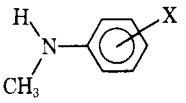
TABLE II

4-METHYLAMINOBENZALDEHYDES



X	Yield, %	Mp, °C[a]	Crystn solvent[b]	Formula[c]
3-Br	61	75.0–76.0[d]	I, IE	C_8H_8BrNO
3-I	44	81.0–82.0[e]	IE	C_8H_8INO[f]
3,5-Br_2	60	73.0–73.5	I	$C_8H_7Br_2NO$
3,5-Cl_2	12	85.0–85.6	I, IE	$C_8H_7Cl_2NO$

[a] Determined with Mel-Temp melting point apparatus. [b] I, mixed isomeric branched hexanes; IE, *i*-Pr_2O. [c] All compounds were analyzed for C and H by Galbraith Laboratories except where indicated otherwise; analytical results were within ±0.3% of the theoretical values. [d] Reaction mixture was stirred 10 min and poured into 1300 ml of H_2O; a few g of $NaHSO_3$ in H_2O were added, the mixture was filtered and washed repeatedly with H_2O. [e] Isooctane extractions treated with sodium thiosulfate and concentrated to obtain additional material. [f] Not analyzed.

was prepared by reacting *t*-BuOCl with 4-dimethylaminobenzaldehyde.[7] 2-Chloro- and 3-bromo-4-dimethylaminobenzaldehyde were prepared by the halogenation of 4-dimethylaminobenzaldehyde according to the method of Brady and Truskowski,[8] but using an equivalent amount of NaOAc in the reaction. The 3-chloro-, 3-bromo-, 3,5-dichloro-, and 3,5-dibromo-4-methylaminobenzaldehydes were prepared similarly. In making the 3-chloro compound most of the AcOH was evaporated under vacuum, and the remaining material poured into 2 l. of H_2O and neutralized with $NaHCO_3$. The resulting oil and/or ppt was dissolved in C_6H_6 and chromatographed on silica gel. During elution with C_6H_6 the 3,5-dichloro compound passed through first, and then the 3-chloro derivative. The 3,5-dichloro compound, however, was obtained principally using 2 equiv of Cl_2/equiv of aldehyde and stirring the reaction mixture for 2 hr. 3-Iodo-4-methylaminobenzaldehyde was prepared by adding 24.2 g of ICl dropwise with stirring to 20 g (0.148 mol) of 4-methylaminobenzaldehyde in 70 ml of AcOH at 12–25°. After standing 3 hr the mixture was hydrolyzed over ice and neutralized with NaOH and $NaHCO_3$. 4-Amino-3,5-dichlorobenzaldehyde was obtained by adding dropwise a solution of Cl_2 in AcOH to a dilute AcOH solution of the HCl salt of 4-aminobenzaldehyde. The product was obtained according to the method of van de Bunt.[9] 4-Amino-3,5-dibromobenzaldehyde was prepared from 3-bromo-4-dimethylaminobenzaldehyde perbromide hydrochloride.[10,11]

1-(3-Chloro-4-dimethylaminobenzylidene)-3-(α-hydroxy-3-chloro-4-dimethylaminobenzyl)indene [isolated and analyzed as the dipicrate (*Anal.* ($C_{49}H_{42}Cl_2N_8O_{15}$) C, H, Cl; H: calcd, 3.49; found, 4.04)] and 1-(3,5-dibromo-4-methylaminobenzylidene)-3-(α-hydroxy-3,5-dibromo-4-methylaminobenzyl)indene (*Anal.* ($C_{25}H_{20}Br_4N_2O$) C, H) were obtained as by-products in the preparation of 1-(3-chloro-4-dimethylaminobenzylidene)indene and 1-(3,5-dibromo-4-methylaminobenzylidene)indene, respectively.

(7) D. Ginsburg, *J. Amer. Chem. Soc.*, **73**, 703 (1951).
(8) D. L. Brady and R. Truskowski, *J. Chem. Soc.*, 2434 (1923).
(9) C. van de Bunt, *Rec. Trav. Chim. Pays-Bas*, **48**, 121-146 (1929).
(10) C. T. Bahner, *et al.*, *J. Org. Chem.*, **25**, 2053 (1960).
(11) J. J. Blanksma, *Chem. Zentralbl.*, **1**, (1910).

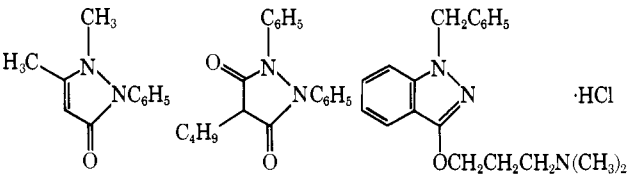
Synthesis and Alkylation of Tetrahydrocyclopentapyrazolols

RICHARD P. WILLIAMS, VICTOR J. BAUER, AND S. R. SAFIR

Organic Chemical Research Section, Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965

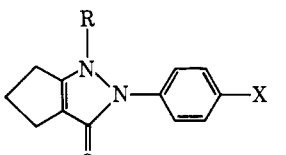
Received February 6, 1970

Antipyrine (**1**) has long been recognized as an analgetic–antipyretic agent;[1] phenylbutazone (**2**) has become a widely used analgetic–antiinflammatory drug;[1] and benzydamine (**3**) has received notice as a potentially useful analgetic–antiinflammatory agent in man.[1,2] Although in many ways dissimilar, certain structural features common to **1**, **2**, and **3** may be

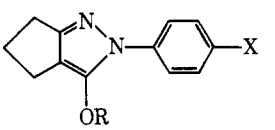


1 **2** **3**

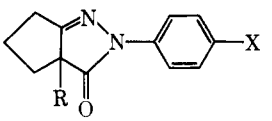
recognized. Each compound possesses an oxygen-bearing pyrazole heterocycle which supports an aryl or alkyl N substituent and a C substituent. The tetrahydrocyclopentapyrazolones **4**, **5**, and **6**, synthesized by Mannich in 1929,[3,4] combine these structural units in a different manner. We undertook to repeat this work, and to prepare a brief series of analogs for examination in an antiinflammatory screening program.



4, R = X = H
5, R = H; X = Br
6, R = CH_3; X = H
7, R = $CH_2CH{=}CH_2$; X = H
8, R = $CH_2C_6H_5$; X = Br
9, R = $CH_2C_6H_5$; X = F



10, R = X = H
11, R = H; X = Br
12, R = H; X = F
13, R = CH_3; X = H
14, R = $CH_2C_6H_5$; X = F

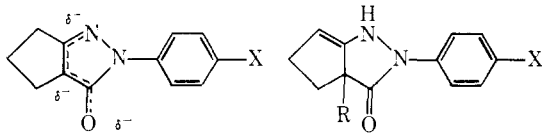


15, R = H; X = H
16, R = H; X = Br
17, R = H; X = F
18, R = CH_3; X = H
19, R = $CH_2CH{=}CH_2$ X = H
20, R = $CH_2C_6H_5$; X = Br
21, R = $CH_2C_6H_5$; X = F

(1) W. C. Cutting, "Handbook of Pharmacology," 3rd ed, Appleton-Century-Crofts, New York, N. Y., 1967, pp 511–515.
(2) M. DeGregorio, "International Symposium on Nonsteroidal Antiinflammatory Drugs, Milan, 1964," S. Garattini and M. N. G. Dukes, Ed., Excerpta Medica Foundation, Amsterdam, 1965, pp 422–429.
(3) C. Mannich, *Arch. Pharm.*, **267**, 699 (1929).
(4) C. Mannich, German Patent 464482 (Aug 18, 1928).

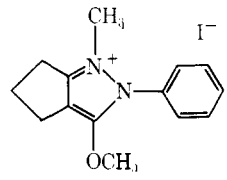
As reported by Mannich, reaction of ethyl cyclopentanone-2-carboxylate with phenylhydrazine and *p*-bromophenylhydrazine, and subsequent cyclization of the crude phenylhydrazones at high temperature under strongly basic conditions, provided crystalline products whose empirical formulas were consistent with the proposed structures **4** and **5**.[3,4] The solid state ir spectra, however, fail to display CO bands below 6.15 μ, and strongly H bonded tautomeric cyclopentapyrazolol structures **10** and **11** are therefore preferred to **4** and **5**. In dilute $CHCl_3$ solution, CO absorption at 5.87 μ is exhibited by **10** and **11**, which must therefore exist as the unconjugated keto tautomers **15** and **16**. The conjugated forms **4** and **5** are excluded by the absence of absorption at 6.0 μ (see below). A similar reaction with *p*-fluorophenylhydrazine gave the fluoro analog, which exists in the solid state as **12** and in solution as **17**.[5]

Alkylation of **10** with MeI or allyl chloride in the presence of NaOMe, or of **11** with benzyl bromide and base, gave, in each case, mixtures of two isomeric products with CO bands at 5.82–5.85 μ and 5.98–6.04 μ. Alkylation of the cyclopentapyrazolol **10** with methyl *p*-toluenesulfonate gave a third isomer **13** which failed to display CO absorption. Under basic conditions,



22

23



24

tridentate anions **22** may be formed by the cyclopentapyrazolols **10** and **11**, and alkylation of these anions can yield N, C, or O substituted products. In this series, the C-alkyl structures **18**, **19**, and **20** correspond to the products with 5.84 μ bands, the N-alkyl compounds **6**, **7**, and **8** to those with 6.0 μ bands, and the O-alkyl derivative **13** to that with no CO absorption.

In the case of the C substituted products, placement of the remaining double bond between N and bridgehead C was indicated by their nmr spectra which fail to show the vinyl proton resonances required for other alternatives such as **23**. Reaction of **12** with benzyl bromide gave the three possible isomeric products **9** (6.00 μ), **21** (5.86 μ), and **14** (no CO absorption below 6.20 μ).

In the alkylation of **10** with MeI, the possibility that the O-Me compound **13** might serve as an intermediate in the formation of **6** and **18** was examined in greater detail. First it was shown that treatment of **13** with excess NaI or NaOMe effected no change. Mild reaction of **13** with MeI gave a quaternary salt **24**, which decomposed upon boiling in MeOH to the N-Me compound **6**; no **18** was formed. Compound **13**, therefore, cannot be a precursor to **18** in the alkylation of **10**. Since the reaction of **10** with MeI leads to a mixture of **6** and **18** in which **18** predominates, the major course of reaction cannot involve **13**. The intermediacy of **13** in that portion of the reaction which produces **6**, however, has not been excluded.

Oral administration of the cyclopentapyrazoles at 250 mg/kg failed to inhibit significantly the carrageenin induced rat paw edema[6] when assayed by the method of Winter, *et al.*[7]

Experimental Section[8]

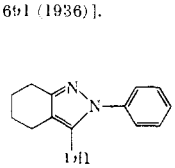
2,4,5,6-Tetrahydro-2-phenylcyclopentapyrazol-3-ol (10).—A modification of the procedure of Mannich[3] was employed. A solution of 7.8 g (0.05 mol) of ethyl cyclopentanone-2-carboxylate, 5.4 g (0.05 mol) of phenylhydrazine, and 100 ml of EtOH was heated under reflux for 24 hr, and then concentrated to a yellow oil. The oil was dissolved in 100 ml of MeOH, 5.7 g (0.1 mol) of NaOMe was added, and the solvent was distilled until a solid remained. The solid was heated at 160° under N_2 for 2 hr, and then dissolved in H_2O. The solution was treated with charcoal and acidified with HCl; tan crystals, 8.0 g (80%), mp 185–187°, precipitated. Three recrystallizations (EtOH) gave colorless crystals, mp 190–191° (lit.[3] mp 183–184°). *Anal.* ($C_{12}H_{12}N_2O$) C, H, N; ir, no CO band below 6.15 μ.

2-(*p*-Bromophenyl)-2,4,5,6-tetrahydrocyclopentapyrazol-3-ol (11).—The procedure used for the preparation of **10** was employed. From 1.56 g (0.01 mol) of ethyl cyclopentanone-2-carboxylate and *p*-bromophenylhydrazine was obtained 1.9 g (40%) of light tan crystals, mp 202–204° (from MeOH; lit.[3] mp 200°). *Anal.* ($C_{12}H_{11}BrN_2O$) C, H, Br, N; ir, no CO band below 6.15 μ.

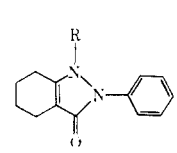
2-(*p*-Fluorophenyl)-2,4,5,6-tetrahydrocyclopentapyrazol-3-ol (12).—The procedure used for the preparation of **10** was employed. From 15.6 g (0.1 mol) of ethyl cyclopentanone-2-carboxylate and *p*-fluorophenylhydrazine was obtained 10.7 g (49%) of tan crystals, mp 186–187° (from EtOH). *Anal.* ($C_{12}H_{11}FN_2O$) C, H, F, N; ir, no CO band below 6.15 μ.

Alkylation of 2,4,5,6-Tetrahydro-2-phenylcyclopentapyrazol-3-ol (10). A. With MeI.—A solution of 20 g (0.1 mol) of **10**, 142 g (1 mol) of MeI, 5.6 g (0.1 mol) of NaOMe, and 350 ml of MeOH was heated under reflux for 15 hr. The solvent was distilled, and the residue was taken up in H_2O. The mixture was extracted with Et_2O, and the Et_2O solution was dried ($MgSO_4$) and concentrated to 12 g of brown oil which was chromatographed on silica gel.

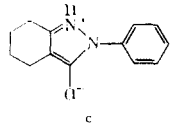
(5) Analogously, the condensation of ethyl cyclohexanone-2-carboxylate with phenylhydrazine [H. Ruhkopf, *Ber.*, **70**, 939 (1937)] gave a compound which fails, in the solid state, to exhibit a band in the CO region below 6.10 μ, and must therefore be 4,5,6,7-tetrahydro-2-phenyl-2*H*-indazol-3-ol (**a**) rather than the keto tautomer **b**. G. deStevens, A. Halamandaris, P. Wenk, and L. Dorfman, *J. Amer. Chem. Soc.*, **81**, 6292 (1959), proposed the dipolar structure **c** for this compound. In $CHCl_3$, **a** exhibits a band at 5.86 μ, and must therefore exist as the keto tautomer **d**. Alkylation of **a** with MeI gives **e** (CO at 6.03 μ) as reported [J. Lee and W. G. Christiansen, *J. Amer. Pharm. Assoc.*, **25**, 691 (1936)].



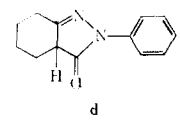
a



b, R = H
e, R = CH$_3$



c



d

(6) Animal testing was carried out by Dr. A. E. Sloboda of the Experimental Therapeutics Research Section of these laboratories.

(7) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).

(8) Melting points were determined in a Hershberg apparatus and are uncorrected. Analytical results, determined by Mr. L. M. Beaucage and staff, obtained for elements indicated by symbols were within ±0.4% of the theoretical values. Ir (KBr disks, unless otherwise noted) and nmr (Varian Associates A-60 Spectrometer, TMS internal standard) spectra were determined by Mr. W. Fulmor and staff.

Elution of the column with Et_2O gave 6.1 g (28%) of orange crystals, mp 64–66° Recrystallization (cyclohexane) gave light tan crystals of 3a,4,5,6-tetrahydro-3a-methyl-2-phenylcylcopentapyrazol-3(2*H*)-one (**18**), mp 68–69°. *Anal.* ($C_{13}H_{14}N_2O$) C, H, N; ir, 5.85 μ (C=O); nmr (DMSO-d_6) τ 8.62 (s, 3, CCH_3), 8.44–7.16 (m, 6, CH_2), and 3.00–205 (5, phenyl).

Elution of the column with Et_2O–MeOH (4:1) gave 2.8 g (13%) of tan crystals, mp 123–127°. Recrystallization (EtOH) gave colorless crystals of 1,4,5,6-tetrahydro-1-methyl-2-phenylcyclopentapyrazol-3(2*H*)-one (**6**), mp 127–128° (lit.[3] mp 128°). *Anal.* ($C_{13}H_{14}N_2O$) C, H, N; ir, 6.01 μ (C=O).

B. With Methyl *p*-Toluenesulfonate.—A solution of 2.0 g (0.01 mol) of **10**, 20 ml of DMF, 0.44 g (0.01 mol) of 55% NaH dispersion, and 1.86 g (0.01 mol) of methyl *p*-toluenesulfonate was heated at 120° with stirring for 2 hr. The solution was cooled, diluted with 100 ml of H_2O, and extracted with Et_2O. The Et_2O solution was dried ($MgSO_4$) and concentrated to a brown oil which was chromatographed on silica gel. Eluted with cyclohexane–Et_2O (9:1) was 0.9 g (42%) of an oil. Short-path distillation at 115° (0.2 mm) gave 2,4,5,6-tetrahydro-3-methoxy-2-phenylcyclopentapyrazole (**13**) as a pale yellow. *Anal.* ($C_{13}H_{14}N_2O$) C, H, N; nmr (DMSO-d_6) τ6.04 (s, 3, OCH_3); ir (liq film), no CO band below 6.15 μ.

C. With Allyl Chloride.—A solution of 4.0 g (0.02 mol) of **10**, 1.53 g (0.02 mol) of allyl chloride, 1.08 g (0.02 mol) of NaOMe, and 50 ml of EtOH was heated under reflux with stirring for 18 hr, and then concentrated to dryness. The residue was taken up in H_2O, and the mixture was extracted with Et_2O. The Et_2O solution was dried ($MgSO_4$) and concentrated to a yellow oil which was chromatographed on alumina.

Elution of the column with C_6H_6 gave 1.5 g (31%) of a yellow oil. Evaporative distillation at 110° (0.05 mm) gave 3a-allyl-3a,4,5,6-tetrahydro-2-phenylcylopentapyrazol-3(2*H*)-one (**19**) as a colorless oil. *Anal.* ($C_{15}H_{16}N_2O$) C, H, N; ir (liq film) 5.82 μ (C=O).

Elution of the column with Et_2O–MeOH (1:1) gave 1.0 g (21%) of brown crystals, mp 92–93°. Recrystallization (cyclohexane) gave tan crystals of 1-allyl-1,4,5,6-tetrahydro-2-phenylcyclopentapyrazol-3(2*H*)-one (**7**), mp 93–94°. *Anal.* ($C_{15}H_{16}N_2O$) C, H, N; ir, 6.04 μ (C=O).

Benzylation of 2-(*p*-Bromophenyl)-2,4,5,6-tetrahydrocyclopentapyrazol-3-ol (11).—A solution of 2.8 g (0.01 mol) of **11**, 1.7 g (0.01 mol) of $PhCH_2Br$, 0.54 g (0.01 mol) of NaOMe, and 25 ml of EtOH was heated under reflux for 15 hr, and then concentrated to dryness. The residue was taken up in H_2O, and the mixture was extracted with Et_2O. The Et_2O solution was dried ($MgSO_4$) and concentrated to a yellow oil which was chromatographed on alumina.

Elution of the column with C_6H_6 gave 1.2 g (32%) of colorless crystals, mp 85–95°. Recrystallization (hexane) provided colorless crystals of 3a-benzyl-2-(*p*-bromophenyl)-3a,4,5,6-tetrahydrocyclopentapyrazol-3(2*H*)-one (**20**), mp 110–111°. *Anal.* ($C_{19}H_{17}BrN_2O$) C, H, Br, N; ir, 5.83 μ (C=O).

Elution of the column with MeOH gave 1.0 g (27%) of tan crystals, mp 113–115°. Recrystallization (cyclohexane) gave colorless needles of 1-benzyl-2-(*p*-bromophenyl)-1,4,5,6-tetrahydrocyclopentapyrazol-3(2*H*)-one (**8**), mp 117–118°. *Anal.* ($C_{19}H_{17}BrN_2O$) C, H, Br, N; ir, 5.98 μ (C=O).

Benzylation of 2-(*p*-Fluorophenyl)-2,4,5,6-tetrahydrocyclopentapyrazol-3-ol (12).—The procedure used for the benzylation of **11** was employed. From 2.2 g (0.01 mol) of **12**, 1.7 g (0.01 mol) of benzyl bromide, 0.54 g (0.01 mol) of NaOMe, and 25 ml of EtOH was obtained an oil which was chromatographed on alumina.

Elution of the column with hexane–Et_2O (3:1) gave 0.09 g (3%) of colorless crystals, mp 75–76°. Recrystallization (hexane) provided colorless crystals of 3-benzyloxy-2-(*p*-fluorophenyl)-2,4,5,6-tetrahydrocyclopentapyrazole (**14**), mp 77°. *Anal.* ($C_{19}H_{17}FN_2O$) C, H, F, N; ir, no CO band below 6.20 μ.

Elution of the column with hexane–Et_2O (1:1) provided 0.51 g (17%) of colorless crystals, mp 90–94°. Recrystallization (hexane) gave colorless crystals of 3a-benzyl-2-(*p*-fluorophenyl)-3a,4,5,6-tetrahydrocyclopentapyrazol-3(2*H*)-one (**21**), mp 98–99°. *Anal.* ($C_{19}H_{17}FN_2O$) C, H, F, N; ir, 5.86 μ (C=O).

Elution of the column with Et_2O–MeOH 149:1) provided 0.83 g (27%) of yellow crystals, mp 90–92°. Recrystallization (cyclohexane) gave colorless crystals of 1-benzyl-2-(*p*-fluorophenyl)-1,4,5,6-tetrahydrocyclopentapyrazol-3(2*H*)-one (**9**), mp 112°. *Anal.* ($C_{19}H_{17}FN_2O$) C, H, F, N; ir, 6.00 μ.

2,4,5,6-Tetrahydro-3-methoxy-1-methyl-2-phenylcyclopentapyrazolium Iodide (24).—A solution of 4.0 g (0.02 mol) of **13** and 6 ml of MeI was allowed to stand at room temperature for 15 hr. The solution was diluted with 200 of Et_2O and filtered to give 1.45 g (20%) of crystals, mp 108–110°. Recrystallization (MeOH–Et_2O) gave colorless crystals, mp 109–110° dec. *Anal.* ($C_{14}H_{17}IN_2O$) C, H, I, N.

Pyrolysis of 2,4,5,6-Tetrahydro-3-methoxy-1-methyl-2-phenylcyclopentapyrazolium Iodide (24).—A solution of 170 mg of **24** and 4 ml of MeOH was heated under reflux for 24 hr. Evaporation of the solvent left 87 mg of **6**, mp 123–125°. Ir and tlc examination of the product failed to indicate the presence of **18**.

Puromycin Analogs. Aminoacyl Derivatives of 9-(3′-Amino-3′-deoxy-β-D-arabinofuranosyl)adenine[1]

LINDA V. FISHER, WILLIAM W. LEE, AND LEON GOODMAN

Life Sciences Division, Stanford Research Institute, Menlo Park, California 94025

Received January 5, 1970

Puromycin (**1**), an antibiotic with antitumor activity,[2] has been used as an important biochemical tool in the study of protein synthesis. Many structural analogs of **1** have been prepared in an effort to exploit the biological properties of the antibiotic. These include analogs where other aminoacyl groups replace the *p*-methoxyphenylalanine moiety of **1**,[3-5] compounds where the *p*-MeO of **1** is replaced by other substituents,[6] the derivative where the 3′-aminoribofuranose of **1** is replaced by 3′-aminoglucopyranose,[7] and the 2′-*O*-Ac derivative[8] of **1**. In an extension of these investigations, we have prepared a number of aminoacyl derivatives of 9-(3-amino-3-deoxy-β-D-arabinonofuranosyl)adenine (**3**),[9] a 2′ epimer of **2**. See Table I.

The aminoacyl derivatives **4** of **3** were prepared by standard methods of peptide synthesis, the method of choice for each compound being dependent on the relative ease of formation and facility of purification from by-products. The choice of solvents was severely restricted by the low solubility of **3**, with DMF solvent mixtures generally being the most useful. As in the work of Baker, *et al.*,[3] unblocked **3** could be used in these coupling reactions. In contrast, blocking of the OH groups was essential to successful aminoacylation of 1-(3-amino-3-deoxy-β-D-glucopyranosyl)uracil.[10]

The two coupling procedures used were A, the mixed anhydride method using isobutyl chloroformate[11]

(1) This work was performed under the auspices of Chemotherapy, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. PH-43-64-500. The opinions expressed here are those of the authors and not necessarily those of Chemotherapy.

(2) B. L. Hutchings, *Chem. Biol. Purines, CIBA Found. Symp.*, **1956**, 777 (1957).

(3) B. R. Baker, J. P. Joseph, and J. H. Williams, *J. Amer. Chem. Soc.*, **77**, 1 (1955).

(4) R. H. Symons, R. J. Harris, L. P. Clarke, J. F. Wheldrake, and W. H. Elliott, *Biochem. Biophys. Acta*, **179**, 248 (1969).

(5) A. O. Hawtrey, S. I. Biedron, and S. H. Eggers, *Tetrahedron Lett.*, 1693 (1967).

(6) A. M. Small, H. M. Kissman, J. P. Joseph, and M. J. Weiss, *J. Med. Pharm. Chem.*, **2**, 375 (1960).

(7) F. W. Lichtenthaler and H. P. Albrecht, *Angew. Chem.*, **80**, 440 (1968).

(8) H. Neumann, V. E. Shashoua, J. F. Sheehan, and A. Rich, *Proc. Nat. Acad. Sci. U. S.*, **61**, 1207 (1968).

(9) A. P. Martinez, D. F. Calkins, E. J. Reist, W. W. Lee, and L. Goodman, *J. Heterocycl. Chem.*, **7**, in press.

(10) H. A. Friedman, K. A. Watanabe, and J. J. Fox, *J. Org. Chem.*, **32**, 3775 (1967).

(11) G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *J. Amer. Chem. Soc.*, **89**, 5012 (1967).