Probable Conformations of Some Reversed Esters of Meperidine as Solutes in Water. Conformational Factors in 4-Phenylpiperidine Analgetics

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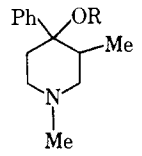
It has previously been shown how the pmr characteristics of α- and β-1,3-dimethyl-4-phenylpiperidin-4-ol (bases and hydrochlorides) provide evidence of their probable conformations.[1] These studies are now extended to include esters of the same piperidinols (**1**).



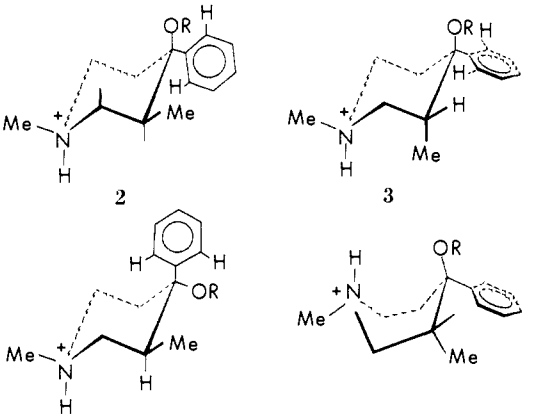
1a, R = H
b, R = COMe
c, R = COEt
d, R = COC_3H_7-*n*

some of which are potent analgetics (*e.g.*, the propionate hydrochlorides **1c**, α- and β-prodine).

Pmr characteristics of the acetate, propionate, and *n*-butyrate esters of α- and β-1,3-dimethyl-4-phenylpiperidin-4-ol hydrochlorides are given in Table I. These data support structures **2** and **3** as the most probable conformations, respectively, of the α- and β-isomeric ester hydrochlorides as solutes in deuteriochloroform ($CDCl_3$). Specific points are as follows (see ref 1 for details of the interpretation). (1) The aromatic signals of the α esters are broader than those of the corresponding β isomers (chemical shift differences among aromatic protons should be more pronounced in **2**). (2) The chemical shifts of the α-3-methyl signals have an 18–20 cps higher field position than the β signals (protonated nitrogen deshields axial 3-methyl in **3** to a greater extent than it does the further removed, equatorial 3-methyl of **2**). (3) The chemical shifts of the β-acyloxy groups are upfield (by 8–12 cps) of the corresponding α signals. In conformer **3**, the ester group will spend some of its time above the plane of the phenyl group, *i.e.*, within the aromatic shielding zone, if the plane of the C_4–O bond and the aromatic ring are approximately perpendicular. Proton groups adjacent to the ester carbonyl should be more screened than those further removed, as is observed experimentally.

Estimations of the relative proportions of the two chair conformations based upon conformational, free-energy difference ($-\Delta G^\circ_x$) values lead to the prediction of almost 100 and 75–80% populations of the more stable (e-phenyl) conformation for the α and β isomers, respectively; $-\Delta G^\circ_x$ values for OH and OCOR are assumed to be similar.[2]

Resonance signals due to the aromatic, N-methyl and acyloxy proton groups of the ester hydrochlorides in deuterium oxide (D_2O) differ at most by only a few cycles per second from those of corresponding signals of the $CDCl_3$ spectra (tetramethylsilane reference, internal in the latter and external in the former solvent) and no pronounced difference between Δ values (chemical shift in D_2O minus chemical shift in $CDCl_3$ for an α,β pair of signals is found in the above cases, Table I). However, Δ values for the α- and β-3-methyl signals differ markedly (α near zero, β near −20 cps), the similar chemical shift values of these groups in D_2O being in sharp contrast to the difference displayed when $CDCl_3$ is the solvent. A similar (but smaller) solvent-induced decrease in the chemical shift difference between α- and β-3-methyl groups is noted in the case of the piperidinol hydrochlorides from which the esters are derived (Table I). Hence, in all these cases, the deshielding influence of protonated nitrogen upon the β-3-methyl group is reduced when $CDCl_3$ is replaced by D_2O, a result which is considered due to a solvent-induced decrease in the conformational preference of the axial 3-methyl conformers **3**, *i.e.*, those in which the $^+$NH–Me distance is a minimum.[3] Of alternative conformations, both the axial 4-phenyl chair (**4**) and the skew-boat[2] conformation (**5**) place protonated nitrogen at a greater distance from the 3-methyl group, the chemical shift of this group then being expected



R = COR′

to approach that of 3-methyl in the α isomer. Evidence of the relative importance of conformations **4** and **5** may be derived from a consideration of the probable orientations of the aromatic and piperidine rings and the likely influence of the aromatic group upon the acyloxy proton resonance signals. In the skew-boat **5**, the steric disposition of the 4-phenyl and 3-methyl substituents is similar to that obtained in the equatorial 4-phenyl chair **3**, in which a perpendicular orientation of the aromatic and piperidine ring planes (as in **2**) is unfavored because of *ortho*-aromatic, hydrogen-axial

(1) A. F. Casy, *Tetrahedron*, **22**, 2711 (1966).

(2) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N. Y., 1965.

(3) Close identity of the pK_a' values of α- and β-prodine (measured in 50% EtOH–H_2O) discount ionization differences as an explanation for reduced β-3-methyl deshielding in D_2O, while the nonidentical β-3-methyl Δ values for the esters and the parent piperidinol (Table I) make unlikely the possibility that the deshielding influence of protonated nitrogen is reduced when this center is solvated (as in D_2O). Attempts at distinction between reduced deshielding due to direct solvation effects and that due to conformational factors, by a study of the solvent dependence of 9-methyl chemical shifts in salts of rigid α- and β-benzomorphans (the 9-e-Me isomer is equivalent to α-, and the 9-a-Me to β-prodine)[4] will be reported elsewhere.

(4) S. E. Fullerton, E. L. May, and E. D. Becker, *J. Org. Chem.*, **27**, 2141 (1962).

TABLE I

PMR CHARACTERISTICS OF SOME DIASTEREOISOMERIC 1,3-DIMETHYL-4-HYDROXY-(AND -4-ACYLOXY-) 4-PHENYLPIPERIDINE HYDROCHLORIDES

No.	4-Oxygen function	Proton group	Chemical shift[a] (W_H) in D_2O	Chemical shift[a] (W_H) in $CDCl_3$	Difference (Δ)
1	OH[i]	α-Ph	447.5[b]	441[c] (19)	+6.5
		β-Ph	446.5[b]	443[c] (8)	+3.5
		α-N-Me[b]	175	167	+8
		β-N-Me[b]	173	163	+10
		α-3-Me[d]	37.5	39.5	−2
		β-3-Me[d]	45	58	−13
2	OCOMe	α-Ph	441[c] (4)	436[c] (4)	+5
		β-Ph	439[b]	437[c] (1)	+2
		α-N-Me	175[c]	172[e]	+3
		β-N-Me	173[b]	174[e]	−1
		α-3-Me[d]	44	44	0
		β-3-Me[d]	41	61	−20
		α-COMe[h]	136	136	0
		β-COMe[b]	124	125.5	−1.5
3	OCOEt	α-Ph	439[c] (4)	435.5[c] (4)	+3.5
		β-Ph	443.5[b] (1.5)	438[b] (1.5)	+5.5
		α-N-Me	174.5[b]	171.5[e]	+3
		β-N-Me	174.5[b]	173.5[e]	+1
		α-3-Me[d]	43.5	44	−0.5
		β-3-Me[d]	43.5	62	−18.5
		α-COCH_2Me[f]	155.5	155.5	0
		β-COCH_2Me[f]	146	143	+3
		α-COCH$_2$*Me*[g]	69.5	73.5	−4
		β-COCH$_2$*Me*[g]	62	64	−2
4	OCO-*n*-Pr	α-Ph	434[b] (2)	436[c] (4)	−2
		β-Ph	440[b] (1.5)	437[b] (1)	+3
		α-N-Me	174[b]	171[e]	+3
		β-N-Me	174[b]	174[e]	0
		α-3-Me[d]	40	44	−4
		β-3-Me[d]	42.5	61	−18.5
		α-COCH_2Et[g]	150	151	−1
		β-COCH_2Et[g]	141	139	+2
		α-COCH$_2$$CH_2$Me[h]	98	105	−7
		β-COCH$_2$$CH_2$Me[h]	92	94	−2
		α-CO(CH$_2$)$_2$*Me*[g]	55.5	62	−6.5
		β-CO(CH$_2$)$_2$*Me*[g]	50	53.5	−3.5

[a] In cps from TMS (internal with $CDCl_3$, and external with D_2O as solvent) spectra being measured at a frequency of 60 Mcps; coupling constants and widths at half-height (W_H) in cps. [b] Singlet. [c] Main peak of multiplet. [d] Doublet (J = 6.5–7 cps). [e] Doublet (J = 5 cps) due to spin–spin coupling with N^+H proton; singlet when D_2O is added. [f] Quartet (J = 7 cps). [g] Triplet (J = 6.5–7 cps). [h] Center of multiplet (four main peaks). [i] Pmr data in D_2O previously reported with DSS as internal standard.[1]

methyl interactions. The more probable aromatic orientation, shown in **5** (in which the two rings approach coplanarity), will have a shielding influence upon the acyloxy protons for reasons previously given. In the axial 4-phenyl chair conformation, of the two extreme aromatic-piperidine ring orientations (aryl plane coplanar or at right angles with a plane passing through N-1 and C-4 of the heterocyclic ring), the one shown in **4** is the more likely because it removes *ortho*-aromatic hydrogen from the vicinity of the equatorial 3-methyl group.[5] In conformation **4**, the 4-acyloxy function does not pass above the aromatic plane during the course of its rotation about the C_4–O bond, the phenyl–acyloxy orientation being similar to that present in the preferred α conformer **2** (in α isomers, conformational preferences are probably alike in both $CDCl_3$ and D_2O; see below). Hence, the facts that the chemical shifts of the β-acyloxy groups are upfield of the corresponding α signals and in extent that they do not differ significantly from those observed in $CDCl_3$, together with the large $-\Delta G^\circ_x$ value of a phenyl substituent in saturated, six-membered, cyclic systems (3.1 kcal/mole is an average value),[2] support the skew-boat **5** as the preferred conformation of β ester (1) hydrochlorides as solutes in D_2O.

These changes in conformational equilibria induced by solvent changes may be accounted for in terms of solvation effects. A considerable increase in the degree of solvation of both the protonated basic center and the oxygen function at C-4 is probable when $CDCl_3$ is replaced by D_2O as solvent; in consequence, the effective bulk of these structural features should become greater. While such increases should not significantly alter conformational preferences in the α derivatives, preference for the β conformer **3** would be expected to decrease, since the destabilizing methyl–N^+H and oxygen function–H 1,3-diaxial interactions obtained in **3** will be larger in the more solvated molecule. It is known, for example, that the $-\Delta G^\circ_x$ value of the hydroxyl group is significantly greater in D_2O than in CCl_4 (1.0 for CCl_4, 1.25 for D_2O at 28°).[7] Solvation

(5) In the absence of this group a conformation in which the plane of axial phenyl is approximately perpendicular to that of the piperidine ring is more probable (*cf.* ref 6).

(6) N. L. Allinger, J. Allinger, M. A. DaRooge, and S. Greenberg, *J. Org. Chem.*, **27**, 3603 (1962).

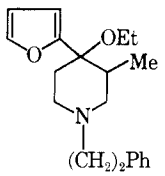
(7) F. A. L. Anet, *J. Am. Chem. Soc.*, **84**, 1053 (1962).

effects would also be expected to raise the energy of the skew-boat **5** (through enhanced bow sprit–flagpole substituent interactions), but the influence of solvent is considered to be more significant in the β chair where three nonbonded interactions are involved. The contributions of the solvated acetoxy, propionoxy, and butyroxy functions to destabilizing the e-phenyl chair conformation **3** appear to be alike (Δ values of the 3-methyl signals are near 20 cps for all three esters) and significantly greater than that of solvated hydroxyl. The corresponding Δ value is 13 cps for the β-piperidinol salt.

The postulate of a skew-boat conformation being favored in a piperidine derivative when 1,3-diaxial interactions in the corresponding chair are enhanced through solvation effects is supported by the solvent dependence of N-methyl chemical shifts in some piperidine methiodides. In isomeric N-methyl-N-substituted piperidinium and tetrahydropyridinium salts a-N-methyl generally has a higher field position than e-N-methyl when $CDCl_3$ is the solvent.[8] Bottini and O'Rell,[9] however, have observed a reversal of a- and e-N-methyl signals in *cis*- and *trans*-4-*t*-butyl-N-benzyl-N-methylpiperidinium chlorides when $CDCl_3$ is replaced by D_2O. This result may be accounted for by solvent-induced conformational changes of a type similar to those presently proposed. In the a-methyl chair-*cis* (*t*-Bu–Me) quaternary salt conformation, 1,3 interactions involving the N-substituent will be greater in D_2O than in $CDCl_3$, making the skew-boat (in which the N-methyl environment approaches that of an e rather than an a substituent) correspondingly more favored. The same arguments predict a near-axial environment for N-methyl in the *trans* isomer as a solute in D_2O.

Discussion[10]

The results of animal tests for analgesia for diastereoisomeric esters of 3-methyl-4-phenylpiperidin-4-ols are given in Table II; values for the acetoxy and butyroxy esters are novel and thanks are due to Dr. Paul Janssen (Janssen Pharmaceutica) for these data. It is noteworthy that among the active pairs, the more potent member (β) has the *cis*-3-alkyl–4-Ph configuration.[11] Significantly, the potent 4-ethoxy-4-(2-furyl)piperidine (**6**)[13] has the same configuration (unpublished results).



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(8) A. F. Casy, A. H. Beckett, and M. A. Iorio, *Tetrahedron*, **22**, 2751 (1966), and references therein cited.

(9) A. T. Bottini and M. K. O'Rell, *Tetrahedron Letters*, 429 (1967).

(10) The conclusions of this discussion are subject to the usual provisos of the compounds cited being morphine-like analgetics acting at the same receptor (all are at least as active as meperidine and fairly closely related chemically) and of potency variations among isomers being largely due to differences in drug–receptor associations and only in minor degree to factors such as drug transport, etc.

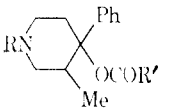
(11) The more active isomer of the related 3-allyl-1-methyl-4-phenyl-4-propionoxypiperidine pair is a possible exception, but its configuration has not been unequivocally established.[12]

(12) A. Ziering, A. Motchane, and J. Lee, *J. Org. Chem.*, **22**, 1521 (1957).

(13) A. F. Casy, A. H. Beckett, G. H. Hall, and D. K. Vallance, *J. Med. Pharm. Chem.*, **4**, 535 (1961).

TABLE II

ANALGETIC ACTIVITIES[a] OF SOME DIASTEREOISOMERIC ESTERS OF 3-METHYL-4-PHENYLPIPERIDIN-4-OLS IN MICE

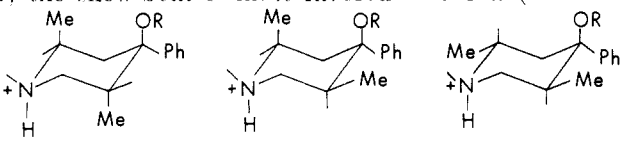


No.	R	R'	Isomer	Potency ratio (morphine = 1)
1[b]	Me	Me	α	0.4
			β	2.2
2[c]	Me	Et	α	2
			β	8.7
3[d]	Me	*n*-Pr	α	1.3
			β	2.9
4[e]	$(CH_2)_2Ph$	Et	α	4.5
			β	22

[a] By subcutaneous injection using an adaptation of the hot plate method. [b] ED_{50} (mg/kg): α, 25; β, 4.6; morphine, 10. [c] Reference 19. [d] ED_{50} (mg/kg): α, 7.5; β, 3.5. [e] A. H. Beckett, A. F. Casy, and G. Kirk, *J. Med. Pharm. Chem.*, 1, 37 (1959). The configurations of these isomers have recently been confirmed by pmr spectroscopy: A. F. Casy, M. A. Iorio, and P. Pocha, *J. Chem. Soc., C*, 942 (1967).

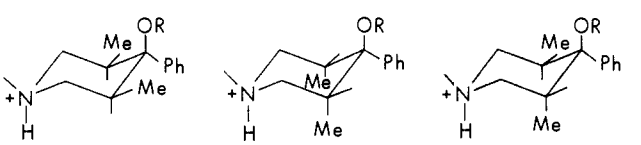
Evidence has been presented that the preferred conformation of the β ester **1** hydrochlorides in D_2O (and, hence, also in water, the medium of greatest biological significance) is the skew-boat **5**. It is likely that the β-4-(2-furyl) ether **6** adopts a similar conformation in water, since the Δ value (chemical shift of D_2O − chemical shift of $CDCl_3$) observed for the 3-methyl group of this compound (as hydrochloride) is close to −20 cps, *i.e.*, almost identical with that noted for 3-methyl in the β esters **1** (Table I).

In view of the lower activity of the α esters **1** (in which a nonchair conformation is improbable), it may be postulated that the skew-boat conformation represents an optimum arrangement of structural features in 4-phenylpiperidine analgetics and that derivatives which might be expected to have high skew-boat populations may well be potent analgetics. Support for this proposition is provided by the following examples. Of the three isomeric 1,2,5-trimethylpiperidine esters **7**, the skew-boat is most favored in the α (with two



7-α **7-β** **7-γ**

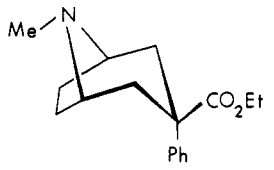
axial methyl groups in the e-phenyl chair, **7-α**) and least in the γ form (with two equatorial methyl groups in the chair, **7-γ**), compounds of the highest and lowest activity, respectively, among the trio.[14] In the 1,3,5-trimethyl derivatives **8**, factors unfavorable toward a skew-boat conformer obtained in all three isomers



8-α **8-β** **8-γ**

(14) I. N. Nazarov, N. S. Prostakov, and N. I. Shvetsov, *J. Gen. Chem. USSR*, **26**, 2798 (1956); N. S. Prostakov, B. E. Zaitsev, N. M. Miklailova, and N. N. Mikheeva, *ibid.*, **34**, 463 (1964), and references there cited.

(nonbonded interactions of e-Me groups in 8-α and -γ are raised in boat forms, and models show that the *cis*-1,3-diaxial Me–Me interaction of 8-β is not relieved in the corresponding boat), the sole active member (γ) being about as active as the γ-1,2,5-trimethyl isomer.[15] Ethyl 3-α-phenyltropane-3-β-carboxylate, which is somewhat more potent than meperdine,[16] would be expected to have a significantly large skew-boat **10** population because the chair conformer **9** is destabilized



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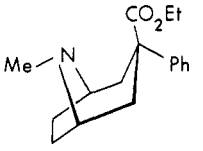

10

by a-Ph–bimethylene bridge interactions. Spectroscopic evidence supports this contention for related β-ethyl and phenyl ketones.[17]

In a recent analysis of stereochemical factors in narcotic analgetics, Portoghese[18] stated that the conformational requirements for most of the 4-phenylpiperidine analgetics appear to be minimal. From the present evidence, however, it is probably more accurate to state that although a fairly wide range of 4-phenylpiperidine conformations are compatible with activity, those in which the aromatic and piperidine rings approach coplanarity (as in the skew-boat with phenyl in the bow-sprit position) may be most effective in evoking a response.

Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within $\pm 0.4\%$ of the theoretical values.

The pmr spectra were recorded on a Varian A-60 spectrometer operating at the normal running temperature with TMS as standard (internal with $CDCl_3$ and external with D_2O as solvent). α-1,3-Dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride (α-prodine), mp 222° (lit.[19] 220–221°), and the corresponding β isomer (β-prodine), mp 199–200° (lit.[19] 195–196°), were obtained by heating the α- and β-piperidinols **1a** with propionic anhydride and pyridine.[19] New esters prepared in this way were as follows (uncorrected melting points determined with a Buchi-Tottoli apparatus in capillary tubes).

α-4-Acetoxypiperidine (**1b**) hydrochloride, mp 216–218°, from *i*-PrOH–Et_2O. *Anal.* ($C_{15}H_{22}ClNO_2$) C, H, N.

β-4-Acetoxypiperidine (**1b**) hydrochloride, mp 211–213°, from EtOH–Me_2CO. *Anal.* C, H, N.

α-4-Butyoxypiperidine (**1d**) hydrochloride, mp 196–197°, from EtOH–MeCOEt. *Anal.* ($C_{17}H_{26}ClNO_2$) C, H, N.

β-4-Butyroxypiperidine (**1d**) hydrochloride, mp 202°, from EtOH–MeCOEt; ν_{max} 3400 cm^{-1}. *Anal.* C, H, N (low C value due to water of crystallization).

All of the esters had ν_{max}^{Nujol} near 1720 cm^{-1} (ester C=O). The pK_a' values of the prodine isomers in 50% EtOH–H_2O, determined by Albert's and Sergeant's method,[20] were α, 7.68 ± 0.06, and β, 7.75 ± 0.06.

Acknowledgment.—The author acknowledges Drs. M. A. Iorio and P. Pocha for assistance in this work.

(15) O. I. Sorokin, *Izv. Akad. Nauk. SSSR*, 460 (1961).
(16) M. R. Bell and S. Archer, *J. Am. Chem. Soc.*, **82**, 4638 (1960).
(17) M. R. Bell and S. Archer, *ibid.*, **82**, 151 (1960).
(18) P. S. Portoghese, *J. Pharm. Sci.*, **55**, 865 (1966).
(19) A. H. Beckett, A. F. Casy, G. Kirk, and J. Walker, *J. Pharm. Pharmacol.*, **9**, 939 (1957).
(20) A. Albert and E. P. Sergeant, "Ionization Constants of Acids and Bases," Methuen, London, 1962.

Effects of Certain Arylhydroxamic Acids on Deoxyribonucleic Acid Synthesis by Ehrlich Ascites Tumor Cells *in Vitro*[1]

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A recent report[2] described a selective inhibition by salicylhydroxamic acid (I) of deoxyribonucleic acid (DNA) synthesis in Ehrlich ascites tumor cells. Characteristics of the inhibition were similar in some respects to the actions of hydroxyurea[3] and of oxamylhydroxamic acid,[4,5] the hydroxamic acid analogs of carbamic acid and oxamic acid, respectively. Effects on the synthesis of ribonucleic acid (RNA) and of protein were nominal and were considered to be of a secondary nature as a consequence of the lowered rate of DNA formation. The inhibition by I was further evident immediately upon adding the compound to the cells; that is, no preincubation was necessary to evoke the effect. The rate of DNA synthesis resumed the control rate upon removal of the inhibitor by washing the cells, indicating no firm binding to the cells and no irreversible alteration of the cells by the compound.

The work herein described was initiated to determine the ways in which structural features of compounds related to I may influence the course of nucleic acid synthesis in a tumor-cell test system.

Biological Data.—Table I shows the 50 and 90% inhibitory concentrations of each compound on DNA synthesis in Ehrlich ascites tumor cells. With one exception, data are presented as obtained with no preincubation (*i.e.*, inhibitor and isotopic precursor were added to the cell suspension simultaneously) and, also, following 1-hr preincubation of the cells with each compound prior to addition of the isotopic precursor. The relative potency of 9 of the 12 compounds was increased by the 1-hr preincubation period, the most striking example being that of XII. Slopes of the regression lines were fairly closely grouped when inhibitor and precursor were added simultaneously but varied erratically following the 1-hr preincubation period.

Figure 1 shows the effects of each of the 12 compounds on DNA, RNA, and protein synthesis in Ehrlich ascites tumor cells. The selectivity of action of I on DNA synthesis was confirmed; that is, the rate of DNA synthesis was depressed almost 80% after 1-hr exposure of the cells to the compound with no appreciable diminution in the rate of RNA or protein synthesis. Com-

(1) This work was aided by Grant GM-13958 from the National Institutes of Health, U. S. Public Health Service.
(2) G. R. Gale, *Proc. Soc. Exptl. Biol. Med.*, **122**, 1236 (1966).
(3) (a) J. W. Yarbro, B. J. Kennedy, and C. P. Barnum, *Proc. Natl. Acad. Sci. U. S.*, **53**, 1033 (1965); (b) J. W. Yarbro, W. G. Niehaus, and C. P. Barnum, *Biochem. Biophys. Res. Commun.*, **19**, 592 (1965); (c) R. L. P. Adams, R. Abrams, and I. Lieberman, *J. Biol. Chem.*, **241**, 903 (1966).
(4) G. R. Gale, *Cancer Res.*, **26**, 2340 (1966).
(5) G. R. Gale, *J. Natl. Cancer Inst.*, **38**, 51 (1967).