The Synthesis of Pyrano- and Furanopyrimidines from 3-Halopropyl- and 2-Halopropylbarbituric Acids

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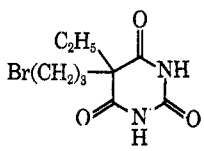
In attempts to obtain intramolecular *N*-alkylated bicyclo compounds from 5-haloalkylbarbituric acids, only *O*-alkylated compounds could be obtained. The resulting pyranopyrimidine, **7**, and furanopyrimidine, **9**, could be opened with alcohols to give the corresponding ether in the side chain of the barbituric acid. With water the side chain alcohol was obtained.

Baumler and coworkers reported the intramolecular nitrogen alkylation of 5-ethyl-5-(3-bromopropyl)barbituric acid (**1**) in the presence of pyridine.[2] A program designed to prepare bridged bicyclic barbituric acids, **2**, as potential anticonvulsants was initiated in these laboratories and it was thought that Baumler's method could be applied in this work.



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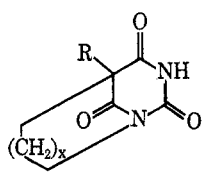
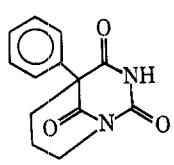


2

The initial compound desired for pharmacologic testing was 5-phenyl-2,4,9-triketo-1,3-diazobicyclo-[3.3.1]nonane (**3**). Light-catalyzed addition of hydrogen bromide to 5-phenyl-5-allybarbituric acid (**4**) produced the primary bromo derivative, **5a**, in quantitative yield.



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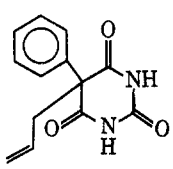

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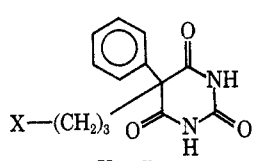
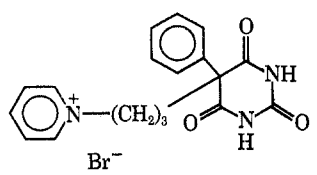


5a, X = Br
b, X = I
c, X = OC_2H_5
d, X = OCH_3
e, X = OH
f, X = OTs

Attempts to cyclize the tosylate derivative, **5f**, utilizing pyridine as the catalyst, resulted in the formation of a water soluble pyridinium salt, **6**. The iodo compound **5b** was treated in a similar manner and also failed to give the cyclized compound **3**. Various other bases also failed to give the desired bicyclic compound. When dry silver oxide in dimethylformamide (DMF) was used, 5-phenyl-5-(3-ethoxypropyl)barbituric acid (**5c**) was obtained on chromatographing on silica gel. This primary ether was also obtained by the ring opening of the intermediate pyranopyrimidine (**7**).



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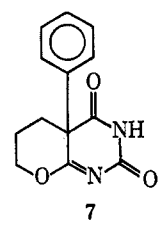

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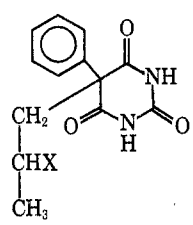
When **5a** was allowed to react with Triton B in refluxing methanol, the major product was the primary ether, 5-phenyl-5-(3-methoxypropyl)barbituric acid (**5d**). With **5b** a mixture of the primary alcohol, **5e**, and the ether, **5d**, was obtained.

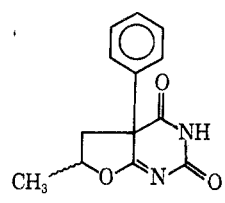
When **5b** was treated with silver benzoate in benzene, the product isolated from the reaction was 4(*a*)-phenyl-6*H*,7*H*-pyrano[2,3-*d*]-$\Delta^{1,8a}$-2,4-(3*H*)-pyrimidinedione (**7**). Hydrolysis of **7** with acid gave the primary alcohol **5e** and with anhydrous methanol the methyl ether **5d**.

The use of sodium hydride and DMF favored *N*-alkylation; however, the reactions were complicated by the formation of polymeric products resulting from intermolecular alkylation and no intramolecularly alkylated compound could be found.

A secondary bromobarbituric acid, 5-phenyl-5-(2-bromopropyl)barbituric acid (**8a**), was prepared by the addition of hydrogen bromide to alphenal (**4**). Treatment of **8a** with bases such as sodium ethoxide in ethanol and sodium hydride in DMF yielded the secondary alcohol, **8b**. When **8a** was refluxed in absolute ethanol



8a, X = Br
b, X = OH



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(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) J. Baumler, E. Sorkin, and H. Erlenmeyer, *Helv. Chim. Acta*, **34**, 459 (1951).

followed by treatment with water, only the secondary alcohol, **8b**, was obtained.

The formation of **8b** proceeds *via* the enol ether intermediate **9**. The *O*-alkylated barbituric acid, 4(a)-phenyl-6-methyl-5*H*,6*H*-furo[2,3-*d*]-$\Delta^{1,7a}$-2,4-(3*H*)pyrimidindione (**9**), was prepared and isolated by treating the bromo derivative **8a** with silver benzoate in refluxing benzene. Acid hydrolysis of **9** produced **8a**.

Baumler, *et al.*,[2] presented no spectral data in support of their proposed structure. In light of our inability to obtain compound **3** by their method, no attempt was made to ascertain whether they reported an incorrect structure or whether there is a steric effect involved in the cyclization of the 5-ethyl- and 5-phenylbarbituric acids investigated.

Experimental Section[3]

5-Phenyl-5-(3-bromopropyl)barbituric Acid (5a).—A suspension of 5-phenyl-5-allybarbituric acid (**4**) (50.0 g, 0.163 mol) in toluene (1000 ml) was irradiated (G. E. Sunlamp, 275 W, 110–125 V) for 90 min with stirring. HBr was added over a 45-min interval with irradiation, followed by additional stirring for 45 min. The reaction vessel was opened and the excess HBr was allowed to evaporate. The solids were removed by filtration and washed with toluene. Recrystallization [Me_2CO–petroleum ether (60–68°)] gave **5a** (51.1 g, 96%): mp 202–205°; ir (KBr) 3.12, 3.22, 5.70–5.85; nmr (CF_3CO_2H) 2.01 (2 H, multiplet, CH_2), 2.78 (2 H, multiplet, CH_2), 3.45 (2 H, triplet, CH_2Br), 7.45 (5 H, singlet, aromatic).

Anal. Calcd for $C_{13}H_{13}N_2O_3Br$: C, 48.02; H, 4.03; N, 8.62; Br, 24.50. Found: C, 48.25; H, 3.93; N, 8.49; Br, 25.60.

5-Phenyl-5-(3-iodopropyl)barbituric Acid (5b).—A solution of NaI (4.62 g, 30.8 mol) in Me_2CO (50 ml) was added with stirring to 5-phenyl-5-(3-bromopropyl)barbituric acid (**5a**) (10.0 g, 30.8 mmol) in Me_2CO (50 ml). The reaction was heated for 15 min and the NaBr was filtered. The Me_2CO was removed *in vacuo* and the product was washed repeatedly with H_2O and dried. Recrystallization [Me_2CO–petroleum ether (60–68°)] afforded **5b** (10.9 g, 95%): mp 224.5–226.5°; ir (KBr) 3.12, 3.22, 5.60–5.92; nmr (CF_3CO_2H) 1.83 (2 H, multiplet, CH_2), 2.50 (2 H, multiplet, CH_2), 3.05 (2 H, triplet, CH_2I), 7.30 (5 H, singlet, aromatic).

Anal. Calcd for $C_{13}H_{13}N_2O_3I$: C, 41.95; H, 3.52; N, 7.53. Found: C, 42.21; H, 3.70; N, 7.56.

5-Phenyl-5-(3-pyridiniumpropyl)barbituric Acid Bromide (6).—A solution of **5a** (4.00 g, 13 mmol) in C_5H_5N (100 ml) was placed in a glass, high-pressure reaction flask and allowed to stand for 7 days. No precipitate appeared. The flask was heated on a steam bath for 3 hr and allowed to cool to room temperature. The solid material was filtered, washed with $CHCl_3$ and Me_2CO, and dried. Recrystallization (absolute EtOH) afforded **6** (4.87 g, 95%): mp 261–263°; ir (KBr) 2.90–2.95, 5.70–5.95; nmr (D_2O) 1.83–2.75 (4 H, multiplet, CH_2), 4.70–4.95 (multiplet, H_2O and CH_2), 7.45 (5 H, singlet, aromatic), 8.00–8.36 (2 H, multiplet, meta-aromatic), 8.51–8.75 (1 H, multiplet, para-aromatic), 8.78–9.08 (2 H, multiplet, ortho-aromatic).

Anal. Calcd for $C_{13}H_{13}N_3O_3Br \cdot H_2O$: C, 51.19; H, 4.77; N, 9.95. Found: C, 51.05; H, 4.50; N, 9.97.

5-Phenyl-5-(3-methoxypropyl)barbituric Acid (5d).—Triton B (2.57 g, 15.4 mmol, 40% in MeOH) was added to a solution of 5-phenyl-5-(3-bromopropyl)barbituric acid (**5a**) (5.00 g, 15.4 mmol) in anhydrous MeOH (100 ml). The reaction mixture was refluxed for 12 hr, cooled, and neutralized with 10% HCl. The MeOH was evaporated and solids were washed with H_2O and dried. Recrystallization [Me_2CO–petroleum ether (60–68°)] afforded **5d** (3.87 g, 89%): mp 182–183°; ir (KBr) 3.10, 3.23, 5.75–5.90, 9.55; nmr (CF_3CO_2H) 2.00 (2 H, multiplet, CH_2), 2.65 (2 H, multiplet, CH_2), 4.04 (3 H, singlet, OCH_3), 4.55 (2 H, triplet, $-CH_2OMe$), 7.42 (5 H, singlet, aromatic).

Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.96; H, 5.65; N, 10.23.

5-Phenyl-5-(3-ethoxypropyl)barbituric Acid (5c).—A mixture of 5-phenyl-5-(3-iodopropyl)barbituric acid (**5b**) (2.00 g, 5.37 mmol) in DMF (200 ml) and Ag_2O (0.712 g, 3.08 mmol) was stirred at 80° for 2 hr. The reaction mixture was cooled to room temperature and the silver salts were filtered off. The DMF was removed *in vacuo*, and the residue was extracted with hot absolute EtOH (200 ml) and filtered. Silica gel was added and the EtOH was removed *in vacuo* below 80°. Chromatography on silica gel ($CHCl_3$–10% 2-propanol) gave **5c** (0.496 g, 32%): mp 204–206° [Me_2CO–petroleum ether (60–68°)]; ir (KBr) 3.10, 3.23, 5.77–5.90, 9.65; nmr (CF_3CO_2H) 1.48 (3 H, triplet-fine splitting, CH_3), 1.70–2.90 (4 H, multiplet, CH_2), 4.50 (2 H, multiplet, CH_3CH_2–O), 5.05 (2 H, triplet, CH_2CH_2–OEt), 7.45 (5 H, singlet, aromatic).

Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.24; N, 9.65. Found: C, 61.97; H, 6.39; N, 9.79.

5-(2-Bromopropyl)-5-phenylbarbituric Acid (8a).—A solution of allylphenylbarbituric acid (24.4 g, 0.1 mol) in Et_2O (240 ml) was stirred for several minutes and cooled. Gaseous HBr was added. After 7 hr the reaction mixture was allowed to warm to room temperature. On filtration, a cream colored material, mp 218–220° dec, was obtained. The solid was washed successively with $NaHCO_3$ solution and H_2O, and recrystallized (EtOH) to give white, solid **8a** (22 g, 68.8%): mp 221–222° dec.

Anal. Calcd for $C_{13}H_{13}N_2O_3Br$: C, 48.02; H, 4.03; N, 8.62; Br, 24.58. Found: C, 48.36; H, 4.13; N, 8.52; Br, 24.76.

4(a)-Phenyl-6*H*,7*H*-pyrano[2,3-*d*]-$\Delta^{1,8a}$-2,4-(3*H*)-pyrimidinedione (7).—A suspension of 5-phenyl-5-(3-iodopropyl)barbituric acid (**5b**) (2.00 g, 5.36 mmol) and AgOBz (1.23 g, 5.36 mmol) in anhydrous C_6H_6 (100 ml) was allowed to refluxed for 2 hr. The reaction mixture was cooled and filtered, and the C_6H_6 was removed *in vacuo*. The residue was taken up in hot C_6H_6 (40 ml) and filtered, and the filtrate was allowed to stand. Crystallization from the solvent gave **7** (0.862 g, 62%): mp 208–211°; ir (KBr) 3.28, 3.42, 5.85, 5.92, 6.24; nmr (DMSO-d_6) 1.15–2.40 (4 H, multiplet), 3.60–4.50 (2 H, multiplet), 7.20–7.70 (5 H, multiplet, aromatic), 9.83 (1 H, imide), *m/e* 244.

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 63.86; H, 4.96; N, 11.35.

Treatment of **7** in either H_2O or CH_3OH with a trace of CF_3CO_2H gave the primary alcohol, **5e**, or methyl ether, **5d**, respectively. The ir, nmr, and tlc (silica gel, 80% $CHCl_3$–20% EtAc) of **5d** and **5e** were identical with the known compounds prepared by alternate methods.

4(a)-Phenyl-6-methyl-5*H*,6*H*-furo[2,3-*d*]-$\Delta^{1,7a}$-2,4-(3*H*)-pyrimidinedione (9).—A mixture of 5-phenyl-5-(2-bromopropyl)barbituric acid (**8a**) (2.00 g, 6.16 mmol) and AgOBz (1.41 g, 6.16 mmol) in C_6H_6 (250 ml) was allowed to react according to the procedure outlined for **7**. The furopyrimidine **9** (0.511 g, 34%) crystallized from C_6H_6: mp 170–174°; ir (KBr) 3.25, 3.35, 5.75, 5.90, 6.15; nmr (DMSO-d_6) 1.00 (3 H, doublet, CH_3), 2.40–3.50 (2 H, multiplet, CH_2), 4.80–5.20 (1 H, multiplet, CH), 7.46 (5 H, singlet, aromatic), 11.16 (1 H, imide).

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 63.57; H, 4.76; N, 11.26.

Acid hydrolysis of **9** gave the alcohol **8b**, mp 229–231°, which gave a positive iodoform test.

Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.78; H, 5.42; N, 10.76.

Registry No.—**5a**, 25860-47-3; **5b**, 25907-99-7; **5c**, 25860-48-4; **5d**, 25860-49-5; **6**, 25860-50-8; **7**, 25860-51-9; **8a**, 25860-52-0; **8b**, 25860-53-1; **9**, 25860-54-2.

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

(3) 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, The University of Kansas. Infrared spectra were recorded on Beckman IR-8 and IR-10 spectrophotometers. Nuclear magnetic resonance spectra were recorded and A-60, A-60A, and HA-100 analytical spectrophotometers with tetramethylsilane as a standard or in deuterium oxide when 3-trimethylpropanesulfonic acid sodium salt was employed. Nuclear magnetic resonance data are reported as δ values (ppm). Molecular weights were determined on the Finnigan 1015 mass spectrometer.