crystallization of the residue from acetic acid gave 5 g. of 3-acetylsulfamyl-4-chlorobenzoic acid, m.p. 235–240°.

Anal. Calcd. for $C_9H_8ClNO_5S$: C, 38.96; H, 2.9; N, 5.05. Found: C, 38.74; H, 2.73; N, 4.86.

2-Chloro-5-formylbenzenesulfonamide.—Ethanol (750 ml.) containing the triacetate VIII (118 g., 0.325 mole) and 350 ml. of 2 *N* HCl was boiled under reflux for 20 min. The ethanol was evaporated under reduced pressure, and the residue was diluted with water to precipitate a colorless solid. Crystallization from 2-propanol gave 31 g. (43.5%) of pure aldehyde with m.p. 169–170°.

Anal. Calcd. for $C_7H_6ClNO_3S$: C, 38.27; H, 2.75; Cl, 16.14; N, 6.38. Found: C, 38.22; H, 3.00; Cl, 16.40; N, 6.18.

Subsequent fractions of crystals from the liquors, although having good melting points (164–167°), were shown by infrared spectra to contain varying proportions of partially hydrolyzed material.

Infrared spectra showed pure aldehyde (Nujol mull): >C=O (1694 cm.$^{-1}$), SO_2NH_2 (1168 and 1330 cm.$^{-1}$), NH_2 (3400, 3370, 3295, and 3220 cm.$^{-1}$); mixtures (Nujol mull): split carbonyl at 1694 (CHO) and 1725 cm.$^{-1}$.

2,4-Dinitrophenylhydrazone, m.p. 301–302°, from dimethylformamide–ethanol.

Anal. Calcd. for $C_{13}H_{10}ClN_5O_6S$: N, 17.6. Found: N, 17.45.

3-(4-Chloro-3-sulfamoylphenyl)-3,4-dihydro-(2H)-1,2,4-benzothiadiazine 1,1-Dioxide.—Diglyme (40 ml.) containing *o*-aminobenzenesulfonamide (3.44 g., 0.02 mole), 2-chloro-5-formylbenzenesulfonamide (4.7 g., 0.02 mole), and 0.2 ml. of ethyl acetate saturated with anhydrous HCl was heated at 90–100° for 4 hr. The resulting solution was cooled and poured onto 200 ml. of water to precipitate a sticky solid. Trituration with ether gave a colorless solid. Repeated crystallization from diglyme–water gave an analytical sample, m.p. 262–264°.

Anal. Calcd. for $C_{13}H_{12}ClN_3O_6S_2$: C, 41.76; H, 3.24; N, 11.24. Found: C, 41.75; H, 3.37; N, 11.00.

Subsequent fractions had m.p. 259–261° which could not be improved. The compounds listed in Table II were prepared by the same general procedure.

Notes

Structures Related to Morphine. XXX.[1] N-Hexyl- and 5-Butyl-, -Amyl-, and -Hexyl-6,7-benzomorphans

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Recently it was reported[3] that optimal analgetic behavior in the 5,9-dialkyl-2′-hydroxy-2′-methyl-6,7-benzomorphan series was shown when the sum of the carbon atoms of these two alkyl substituents was 2–4. It is also known that there is complete loss of activity when the methyl group on the nitrogen of 2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan is replaced by ethyl, propyl, or butyl, but that activity is restored when the group on nitrogen becomes amyl.[4] To further define structural limits at the 2(nitrogen)- and 5-positions, 2-hexyl-2′-hydroxy-α-5,9-dimethyl-6,7-benzomorphan (III)[5] and 5-butyl-, -amyl-, and -hexyl-2′-hydroxy-2-methyl-6,7-benzomorphans (II) have been synthesized, assessed for analgetic activity, and compared with the lower homologs.

The method of synthesis used for II *via* I was a modification of the Stevens rearrangement and has been described before[3,6] for various analogs. Acid cyclization of I proceeded in much lower yields than was the case with lower homologs[3,6] and with 3,4-dialkyl-1,2,5,6-tetrahydropyridines when the alkyl group at position 4 was methyl to propyl.[3,6,7] Phosphoric acid (85%) at 150–160° proved superior to boiling 48% HBr.

Compound IIIa was synthesized from 2′-methoxy-α-2,5,9-trimethyl-6,7-benzomorphan essentially as described for lower N-alkyl homologs.[4a] Benzomorphan Ia was converted to the methyl ether (with diazomethane) which, as the methiodide, was cleaved to 1,2-dihydro(2-dimethylaminoethyl)-1-hexyl-7-methoxynaphthalene with hot, aqueous NaOH. This methine was hydrogenated to the corresponding tetrahydronaphthalene which was tested for diuretic activity.[8]

As shown in Table I, in the 5-alkyl series, compounds

TABLE I

ANALGETIC ACTIVITY OF 5-ALKYL-2′-HYDROXY-2-METHYL-6,7-BENZOMORPHANS (II) AND OF α-2-ALKYL-2′-HYDROXY-5,9-DIMETHYL-6,7-BENZOMORPHANS (III)

II			III		
No.	R	ED_{50}[a]	No.	R_1	ED_{50}[a]
IId	Me	10.4[b]	IIIb	Me	3.0[b]
IIe	Et	2.3[b]	IIIc	Et	I[c]
IIf	Pr	2.1[b]	IIId	Pr	I[c]
IIa	Bu	2.0	IIIe	Bu	I[c]
IIb	Am	3.4	IIIf	Am	2.1[d]
IIc	Hex	10.8	IIIa	Hex	1.5
Morphine		2.1			

[a] Expressed in mg./kg. of hydrochloride salt (mice, subcutaneous administration): see N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953). [b] See ref. 3. [c] Inactive; see ref. 4. [d] See ref. 4.

IIe, IIf, and IIa are equipotent and comparable to morphine.[9] Activity begins to drop with amyl (IIb) and decreases sharply with hexyl (IIc) which is almost identical with the 5-methyl homolog (IId). Thus, like the 5,9-dialkyl series, maximum activity obtains when the carbon total numbers 2–4. In contrast,

(1) Previous paper: C. F. Chignell and E. L. May, *J. Med. Chem.*, **8**, 385 (1965).

(2) (a) Visiting Scientist from Allahabad University, India. (b) Visiting Fellow from the Chelsea School of Pharmacy, London, England.

(3) J. H. Ager, S. E. Fullerton, and E. L. May, *J. Med. Chem.*, **6**, 322 (1963).

(4) (a) J. H. Ager and E. L. May, *J. Org. Chem.*, **25**, 984 (1960); (b) S. Archer, N. F. Albertson, L. S. Harris, A. K. Pierson, and J. G. Bird, *J. Med. Chem.*, **7**, 125 (1964), have found that the N-propyl compound is one of the most potent morphine antagonists known.

(5) For proof of configuration at position 9 and an explanation of the α- and β-designations, see S. E. Fullerton, E. L. May, and E. D. Becker, *J. Org. Chem.*, **27**, 2144 (1962).

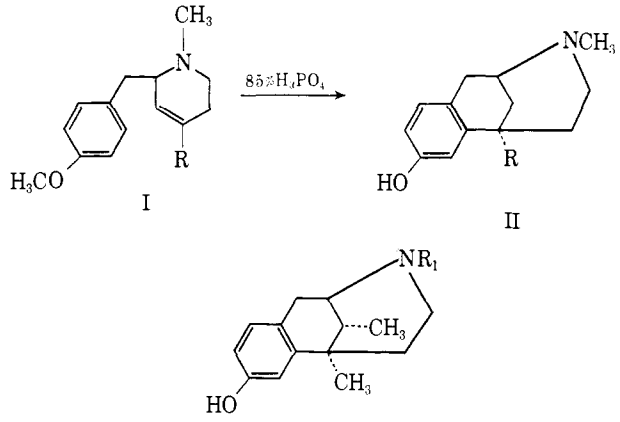
(6) (a) E. M. Fry and E. L. May, *ibid.*, **26**, 2592 (1961); (b) S. Saito and E. L. May, *ibid.*, **27**, 948 (1962).

(7) J. H. Ager, S. E. Fullerton, E. M. Fry, and E. L. May, *ibid.*, **28**, 2470 (1963).

(8) By Smith Kline and French Laboratories.

(9) Considering optical activity, morphine is only half as potent on the reasonable assumption that most of the activity of II (racemates) resides in one antipode.

2-hexyl-2′-hydroxy-α-5,9-dimethyl-6,7-benzomorphan (IIIa) is even more potent than the N-amyl (IIIf) and N-methyl (IIIb) relatives (Table I) indicating that maximum activity has not yet been reached in the N-alkyl series.[10]



I II III

I and IIa, R = C_4H_9
b, R = C_5H_{11}
c, R = C_6H_{13}
IIIa, R_1 = C_6H_{13}

Experimental

Melting points (capillary) are corrected. Microanalyses are by Evelyn Peake, Paula Parisius, Alice Wong, and Byron Baer of this laboratory.

4-Butylpyridine Methiodide.—To 100 g. of 4-butylpyridine[11] in 100 ml. of benzene was added dropwise (stirring, ice cooling) 131 g. of methyl iodide in 50 ml. of acetone. The solution was refluxed for 2 hr. and stored at −5° overnight to give 162 g. (80%) of needles (from acetone), m.p. 91–92°.

Anal. Calcd. for $C_{10}H_{16}IN$: C, 43.4; H, 5.7; N, 5.1. Found: C, 43.4; H, 5.7; N, 5.3.

4-Amylpyridine Methiodide.—This compound was obtained in 97% yield from 4-amylpyridine[12]; m.p. 81–82°.

Anal. Calcd. for $C_{11}H_{18}IN$: C, 45.6; H, 6.1; I, 44.0; N, 4.8. Found: C, 45.5; H, 6.3; I, 43.7; N, 4.8.

4-Hexylpyridine[11] methiodide, m.p. 79–80°.

4-Butyl-1-*p*-methoxybenzyl-1-methyl-1,2,5,6-tetrahydropyridinium Chloride (IV).—To a stirred solution of 20 g. of 4-butylpyridine methiodide in 200 ml. of 1 *N* NaOH was added in one lot, 2.8 g. of $NaBH_4$ in 80 ml. of water. The mixture was kept at 50–55° for 2 hr., cooled, and extracted with three 150-ml. portions of ether. Drying and evaporation of the ether left 9.3 g. of oil which was treated with 9.5 g. of *p*-methoxybenzyl chloride,[6b] in warm acetone. After 1 hr. the mixture was stored overnight at −5° and yielded 13 g. (63%) of plates from acetone–ether; m.p. 158–159°.

Anal. Calcd. for $C_{18}H_{28}ClNO$: C, 69.8; H, 9.1; N, 4.5. Found: C, 69.3; H, 8.8; N, 4.7.

4-Amyl-1-*p*-methoxybenzyl-1-methyl-1,2,5,6-tetrahydropyridinium chloride (V) was prepared essentially as described for IV except that methanol–water was used instead of water in the borohydride reduction; m.p. 179–180°.

Anal. Calcd. for $C_{19}H_{30}ClNO$: C, 69.8; H, 9.4; Cl, 10.9; N, 4.6. Found: C, 70.3; H, 9.6; Cl, 10.6; N, 4.3.

4-Hexyl-1-*p*-methoxybenzyl-1-methyl-1,2,5,6-tetrahydropyridinium chloride (VI) was prepared as described for V above; m.p. 173° (from acetone).

Anal. Calcd. for $C_{20}H_{32}ClNO$: C, 71.3; H, 9.5; Cl, 10.4; N, 4.5. Found: C, 71.1; H, 9.5; Cl, 10.5; N, 4.1.

4-Hexyl-2-(*p*-methoxybenzyl)-1-methyl-1,2,5,6-tetrahydropyridine (Ic) Picrate.—To 10.9 g. of chloride VI covered with dry ether was added (stirring) 42 ml. of 2 *M* ethereal phenyllithium at such a rate to cause brisk refluxing. After the initial reaction had subsided, gentle refluxing was continued for 1–2 hr. The mixture was poured into ice water and the ethereal layer extracted with excess 10% HCl (three 50-ml. portions). The combined extracts were made basic with concentrated NH_4OH and extracted with ether. Drying (Na_2SO_4) and evaporation of the ether left 8.4 g. of crude Ic. It was converted to 9 g. (55%) of picrate in acetone–ethyl acetate; m.p. 98.5° (from acetone).

Anal. Calcd. for $C_{26}H_{34}N_4O_8$: C, 59.2; H, 6.3; N, 10.9. Found: C, 58.9; H, 6.4; N, 10.6.

5-Butyl-2′-hydroxy-2-methyl-6,7-benzomorphan (IIa).—As described in the preparation of Ic, 19.7 g. of chloride IV and 120 ml. of 2 *M* ethereal phenyllithium gave 10 g. of crude Ia, b.p. 127–131° (0.1 mm.). This material (4 g.) and 25 ml. of 85% H_3PO_4 were stirred at a bath temperature of 150–155° for 40 hr., cooled, made basic with cold NH_4OH, and extracted with chloroform. The residue from the dried (Na_2SO_4) chloroform extracts was evaporatively distilled (0.1 mm., bath temperature 180–200°) to give 1.5 g. of oil which crystallized (at 0°) from 2–3 ml. of acetone; yield 0.63 g. (8% from IV), m.p. 183–186°; ellipsoids from acetone, m.p. 172–174° with solidification and remelting at 184–188°. When temperature rise is very slow the melting point is 173–188°.

Anal. Calcd. for $C_{17}H_{25}NO$: C, 78.7; H, 9.7. Found: C, 78.7; H, 9.9.

The **hydrochloride** crystallized from acetone–ethanol as the hemihydrate, m.p. 204–210°.

Anal. Calcd. for $C_{17}H_{26}ClNO \cdot 0.5H_2O$: C, 67.0; H, 8.9. Found: 67.1; H, 9.1.

The anhydrous hydrochloride was obtained on drying the hemihydrate at 100°.

Anal. Calcd. for $C_{17}H_{26}ClNO$: C, 69.0; H, 8.9. Found; C, 69.2; H, 8.5.

5-Amyl-2′-hydroxy-2-methyl-6,7-benzomorphan (IIb) **Hydrochloride.**—As described in the preparation of Ic, 20 g. of chloride V and 40 ml. of 2 *M* ethereal phenyllithium gave 16.4 g. of evaporatively distilled (at 0.1 mm., 160–180°) but impure Ib. This Ib (7 g.) was cyclized with 45 ml. of 85% H_3PO_4 as described above for Ia. The distilled IIb crystallized from ether in a yield of 1.4 g. (18% from V), m.p. 161–162°. It was converted to the hydrochloride (ethereal HCl) which crystallized from acetone as the hemihydrate, m.p. 187–190°.

Anal. Calcd. for $C_{18}H_{28}ClNO \cdot 0.5H_2O$: C, 67.6; H, 9.1; Cl, 11.4; N, 4.4. Found: C, 67.7; H, 9.1; Cl, 11.1; N, 4.4.

The anhydrous compound was obtained after keeping the hemihydrate at 55° (high vacuum) overnight. The weight loss was 2.2% (calcd. for 0.5 mole of H_2O, 2.6%).

Anal. Calcd. for $C_{18}H_{28}ClNO$: C, 69.8; H, 9.0. Found: C, 69.6; H, 9.2.

5-Hexyl-2′-hydroxy-2-methyl-6,7-benzomorphan (IIc).—Pure Ic (4.1 g. obtained from 8 g. of picrate with ligroin–LiOH) and 25 ml. of 85% H_3PO_4 gave, as described in the cyclization of Ia and Ib, 1.8 g. of distilled (bath temperature 175–180°, 0.1 mm.) IIc. It crystallized from acetone in a yield of 0.9 g. (21%), m.p. 163.5–164°.

Anal. Calcd. for $C_{19}H_{29}NO$: C, 79.3; H, 9.8; N, 4.8. Found: C, 79.4; H, 10.1; N, 4.9.

The **hydrobromide,** m.p. 196–198°, was recrystallized from acetone.

Anal. Calcd. for $C_{19}H_{30}BrNO$: Br, 21.7. Found: Br, 21.7.

2-Hexyl-2′-methoxy-α-5,9-dimethyl-6,7-benzomorphan Hydrochloride.—Crude 2′-methoxy-5,9-dimethyl-6,7-benzomorphan[4a] (2.8 g.), 10 ml. of dimethylformamide, 1.5 g. of K_2CO_3, and 2.5 g. of hexanoyl chloride were refluxed for 2 hr. (stirring),[13] diluted with water, and extracted with ether. The dried (Na_2SO_4) extracts were evaporated to dryness, and the residue (crude hexanoic amide) in 10 ml. of ether was treated during 40 min. with 1.6 g. of powdered $LiAlH_4$. After refluxing for 6–8 hr., 5–8 ml. of water was added very carefully (stirring). The solid was filtered and washed with ether. Drying and evaporation

(10) N-amyl- and N-hexylnormorphines [C. A. Winter, P. D. Orahovats, and E. G. Lehman, *Arch. intern. pharmacodyn.*, **110**, 186 (1957)] and 3-hydroxy-N-amyl- and N-hexylmorphinans (J. Hellerbach, H. Besendorf, B. Pellmont, and O. Schnider, "Synthetic Analgesics, Part II-A, Morphinans," Pergamon Press Ltd., Oxford, England, in press; O. Schnider, personal communication) are somewhat less potent than the respective N-methyl analogs.

(11) From Reilly Tar and Chemical Corp.

(12) From Chemical Intermediates and Research.

(13) See A. Grüssner, J. Hellerbach, and O. Schnider, *Helv. Chim. Acta*, **40**, 1232 (1957).

of the ether left 1.8 g. of oil which gave (from acetone–HCl gas) 1.5 g. (38% over-all after recrystallization from acetone) of hydrochloride, m.p. 202–203°.

Anal. Calcd. for $C_{21}H_{34}ClNO$: C, 71.7; H, 9.7. Found: C, 71.6; H, 9.9.

2-Hexyl-2′-hydroxy-α-5,9-dimethyl-6,7-benzomorphan (IIIa).—The preceding hydrochloride (1.5 g.) and 15 ml. of 48% HBr were refluxed for 15 min. The mixture was cooled and made alkaline with NH_4OH, and the liberated base was extracted with chloroform. Drying and distillation of the solvent *in vacuo* left a residue which was evaporatively distilled (0.5 mm., 170–180°). The distillate crystallized from acetone in a yield of 0.27 g. (20%), m.p. 130–132°, with bubbling. Analysis indicated a molecule of acetone of solvation, not removed on prolonged heating at 80° *in vacuo*.

Anal. Calcd. for $C_{20}H_{31}NO \cdot CH_3COCH_3$: C, 76.8; H, 10.4. Found: C, 76.3; H, 10.6.

The solvate-free IIIa was obtained by heating the solvated compound to its melting point.

Anal. Calcd. for $C_{20}H_{31}NO$: C, 79.7; H, 10.2. Found: C, 79.9; H, 10.5.

The **hydrochloride** of IIIa, prepared from acetone-HCl, crystallized from acetone containing a little methanol in short rods, m.p. 205–207°.

Anal. Calcd. for $C_{20}H_{32}ClNO$: C, 71.1; H, 9.5. Found: C, 71.3; H, 9.8.

5-Hexyl-2′-methoxy-2-methyl-6.7-benzomorphan Methiodide.—Methanol (5 ml.), 0.75 g. of IIc, and 35 ml. of 3% ethereal diazomethane were stirred for 46 hr. A 15-ml. portion of CH_2N_2 was then added. After another 22 hr., solvents were distilled, and the residue was evaporatively distilled (bath temperature 140–150°, 0.1 mm.). The distillate in acetone was treated with 0.5 ml. of methyl iodide to give 1.2 g. (90%) of crystals, m.p. 225–226°.

Anal. Calcd. for $C_{21}H_{34}INO$: C, 56.8; H, 7.4; I, 28.9. Found: C, 56.9, H, 7.7; I, 28.9.

1-Hexyl-7-methoxy-1-(2-dimethylaminoethyl)-1,2,3,4-tetrahydronaphthalene Hydrochloride.—The above methiodide (1.2 g.) and 12 ml. of 10% NaOH were refluxed for 2–3 hr. The resultant oil was dried (Na_2SO_4) in ether and hydrogenated (0.1 g. of platinum oxide) in alcohol with absorption of 1 *M* equiv. of hydrogen. The product was converted to the hydrochloride (ethereal HCl) which was recrystallized from acetone-ether; over-all yield from methiodide 0.7 g. (75%), m.p. 195–196°.

Anal. Calcd. for $C_{21}H_{36}ClNO$: C, 71.3; H, 10.2. Found: C, 71.0; H, 10.2.

Structures Related to Morphine. XXXII.[1] α- and β-2,9-Dimethyl-5-propyl-6,7-benzomorphan from 3-Methyl-4-propylpyridine

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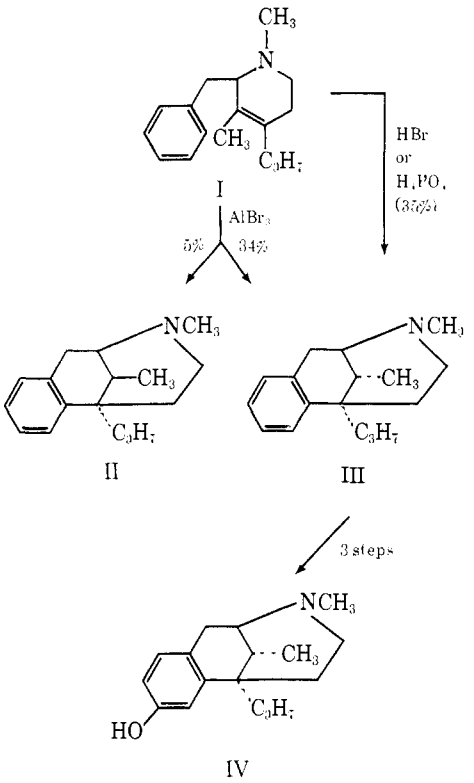
In the synthesis of two relatively strong analgesics, α- and β-2,9-dimethyl-5-propyl-6,7-benzomorphan (III and II, respectively), from 3,4-dihydro-2(1H)-naphthalenone (β-tetralone) by stereo-controlled reactions, the yields are very low.[3] In order to provide sufficient material for pharmacological study of II and III and to further confirm their structure we have effected a three-step synthesis from 3-methyl-4-propylpyridine and have converted the α-compound (III) into the also known α-2,9-dimethyl-2′-hydroxy-5-propyl-6,7-benzomorphan (IV). This establishes the structure of II and III beyond reasonable doubt.

The cyclization of 2-benzyl-1,3-dimethyl-4-propyl-1,2,5,6-tetrahydropyridine (I) (prepared by sodium borohydride reduction of 2-benzyl-1,2-dihydro-1,3-dimethyl-4-propylpyridine in turn prepared by the Freund reaction using benzylmagnesium chloride and 3-methyl-4-propylpyridine)[4] with aluminum bromide in carbon disulfide gave a mixture of II (34%) and III (5%) (see Scheme I).[5] With either 48% hydrobromic acid or 85% phosphoric acid, the α-isomer (III) was isolated in 30–35% yield, no β-isomer (II) being detected. Nitration of III followed by hydrogenation and nitrous acid oxidation of the resultant 2′-amino derivative[4] gave the known 2′-hydroxy relative (IV).[6] Analgetic activities of II and III are comparable to morphine and codeine, respectively.[3]

SCHEME I



Experimental

2-Benzyl-1,3-dimethyl-4-propyl-1,2,5,6-tetrahydropyridine (I) Hydrochloride.—To an ice-cooled, stirred suspension of 50 g. of 1,3-dimethyl-4-propylpyridinium iodide[6] was added, during 15–20 min., freshly prepared benzylmagnesium chloride (from 32 g. of $C_6H_5CH_2Cl$, 6 g. of Mg turnings, and 150 ml. of ether). The mixture was stirred for 1.5 hr. without cooling and poured

(1) Paper XXXI: A. E. Jacobson and E. L. May, *J. Med. Chem.*, **8**, 563 (1965).

(2) Visiting Associate from the University of Allahabad, India.

(3) C. F. Chignell and E. L. May, *J. Med. Chem.*, **8**, 385 (1965).

(4) For a leading reference see A. E. Jacobson and E. L. May, *ibid.*, **7**, 400 (1964).

(5) This is a less favorable ratio of β-isomer and a lower yield of each isomer than had hitherto been obtained with lower homologs: J. H. Ager, S. E. Fullerton, E. M. Fry, and E. L. May, *J. Org. Chem.*, **28**, 2470 (1963).

(6) C. F. Chignell, J. H. Ager, and E. L. May, *J. Med. Chem.*, **8**, 235 (1965).