# The Synthesis and Rearrangement of 5-Phenyl-7-methoxy-2,4,9-triketo-1,3-diazabicyclo[3.3.1]nonane

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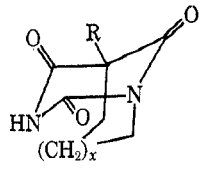
The synthesis and proof of structure of the bicyclobarbiturate, 5-phenyl-7-methoxy-2,4,9-triketo-1,3-diazabicyclo[3.3.1]nonane (**2**), is described. An attempt was made to demethylate **2** utilizing boron trichloride and resulted in the formation of a γ-lactone. A plausible mechanism for this transformation is given.

A study of the steric aspects of antiepileptic drug action was initiated by investigating the synthesis of bridged barbituric acids (**1**).

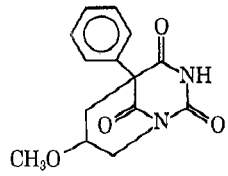


**1**

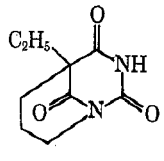
R = alkyl, aryl

$x = 0, 1, 2$

The initial approach to this desired system involved a base catalyzed intramolecular attack by an imide nitrogen on a suitable substituent located on a 5-alkyl side chain of a barbituric acid. In these laboratories 5-phenyl-7-methoxy-2,4,9-triketo-1,3-diazabicyclo-[3.3.1]nonane (**2**) was prepared by this route. Baumler and coworkers[2] have reported the synthesis of 5-ethyl-



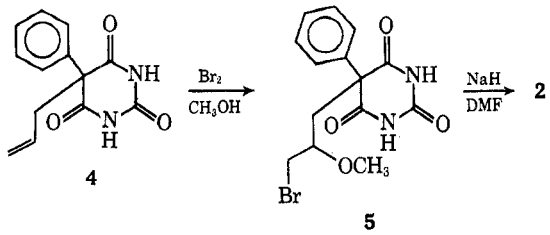
**2**



**3**

2,4,9-triketo-1,3-diazabicyclo[3.3.1]nonane (**3**) by a similar method; however, there is reason to believe that their structure assignment was erroneous[3] and thus a rigorous structure proof of the bicyclic system was undertaken.

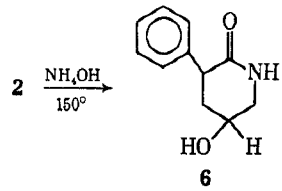
The synthesis of the bicyclic barbiturate **2** involved the conversion of 5-phenyl-5-allylbarbituric acid (**4**) to 5-phenyl-5-(2-methoxy-3-bromopropyl)barbituric acid (**5**) by treatment with bromine in methanol. The structure of the bromo ether, **5**, was confirmed by nmr



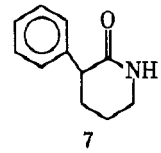
**4** **5**

in that the spectrum had a doublet at δ 3.10–3.30 ($-CH_2Br$) and a broad multiplet at δ 4.50–4.90 ($>CHOCH_3$). Treatment of the bromo ether, **5**, with sodium hydride produced the desired bicyclic barbiturate, **2**. The absence of absorption at 1625–1650 $cm^{-1}$ (>C=N– stretch) in the infrared spectrum of **2** eliminated the possibility of an *O*-alkylated product.[3]

Further proof of *N*-alkylation was obtained by degradation of the barbiturate ring under basic conditions. When the bicyclic system, **2**, was treated with ammonium hydroxide, 5-hydroxy-3-phenyl-2-piperidone (**6**) was obtained. Its infrared spectrum showed a band at 3390 $cm^{-1}$ (OH stretch) while the remainder of the spectrum was almost identical with that of 3-phenyl-2-piperidone (**7**).[4]



**6**



**7**

The demethylation of **2** during the hydrolysis constitutes a somewhat anomalous situation, considering the basic conditions utilized. The degradation product, however, supports the assignment of compound **2** as the *N*-alkylated structure.

An attempt to demethylate **2** utilizing boron trichloride[5] resulted in the formation of a γ-lactone **8**. The nmr spectrum of **8** showed the absence of *O*-methyl-protons and a shift of one NH proton from δ 10.0 (observed for barbituric acid imide protons in DMSO)[6] to δ 7.90. Infrared spectroscopy indicated the presence of a γ-lactone carbonyl (1780 $cm^{-1}$).

The formation of this lactone in high yield indicates that the methyl ether in **2** is probably in an exo configuration (in relation to the C-9 ketone) since cleavage of methyl ethers with other strong Lewis acids has been shown to proceed with retention of configuration.[7] A

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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).

(3) E. E. Smissman and R. A. Robinson, *J. Org. Chem.*, **35**, 3532 (1970).

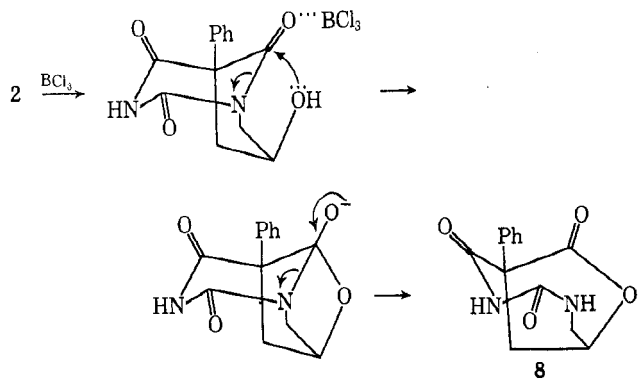
(4) R. K. Hill, C. E. Glassik, and E. J. Fleinder, *J. Amer. Chem. Soc.*, **81**, 737 (1959).

(5) F. M. Dean, J. Goodchild, L. E. Houghton, J. A. Martin, R. B. Morton, B. Parton, A. W. Price, and N. Somvichien, *Tetrahedron Lett.*, 4153 (1966).

(6) G. M. Kheifets, N. V. Khromov, A. I. Borison, A. I. Koltsov, and M. V. Volkenstein, *Tetrahedron*, **23**, 1197 (1967).

(7) C. R. Narayanan and K. N. Iyer, *J. Org. Chem.*, **30**, 1734 (1965).

plausible mechanism for this transformation is shown below.



8

The syntheses of bicyclic hydantoins, oxazolidindiones, glutarimides, and succinimides are currently being investigated.

## Experimental Section[8]

**5-Phenyl-5-(2-methoxy-3-bromopropyl)barbituric Acid (5).**—A solution of 5-phenyl-5-allylbarbituric acid (4) (6.10 g, 0.025 mol) in MeOH (90 ml), cooled to 10°, was slowly added to a cold solution of $Br_2$ (4.00 g, 0.025 mol) in MeOH (20 ml). The mixture was stirred for 2 hr at 10° and allowed to warm to 25°. The precipitate was filtered and air dried. Recrystallization from EtOH gave **5** (7.70 g, 87%): mp 209–209.5°; ir (Nujol) 3310, 1745, 1735; nmr ($CF_3CO_2H$) 2.40–2.80 (2 H, multiplet, $CH_2$), 3.10–3.30 (2 H, doublet, $-CH_2Br$), 3.58 (3 H, singlet, $-OCH_3$), 4.50–4.90 (1 H, multiplet, HCOCH$_3$), 7.10 (5 H, aromatic).

*Anal.* Calcd for $C_{14}H_{15}N_2O_4Br$: C, 47.34; H, 4.26; N, 7.89; Br, 22.50. Found: C, 47.44; H, 4.48; N, 7.95; Br, 22.20.

**5-Phenyl-7-methoxy-7-2,4,9-triketo-1,3-diazabicyclo[3.3.1]nonane (2).**—To 5-phenyl-5-(2-methoxy-3-bromopropyl)barbituric acid (4.00 g, 0.011 mol) in DMF (100 ml) (anhydrous) at 25° was added 50% NaH–mineral oil suspension (0.54 g, 0.011 mol). The mixture evolved $H_2$ immediately and was stirred at 25° for 20 hr. The DMF was removed at 100° under a stream of $N_2$ to afford a solid and a reddish-brown oil. The oil was dissolved in acetone, filtered, and cooled to afford a white solid, mp 237–240°. The filtered solid was washed with $H_2O$, and crystallization (MeOH) afforded **2** (0.78 g, 25.2%): mp 240.5–242.5°; ir (KBr) 3390, 3180, 3080, 1740, 1700; nmr ($CF_3CO_2H$) 3.10–3.70 [5 H, singlet ($-OCH_3$) and multiplet ($-CH_2$)], 3.80–4.80 (2 H, multiplet, $CH_2$), 5.00 (1 H, multiplet, CH), 7.40 (5 H, singlet, aromatic).

*Anal.* Calcd $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.15; N, 10.21; mol wt, 274. Found: C, 60.91; H, 5.41; N, 10.11; mol wt, 274 (mass spectrum).

**3-Phenyl-5-hydroxy-2-piperidone (6).**—A suspension of 5-phenyl-7-methoxy-2,4,9-triketo-1,3-diazabicyclo[3.3.1]nonane, **2** (0.50 g, 1.41 mmol), in a solution of 30% $NH_4OH$ (6 ml) and $H_2O$ (34 ml) was heated at 150° in a steel autoclave. After 48 hr the reaction was cooled to 25°, and evaporation of the aqueous solution gave a red residue which was dissolved in 95% EtOH, filtered, and was allowed to stand. The hydroxypiperidone (**6**) (0.18 g, 65%) crystallized: mp 202–205°; ir (KBr) 3390 (OH), 3178, 3025, 2900, 1625 (lactam >C=O); nmr (DMSO-$d_6$) 1.83–2.20 (2 H, multiplet, $CH_2$), 3.00–4.18 (4 H, multiplet), 5.00 (1 H, multiplet, OH), 7.20 (5 H, singlet, aromatic), 7.41 (1 H, broad singlet, amide).

*Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.34. Found: C, 68.68; H, 6.92; N, 7.33.

**Reaction of 5-Phenyl-7-methoxy-2,4,9-triketo-1,3-diazabicyclo[3.3.1]nonane (2) with Boron Trichloride.**—To a stirred suspension of **2** (0.10 g, 0.73 mmol) in methylene chloride (50 ml) at −70° was added an excess of $BCl_3$. The mixture was stirred for 2 hr and allowed to warm to 25°. The solvent was removed *in vacuo* and the residue was washed several times with hot $H_2O$, filtered, and dried. Recrystallization ($Me_2CO$–$Et_2O$) yielded lactone **8** (0.08 g, 85%): mp 182–184°; ir (KBr) 3250, 3050, 2875, 1780 (lactone >C=O), 1660–1680; nmr (DMSO-$d_6$) 2.80–3.10 (4 H, multiplet, $CH_2$), 4.80–5.10 (1 H, multiplet, methine), 7.20–7.90 (6 H, multiplet, aromatic and amide), 10.0 (1 H, broad singlet, imide).

*Anal.* Calcd for $C_{13}H_{12}N_2O_4$: C, 59.99; H, 4.64; N, 10.77; mol wt, 260. Found: C, 59.75; H, 4.42; N, 10.80; *m/e* 217 [loss of HNCO (43)].

(8) Melting points were obtained on a calibrated Thomas–Hoover Unimelt and are corrected. Ir data were recorded on Beckman IR-8 and IR-10 spectrophotometers and are reported in $cm^{-1}$. Nmr data were recorded on Varian Associated Model A-60, A-60A, and HA-100 spectrophotometers (TMS) and are reported as ppm ($\delta$). Microanalyses were conducted by Midwest Microlab, Inc., Indianapolis, Ind., and on an F & M Model 185, University of Kansas. Molecular weights were determined on a Finnigan 1015 mass spectrometer.

**Registry No.**—**2**, 25860-23-5; **5**, 25860-24-6; **6**, 25860-25-7; **8**, 25860-26-8.

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