The Synthesis of Bicyclo[4.3.0]nonanebarbituric and -thiobarbituric Acid Derivatives and a Bicyclo[4.4.0]decanebarbituric Acid Derivative

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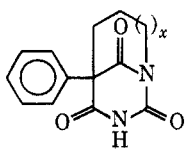
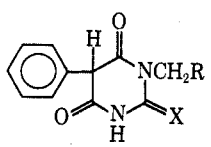
In attempting to prepare intramolecularly C-alkylated bicyclic barbituric and thiobarbituric acids from *N*-haloalkylbarbituric and *N*-haloalkylthiobarbituric acids, only O-alkylated compounds were obtained. The structures were assigned on the basis of spectral data and by degradation of the products to known entities.

Recent reports from this laboratory[2] indicate that barbituric acids with a displaceable group on an alkyl side chain attached to the C-5 carbon will undergo intramolecular alkylation to give O-alkylation in preference to N-alkylation. In a continuation of a program designed to prepare bicyclic barbituric acids **1** as selective CNS agents for potential use as anticonvulsants, the *N*-alkylbarbituric acids **2**, **4**, and **5** and the *N*-alkylthiobarbituric acid **3** were prepared[1] and investigated as possible precursors to compound **1**.

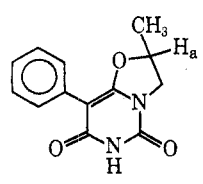


1, $x = 0, 1, 2$



2, X = O; R = CH=CH$_2$
3, X = S; R = CH=CH$_2$
4, X = O; R = CH$_2$OH
5, X = O; R = CH$_2$CH$_2$Br
6, X = O; R = CHBrCH$_3$
7, X = O; R = CH$_2$Br

An acid-stable crystalline substance was obtained upon treatment of the *N*-allylbarbituric acid **2** with hydrogen bromide in acetic acid. Elemental analysis indicated the structure could be either **8** or **9**.



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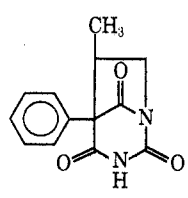

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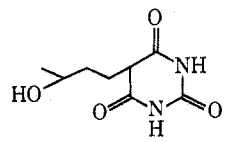
Structure **8** is supported by ir and nmr spectral data. Nuclear magnetic resonance analysis shows a one-proton multiplet centered at δ 5.1 which is consistent with H$_a$ (**8**) but is downfield from the chemical shift to be expected for any protons in **9**. The unexpected acid stability for the vinyl ether function in **8** was found in a similar system, the conversion of the barbiturate **10** to the bicyclic compound **11**, by Senda, Fujimura, and Izumi.[3]



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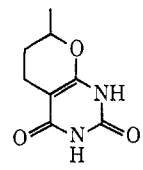
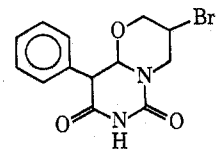


11

A plausible mechanism for the formation of **8** would involve enolization of **6**, followed by displacement of the secondary bromide by the enolic oxygen. When compound **2** was allowed to react with bromine in carbon tetrachloride and in ethylene glycol dimethyl ether, a crystalline product was obtained whose elemental analysis and spectral qualities were consistent with either structure **12** or **13**. The product was



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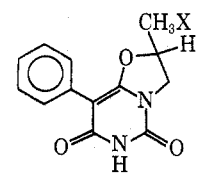
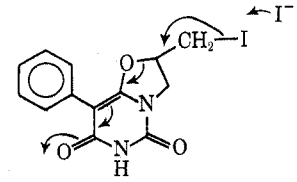


13, X = Br
14, X = OCOCH$_3$
15, X = OCOC$_6$H$_5$
16, X = I

shown to be 2,4-diketo-8-bromomethyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (**13**) by nmr analysis of its acetate **14** and benzoate **15**. If the product were **12** rather than **13**, it would be expected that the absorbance of the methine proton rather than the methylene protons would be shifted on conversion to the esters **14** and **15**.

The iodo compound **16** was formed by allowing the bromo compound **13** to reflux with excess sodium iodide in acetone. Compound **2** was also obtained in this reaction, probably by an elimination with cleavage as shown below.

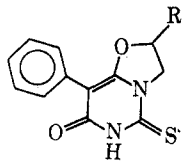


(1) Taken in part from the dissertation presented by J. W. Ayres, Aug 1970, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

(2) E. E. Smissman, R. A. Robinson, and A. J. B. Matuszak, *J. Org. Chem.*, **35**, 3823 (1970).

(3) S. Senda, H. Fujimura, and H. Izumi, Japanese Patent 6,824,193 (1968); *Chem. Abstr.*, **70**, 78001r (1969).

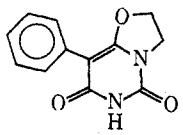
The sulfur-containing analogs **17–20** were prepared in a similar manner to the oxygen-containing compounds starting with **3**. The reaction of sodium benzoate in dimethylformamide with the bromide **18** did not pro-



17, R = CH_3
18, R = CH_2Br
19, R = CH_2OCOCH_3
20, R = $=CH_2$

duce the corresponding benzoate as it had in the oxygen series but instead 4-keto-2-thio-5-phenyl-Δ^5-7-oxa-8-methylene-1,3-diazabicyclo[4.3.0]nonane (**20**) was obtained.

When the alcohol **4** was treated with 32% hydrogen bromide in acetic acid, the only product isolated was 2,4-diketo-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]-nonane (**21**). Presumably, this compound was obtained *via* the intermediate bromide **7**. Compound **5**



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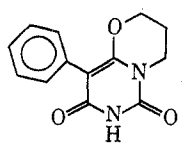
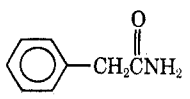


22

was converted to 2,4-diketo-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.4.0]decane (**22**) by allowing it to stand in pyridine.

Further evidence for O-alkylation as opposed to C-alkylation in the above series of bicyclic compounds was provided by the degradation of compounds **18**, **21**, and **22**. These compounds were treated with 58% ammonium hydroxide and 21% ammonium sulfide at 150° in a steel reaction vessel. In each case, the only identifiable product obtained from this hydrolytic procedure was α-phenylacetamide (**23**), thus indicating that no alkylation had occurred on the carbon adjacent to the aromatic ring.



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Experimental Section[4]

2,4-Diketo-8-methyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]-nonane (8).—A solution of *N*-allyl-5-phenylbarbituric acid (**2**) (25 g, 0.10 mol) in 100 ml of 32% HBr–HOAc in a stoppered Wheaton glass pressure bottle was stirred overnight and then allowed to stand at 25° for 5 days. Compound **8** was filtered and the filtrate diluted with 200 ml of H_2O and used to wash **8** several times. After drying the yield was 88% (22 g): mp 259–261° (Me_2CO); ir (KBr) 3400 (NH), 1700 (C=O), 1620 cm^{-1} [C=CC(=O)N]; nmr (DMSO-d_6) δ 1.42 (d, 3 H, CH_3), 3.8 (m, 2 H, NCH_2C), 5.1 (m, 1 H, OCH), 11.1 (br s, 1 H, NH).

(4) Melting points were obtained on a calibrated Thomas-Hoover Unimelt and are corrected. Ir data were recorded on a Beckman IR 10 spectrophotometer and nmr data on Varian Associates A-60, A-60-A, and HA-100 spectrometers (TMS). Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., and on an F & M 185 C, H, N analyzer, University of Kansas.

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.46. Found: C, 64.10; H, 5.02; N, 11.41.

2,4-Diketo-8-bromomethyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo-[4.3.0]nonane (13).—Bromine (25.6 g, 0.16 mol) was added all at once to a stirred solution of *N*-allyl-5-phenylbarbituric acid (**2**) (40 g, 0.16 mol) in 750 ml of ethylene glycol dimethyl ether which was cooled in an ice bath. The suspension was allowed to stir for 30 min and then N_2 was bubbled through the suspension to remove Br_2 vapors. The solvent was removed *in vacuo* and the residue washed with 40 ml of Me_2CO to yield **13** (31.7 g). The Me_2CO was evaporated to leave an oil which was dissolved in EtOAc and decolorized with a solution of Na_2SO_3 in H_2O. The organic layer was dried ($MgSO_4$) and evaporated to leave a solid which was washed with 200 ml of hot C_6H_6 and dried to yield another 9 g of **13** (total yield 40.7 g, 79%): mp 230° (Me_2CO); nmr (DMSO-d_6) δ 4.0 (m, 4 H, CH_2Br, CH_2N), 5.3 (m, 1 H, OCH), 11.2 (br s, 1 H, NH).

Anal. Calcd for $C_{13}H_{11}BrN_2O_3$: C, 48.31; H, 3.43; N, 8.66. Found: C, 48.67; H, 3.34; N, 8.93.

2,4-Diketo-8-acetoxymethyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (14).—A stirred suspension of 2,4-diketo-8-bromomethyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (**13**) (2.0 g, 6.2 mmol) and AgOAc (2.0 g, 12 mmol) in 5 ml of DMSO, 5 ml of DMF, and 5 ml of HOAc was heated at 100° for 1 hr. The suspension was filtered and the filtrate diluted with 100 ml of H_2O and made acidic with 10% HCl. The gummy precipitate was filtered and recrystallized twice to yield **14** (1.1 g, 59%): mp 198–200° (EtOAc); nmr (DMSO-d_6) δ 4.0 (m, 2 H, NCH_2), 4.4 (m, 2 H, OCH_2), 5.2 (m, 1 H, OCH), 11.0 (br s, 1 H, NH).

Anal. Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.66; N, 9.26. Found: C, 59.85; H, 4.80; N, 9.05.

2,4-Diketo-8-benzoxymethyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (15).—A stirred solution of 2,4-diketo-8-bromomethyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (**13**) (2.0 g, 6.2 mmol) and NaOBz (1.0 g, 7.0 mmol) in 20 ml of DMF was refluxed 4 hr, cooled, and poured into 150 ml of H_2O. The suspension was made acidic (10% HCl) and the gummy precipitate collected to yield **15** (1.0 g, 44.3%): mp 210–212° (EtOAc–petroleum ether 60–70°); nmr (DMSO-d_6) δ 4.2 (m, 2 H, NCH_2), 4.7 (m, 2 H, OCH_2), 5.3 (m, 1 H, OCH), 11.2 (br s, 1 H, NH).

Anal. Calcd for $C_{20}H_{16}N_2O_5$: C, 65.92; H, 4.42; N, 7.68. Found: C, 65.64; H, 4.61; N, 7.77.

2,4-Diketo-8-iodomethyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo-[4.3.0]nonane (16).—A solution of 2,4-diketo-8-bromomethyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (**13**) (20 g, 0.06 mol) and NaI (45 g, 0.32 mol) in 1500 ml of Me_2CO was refluxed overnight. The solvent was removed *in vacuo* and the black residue decolorized with Na_2SO_3 in H_2O. The solid was collected on a filter to yield **16** (8.3 g), mp 226–228° dec (Me_2CO); the spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{13}H_{11}IN_2O_3$: C, 42.08; H, 2.99; N, 7.56. Found: C, 42.00; H, 2.92; N, 7.18.

The above filtrate was made acidic (10% HCl) and the precipitate collected by filtration. The solid was washed with 200 ml of boiling EtOAc and the insoluble material filtered to yield more **16** (4.6 g, total yield 51.6%). Concentration of the filtrate yielded *N*-allyl-5-phenylbarbituric acid (**2**) (6.0 g, 39.8%).

4-Keto-2-thio-8-methyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo-[4.3.0]nonane (17).—A stirred solution of *N*-allyl-5-phenylthiobarbituric acid (**3**) (25 g, 0.09 mol) in 100 ml of 32% HBr–HOAc (Eastman) was refluxed 8 hr in a stoppered Wheaton glass pressure bottle and then allowed to stir overnight at 25°. The solid was collected and washed with 150 ml of Me_2CO to yield **17** (16.6 g, 66.5%), mp 239–242° dec (Me_2CO); the spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{13}H_{12}N_2O_2S$: C, 59.98; H, 4.64; N, 10.76. Found: C, 60.26; H, 4.85; N, 10.56.

4-Keto-2-thio-8-bromomethyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (18).—A solution of Br_2 (24.6 g, 0.154 mol) in 100 ml of CCl_4 was added all at once to a stirred suspension of *N*-allyl-5-phenylthiobarbituric acid (**3**) (40.0 g, 0.154 mol) in 500 ml of ethylene glycol dimethoxy ether cooled in an ice bath. The mixture was stirred 30 min, refluxed 1 hr, and concentrated *in vacuo*. The oily residue was washed with 200 ml of Me_2CO–petroleum ether (60–70°) and the solid collected to yield **18** (44.2 g, 85%), mp 238–239° dec (Me_2CO–petroleum ether 60–70°); the spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{13}H_{11}BrN_2O_2S$: C, 46.03; H, 3.26; N, 8.25. Found: C, 46.12; H, 3.9; N, 8.38.

4-Keto-2-thio-8-acetoxymethyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (19).—A stirred suspension of 4-keto-2-thio-8-bromomethyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (**18**) (3.0 g, 8.9 mmol) and AgOAc (1.6 g, 10 mmol) in 30 ml of HOAc was refluxed 1.25 hr and the solid filtered. The filtrate was concentrated *in vacuo* and added to 50 ml of H_2O which was made acidic (10% HCl). The precipitate was collected to yield **19** (1.5 g, 52%), mp 202–204° (EtOAc–Me_2CO); the spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{15}H_{14}N_2O_4S$: C, 56.59; H, 4.43; N, 8.79. Found: C, 56.35; H, 4.52; N, 8.79.

4-Keto-2-thio-8-methylene-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (20).—A stirred solution of 4-keto-2-thio-8-bromomethyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (**18**) (4.00 g, 11.8 mmol) and NaOBz (1.87 g, 13.0 mmol) in 10 ml of DMF was refluxed 5 hr, cooled, and poured into 200 g of crushed ice. The suspension was made acidic (10% HCl) and the precipitate collected and decolorized with activated charcoal in Me_2CO. The Me_2CO was removed *in vacuo* to yield **20** (0.5 g, 16.4%), mp 186–187° (Me_2CO); the spectral data were consistent with the assigned structure.

Anal. Calcd for $C_{13}H_{10}N_2O_2S$: C, 60.45; H, 3.90; N, 10.84. Found: C, 60.07; H, 3.74; N, 10.54.

2,4-Diketo-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (21).—A stirred solution of *N*-(2-hydroxyethyl)-5-phenylbarbituric acid (**4**) (10.0 g, 0.04 mol) in 100 ml of 32% HBr–HOAc (Eastman) was refluxed overnight in a stoppered Wheaton glass pressure bottle. The HOAc was removed *in vacuo* and the residue added to 400 ml of crushed ice. The H_2O was decanted and the gummy residue crystallized to yield **21** (4.25 g, 46.2%), mp 267–268° (Me_2CO); the spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.37; N, 12.16. Found: C, 62.46; H, 4.48; N, 12.15.

2,4-Diketo-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.4.0]decane (22).—A solution of *N*-(3-bromopropyl)-5-phenylbarbituric acid (**5**) (1.0 g, 3.0 mmol) in 30 ml of C_5H_5N was stirred 3 days and then concentrated *in vacuo*. The residue was dissolved in 10 ml of H_2O and the solution made acidic (10% HCl). The precipitate was collected to yield **22** (400 mg, 54.6%), mp 290.5–291.5 dec (Me_2CO); the spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.46. Found: C, 64.15; H, 5.03; N, 11.57.

α-Phenylacetamide (23). A. Hydrolysis of 4-Keto-2-thio-8-bromomethyl-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (18).—A solution of **18** (3.0 g, 8.8 mmol) in 10 ml of 58% NH_4OH and 20 ml of 21% $(NH_4)_2S$ was maintained at 150° in a steel reaction vessel for 3 days. The solvent was removed *in vacuo* and the residue dissolved in $CHCl_3$, decolorized (activated charcoal), dried ($MgSO_4$), and evaporated to yield **23** (0.30 g, 26%), mp 154–155° ($CHCl_3$–Et_2O) (lit.[5] mp 154–155°). The spectral data were identical with those for α-phenylacetamide.[6]

B. Hydrolysis of 2,4-Diketo-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]nonane (21).—The procedure utilized was identical with that in A. Compound **23**, mp 151–152° ($CHCl_3$–Et_2O), was obtained.

C. Hydrolysis of 2,4-Diketo-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.3.0]decane (22).—The procedure utilized was identical with that in A and B. Compound **23**, mp 154–155 ($CHCl_3$–Et_2O), was obtained.

Registry No.—**8**, 30345-98-3; **9**, 30345-99-4; **14**, 30346-00-0; **15**, 30346-01-1; **16**, 30346-02-2; **17**, 30346-03-3; **18**, 30409-27-9; **19**, 30346-04-4; **20**, 30346-05-5; **21**, 30346-06-6; **22**, 30349-28-0.

Acknowledgment.—The authors gratefully acknowledge the support of this project by the National Institutes of Health Grants GM-09254 and GM-01341. We appreciate the assistance rendered by Mr. Darrell Abernethy in the preparation of starting materials.

(5) "The Merck Index," 7th ed, Merck and Co., Inc., Rahway, N. J., 1960, p 799.

(6) "The Sadtler Standard Spectra," Sadtler Research Laboratories, Philadelphia, Pa., 1970, Prism No. 2236, nmr no. 6588.

The Synthesis of the Thalictrum Alkaloids, Adiantifoline and Thalicsimidine[1]

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A total synthesis is described for adiantifoline (**1**) involving, in the final step, the joining by the Ullmann reaction of the two components (+)-(*S*)-6′-bromolaudanosine (**12**) and (+)-(*S*)-1,2,3,10-tetramethoxy-9-hydroxyaporphine (**4**), thus establishing the structure for the alkaloid. The aporphine intermediate **4** was formed by two routes, both leading to the same Pschorr cyclization reactant, 1-(3′-benzyloxy-4′-methoxy-6′-nitrobenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**8**). One pathway started with *N*-(2,3,4-trimethoxyphenylethyl)-3′-benzyloxy-4′-methoxyphenylacetamide (**5**) with the nitro group being introduced to the tetrahydroisoquinoline **7**, while the other procedure started with *N*-(2,3,4-trimethoxyphenylethyl)-3′-benzyloxy-4′-methoxy-6′-nitrophenylacetamide (**9**). Only polyphosphoric ester was successful in cyclizing compound **9** in the Bischler–Napieralski reaction. Methylation of compound **4** to (+)-(*S*)-1,2,3,9,10-pentamethoxyaporphine (**13**) or thalicsimidine constitutes its total synthesis and confirms its structure earlier assigned on the basis of spectroscopic evidence. Four pentaoxygenated benzyltetrahydroisoquinolines, **14–17**, were obtained from intermediates in the synthesis.

Adiantifoline, the fourth member of a novel group dimeric benzylisoquinoline–aporphine alkaloids, was isolated from *Thalictrum minus* L. var. *adiantifolium* Hort., and was assigned structure **1** from physical and chemical evidence.[3] A confirmation of this structure was necessary and was obtained by a total synthesis of (+)-adiantifoline,[4] since scarcity of the alkaloid precluded further degradative studies and the evidence at hand was also consistent with structure **2**. In addition, a quantity of the alkaloid could now be made available for pharmacological testing,[5] which otherwise would not have been possible.

(1) Alkaloids of Thalictrum. XII. Paper XI: R. W. Doskotch, P. L. Schiff, Jr., and J. L. Beal, *Lloydia*, **32**, 29 (1969). This investigation was supported by Public Health Service research grants HE-07502 and FR-00328, the latter for purchase of a Varian A-60A nmr spectrometer with accessories.

(2) Acknowledges with thanks the receipt of a Wellcome Research Travel Grant. Permanent address: Department of Pharmacy, Chelsea College, University of London, London, United Kingdom.

(3) (a) R. W. Doskotch, P. L. Schiff, Jr., and J. L. Beal, *Tetrahedron Lett.*, 4999 (1968). (b) The isolation procedure is found in paper XI.[1]

(4) A preliminary report of this work has appeared: R. W. Doskotch, J. D. Phillipson, A. B. Ray, and J. L. Beal, *Chem. Commun.*, 1083 (1969).

(5) Testing for antitumor activity will be of special interest because of the success thalicarpine (**3**) has been having in the evaluation program of the Cancer Chemotherapy National Screening Center; see R. E. Perdue and J. L. Hartwell, *Morris Arbor. Bull.*, **20**, 35 (1969).