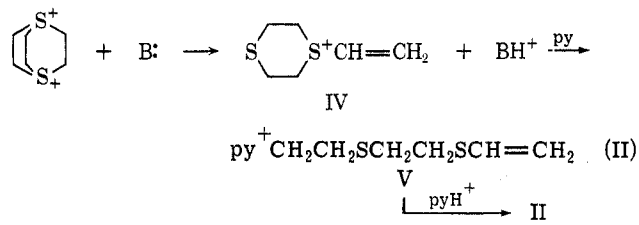
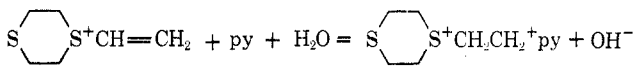


through intermediate IV (mechanism II). (1) The reaction of 1 equiv of sodium hydroxide with aqueous disulfonium perchlorate yields IV. (2) Both I and IV have been isolated[1] and shown to be interconvertible *via* the rapid equilibrium III. (3) When the pyridine–



disulfonium reaction is run in dimethylformamide, the pmr spectra of the reaction solutions exhibit signals characteristic of vinyl protons and V is obtained as a by-product. Independent experiments show that II will not undergo elimination to give V under the reaction conditions and therefore V arises from nucleophilic attack by pyridine on IV (which is not expected to yield *p*-dithiane and *N*-vinylpyridinium ion in light of the inertness of vinyl halides to nucleophilic attack[35]). (4) Doering[36] has shown that the reaction of hydroxide ion with 2-bromoethyldimethylsulfonium ion rapidly yields the vinyldimethylsulfonium ion by elimination of HBr. (He has also observed that hydroxide rapidly attacks 1-thioniabicyclo[2.2.1]heptane.[37])

(35) L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold, New York, N. Y., 1961, p 341.
(36) W. von E. Doering and K. Schreiber, *J. Amer. Chem. Soc.*, **77**, 514 (1955).
(37) W. von E. Doering and A. K. Hoffmann, *ibid.*, 521 (1955).

The magnitudes of the rates of OH^- attack on the two disulfonium centers, relative to H–D exchange, are indicated by the observation that, when molar deuterioxide is allowed to react with disulfonium chloride, mass spectral analysis of the resultant *p*-dithiane shows that it has undergone exactly 50% H–D exchange. This can be understood if deuterioxide rapidly attacks the disulfonium ion before H–D exchange can take place, giving either intermediate IV or the –OD analog of intermediate I. This intermediate is then subject to deuterioxide-catalyzed H–D exchange *via* the accepted mechanism for sulfonium ions.[38] Thus only those hydrogens on carbons bound to the sulfonium sulfur will exchange before the second, slower hydroxide attack occurs, leading to the observed 50% deuterium content of the *p*-dithiane product.

Registry No.—Disulfonium tetrachlorozincate, 35616-90-1; *p*-dithiane, 505-29-3; disulfonium perchlorate, 35624-14-7; disulfonium chloride, 5344-51-4; disulfonium tetraphenylborate, 35616-91-2; tetra(disulfonium)cobalt(II) decachloride hydrate, 35616-92-3; dipyridinium 1,1′-[ethylenebis(thioethylene)]diperchlorate, 35624-16-9; *N*-[3,6-bis(thia)-7-octenyl]pyridinium perchlorate, 35624-17-0; dipyridinium 1,1′-ethylenediperchlorate, 6601-41-8.

Acknowledgments.—Funds for this work were provided by ARPA and by a Du Pont Young Faculty Grant. The author is grateful to Dr. Ernst Habicht, Jr., for originally bringing the disulfonium ion to his attention, as well as to Dr. JoAnn Molin-Case, Professor E. Fleischer, Professor R. Elder, and Mr. G. Christoph for invaluable assistance with the X-ray analysis.

(38) C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press, New York, N. Y., 1962, pp 153–155.

The Synthesis of 2,4-Diketo-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.4.0]decane and 2,4-Diketo-3-phenyl-Δ^5-7-oxa-1,5-diazabicyclo[4.4.0]decane[1]

EDWARD E. SMISSMAN,* JAMES W. AYRES, PETER J. WIRTH, AND DARRELL R. ABERNETHY

Department of Medicinal Chemistry, School of Pharmacy, The University of Kansas, Lawrence, Kansas 66044

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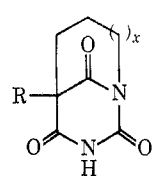
In an attempt to secure 5-phenyl bicyclo barbiturates, *N*-(haloalkyl)-5-phenylbarbituric acids were prepared and converted to their corresponding thallous salts. Nitrourea and alkanolamines were allowed to react to produce *N*-(hydroxyalkyl)ureas, which were converted to the corresponding *N*-(hydroxyalkyl)-5-phenylbarbituric acids and *via* these alcohols to the halides. When cyclization of the thallous salts of the *N*-(halopropyl)-5-phenylbarbituric acids was attempted in benzene-water, no intramolecular C-alkylation occurred and the only product isolated was 2,4-diketo-3-phenyl-Δ^5-7-oxa-1,5-diazabicyclo[4.4.0]decane. Utilizing anhydrous benzene as the solvent for the cyclization reaction, the product obtained was 2,4-diketo-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo-[4.4.0]decane.

As part of a study on the steric aspects of selective central nervous system depression, attempts have been made to find general synthetic routes to bridged barbiturates, **1**, to be investigated as antiepileptic agents.

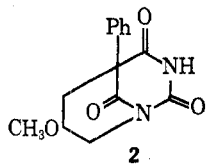
One such barbituric acid, 5-phenyl-7-methoxy-2,4,9-triketo-1,3-diazabicyclo[3.3.1]nonane (2), was prepared by base-catalyzed intramolecular attack of an



1
R = alkyl, aryl
x = 0, 1, 2

imide nitrogen on the primary bromo function of 5-phenyl-5-(2-methoxy-3-bromopropyl)barbituric acid

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



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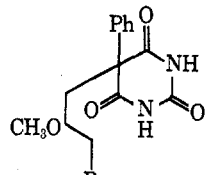
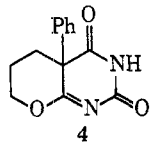
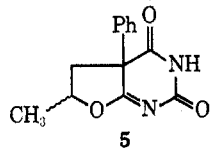


3

(3).[2] This did not prove to be a general method for the desired compounds, since intramolecular cyclization of 5-substituted 3-halopropyl- and 2-halopropylbarbituric acids failed to give the N-alkylated system but rather the O-alkylated pyrano- and furopyrimidines, **4** and **5**, respectively.[3]

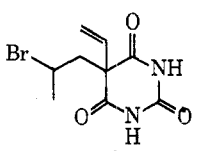


4

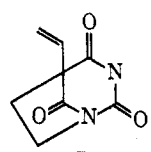


5

The intramolecular N-alkylation of **6** was reported to give the bicyclo barbiturate 5-vinyl-2,4,8-triketo-1,3-diazabicyclo[3.2.1]barbituric acid (**7**) through N-alkylation.[4] The data reported (ir absorption at 1650 cm^{-1}, acid lability) indicates that the structure reported as **7** is actually **8**.



6



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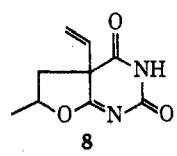
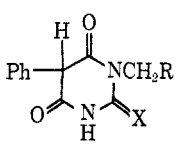


8

Taylor and McKillop[5] have reported exclusive C-alkylation upon heating the thallous salts of 1,3-dicarbonyl compounds with alkyl iodides. In order to prepare the desired compounds utilizing their method, it was necessary to synthesize barbituric acids with functional groups located on an N-alkyl side chain. These compounds could give the barbiturate **1** by intramolecular attack of the carbon atom at C-5 on the proper side chain substituent.

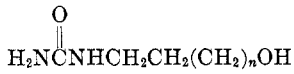
N-Allyl-5-phenylbarbituric acid (**9**) and *N*-allyl-5-phenylthiobarbituric acid (**10**) were obtained by allowing allylurea or allylthiourea to react with diethyl phenylmalonate in the presence of sodium ethoxide.



9, X = O; R = CH=CH$_2$
10, X = S; R = CH=CH$_2$
11, X = O; R = CH_2CH_2Br
12, X = O; R = CH_2OH
13, X = O; R = CH_2CH_2OH
14, X = O; R = $CH_2CH_2CH_2OH$
15, X = O; R = $CH_2CH_2CH_2Br$
16, X = O; R = CH_2CH_2I
17, X = O; R = CH_2CH_2OTs

An attempt was made to obtain the *N*-bromopropyl compound **11** by reaction of **9** with hydrogen bromide under free-radical conditions; however, no identifiable products could be isolated.

The treatment of nitrourea with ethanolamine was reported[6] to give *N*-(2-hydroxyethyl)urea (**18**). In a similar manner, *N*-(3-hydroxypropyl)urea (**19**) and

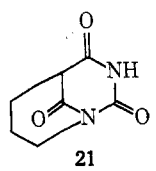


18, *n* = 0
19, *n* = 1
20, *n* = 2

N-(4-hydroxybutyl)urea (**20**) now have been prepared. The condensation of **18**, **19**, and **20** with diethyl phenylmalonate produced **12**, **13**, and **14**, respectively. The treatment of **13** or **14** with hydrogen bromide in acetic acid produced the corresponding bromides **11** and **15**.

The thallous salts of **11** and **16** were prepared by the addition of thallium ethoxide in dimethoxyethane (DME) to a solution of the barbiturate in the same solvent. Kornblum[7] and coworkers reported the importance of solvent in determining the ratio of C-alkylation to O-alkylation in the alkylation of ambident anions. Higher ratios of the C-alkylated products were obtained when the reactions were performed in water or fluorinated alcohols. With this fact in mind, the thallous salts of the barbiturates **11** and **16** were refluxed in a 50:50 benzene–water solvent system.

The product isolated had an empirical formula consistent with the bicyclic structures **21**, **22**, and **23**. The nmr spectrum [δ 3.4 (s), one proton)] indicated structure **23**, which is the only possibility with a benzylic proton. The presence of an ir peak at 1630 cm^{-1} (C=N) is consistent with **23** and eliminates **21**. A minor impurity proved to be **22**.



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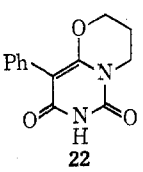

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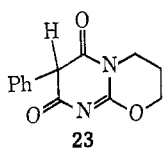

23

When the thallous salt of **11** was refluxed in anhydrous benzene the only product isolated was **22**. This compound had no benzylic absorption in the nmr but showed a one-proton singlet at δ 11.2 for the imide hydrogen, which is consistent with the assigned structure which has been reported previously.[8]

Experimental Section[9]

N-Allyl-5-phenylbarbituric Acid (**9**).—A mixture of allylurea (40 g, 0.40 mol) and diethyl phenylmalonate (94 g, 0.40 mol) was added to a solution of Na (18 g, 0.78 g-atom) in dry EtOH (600 ml) and refluxed for 2 days. The EtOH was removed *in vacuo* and the residue was dissolved in 500 ml of H_2O. The solution was made acidic with 10% HCl and the precipitate was collected and washed with 300 ml of hot C_6H_6. Recrystallization ($C_6H_5CH_3$) yielded **9** (57 g, 60%), mp 122–123°.

(2) E. E. Smissman, R. A. Robinson, J. B. Carr, and A. J. Matuszak, *J. Org. Chem.*, **35**, 3821 (1970).
(3) E. E. Smissman, R. A. Robinson, and A. J. B. Matuszak, *ibid.*, **35**, 3823 (1970).
(4) M. Konieczny, *Arch. Immunol. Ther. Exp.*, **15**, 920 (1967).
(5) E. C. Taylor and A. McKillop, *Accounts Chem. Res.*, **3**, 338 (1970).
(6) R. W. Charlton and A. R. Day, *J. Org. Chem.*, **1**, 552 (1937).
(7) N. Kornblum, P. J. Berrigan, and W. J. LeNoble, *J. Amer. Chem. Soc.*, **85**, 1141 (1963).
(8) E. E. Smissman and J. W. Ayres, *J. Org. Chem.*, **36**, 2407 (1971).
(9) Melting points were obtained on a calibrated Thomas-Hoover Unimelt and are corrected. Ir data were recorded on a Backman IR-10 spectrophotometer and nmr data on Varian Associates A-60, A-60A, 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, 63.72; H, 4.74; N, 11.69.

N-**Allyl-5-phenylthiobarbituric Acid (10).**—A mixture of allylthiourea (52.6 g, 0.453 mol) and diethyl phenylmalonate (107.0 g, 0.453 mol) was added to a stirred solution of Na (20.8 g, 0.905 g-atom) in 500 ml of dry EtOH and refluxed overnight. The EtOH was removed *in vacuo* and the residue was dissolved in 500 ml of H_2O. The solution was made acidic (10% HCl) and the precipitate was collected to yield **10** (112 g, 95%), mp 198–201° (Me_2CO).

Anal. Calcd for $C_{13}H_{12}N_2O_2S$: C, 59.98; H, 4.64; N, 10.76. Found: C, 60.21; H, 4.61; N, 10.89.

N-(**2-Hydroxyethyl**)**urea (18).**—The procedure used was essentially that of Charlton and Day.[6] Nitrourea (25 g, 0.238 mol) was added slowly to a stirred solution of aminoethanol (12.2 g, 0.200 mol) in 15 ml of H_2O cooled in an ice bath. The mixture was allowed to stir overnight and the H_2O was removed *in vacuo*. The residual oil solidified on standing in the freezer and was crystallized from a large volume of dioxane to yield **18** (14.6 g, 70.4%), mp 95° (lit. mp 94–95°).

Anal. Calcd for $C_3H_8N_2O_2$: C, 34.61; H, 7.74; N, 27.14. Found: C, 34.68; H, 8.04; N, 27.14.

N-(**3-Hydroxypropyl**)**urea (19).**—Nitrourea (50.0 g, 0.475 mol) was added in small portions to a stirred solution of aminopropanol (30.0 g, 0.400 mol) in 40 ml of H_2O cooled in an ice bath. The mixture was stirred for 24 hr and the H_2O was removed *in vacuo*. The residual oil formed a waxy solid after standing for 4 days to give a quantitative yield of **19**, mp 50–52°.

Anal. Calcd for $C_4H_{10}N_2O_2$: C, 40.66; H, 8.53; N, 23.71. Found: C, 40.97; H, 8.79; N, 23.90.

N-(**4-Hydroxybutyl**)**urea (20).**—Nitrourea (14.28 g, 0.136 mol) was added over a period of 45 min to a stirred solution of 4-amino-1-butanol (11.0 g, 0.124 mol) in 40 ml of H_2O while being cooled in an ice bath. The reaction mixture was allowed to warm to 25° and stirred for 10 hr. The H_2O was removed *in vacuo* to yield a yellow oil. The oil was washed three times with C_6H_6; the last time the C_6H_6 was removed by distillation in order to azeotrope traces of H_2O. The yellow oil (14.2 g, 87%) did not crystallize. The spectral data were consistent with the assigned structure.

N-(**2-Hydroxyethyl**)**-5-phenylbarbituric Acid (12).**—A mixture of diethyl phenylmalonate (26.9 g, 0.114 mol) and *N*-(2-hydroxyethyl)urea (**13**) (11.4 g, 0.114 mol) was added to a stirred solution of Na (5.30 g, 0.230 g-atom) in 120 ml of dry EtOH and refluxed overnight. The EtOH was removed *in vacuo* and the residue was dissolved in H_2O. The solution was made acidic (10% HCl) and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to leave an oil which was triturated with Et_2O to yield **12** (18.7 g, 66%), mp 120° [EtOAc–petroleum ether (bp 60–70°)].

Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 58.29; H, 4.90; N, 11.22.

N-(**3-Hydroxypropyl**)**-5-phenylbarbituric Acid (13).**—A mixture of diethyl phenylmalonate (60.0 g, 0.254 mol) and *N*-(3-hydroxypropyl)urea (**19**) (30.0 g, 0.254 mol) was added to a stirred solution of Na (11.5 g, 0.500 g-atom) in 300 ml of dry EtOH and refluxed overnight. The EtOH was removed *in vacuo* and the residue was dissolved in H_2O. The solution was made acidic (10% HCl) and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to yield **13** (32.5 g, 49%), mp 170° (EtOAc).

Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.32; H, 5.54; N, 10.45

N-(**4-Hydroxybutyl**)**-5-phenylbarbituric Acid (14).**—Essentially the same procedure was utilized as reported above. A white solid was obtained from 29.26 g (0.124 mol) of diethyl phenylmalonate and 16.4 g (0.124 mol) of 4-hydroxy-*n*-butylurea in the presence of 5.7 g (0.248 g-atom) of Na dissolved in 300 ml of EtOH. The solid was recrystallized (EtOAc) to yield 12.5 g (36%) of the desired product **14**, mp 186–188°. The spectral data were consistent with the assigned structure.

Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.85; H, 5.83; N, 10.13. Found: C, 61.03; H, 6.04; N, 10.01.

N-(**3-Bromopropyl**)**-5-phenylbarbituric Acid (11).**—A stirred solution of *N*-(3-hydroxypropyl)-5-phenylbarbituric acid (**10**) (10.0 g, 0.038 mol) in 100 ml of 32% HBr–HOAc was refluxed overnight in a stoppered Wheaton glass pressure bottle. The HOAc was removed *in vacuo* and the residue was added to 400 ml of crushed ice. The solution was made acidic and decanted from the gummy precipitate, which was dissolved in Me_2CO, dried ($MgSO_4$), and concentrated to leave a solid which was washed with Et_2O to yield 11 (9.2 g, 74.2%), mp 120° (EtOAc–petroleum ether).

Anal. Calcd for $C_{13}H_{13}N_2O_3Br$: C, 48.01; H, 4.02; N, 8.61. Found: C, 47.71; H, 4.08; N, 8.59.

N-(**4-Bromobutyl**)**-5-phenylbarbituric Acid (15).**—The procedure was essentially that used for the preparation of **11**. The crude product was recrystallized from Me_2CO–petroleum ether (bp 60–68°) to yield white crystals (70%), mp 125–127°.

Anal. Calcd for $C_{14}H_{15}N_2O_3Br$: C, 49.57; H, 4.46; N, 8.26. Found: C, 49.56; H, 4.26; N, 8.55.

2,4-Diketo-3-phenyl-Δ^5-7-oxa-1,5-diazabicyclo[4.4.0]decane (23).—*N*-(3-bromopropyl)-5-phenylbarbituric acid (**11**) (2.0 g, 0.006 mol) was dissolved in 250 ml of anhydrous dimethoxyethane (DME) at 25°. To this solution was added, at one time, a solution of thallium ethoxide ($TlOC_2H_5$) (1.54 g, 0.006 mol) in 50 ml of anhydrous DME. A white, crystalline product formed immediately. This material was filtered, washed with water, and refluxed in 500 ml of C_6H_6–H_2O (1:1) for 12 hr. The two-phase system was cooled and the aqueous layer was acidified with 10% HCl and extracted with EtOAc (3 × 150 ml). The extracts were combined, dried ($MgSO_4$), and filtered and the solvent was removed to yield 0.81 g (55%) of **23** as a white solid which was recrystallized from EtOAc: mp 294–297° dec; ir (KBr) 3400, 3190, 1700, 1630, 1590, 1490, 1280 cm^{-1}; nmr (DMSO-d_6) δ 2.0–2.5 (2 H, multiplet, $-CH_2CH_2CH_2-$), 3.4 (1 H, singlet, benzylic H), 3.8–4.0 (2 H, triplet, $-NCH_2-$), 4.3–4.5 (2 H, triplet, $-OCH_2-$), 7.4 (5 H, singlet, aromatic).

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.46. Found: C, 64.22; H, 5.09; N, 11.30.

The same procedure utilizing the thallous salt of *N*-(3-iodopropyl)-5-phenylbarbituric acid (**16**) afforded a 28% yield of **23**.

2,4-Diketo-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.4.0]decane (22).—The thallous salt of **11** was prepared as in the preparation of **23** and 1.55 g (0.0029 mol) of the white solid was refluxed in anhydrous C_6H_6 for 8 hr. Water was added to dissolve the yellow precipitate (TlBr) The aqueous layer was acidified with 10% HCl and extracted with EtOAc (3 × 150 ml). The extracts were combined, dried ($MgSO_4$), and filtered and the solvent was removed to yield 350 mg (49%) of **22** as a white solid which was recrystallized from EtOAc: mp 292–295°; ir (KBr) 3400, 3160, 2990, 1710–1590, 1480, 1430, 1270, 1200, 1170, 1130, 1095 cm^{-1}; nmr (DMSO-d_6) δ 2.0–2.5 (2 H, multiplet, $-CH_2CH_2CH_2-$), 3.7–3.9 (2 H, triplet, $-NCH_2-$), 4.2–4.4, (2 H, triplet, $-OCH_2-$), 7.8 (5 H, singlet, aromatic), 11.2 (1 H, singlet, O=CNHC=O).

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.46. Found: C, 63.98; H, 4.74; N, 11.56.

Registry No.—**9**, 35359-11-6; **10**, 35359-12-7; **11**, 35359-13-8; **12**, 35359-14-9; **13**, 35359-15-0; **14**, 35359-16-1; **15**, 35427-24-8; **18**, 2078-71-9; **19**, 16517-53-6; **20**, 34486-68-5; **22**, 30409-28-0; **23**, 35359-21-8.

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