illustrations very similar to the isoelectron density contours without any increase in sensitivity to electronic alterations.

The electrostatic potential energy was then investigated for its utility to produce either two- or three-dimensional aspects of molecules. These isoelectrostatic energy contours produced pictorially clear illustrations with the additional characteristic of sensitivity to electron shifts and an attacking proton in these molecular projections.

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Three-Dimensional Molecular Illustrations II: Isoelectrostatic Energy Contour Spheres of Influence Applied to Narcotic Molecules

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Received May 21, 1976, from the **College of Pharmacy and the* ‡*Department of Chemistry, University of Rhode Island, Kingston, RI 02881.* Accepted for publication April 1, 1977.

Abstract □ A computer-generated method using quantum mechanics was applied to the calculation and subsequent plotting of nonperspective three-dimensional illustrations of molecules *in vacuo*. The purpose was to generate isoelectrostatic energy contour spheres for larger molecules and current drugs. The molecules chosen, morphine, meperidine, and alphaprodine, possess similar pharmacological properties. Minor configurational manipulation of the meperidine and alphaprodine molecules was made to approximate the spatial configuration of the rigid morphine molecule so that direct comparisons were possible. Common areas of reactivity, potential energy minima, net atomic charges, spatial regions, and near neighbor influences are considered.

Keyphrases □ Molecular structure—three-dimensional illustrations of narcotic molecules calculated and plotted with computer-generated method using electrostatic energy contours □ Narcotic molecules—three-dimensional illustrations of molecular structure calculated and plotted with computer-generated method using electrostatic energy contours □ Electrostatic potential energy—considered in depicting three-dimensional illustrations of molecular structure of narcotic molecules

In this study, molecular projections utilizing electrostatic potential energy contours were prepared for morphine, meperidine, and alphaprodine. These narcotic agents were chosen because their large molecular sizes show that the methods developed are adaptable to large molecular systems characteristic of most medicinal agents. Moreover, although the spatial configurations of the molecules are dissimilar, they possess common pharmacological properties. The molecular illustrations derived from the electrostatic potential energy function show that these molecules possess common regions of reactivity in their molecular environments.

BACKGROUND

The stereochemical configuration of compounds possessing narcotic activity was presented (1–5) and reviewed (6). Another study (7) dealt

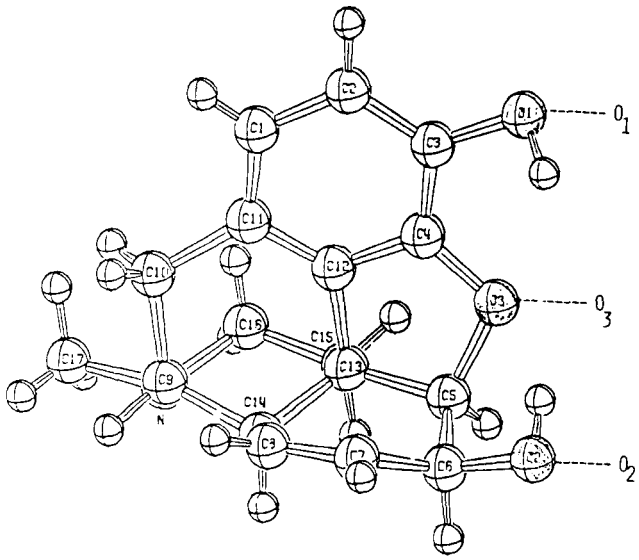

Figure 1—*Skeletal illustration of morphine depicting the spatial relationships of the atoms obtained from the ORTEP program.*

with the topography of the narcotic receptor. Binding modes by the use of free energy relationships were presented (8), and receptor perturbation by interacting molecules was suggested (9). The possibility of unrelated chemical species assuming a conformation similar to active compounds also was discussed (10). The chemical configuration of opium alkaloids (11, 12) and the total synthesis of codeine and morphine (13) confirmed earlier studies.

The structure of the phenanthrene fragment and its relative configuration were reported (14). Independent studies (15–18) confirmed this work. Stereochemical configurations from X-ray crystallographic studies of this type of compound were derived (19, 20), and the absolute configurations were determined by chemical means (21). Subsequent three-dimensional analysis of crystallographic data confirmed the absolute stereochemistry of morphine (22) and codeine (23). Through similar methods, the stereochemistry of several synthetic narcotics was determined (24–26).

PROCEDURES

Computations—The calculation of electrostatic potential energy was accomplished with a computer[1] utilizing Fortran IV language. These procedures were described in Part I. The molecular projections or illustrations were effected by the use of an available program[2] and an incremental plotter[3] slaved to the computer output.

Electrostatic Potential Energy Projections—*Morphine*—All molecules discussed in Part I had relatively small structures. To demonstrate the applicability of this method to large molecular systems of more practical interest, the electrostatic potential energy computations were performed on several narcotic agents. Morphine was chosen because of its potent pharmacological properties, widespread interest, and well-defined conformation.

A skeletal illustration of this molecule, utilizing the ORTEP method (27), is found in Fig. 1. The characteristic features of this molecule include a piperidine and phenyl ring joined by a common asymmetric carbon atom, C-13. Two more six-membered rings and a five-membered ring containing an ether linkage, O-3, complete the main structure. Peripheral groups necessary for pharmacological activity include a methyl, C-17, an alcoholic hydroxyl, O-2, and a phenolic hydroxyl, O-1. The basic structure consists of five ring systems bonded to each other at multiple points. This structure is rigid and may preclude any significant conformational changes caused by biological systems. The skeletal configuration and numbering system for this molecule were taken from the crystallographic data of Gylbert (22), as corrected[4].

[1] IBM 370/155.
[2] ORTEP.
[3] Broomall Industries M-2000 drum-type.
[4] The correct x positional coordinate, in Table I of Ref. 22, for C-3 is 1806 (5) (Dr. Leif Gylbert, Department of Medical Physica, Karolinska Institutet, S-104-01 Stockholm 60, Sweden, personal communication, Sept. 1974).

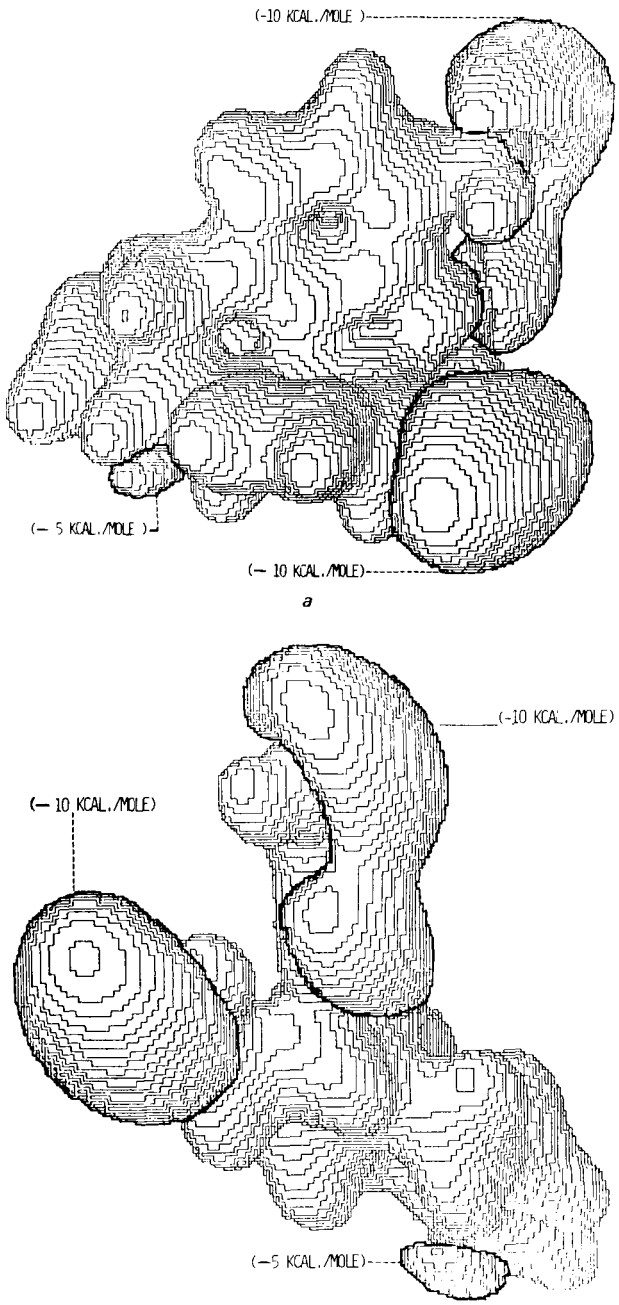

Figure 2—(a) *Illustration of the electrostatic potential energy contours of morphine (ORTEP facing). The negative lobes are at −10 kcal/mole for O-1, O-2, and O-3 and at −5 kcal/mole for N; all other lobes are at +100 kcal/mole.* (b) *Illustration of the electrostatic potential energy contours of morphine from Fig. 2a, where the molecule is rotated 90° about a vertical axis toward the viewer.*

The electrostatic potential energy contours pertaining to morphine are presented in Fig. 2. Figure 2*a* represents a frontal view in which the molecule is positioned identically to Fig. 1. Figure 2*b* is a view after the molecule was rotated 90° about a vertical axis. For comparison, the net atomic charges of the molecular constituents are listed in Table I. These data were calculated from the CNDO/2 valence orbital populations. These populations compare favorably with those published previously (28).

Virtually the entire molecule is surrounded by a field of positive potential. As expected, the potential diminishes near the center of the various ring systems. In Fig. 2*a*, "holes" may be seen in the two six-membered rings parallel to the plane of the page as well as in the ring containing the ether bridge. The *N*-methyl group is readily distinguishable at the far left. The phenolic hydroxyl group is at the upper right,

Table I—CNDO/2 Net Atomic Charges for Morphine

Atom	Net Atomic Charge	Atom	Net Atomic Charge
O-1	−0.2445	C-17	0.0430
O-2	−0.3067	H–O-1	0.1433
O-3	−0.2382	H-1	0.0156
N	−0.1744	H-2	0.0103
C-1	−0.0298	H-5	−0.0001
C-2	−0.0364	H-6	−0.0035
C-3	0.1285	H-7	0.0253
C-4	0.1116	H-8	0.0239
C-5	0.1082	H-9	−0.0253
C-6	0.1397	H-10a	0.0251
C-7	−0.0442	H-10b	0.0022
C-8	−0.0280	H-14	0.0007
C-9	0.0968	H-15a	0.0051
C-10	−0.0282	H-15b	0.0022
C-11	0.0221	H-16a	−0.0117
C-12	−0.0178	H-16b	−0.0009
C-13	0.0288	H-17a	−0.0065
C-14	0.0101	H-17b	0.0169
C-15	−0.0070	H-17c	−0.0094
C-16	0.0752	H–O-2	0.1781

adjacent to the aromatic ring; the alcoholic hydroxyl is positioned at the lower right but is hidden from view.

Four regions of negative potential, each associated with a heteroatom, can be noted.

The minima, expressed in kilocalories per mole, found at the center of each of these energy wells are ranked as follows: −32.2 (O-2, alcoholic hydroxyl) > −24.4 (O-1, phenolic hydroxyl) > −20.7 (O-3, ether) > −7.1 (N). These regions represent prime areas for electrophilic interaction or attack and are of particular interest when considering drug–receptor mechanisms. Each lobe is on the periphery of the molecule, thus providing a relatively large number of possible conformations in its approach to, or interaction with, a biophase.

Because of the close physical proximity of the lobes associated with the phenolic and ether oxygen atoms, the −10-kcal/mole contours merge to form one large, odd-shaped negative site. Within this dumbell-shaped lobe, two wells exist, having minimum energies of −24.4 and −20.7 kcal/mole.

The negative potential corresponding to the ether oxygen atom is nonuniformly distributed about the nucleus. In a molecule where there is no steric hindrance, the negative lobe of an ether linkage would possess a quarter-moon shape and lay on a plane perpendicular to the ether linkage, corresponding to the approximate position of the two lone pairs of electrons. In the present case, the −10-kcal/mole contour associated with the ether oxygen atom is concentrated only on one side of it. The additive effect of the phenolic hydroxyl may partially account for this uneven distribution.

Of greater significance is the alcoholic hydroxyl group at C-6. The O–H bond of this group is directed toward the ether bridge. The O-2–H···O-3 interatomic distance is 2.72 Å, and the angle is 146°. As suggested previously (22), the geometric configurations of these atoms present conditions that may be favorable to intramolecular hydrogen bonding, and the potential for forming a five-membered ring exists.

The partial positive charge on the hydrogen atom, H–O-2, generates a large sphere of positive potential, and a region of negative potential is generated by the excess electrons of the ether. In this case, these atoms are close enough together that the potential energies generated by each blend together, resulting in a net positive electrostatic potential in this entire region.

The illustrated isoelectrostatic energy values were chosen because these values provide a contiguous picture of the entire molecule. Greater or smaller values would cause the illustration to "balloon out" or "become nodules" in space; the values chosen give the best pictorial guide compatible with chemical reasoning.

Table II—CNDO/2 Conformational Energies for Various Configurations of Meperidine

Configuration	Total Energy, kcal/mole
Crystal, from Ref. 24	−107,453
Piperidine ring inverted	−107,455
Phenyl ring rotated about C-3–C-1′ onto a plane perpendicular to N–C-3	−107,452
Ester linkage rotated about C-3–C-7	−107,448

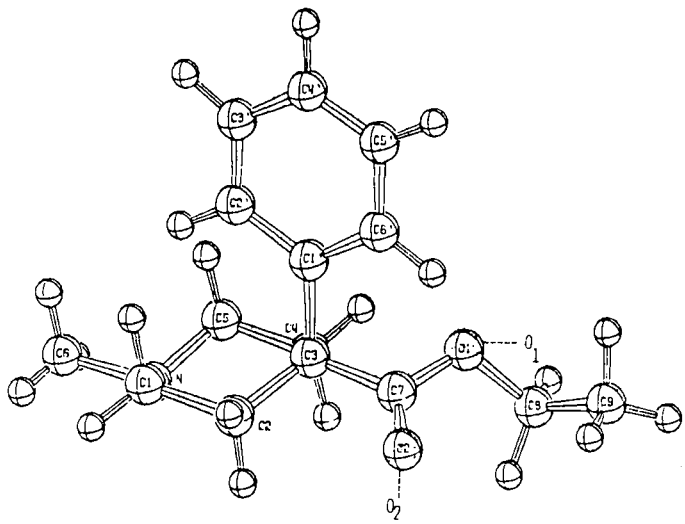

Figure 3—*Skeletal illustration of meperidine depicting the spatial relationships of the atoms obtained from the ORTEP program.*

Meperidine—Meperidine, a synthetic narcotic, has several structural features similar to morphine. This molecule is composed of a piperidine ring, containing an *N*-methyl group, with a phenyl ring and an ester linkage positioned on an asymmetric carbon atom. The crystal structure of this compound (24) indicates the aromatic ring to be equatorial and the ester linkage to be axial to the piperidine ring.

In this investigation, the conformation of meperidine was altered to reposition the negative lobes that might be generated by the heteroatoms. Manipulation of the atomic coordinates allows these lobes to be placed in positions similar to those occupied by the negative lobes of morphine.

When altering the configuration of a molecule, one must also be concerned with the change in conformational energy that may occur. Table II lists the steps used in manipulating the meperidine molecule and the total energy of each resulting conformer.

By inverting the piperidine ring, the phenyl ring now becomes axial and the ester becomes equatorial (Fig. 3). In this position, this molecule is in a configuration similar to the structure of morphine. Conformational energies indicate a small change in total energy between the crystal and inverted configurations.

The next step involves the rotation of the aromatic ring about the C-3–C-1′ axis onto a plane perpendicular to the nitrogen and asymmetric carbon atoms of the piperidine ring. Again, a very small change in the conformational energy is noted. Finally, rotation of the ester fragment about the C-3–C-7 bond allows the two ester oxygen atoms to be positioned in the same relative positions as the ether and alcohol oxygen

Table III—CNDO/2 Net Atomic Charges for Meperidine

Atom	Net Atomic Charge	Atom	Net Atomic Charge
O-1	−0.2735	H-2a	0.0013
O-2	−0.3291	H-2b	0.0039
N	−0.1565	H-4a	−0.0057
C-1	0.0811	H-4b	−0.0042
C-2	0.0086	H-5a	−0.0075
C-3	−0.0184	H-5b	−0.0090
C-4	0.0179	H-6a	−0.0029
C-5	0.0786	H-6b	0.0224
C-6	0.0273	H-6c	0.0003
C-7	0.3985	H-8a	−0.0011
C-8	0.1541	H-8b	−0.0099
C-9	−0.0377	H-9a	0.0117
C-1′	0.0416	H-9b	0.0261
C-2′	−0.0222	H-9c	0.0160
C-3′	0.0110	H-2′	0.0103
C-4′	0.0065	H-3′	−0.0038
C-5′	0.0050	H-4′	−0.0093
C-6′	−0.0273	H-5′	0.0027
H-1a	−0.0166	H-6′	0.0217
H-1b	−0.0117		

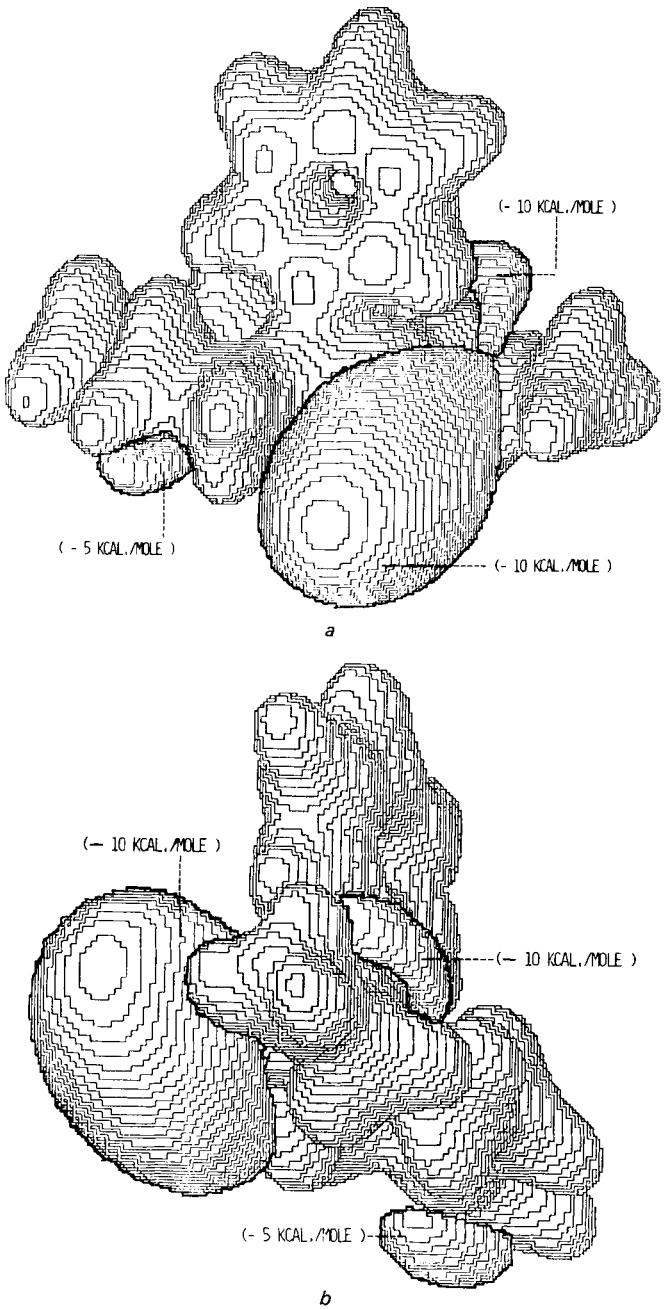

Figure 4—(a) *Illustration of the electrostatic potential energy contours of meperidine (ORTEP facing). The negative lobes are at −10 kcal/mole for O-1 and O-2 and at −5 kcal/mole for N; all other lobes are at +100 kcal/mole.* (b) *Illustration of the electrostatic potential energy contours of meperidine from Fig. 4a, where the molecule is rotated 90° about a vertical axis toward the viewer.*

atoms of morphine. A small loss in the conformational energy of 4 kcal/mole occurs as a result of this step. The net change in conformational energy between the first and the last step is a loss of 5 kcal/mole (Table II).

The skeletal structure of meperidine resulting from these manipulations is found in Fig. 3. This structure is used in all subsequent illustrations. The numbering system is identical to that previously published (24). In Ref. 24, only the positions of the nonhydrogen atoms were reported. In the present investigation, standard bond lengths and bond angles were used to add the hydrogen atoms. Table III lists the net atomic charges calculated from the CNDO/2 orbital populations.

The potential energy contour surfaces corresponding to meperidine are shown in Fig. 4. The energy values represented by the various contours and the orientation of the molecule are identical to the morphine illustrations.

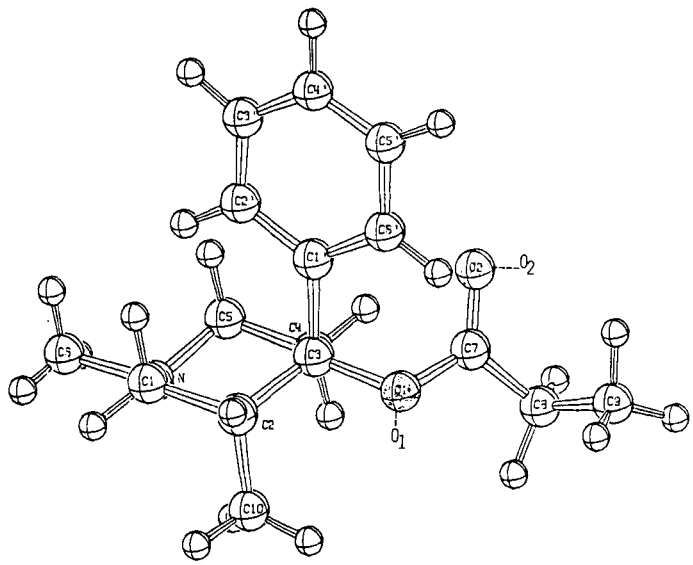

Figure 5—*Skeletal illustration of alphaprodine depicting the spatial relationships of atoms obtained from the ORTEP program.*

Three lobes of negative electrostatic potential energy are found, and each of these energy wells is associated with an atom possessing lone-pair orbitals and a rather large negative net atomic charge. The energy minima, in kilocalories per mole, associated with each lobe are ranked as follows: −41.7 (O-2, carbonyl) > −18.7 (O-1, ether) > −7.8 (N).

The −10-kcal/mole contours generated by the ester oxygens merge in an area approximately midway between the two minima. This phenomenon may not be explicitly evident from these illustrations but was visually confirmed using other viewing angles. The remainder of the molecule is surrounded by a field of positive electrostatic potential.

Alphaprodine—The molecular structure of alphaprodine, another synthetic narcotic agent, is similar to meperidine in that it is composed of a phenyl ring, an ester linkage, and a piperidine ring containing an *N*-methyl group. In alphaprodine, however, the ester linkage is reversed from that in meperidine. The only other feature unique to this compound is a second methyl group substituted on the piperidine ring.

The spatial relationships among the two ring systems and the ester group are identical to the crystal configuration of meperidine (25). The additional methyl group is equatorial to the heterocyclic ring.

Because of the similar stereochemical relationships of meperidine and alphaprodine, it was presupposed that the latter molecule could be subjected to conformational alterations with virtually no change in conformational energy. The resulting configuration is similar to that found in Fig. 5. As seen in the previous illustrations, the ester group may be rotated, within limits, to orient the expected regions of negative potential into positions mimicking meperidine and morphine. As a result of the type of ester found in alphaprodine, only one oxygen atom may be displaced by a rotation about the C-3–O-1 bond. The other oxygen atom, which lies on the axis, cannot be displaced by rotation, but the anticipated lobe of negative potential associated with the ether oxygen atom may be reoriented into a more favorable position.

In the previous illustrations of meperidine, the carbonyl produced the largest region of negative potential. Because of the close stereochemical similarities, the carbonyl of alphaprodine would, in all probability, generate the largest region of low electrostatic potential energy. This portion of the molecule was manipulated independently so that the position of this lobe would reside in the same general area as the lobe generated by the ether group of morphine.

A conformational change of this nature affords the opportunity to assess the difference in the potential energy contour surfaces resulting from interchanging the two types of oxygen atoms. In meperidine, an ether oxygen is located in the same relative spatial position as the ether oxygen of morphine; in alphaprodine, this region is occupied by the carbonyl oxygen.

The nuclear coordinates of the atomic constituents of alphaprodine were taken from the corresponding atoms of the meperidine molecule. The C-10 methyl group was added and the ester linkage was reversed, utilizing standard bond lengths and angles. The ester group was then rotated about the C-3–O-1 bond as described. The resulting configuration (Fig. 5) was utilized in the CNDO/2 computations to determine the

Table IV—CNDO/2 Net Atomic Charges for Alphaprodine

Atom	Net Atomic Charge	Atom	Net Atomic Charge
O-1	−0.2943	H-2	−0.0014
O-2	−0.3376	H-4a	0.0042
N	−0.1588	H-4b	0.0019
C-1	0.0873	H-5a	−0.0027
C-2	0.0127	H-5b	−0.0064
C-3	0.1668	H-6a	−0.0017
C-4	−0.0169	H-6b	0.0229
C-5	0.0843	H-6c	0.0022
C-6	0.0283	H-8a	0.0331
C-7	0.4082	H-8b	0.0145
C-8	−0.0529	H-9a	0.0039
C-9	0.0049	H-9b	0.0147
C-10	−0.0084	H-9c	0.0090
C-1′	−0.0061	H-10a	−0.0097
C-2′	−0.0133	H-10b	0.0105
C-3′	−0.0070	H-10c	0.0082
C-4′	0.0155	H-2′	0.0
C-5′	−0.0194	H-3′	−0.0083
C-6′	0.0242	H-4′	−0.0142
H-1a	−0.0177	H-5′	−0.0006
H-1b	−0.0082	H-6′	0.0282

atomic electron populations, from which the net atomic charges (Table IV) were derived.

Two views of the electrostatic potential energy contour surfaces representing alphaprodine are shown in Fig. 6. The viewing angle in each is the same as the corresponding illustrations of morphine and meperidine. The negative isoenergy contour associated with the nitrogen atom is not drawn at the same energy level as in the previous illustrations. In the present case, this contour represents a value of −2 kcal/mole.

This molecule is unique, among the three narcotics presented, in that the minimum energy in the nitrogen atom region does not attain a value of −5 kcal/mole, the level at which this contour was drawn for the previous molecules. This positive shift in the potential energy may be due to the close proximity of the C-10 methyl group. The positive potential generated by this group partially neutralizes the negative potential radiated by the nitrogen atom, resulting in a net increase in the minimum energy of this lobe.

The energy minima, in kilocalories per mole, associated with each lobe are: −40.5 (O-2, carbonyl) > −22.7 (O-1, ether) > −4.8 (N). As expected, the largest region of negative potential, as well as the lowest minimum, was found in the vicinity of the carbonyl oxygen atom.

DISCUSSION

The atomic coordinates and the spatial orientation of these narcotic compounds have been manipulated so that comparisons may be readily made among them. The illustration pertaining to morphine (Fig. 2*a*) indicates three lobes of negative potential on the right side of the molecule. If the quantity of energy representing these contours is made less negative, it would become apparent that this entire region is attractive to an electrophilic group in a biophase. The region on the opposite side of the molecule is positive and repulsive to a reactant of this type.

Meperidine and alphaprodine each possess a similar large region of positive potential surrounding the phenyl ring and the top of the piperidine ring. They differ from morphine in the shape of their regions of negative potential. In these compounds, the ethane substituent attached to the ester linkage radiates a dense field of positive energy that pierces or attenuates this otherwise large field of negative potential. As a result, an approaching electrophilic agent must be more selective in its direction of attack.

Each of these molecules demonstrates a decreased propensity toward electrostatic interactions in an area directly beneath the nitrogen atoms. The energy minima in these regions are significantly less negative than those generated by the other electronegative atoms. The affinity of these areas for an electrophilic agent is greatly reduced. Of importance also is the greater amount of shielding produced by the surrounding region of positive potential. Unlike the other energy wells, the lobes associated with each nitrogen atom are tucked in close to the underside of the molecule. This shielding effect is more pronounced for alphaprodine, which has a methyl group axial to the piperidine ring. In these regions, the direction from which an electrophilic agent might approach the molecule is more restrictive than when the lobes are associated with the oxygen atoms.

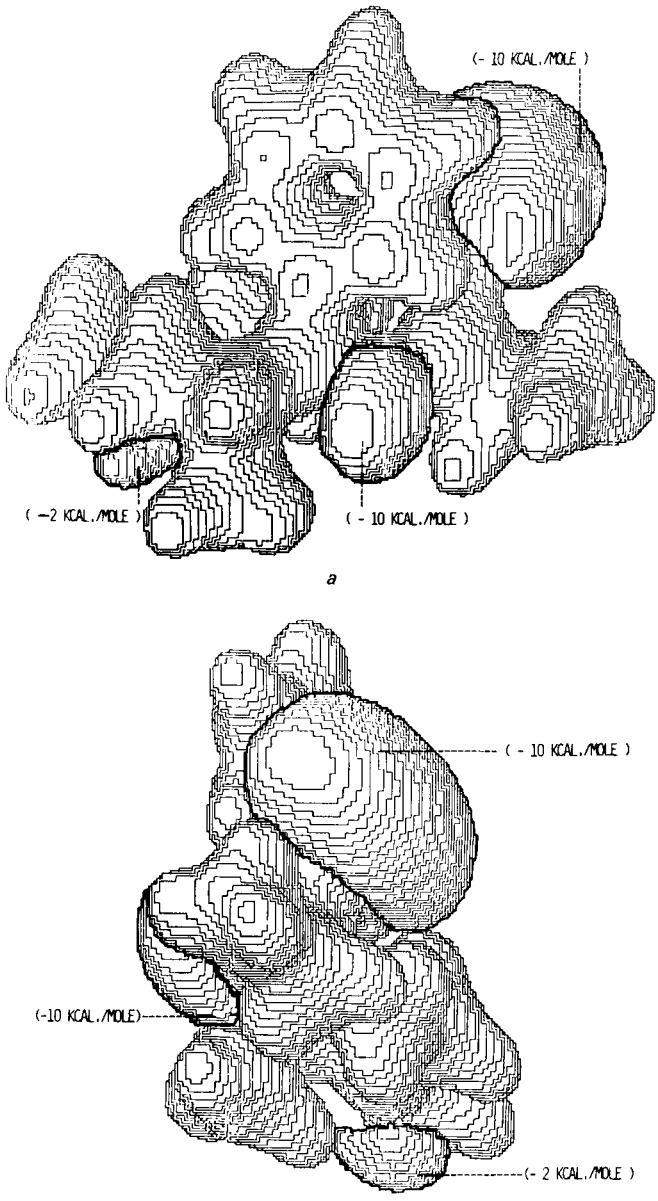

Figure 6—(a) *Illustration of the electrostatic potential energy contours of alphaprodine (ORTEP facing). The negative lobes are at −10 kcal/mole for O-1 and O-2 and at −2 kcal/mole for N; all other lobes are at +100 kcal/mole.* (b) *Illustration of the electrostatic energy contours of alphaprodine from Fig. 6a, where the molecule is rotated 90° about a vertical axis toward the viewer.*

The type of atom involved in these electrostatic potential energy calculations should dictate the magnitude of the energy minimum. An oxygen atom, having a greater ability to attract electrons than a nitrogen atom, is expected to generate an energy minimum somewhat more negative than that produced by a nitrogen atom. This fact is substantiated by the data presented in Table V. Each nitrogen atom generates an energy minimum significantly less negative than any oxygen atom.

The oxygen atoms can be further segregated by the type of group in which they reside. In general, the net atomic charges become more negative as one descends this list of chemical groups. An alcoholic oxygen atom is expected to possess a larger number of excess electrons than an ether oxygen because of the greater ease of extracting an electron from a hydrogen atom. In an ether group, the oxygen atom incurs more competition from the two adjacent carbon atoms, and its net atomic charge is less negative.

A phenolic hydroxyl group is much the same as an alcoholic hydroxyl group, but the resonating aromatic ring competes with the oxygen from the electrons to a greater extent than a single carbon atom. As a result,

Table V—Summary of the Potential Energy Minimums [a] and the Net Atomic Charge [b] Associated with the Noted Atom or Functional Group for the Narcotic Molecules Utilized in This Study

Group	Morphine	Meperidine	Alphaprodine
N	−7.1 [−0.1744]	−7.8 [−0.1565]	−4.8 [−0.1588]
Ether	−20.7 [−0.2382]	−18.6 [−0.2735]	−22.7 [−0.2943]
Phenolic hydroxyl	−24.4 [−0.2554]	—	—
Alcoholic hydroxyl	−32.2 [−0.3067]	—	—
Carbonyl	—	−41.7 [−0.3291]	−40.5 [−0.3376]

[a] Expressed in kilocalories per mole. [b] Values appear in brackets.

Table VII—Summary of the Distances between the Points of Minimum Energy Found in Each Common Region [a] and the Triangular Area Enclosed by These Points for the Narcotic Molecules Utilized in This Study [b]

Molecule	Vector, Å			Area, Å²
	1–2	1–3	2–3	
Morphine	6.8 [5.22]	7.7 [6.50]	4.2 [2.72]	14.3 [6.8]
Meperidine	6.3 [5.10]	5.8 [4.98]	4.2 [2.27]	12.0 [5.6]
Alphaprodine	6.8 [5.39]	5.3 [4.33]	4.2 [2.44]	11.0 [4.7]

[a] See the text for a description of the heteroatoms associated with each region. [b] Values denoted in brackets were derived in a similar manner from the nuclear coordinates of the heteroatoms associated with each region.

the net atomic charge on the oxygen atom is similar to that of an ether oxygen. Finally, a carbonyl oxygen atom has the largest electron-withdrawing capability because of the reduced number of protons, on the single carbon atom, competing with the oxygen atom. To summarize, as the list is descended, the total number of protons on the atoms adjacent to the oxygen atom gain excess electrons. As a result of this ordering of net atomic charges, the energy minima also vary in the same general pattern (Table V).

Another factor also must be considered when discussing the ordering of the energy minima associated with the oxygen atoms. As the list is descended, the number and size of the atoms bonded to the oxygen atom diminish. The number and magnitude of the spheres of influence generated by these nearest neighbors also diminish, resulting in less attenuation of the negative energy lobe.

Of particular interest is the smaller variation of the energy minima among the nitrogen atoms themselves (Table V). In each of the three molecules listed, the net atomic charge of the nitrogen atoms is nearly identical. This fact in itself would lead one to expect identical energy minima. However, the value for alphaprodine is nearly half that of the other molecules. This aberrant behavior pointedly demonstrates the steric effect created by the C-10 methyl group of alphaprodine. The spatial location of this substituent is close enough to the nitrogen atom that its sphere of positive influence mitigates the negative potential generated by the nitrogen atom, thus rendering the minimum less negative. With nearly identical net atomic charges, electron density illustrations would not show any discernible differences in this region of the molecules.

Several other irregularities also demonstrate the significant influence of neighboring atoms on the energy minima (Table V). One would expect the energy minimum to become more negative as the number of electrons in a given atom increases. Comparing the ether groups of morphine and meperidine, one finds the minimum energies to be proportional to the net atomic charges. An analogous situation exists with the meperidine and alphaprodine carbonyl groups.

These trends illustrate the specificity and sensitivity of this method to depict small changes in the electronic character of a molecule and to depict uniquely the steric effects caused by interactions of molecular constituents.

In any discussion of drug–receptor mechanisms, electrostatic interactions between the pharmacophore and receptor must be considered. In a given series of similar pharmacological agents, such as the narcotics presently being discussed, a comparison of their electrostatic potential energy characteristics is essential. Each of these molecules possesses at least three energy wells in similar geometrical or spatial regions. The minimum energies in each region in the molecular environment are listed in Table VI.

Region 1 includes the energy wells generated by the nitrogen atoms, and Region 2 is comprised of the ether oxygens of morphine and meperidine and the carbonyl oxygen of alphaprodine. The alcoholic hydroxyl of morphine, the carbonyl oxygen of meperidine, and the ether oxygen of alphaprodine are located in Region 3. Morphine has a fourth energy well generated by the phenolic hydroxyl group. Meperidine and alphaprodine do not possess a corresponding region of low potential energy.

Table VI—Summary of the Potential Energy Minimums [a] Associated with the Common Spatial Regions for the Narcotic Molecules Utilized in This Study

Molecule	Region [b]			
	1	2	3	4
Morphine	−7.1	−20.7	−32.2	−24.4
Meperidine	−7.8	−18.6	−41.7	—
Alphaprodine	−4.8	−40.5	−22.7	—

[a] Expressed in kilocalories per mole. [b] See the text for a description of the heteroatoms associated with each region.

The energy minima for morphine and meperidine are ranked in the same order but differ slightly in magnitude. In each molecule, the lobes occupying Regions 1 and 2 are generated by a nitrogen atom and an ether oxygen atom, respectively. On this basis, one might expect similar minimum energies, barring any steric influence from neighboring atoms. The lowest potential energy in Region 2 of meperidine is somewhat less negative than the corresponding value for morphine. The sphere of negative potential energy in this region of the morphine molecule possesses spatial contours larger in volume because of the additive effect of the phenolic hydroxyl in Region 4. This condition undoubtedly accounts for the slightly more negative minimum in Region 2 of morphine.

A somewhat larger deviation is found when comparing the minimum energies in Region 3 of morphine and meperidine. These energy wells are generated by an alcoholic hydroxyl and a carbonyl oxygen atom, respectively. Previously, it was noted that the alcoholic oxygen atom possessed a less negative net atomic charge, thus accounting for part of this deviation. A large sphere of positive potential is generated by the alcoholic hydrogen atom, which tends to produce a less negative minimum energy in Region 2 of morphine.

The smaller minimum energy found in Region 1 of alphaprodine has already been discussed in regard to the sphere of influence generated by the extra methyl group in this molecule. The relative strengths of the minima in Regions 2 and 3 of alphaprodine are reversed from those in morphine and meperidine (Table VI), partially as a result of the ester group being approximately 180° out of phase with the same chemical group of meperidine.

The ester groups of these two molecules have about the same geometrical configuration and spatial coordinates. It would be expected that the relative order and magnitudes of the alphaprodine minimums could be made to conform to those of morphine and meperidine by rotation of the ester linkage. In such a configuration, a close correlation would be noted among the energy minima found in nearly identical regions of each of these narcotic molecules.

The electrostatic potential energy surface contours are unique in that they can be utilized to combine elements from both the stereochemical and quantum mechanical approaches to the elucidation of drug–receptor conformations. The magnitude of the electrostatic interactions is an indicator of the intermolecular affinity between two or more species. As noted from the illustrations, these forces are not evenly distributed about the molecule but are localized in specific regions; each region radiates a sphere of influence from its nucleus or point of minimum energy. Therefore, critical distances should not be calculated from the nuclear coordinates of the reactive atoms but from the centers of the minimum energy wells. Since these energy minima are not symmetrically distributed about an atom because of the influence of its neighbors, a more accurate description of the location of the "reactive sites" is obtained from the point of minimum energy.

Table VII lists the distances calculated between these points in similar regions of low electrostatic potential. The regions are numbered by the same convention used in the previous table. For comparison purposes, the distances between the nuclei of the atoms generating these minimum energies are included in brackets. The distance between each pair of minima occupying similar regions are nearly identical among the three molecules. The major exception is the Region 1–3 interval in morphine. This deviation is a consequence of the alcoholic hydroxyl group of Region

3 being approximately one carbon–carbon bond length further removed from the nitrogen atom.

The positions of the energy minima associated with the three negative lobes common to each molecule may be thought of as representing the vertices of a triangle. The similarities of the geometrical configuration of the electrostatic potential energy field surrounding each compound is demonstrated by a comparison of the areas of these triangles (Table VII). The values corresponding to meperidine and alphaprodine are nearly identical. As a result of the increased distance between Regions 1 and 3, the area corresponding to morphine is slightly larger.

The data in Table VII derived from the nuclear coordinates show approximately the same rank correlation as those derived from the positions of minimum energy. The significant feature is the larger magnitude of the distances calculated by the latter method. This result indicates the much larger total sphere of influence a molecule presents to a receptor than might be implied by using measurements taken from the nuclear coordinates.

At the beginning of this investigation, it was noted that the molecular structures of meperidine and alphaprodine were systematically manipulated so that the anticipated positions of the energy wells would occupy approximately the same spatial regions in each molecule. Examination of the illustrations and the data of Table VII shows the manipulations to be effective in achieving this end.

If the original coordinates, derived from the crystallographic data, were used to generate the electrostatic potential energy contour surfaces, the distances between Regions 1 and 2 and 1 and 3 would be reduced for both meperidine and alphaprodine. The vector from Region 2 to Region 3 would not be altered due to the rigidness of the ester group. In these molecules, the inversion of the piperidine ring reorients the ester group from an axial to an equatorial position, resulting in electrostatic potential energy contours that closely mimic those of morphine with a minimum expenditure of conformational energy.

Much smaller variations in the distances between the energy wells may be achieved by rotation of the individual functional groups about their adjacent bonds. With the exception of the carbonyl group, the points of minimum energy are remote from the bond axis. Rotation about a bond would reorient the negative energy lobe.

Rotation about the C–O bonds of the hydroxyl groups of morphine would alter only slightly the positions of the energy minima associated with the oxygen atoms. In meperidine, the ester linkage may be rotated about the C-3–C-7 bond, within the limits dictated by the conformational energy. A similar rotation could be applied to the C-3–O-1 bond of alphaprodine. In each case, the positions of the energy wells would be offset by a small distance. In any case, the effect created by the extra carbon–carbon length between the nitrogen atom and alcoholic hydroxyl of morphine could not be compensated for by these manipulations.

A more important point is the effect of any molecular configurational modification on the magnitudes of the various energy wells. Each negative energy lobe is oriented on a vector away from all other neighboring atoms. Small rotations about the bonds specified would tend to bring these lobes into closer proximity to the neighboring atoms. The steric relationships of these atoms would have a profound effect on the electrostatic energy minima, resulting in less negative values and changes in the shapes of the isopotential surfaces.

If it is assumed that the electrostatic forces play an important role in drug–receptor interactions, these spheres of influence would determine the proper and maximal alignment of a pharmacophore with a receptor. An affinity for the receptor could result if proper alignment could occur. The minimum energies, as well as the spatial location of the negative energy lobes, would be of utmost importance. Under these conditions, the members of a homologous series of pharmacophores would not have to possess identical energy minima at exactly the same spatial locations. Any small deviation from the optimum position for an energy well could be compensated for by a more negative energy minimum associated with that well. In such a situation, the net attractive force between a molecule and a receptor would remain constant.

A comparison of morphine and meperidine can be used to illustrate this principle. If one assumes that the negative energy lobes associated with the nitrogen atom and the oxygen atom of the alcoholic hydroxyl group of morphine are in "perfect" alignment with complementary receptor sites, the meperidine molecule would not physically match these sites identically. In the latter compound, the carbonyl oxygen atom and its corresponding point of minimum energy would be far removed from the receptor site. However, the energy minimum (Table VI, Region 3) in this region is significantly more negative, producing a sphere of influence much larger in volume than that in the corresponding position of morphine. Because of this magnified effect, it is conceivable that this region of low electrostatic potential extends away from the molecule far enough to engage the same receptor site. If the ester group of alphaprodine is rotated, as mentioned previously, this same reasoning would apply to that compound.

The possibility of the receptor itself modifying the conformation of the pharmacophore also must be considered. Just as the drug molecule is considered as a field of electrostatic forces, the receptor must be thought of likewise. The fields of electrostatic attraction and/or repulsion generated by the receptor molecule could perturb the pharmacophore to a small degree. This effect, in turn, could aid in the proper alignment of these species and increase the efficiency of the drug–receptor interaction. This ability of drugs to undergo molecular reorganization upon interacting with a receptor also was recognized by Portoghese (29).

It is also possible to alter the magnitude and position of the minimum energy at a point in the molecular environment by altering neighboring substituent groups. The C-10 methyl group of alphaprodine significantly changed the magnitude of the minimum energy associated with the nitrogen atom to a less negative value. The opposite effect might also be designed into a drug molecule. For example, the addition of an electronegative group on a position in close proximity to one already present in a molecule would enhance the minimum energy, producing a more negative value. This result, in turn, would increase the volume of its sphere of influence. The position of the energy minimum may also be altered by such an additional chemical group.

CONCLUSIONS

The purpose of this study was to devise a method by which three-dimensional illustrations could be produced to allow visualization of the electronic characteristics of a molecule. To devise a viable research tool to accomplish this task, it was necessary to introduce some assumptions and approximations to reduce the computational efforts involved.

The electrostatic potential energy contour surface illustrations were prepared from molecules that admittedly exist *in vacuo*. In reality, a molecule cannot exist as a single entity but always coexists with other molecules of its own or of a differing kind. Such a close relationship of molecular entities tends to influence the electronic structure of each. In an analogous manner, the association of a drug with a receptor could cause mutual perturbations in both the pharmacophore and molecular constituents of the biophase. However, the amount of computational effort necessary to consider the perturbations is beyond the realm of reality at this time. The method presented fulfilled the objectives initially set forth. It allows one to view the physical configuration of a molecule in terms of the electrostatic forces generated by the constituent atoms and to discern how these contours are perturbed by molecular modifications.

The superiority of the electrostatic potential contour surface illustrations may also be substantiated by some features found in the narcotic illustrations. The unsymmetrical shape of the region of negative potential associated with the ether group of morphine provided evidence of possible intramolecular hydrogen bonding.

In comparing the molecules of the narcotic series, the attenuating effect of the fields of electrostatic potential energy about a molecule was noted from the significant influence of the C-10 methyl group of alphaprodine in rendering less negative the minimum energy associated with the nitrogen atom. The electron population assigned to this nitrogen atom is nearly identical to that in meperidine and morphine.

The electrostatic potential energy contour surface illustrations allow one to discern readily the regions in the molecular environment that are attractive or repulsive to an approaching electrophilic group.

A sensitive probe has been developed which makes clearly perceptible one force within a molecule that is important in any discussion of drug interactions in the biophase.

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Potential Hypocholesteremic Derivatives of Styrylacetic Acid II: *cis*- and *trans*-3-Methyl-4-phenyl-3-butenoic Acid Analogs

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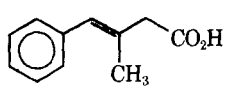
Abstract □ The synthesis and preliminary biological testing for *in vitro* cholesterol biosynthesis inhibitory activity of 2-indeneacetic acid, 2-methyl-1,2-dihydro-2-naphthoic acid, and their 5- and 7-chloro derivatives, respectively, are described. These compounds were prepared as *trans*- and *cis*-analogs of the known antilipemic agent 3-methyl-4-phenyl-3-butenoic acid. Although both series of compounds showed cholesterol biosynthesis inhibitory properties, chloro substitution enchanced potency only in the *cis*-system. These findings are discussed in terms of a possible relationship between the *cis*-compounds and clofibrate-type antilipemic agents.

Keyphrases □ *cis*- and *trans*-3-Methyl-4-phenyl-3-butenoic acid analogs—synthesized, evaluated for effect on cholesterol biosynthesis in rat liver homogenates □ 2-Indeneacetic acid and 5-chloro derivative—synthesized, evaluated for effect on cholesterol biosynthesis in rat liver homogenates □ 2-Naphthoic acids, substituted—synthesized, evaluated for effect on cholesterol biosynthesis in rat liver homogenates □ Cholesterol biosynthesis—effect of 2-indeneacetic acid and substituted 2-naphthoic acids and chloro derivatives, rat liver homogenates □ Structure–activity relationships—effects of 2-indeneacetic acid and substituted 2-naphthoic acids and chloro derivatives on cholesterol biosynthesis in rat liver homogenates

In continuing investigations (1) of the structure–activity relationships for cholesterol biosynthesis inhibition by compounds related to 3-methyl-4-phenyl-3-butenoic acid (benzalbutyric acid) (I), the influence of the double bond stereochemistry on biological activity was examined. Compound I exists in the (*E*)-configuration (2), but it has not been established that this configuration represents the optimal geometry for biological action.



I

In an initial attempt to obtain information relating to this question, the synthesis of indeneacetic acids (II*a* and II*b*) and dihydronaphthoic acids (III*a* and III*b*) as *trans*- and *cis*-congeners of the parent system was undertaken. Although these compounds also differ with respect to the α-carbon substitution pattern, they were believed to be useful as initial probes. This report describes their synthesis and preliminary *in vitro* testing.

DISCUSSION

The synthesis of II*a* and II*b* is outlined in Scheme I (also see *Experimental*). Although the mixture of hydroxy acid X and lactone XI could be converted entirely into the lactone by prolonged stirring in dilute sulfuric acid, for preparative runs it was more convenient to use the mixture directly for the subsequent reaction.

Synthesis of the *cis*-analogs was accomplished according to the sequence outlined in Scheme II.

Interestingly, if the methanolysis of XVIII or the mixture of XVII and XVIII was terminated after refluxing for only 4 hr and the product was saponified, methoxy acid XX could be obtained from the reaction product mixture. This finding is in agreement with the suggestion advanced previously (3) that methanolyses of similar tricyclic lactones, including XI, proceed *via* an intermediate benzyl carbonium ion. This conclusion was based largely on the fact that methanolysis of γ-phenylbutyrolactone afforded methyl 4-methoxy-4-phenylbutanoate instead of the anticipated

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