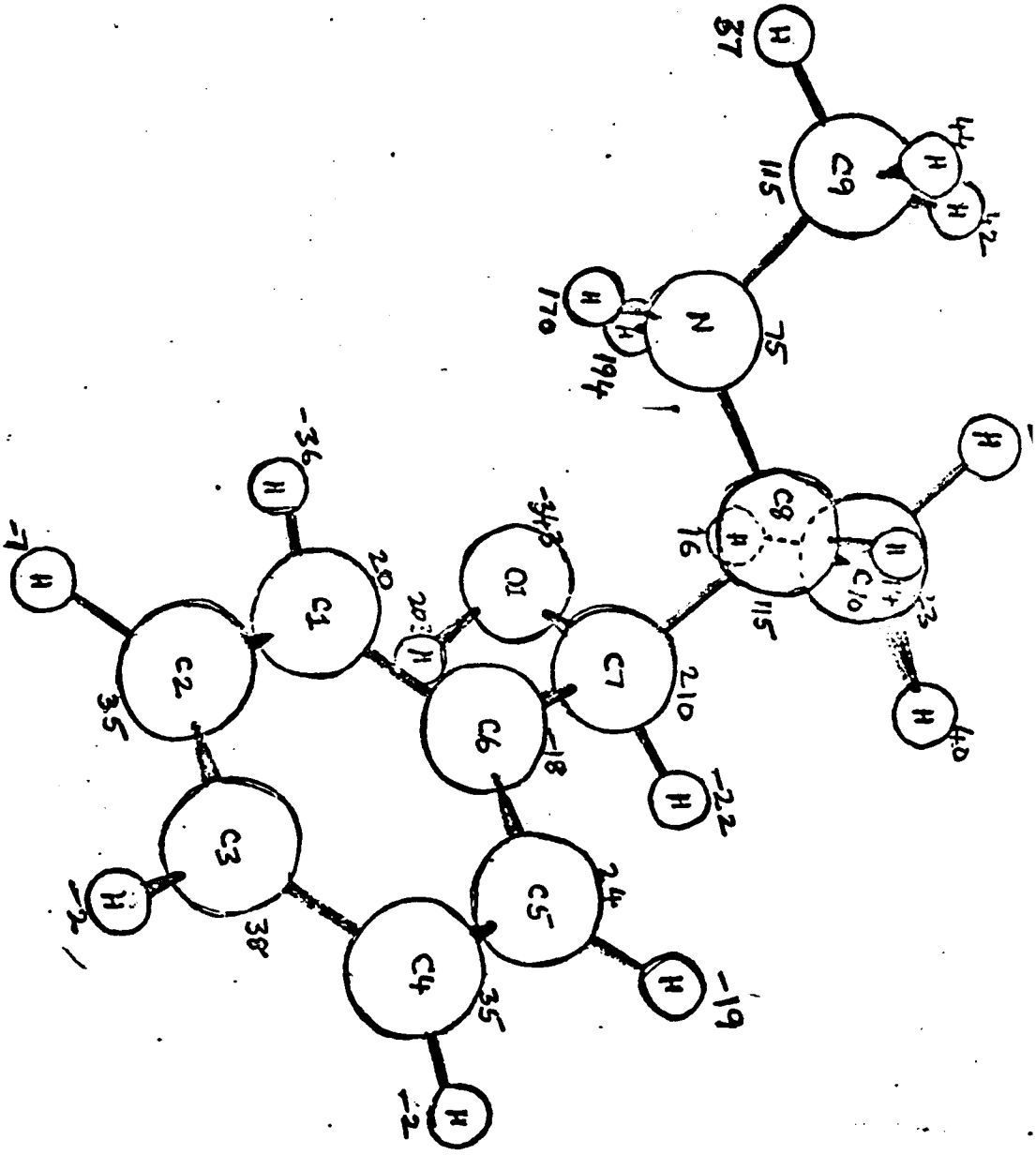

H
87
C9
115
H
44
H
12
H
170
N
75
194
H
C8
16
H
H
C10
115
23
H
40
-36
H
-7
H
C1
20
-34
O1
20
H
C7
210
C2
35
C6
18
-22
H
C3
H
-2
38
C5
24
H
-19
C4
35
H
-2

Figure 30.

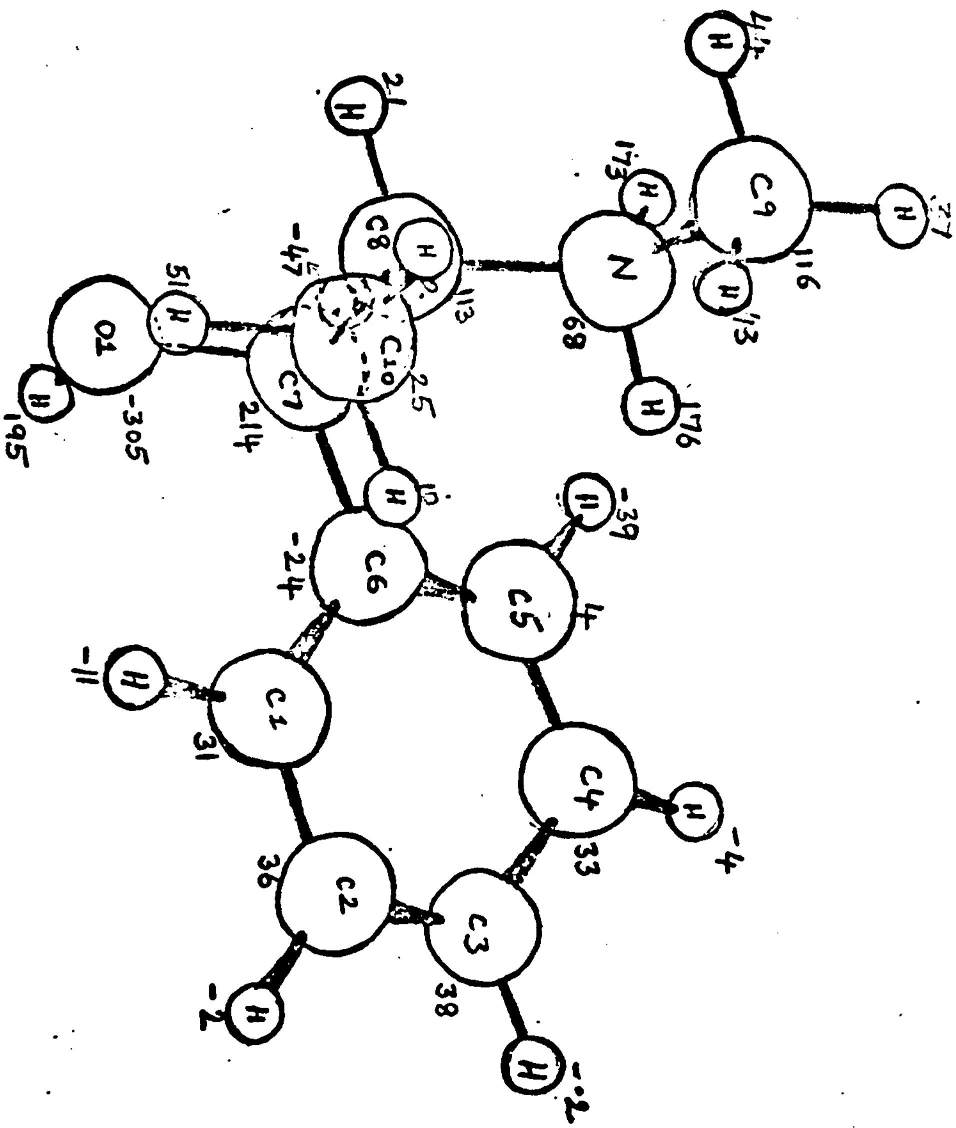
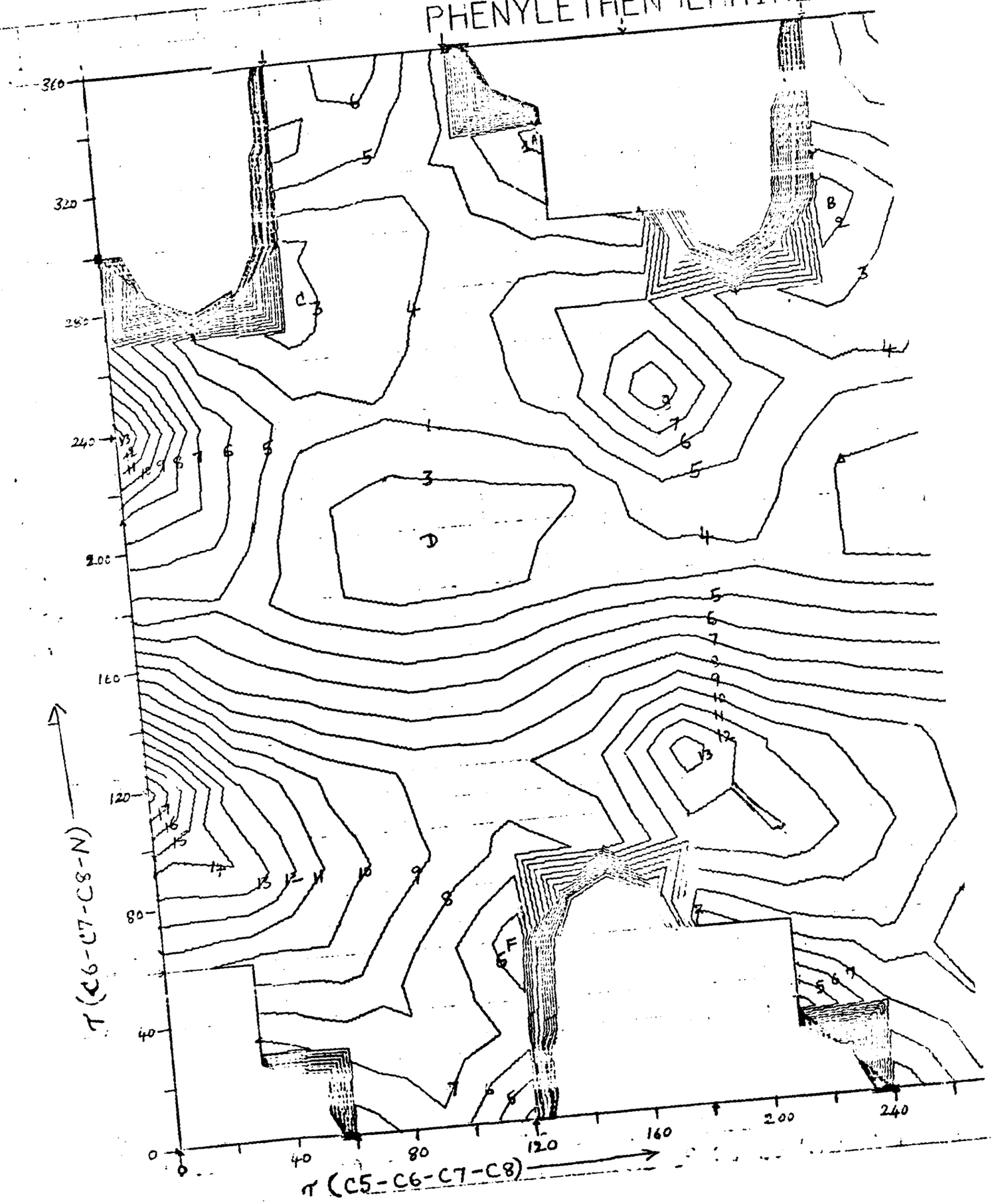
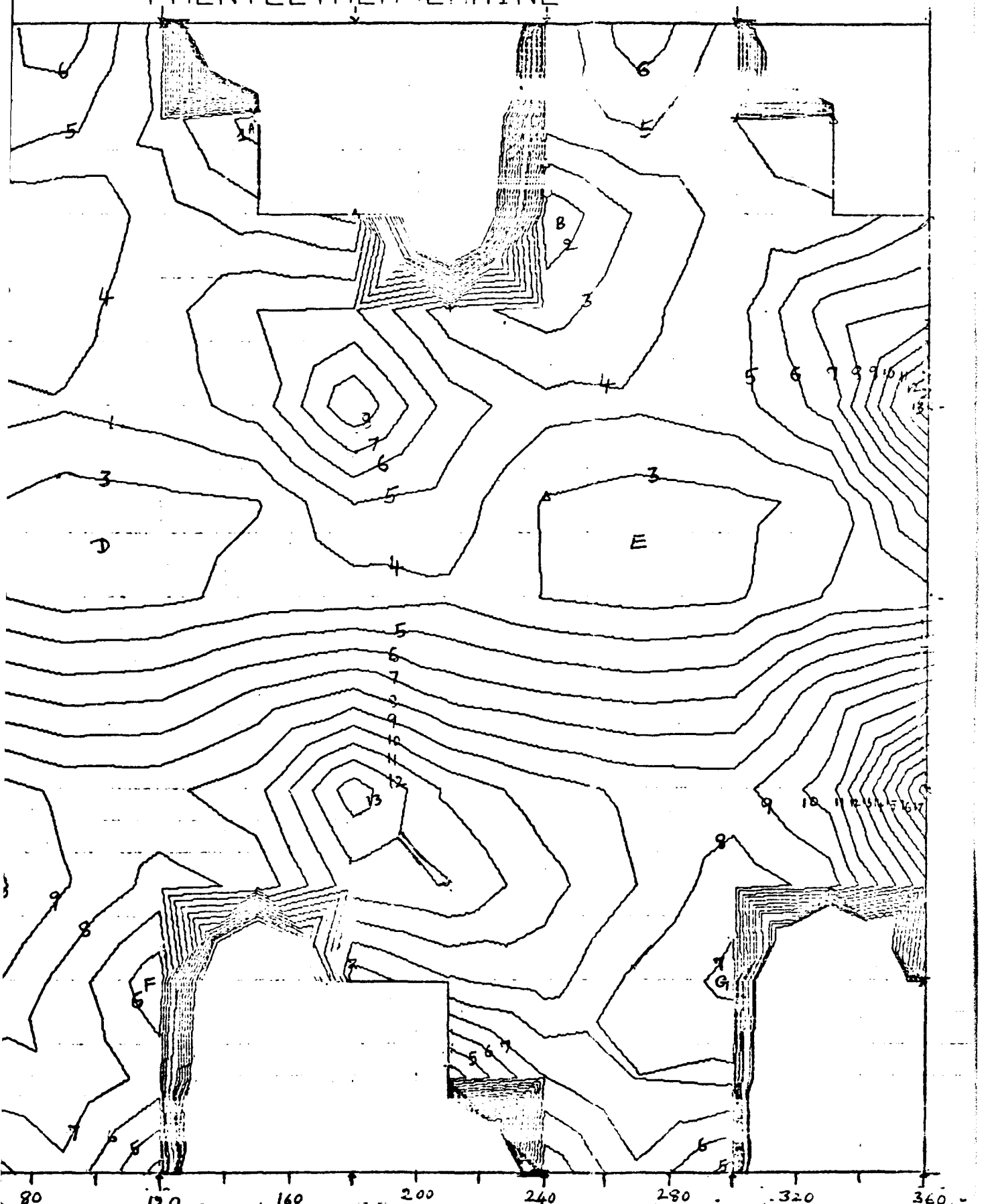


Figure 31.

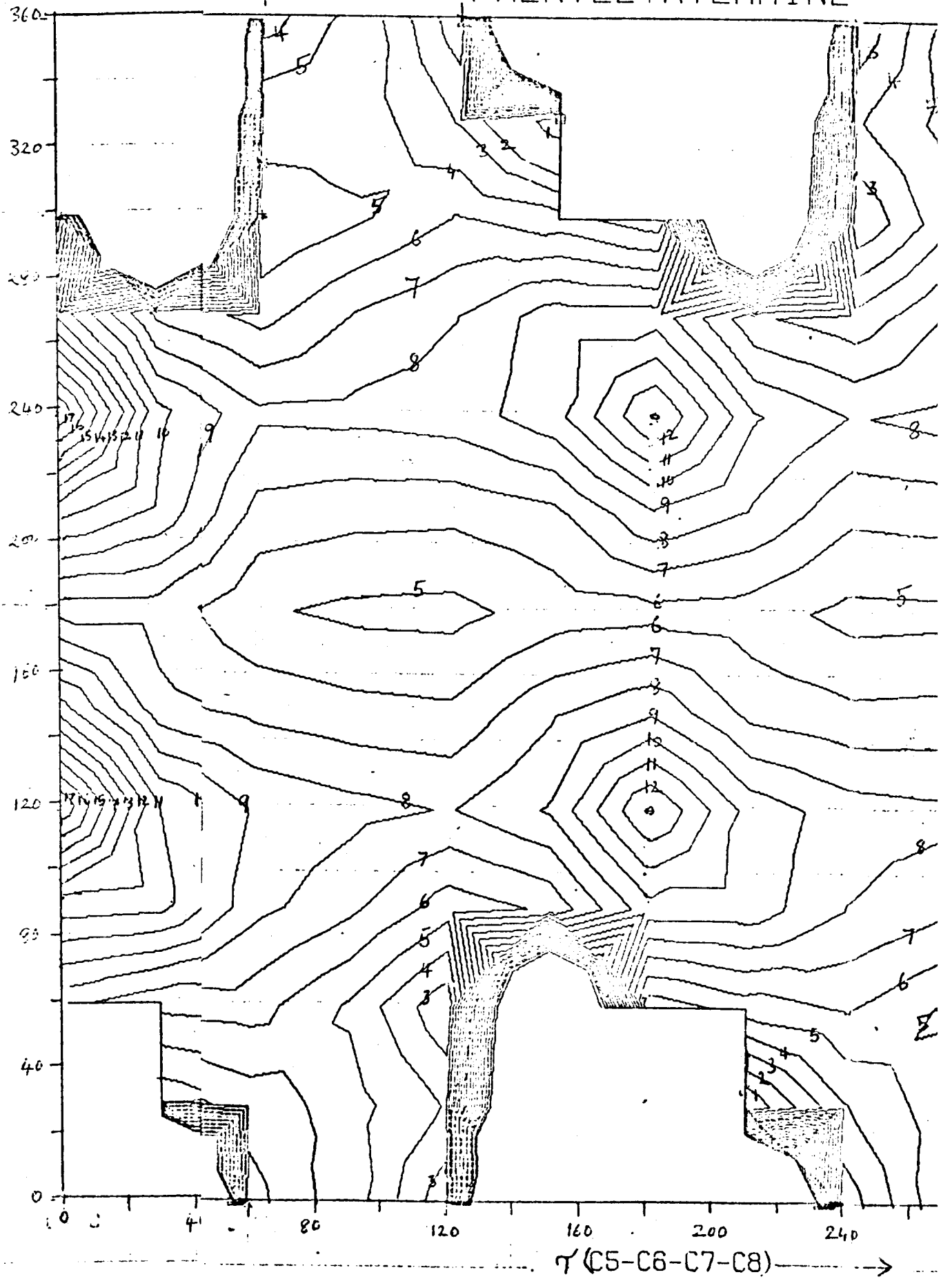
PHENYLETHENYLAMINE



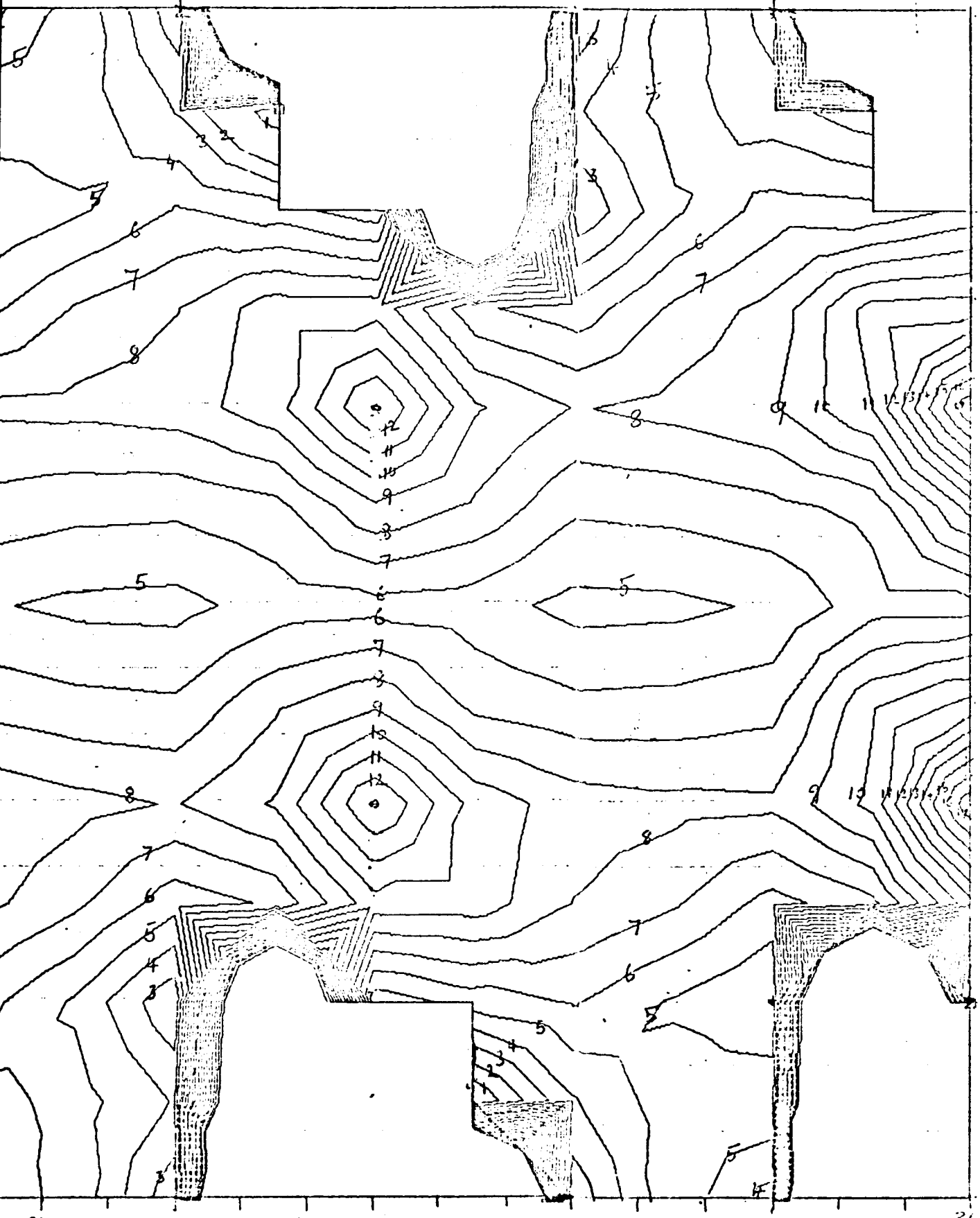
PHENYLETHENYLAMINE



PHENYLETHYLAMINE



PHENYLETHYLAMINE



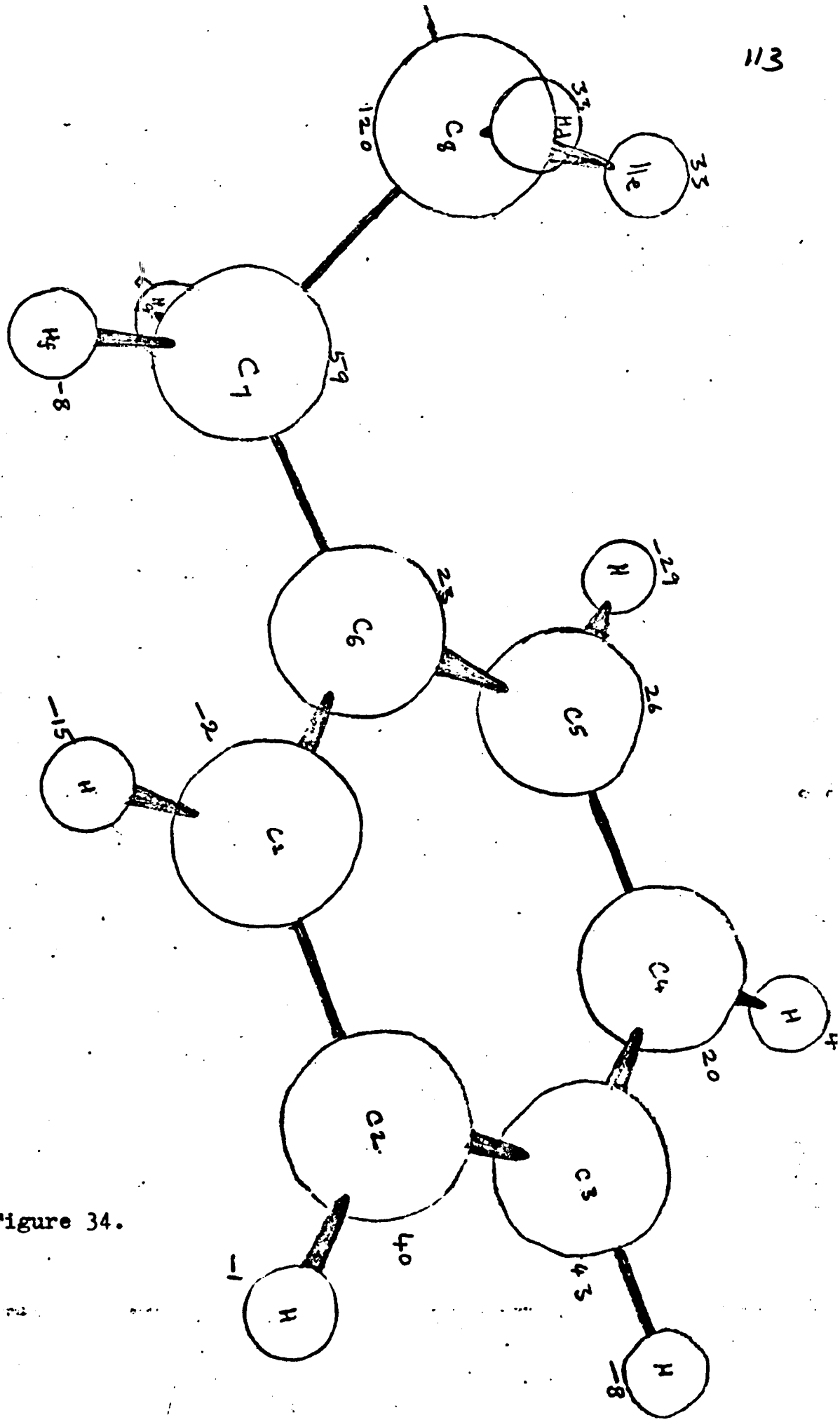


Figure 34.

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