the nmr spectrum taken. The nmr spectrum (reference, water taken as 5 ppm from TMS) showed δ 2.38 (s, 3 H, CH_3), 5.55 (s, 1 H, C-5 vinyl), 6.34 (s, 2 H, C-2 and C-3 vinyls). The above solution was acidified with concentrated HCl and the nmr spectrum of the resulting solution was identical with that of maleylacetone in water. A similar experiment with butenolide **7** was carried out in order to show that it was also hydrolyzed to form maleylacetone.

Monosodium Salt of Maleylacetone (10).—To 0.038 g (0.00024 mol) of maleylacetone in 0.5 ml of D_2O was added 0.054 g (0.00064 mol) of $NaHCO_3$. After CO_2 evolution had ceased the nmr spectrum was taken and showed (reference, HOD taken as 5 ppm from TMS) δ 2.48 (s, 3 H, CH_3), 2.57 (s, 3 H, CH_3), 6.33 and 6.58 (q, 2 H, J = 12.5 Hz, C-2 and C-3 vinyls), 6.5 and 6.76 (q, 2 H, J = 12.5 Hz, C-2 and C-3 vinyls). The pD of this solution was 8.34. The solution from the nmr tube was diluted to 1 l., the pH adjusted to 7.99 with $NaHCO_3$ and HCl, and the uv spectrum run (λ_{max} 312 nm).

Titration of Maleylacetone.—Maleylacetone (0.16176 g, 0.001036 mol) in 20 ml of water was titrated with 0.1219 N NaOH using a glass electrode. The pH was measured after each 0.2 ml addition of base. The first neutralization equivalent required 8.40 ml of NaOH (0.001024 mol). The pK_a's were determined from the pH at addition of half an equivalent of base, the first two ionization constants being 4.2 and 9.4.

Dissociation Constants.—Nine acetic acid–sodium acetate buffer solutions containing lithium perchlorate were prepared to give solutions in which the sum of the acetic acid and sodium acetate concentrations was 0.01 M and the ionic strength was 0.1 M when diluted with a stock solution of maleylacetone. An Orion Model 801 digital pH meter standardized at pH 4 and 7 was used to determined the pH of each solution. Uv spectra were recorded on a Cary 14 spectrophotometer at 25° for each buffer solution containing 2.24×10^{-4} M maleylacetone. The reference cell contains buffer. Complete ionization was assumed at pH 6.43 (*i.e.*, $[anion]_{6.43} = [acid]_0$). Ratios of $[anion]_{pH}/[acid]_0$ were determined at 312 nm and taken as $O.D._{pH}/O.D._{6.43}$. A plot of these ratios gave $pK_a = 3.95$ when $[anion]_{pH}/[acid]_0 = 0.5$.

Registry No.—**4a**, 25517-95-7; **4b**, 25568-65-4; **7**, 25527-98-4; **8**, 25527-99-5; **9**, *cis,cis* (disodium salt), 25568-66-5; **9**, *cis,trans* (disodium salt), 25528-00-1; **10a** (monosodium salt), 25528-01-2; **10b** (monosodium salt), 25528-02-3; **10c** (monosodium salt), 25528-03-4.

Acknowledgment.—We wish to thank Dr. David Christman for recording the mass spectra.

The Prévost Reaction with 5-Substituted 5-Allylbarbituric Acids

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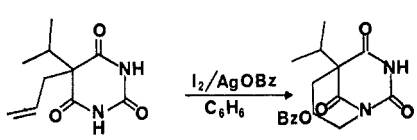
The Prévost reaction utilizing 5-substituted 5-allylbarbituric acids produced furopyrimidines by intramolecular O-alkylation. These compounds could be hydrolyzed readily in the presence of acid or converted to esters by treatment with the corresponding alcohol in the presence of acid.

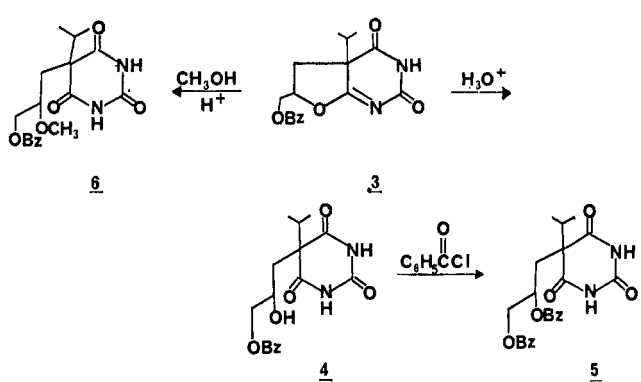
Meltzer and Lewis[2] reported the conversion of 5-isopropyl-5-allylbarbituric acid (**1**) to a bicyclic product **2** by the use of the "dry" Prévost reaction.[3]

In attempting to duplicate the work of Meltzer and Lewis in these laboratories, it was found that the product which they obtained had been assigned an erroneous structure and was not **2**, as they depicted.



1 **2**

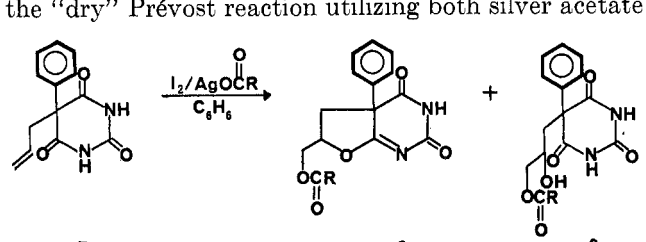
On examination, the cyclized product proved to be an O-alkylated structure, 4(a)-isopropyl-6-benzoyloxymethyl-5H,6H-furo[2,3-*d*]-$\Delta^{1,7a}$-2,4(3H)-pyrimidinedione (**3**). The infrared spectrum of **3** showed intense absorption at 1625 cm^{-1} (>C=N– stretching frequency).[4] The mass spectrum of **3** gave a molecular ion at *m/e* 330, consistent with its ascribed formula. The enol–ether, **3**, underwent facile conversion to 5-isopropyl-5-(2-hydroxy-3-benzoyloxypropyl) barbituric acid (**4**) during acid hydrolysis. The dibenzoate, **5**, was prepared by the treatment of **4** with benzoyl chloride



6 **3** **4** **5**

in pyridine. The alcohol methine proton in **4** was shifted from nmr δ 4.50 (3-proton multiplet) to 5.60 in the acylated product **5**. Compound **3** yielded a methyl ether, **6**, on treatment with methanol in the presence of acid (ether methine proton shifted 1.0 ppm downfield relative to the alcohol, **4**).

5-Phenyl-5-allylbarbituric acid (**7**) was subjected to the "dry" Prévost reaction utilizing both silver acetate



7 **8** **9**

a) R = CH_3

b) R = C_6H_5

(1) Taken in part from the dissertation presented by R. A. Robinson, July 1969, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

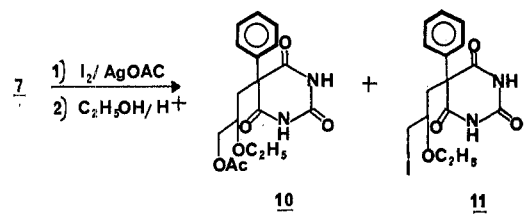
(2) R. I. Meltzer and A. D. Lewis, *J. Org. Chem.*, **21**, 256 (1956).

(3) C. V. Wilson, *Org. React.*, **9**, 360 (1957).

(4) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1962, p 39.

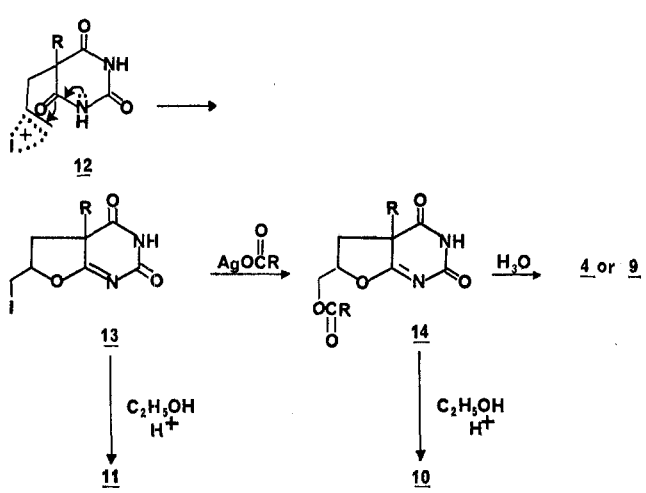
and silver benzoate. The corresponding furopyrimidines, **8a** and **8b**, and the corresponding hydrolysis products, the hydroxy esters, **9a** and **9b**, were isolated from the reactions. Both **8a** and **8b** were readily hydrolyzed to the hydroxy esters **9a** and **9b** in the presence of acid. The formation of **9a** and **9b** in the Prévost procedure can be attributed to partial hydrolysis of the furopyrimidines during chromatographic purification on silica gel.

Acid-catalyzed ethanolysis of a mixture resulting from the treatment of **7** with iodine and silver acetate afforded two compounds, 5-phenyl-5-(2-ethoxy-3-acetoxypropyl)barbituric acid (**10**) and an iodo ether (**11**).



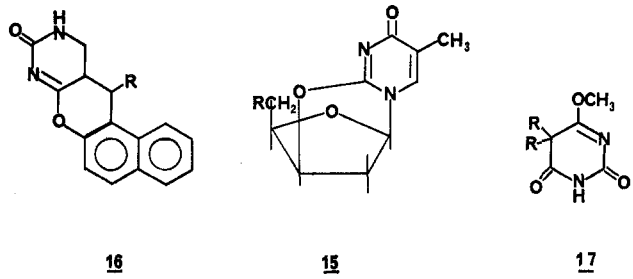
Nmr decoupling studies established the chemical shifts of the ether methylene and methine protons (δ 4.35–4.80) of **10**. The iodo ether was assigned structure **11** based on elemental analysis and spectral similarities (nmr) to **10**.

A plausible mechanism for the formation of the observed products involves the initial formation of an iodonium intermediate **12**, followed by neighboring



group participation of the imide electrons to form an intermediate iodine-containing furopyrimidine, **13**. The esterified product **14** would then be obtained by displacement of the primary iodo group by acetate anion. Acid-catalyzed ethanolysis of **13** and **14** would lead to the observed products, **10** and **11**.

The use of silver salts, particularly in solvents of low polarity, has been shown to favor alkylation in many ambident heterocyclic systems.[5-7] An anhydrothymidine analog, **15**, has been isolated *via* intramolecular alkylation with silver or alkali salts.[8,9] Other cyclic,



16,[10] and noncyclic, **17**,[11] enol ethers similar to the system reported in this paper have also been reported.

Experimental Section[12]

4(a)-Isopropyl-6-benzoyloxymethyl-5H,6H-furo[2,3-*d*]-$\Delta^{1,7a}$ 2,4(3H)-pyrimidinedione (3).—Silver benzoate (11.50 g, 0.05 mol) was suspended in 200 ml of C_6H_6. Iodine (6.35 g, 0.025 mol) (in 100 ml of C_6H_6) was added and the suspension stirred at room temperature for 15 min. To the suspension was added 5-isopropyl-5-allylbarbituric acid (**1**) (5.25 g, 0.025 mol) (suspended in 200 ml of hot C_6H_6), and the reaction was stirred and refluxed for 2 hr, cooled to room temperature, and filtered *in vacuo*. The benzene was removed and the residue chromatographed on silica gel. The column was eluted with $CHCl_3$ to afford a mixture of benzoic acid and **1** followed by 2.28 g (28%) of **3**: mp 170–172° [Me_2CO–petroleum ether (60–68°)] (lit.[1] mp 172–173.5°); ir (KBr) 3250, 1720, 1690, 1625 cm^{-1}; nmr (DMSO-d_6) 1.00 (6 H, triplet, CH_3), 2.00–2.41 (2 H, multiplet, CH_2), 2.50 (DMSO-d_5 and isopropyl methine), 4.46–4.70 (2 H, multiplet, CH_2OBz), 5.08–5.50 (1 H, multiplet, CH), 7.50–7.75 (3 H, aromatic), 7.91–8.10 (2 H, multiplet, *ortho*-aromatic), 10.96 (1 H, broad singlet, >NH).

Anal. Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.90; H, 5.60; N, 8.47.

5-Isopropyl-5-(2-hydroxy-3-benzoyloxypropyl)barbituric Acid (4).—To a solution of 0.100 g (0.303 mmol) of **3** in 5 ml of Me_2CO was added 4 drops of CF_3CO_2H and 2 ml of H_2O. The solution was warmed on a steam bath for 10 min and allowed to stand for 8 hr. The solvent was removed *in vacuo* and the H_2O azeotroped with several portions of C_6H_6. The residue was triturated with Et_2O and the solid material recrystallized from Et_2O–petroleum ether (60–68°) to give **4** (0.088 g, 84%): mp 178–181°; ir (KBr) 3450, 3220, 2910, 1740–1690; nmr (CF_3CO_2H) 0.96–1.33 (6 H, multiplet, CH_3), 1.96–3.00 (3 H, multiplet, CH_2 and isopropyl methine), 4.40–4.66 (3 H, multiplet, CH_2OBz and HCOH), 7.33–7.80 (3 H, multiplet, aromatic), 7.93–8.80 (2 H, multiplet, *ortho*-aromatic).

Anal. Calcd for $C_{17}H_{20}N_2O_6$: C, 58.61; H, 5.79; N, 8.04. Found: C, 58.58; H, 5.94; N, 7.98.

5-Isopropyl-5-(2,3-dibenzoyloxypropyl)barbituric Acid (5).—A solution of **4** (0.200 g, 0.575 mmol) in 15 ml of pyridine and BzCl (0.085 g, 0.575 mmol) was heated at 60° for 2 hr. The reaction mixture was cooled to room temperature, poured into an iced solution of dilute HCl, and extracted with Et_2O. The Et_2O extracts were washed with H_2O, dried ($MgSO_4$), and evaporated *in vacuo* to give an oil which was chromatographed on Silicar CC-4 (Mallinckrodt). The column was eluted with 60%

(5) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Amer. Chem. Soc.*, **77**, 6269 (1955).

(6) G. C. Hopkins, J. P. Jonak, H. Minnemeyer, and H. Tieckelmann, *J. Org. Chem.*, **32**, 4040 (1967).

(7) G. C. Hopkins, J. P. Jonak, H. Tieckelmann, and H. J. Minnemeyer, *ibid.*, **31**, 3969 (1966).

(8) J. J. Fox and N. C. Miller, *J. Org. Chem.*, **28**, 936 (1963).

(9) J. P. Horowitz, J. Chua, J. A. Urbanski, and M. Noel, *ibid.*, **28**, 942 (1963).

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(11) J. A. Snyder and K. P. Link, *J. Amer. Chem. Soc.*, **75**, 1881 (1953).

(12) All melting points were taken on the Thomas–Hoover capillary melting point apparatus and are corrected. Analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., by Weiler and Strauss Microanalytical Laboratory, Oxford, England, and on an F & M Model 185, University of Kansas. Infrared spectra were recorded on Beckman IR-8 and IR-10 spectrophotometers. Nuclear magnetic resonance spectra were recorded on A-60, A-60A, and HA-100 analytical spectrophotometers with tetramethylsilane as a standard. Nuclear magnetic resonance data are reported as δ values (parts per million). Molecular weights were determined on the Finnigan 1015 mass spectrometer.

Et_2O–40% Skellysolve B to yield **5** (0.036 g, 14%): mp 170–172° (Me_2CO–Skellysolve B); nmr (CF_3CO_2H) 9.03–1.13 (6 H, multiplet, CH_3), 2.06–3.00 (3 H, multiplet, CH_2 and isopropyl methine), 4.40–4.63 (2 H, multiplet, CH_2OBz), 5.26–5.82 (1 H, multiplet, HCOBz), 7.43–7.75 (6 H, multiplet, aromatic), 7.83–8.16 (4 H, multiplet, *ortho*-aromatic).

Anal. Calcd for $C_{24}H_{24}N_2O_7$: C, 63.71; H, 5.35; N, 6.19. Found: C, 63.98; H, 5.19; N, 6.22.

5-Isopropyl-5-(2-methoxy-3-benzoyloxypropyl)barbituric Acid (6).—A solution of 0.200 g (0.606 mmol) of **3** in 10 ml of absolute MeOH was treated in the manner previously described for **29** to give 0.160 g (83%) of **6**: mp 178–180.5°. [Me_2CO–petroleum ether (60–68°)]; nmr (CF_3CO_2H) 1.00–1.43 (6 H, multiplet, CH_3) 2.16–3.26 (3 H, multiplet CH_2 and isopropyl methine), 4.16 (3 H, singlet, OCH_3), 4.40–4.83 (2 H, multiplet, CH_2OBz), 5.33–5.96 (1 H, multiplet, $CHOCH_3$), 7.33–7.86 (3 H, multiplet aromatic) 7.90–8.33 (2 H, multiplet, *ortho*-aromatic).

Anal. Calcd for $C_{18}H_{22}N_2O_6$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.89; H, 5.84; N, 7.71.

4(a)-Phenyl-6-benzoyloxymethyl-5H,6H-furo[2,3-*d*]-$\Delta^{1,7a}$-2,4(3H)-pyrimidinedione (8b).—A suspension of AgOBz (4.70 g, 20.5 mmol), iodine (2.60 g, 10.2 mmol) and 5-phenyl-5-allylbarbituric acid (**7**) (2.50 g, 10.2 mmol) in 600 ml of anhydrous C_6H_6 was prepared according to the procedure outlined for **3**. The reaction was refluxed with stirring for 90 min and cooled to room temperature. Filtration and removal of the C_6H_6 *in vacuo* afforded a residue which was taken up in $CHCl_3$ and passed through silica gel (90% $CHCl_3$–10% 2-propanol). An oil was obtained which was chromatographed on Silicar CC-4 (Mallinckrodt). Elution with 90% petroleum ether (60–68°)–10% Et_2O yielded a mixture of **7** and benzoic acid. Increasing the Et_2O concentration to 40% gave **7** followed by 0.687 g 5-phenyl-5-(2-hydroxy-3-benzoyloxypropyl)barbituric acid (**9b**): mp 199–201° (Me_2CO–Skellysolve B); ir (KBr) 3450, 3210, 1750–1700; nmr (CF_3CO_2H) 3.00–3.60 (2 H, multiplet, CH_2), 4.50–4.80 (3 H, multiplet, CH_2–OBz, CHOH), 7.35–7.80 (8 H, multiplet, aromatic), 8.05–8.30 (2 H, multiplet, *ortho*-aromatic).

Anal. Calcd for $C_{20}H_{18}N_2O_6$: C, 62.82; H, 4.74; N, 7.32. Found: C, 6.282; H, 4.66; N, 7.25.

Further elution with 100% Et_2O gave 0.653 g (18%) of the furopyrimidine (**8b**), recrystallized from Me_2CO–petroleum ether (60–68°): mp 185–186.5°; ir (KBr) 3185, 1720, 1630; nmr (DMSO-d_6) 2.80–3.10 (2 H, multiplet, CH_2), 4.50–5.20 (3 H, CH_2OBz, –CHO'), 7.20–7.75 (8 H, multiplet, aromatic), 7.95–8.20 (2 H, multiplet, *ortho*-aromatic), 11.08 (1 H, broad singlet, >NH).

Anal. Calcd for $C_{20}H_{16}N_2O_5$: C, 65.93; H, 4.43; N, 7.69. Found: C, 66.03; H, 4.54; N, 7.61.

Treatment of **8b** with CF_3CO_2H, H_2O, and Me_2CO, as described for **4**, gave **9b** [ir and tlc (Silicar CC-4) (40% Et_2O–petroleum ether 60–68°) were identical with **9b** isolated from the reaction].

4(a)-Phenyl-6-acetoxymethyl-5H,6H-furo[2,3-*d*]-$\Delta^{1,7a}$-2,4(3H)-pyrimidinedione (8a).—A suspension of AgOAc (4.08 g, 24.6 mmol), I_2 (3.12 g, 12.3 mmol), and **32** (3.00 g, 12.3 mmol) in 600 ml of dry C_6H_6 was prepared according to the method outlined for **8b**. The reaction was stirred and refluxed for 90 min, cooled and purified as described for the isolation of **8b**. Elution with 50% Et_2O–50% petroleum ether (60–68°) gave a mixture of **7** and a halogen containing compound. The column was eluted with 100% Et_2O to afford 0.245 g of the hydroxy acetate (**9a**): mp 200–202° [Me_2CO–petroleum ether (60–68°)]; ir (KBr) 3450, 3210, 1750–1700; nmr (CF_3CO_2H) 2.25 (3 H, singlet, CH_3), 2.70–3.25 (2 H, multiplet, CH_2), 4.20–4.68 (3 H, multiplet, CH_2OAc, CHOH), 7.45 (5 H, singlet, aromatic).

Anal. Calcd for $C_{15}H_{16}N_2O_6$: C, 56.24; H, 5.04; N, 8.75. Found: C, 56.45; H, 5.10; N, 8.74.

Further elution with 100% Et_2O gave 0.368 g (10%) of the furopyrimidine (**8a**): mp 160–164° [Me_2CO–petroleum ether (60–68°)]; ir (KBr) 3200, 1750, 1700, 1650; nmr (DMSO-d_6) 2.05 (3 H, singlet, CH_3), 2.65–2.90 (2 H, multiplet, CH_2), 4.15–4.81 (3 H, CH_2OAc, CHO–), 7.30–7.55 (5 H, multiplet, aromatic), 11.03 (1 H, broad singlet, NH).

Anal. Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.40; H, 4.59; N, 9.07.

Compound **8a** was converted to **9a** by acid hydrolysis as described for **3** and **8b** (ir and tlc were superimposable with **9a** isolated from the reaction mixture).

5-Phenyl-5-(3-acetoxy-2-ethoxypropyl)barbituric Acid (10).—A suspension of silver acetate (6.80 g, 0.041 mol), iodine (5.17 g, 0.020 mol), and **7** (5.00 g, 0.020 mol) in 500 ml of dry C_6H_6 was prepared in the manner described for the synthesis of **3**. The reaction was stirred and refluxed for 2 hr, cooled to room temperature, and filtered *in vacuo*. After removal of solvent the residue was taken up in 600 ml of abs EtOH and filtered. A few drops of concentrated HCl were added which resulted in the formation of a precipitate. The mixture was filtered and the EtOH removed *in vacuo* (80°). During evaporation of the solvent, the reaction turned black. The residue was taken up in $CHCl_3$ and chromatographed on silica gel. The column was eluted with 85% $CHCl_3$–15% EtAc to yield 0.940 g of a yellow oil which was taken up in Et_2O. A crystalline solid, 0.690 g, mp 202–205° [Et_2O–petroleum ether (60–68°)] (positive Beilstein), was assigned structure **11**: nmr (CF_3CO_2H) 1.50 (3 H, triplet), 2.80–3.80 (3 H, multiplet), 4.35–4.80 (3 H, multiplet), 7.50 (4 H, singlet, aromatic).

Anal. Calcd for $C_{15}H_{17}N_2O_4I$: C, 43.28; H, 4.12; N, 6.73. Found: C, 43.48; H, 4.09; N, 6.65.

Further elution gave 1.29 g of an oil, resistant to further purification attempts, followed by 0.770 g of **10**, a white solid: mp 234–236° (EtOH); nmr (DMSO-d_6) 1.00 (3 H, triplet, CH_3), 2.00 (3 H, singlet, CH_3), 2.55–3.10 (2 H, multiplet), 3.25–4.45 (5 H, multiplet), 7.30 (5 H, singlet, aromatic).

Anal. Calcd for $C_{17}H_{20}N_2O_6$: C, 58.61; H, 5.79; N, 8.04. Found: C, 58.42; H, 5.45; N, 8.03.

Registry No.—**3,** 25568-67-6; **4,** 25517-96-8; **5,** 25517-97-9; **6,** 25517-98-0; **8a,** 25517-99-1; **8b,** 25518-00-7; **9a,** 25518-01-8; **9b,** 25518-02-9; **10,** 25518-03-0; **11,** 25518-04-1.

Acknowledgment.—The authors gratefully acknowledge support of this project by the National Institutes of Health Grants GM-9254.