Intramolecular Isomerizations of 5-Phenyl-5-(3-aminopropyl)barbituric Acids

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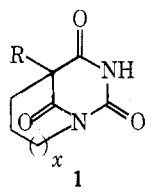
In an attempt to prepare the N-alkylated rigid analog of phenobarbital **1** from 5-phenyl-5-(3-bromopropyl)barbituric acid (**6**) an unexpected intramolecular isomerization occurred. Treatment of **6** with ammonium hydroxide yielded 3-phenyl-3-allophanyl-2-piperidone (**10**), which was further hydrolyzed to 3-phenyl-2-piperidone (**8**). In a similar manner 5-phenyl-5-(2-hydroxypropyl)barbituric acid (**14**) underwent a similar intramolecular isomerization to yield α-phenyl-α-allophanyl-γ-valerolactone (**17**).

As part of a continuing study on the steric requirements for selective central nervous system depression, attempts have been made to develop general synthetic routes to bridged barbituric acids **1**, to be investigated as antiepileptic agents.

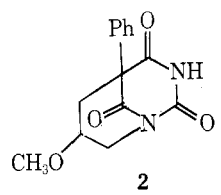


1

R = alkyl, aryl

x = 0, 1, 2

Although attempts to prepare such ring systems have met with great difficulty, one such barbituric acid, 5-phenyl-7-methoxy-2,4,9-triketo-1,3-diazabicyclo[3.3.1]nonane (**2**), has been prepared.[2] Its synthesis was accomplished via an intramolecular imide attack on the primary bromide function of 5-phenyl-5-(2-methoxy-3-bromopropyl)barbituric acid (**3**).



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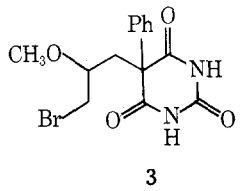

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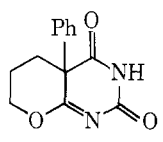

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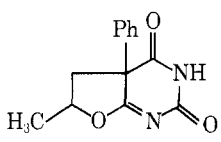

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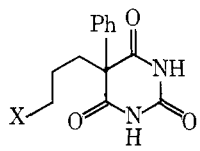
This procedure did not prove to be a general method for the desired compounds, since similar intramolecular alkylations of 5-phenyl-5-(3-halopropyl)- and 5-(2-halopropyl)-barbituric acids yielded the O-alkylated pyrano- and furopyrimidines **4** and **5**, rather than the N-alkylated systems.[3]

Taylor and McKillop[4] have reported exclusive C-alkylation when the thallous salts of 1,3-dicarbonyl compounds were heated with alkyl halides. In an attempt to extend this selectivity to our systems, it was hoped that the thallous salt of **6** could give the barbiturate **1** by intramolecular displacement by the imide nitrogen at N-1 of a proper side-chain substituent.

Kornblum and coworkers[5] have reported the importance of solvent in determining the ratios of C-alkylation to O-alkylation in the alkylation of ambident anions. Higher ratios of C-alkylated products were obtained when the alkylations were performed in fluoro alcohols or water.

With these facts in mind, it was hoped that heating the thallous salt of **6** in an aqueous benzene solvent system would yield the desired N-alkylated product **1** in preference to the O-alkylated pyranopyrimidine **4**.

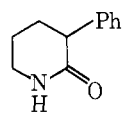
The thallous salt of 5-phenyl-5-(3-bromopropyl)barbituric acid (**6**) was prepared by the addition of thallium ethoxide in anhydrous dimethoxyethane (DME) to a solution of **6** in DME. However, when the thallous salt of **6** was refluxed in a 50:50 water–benzene solvent system, 5-phenyl-5-(3-hydroxypropyl)barbituric acid (**7**) and a colorless gum



6, X = Br

7, X = OH

were obtained. Formation of **7** may have resulted either from direct solvent attack on **6** during reflux or from hydrolysis of the O-alkylated intermediate **4** during purification. The gum, although not completely purified, exhibited R_f values very similar to those of **6** in numerous TLC solvent systems. Treatment of the gum with ammonium hydroxide at 150° led to the formation of 3-phenyl-2-piperidone (**8**), the expected hydrolysis product of **1**. However,



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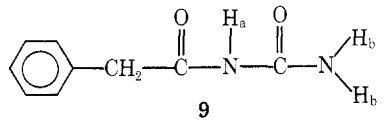
treatment of an authentic sample of **6** under identical conditions also yielded **8** in excellent yield.

In an attempt to isolate intermediates in the formation of **8**, **6** was treated with ammonium hydroxide at 50°, affording a product which was insoluble in dilute acid but soluble in dilute base. The ir spectrum showed three sharp carbonyl absorptions at 1650, 1690, and 1720 cm^{-1} in addition to NH absorptions at 3400, 3350, and 3250 cm^{-1}. The NMR spectrum (DMSO-d_6) showed the presence of one imide proton at δ 10.04 and H_a in phenylacetylurea **9** occurs at δ 10.10. In both compounds the aromatic region integrates for seven protons and in **9** the H_b protons fall under



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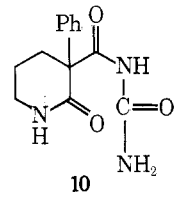
the aromatic protons. These data, therefore, suggested the presence of the allophanyl moiety, $-CONHCONH_2$. Warm-

† Deceased, July 14, 1974.

ing with dilute acid or treatment with nitrous acid converted the product to **8**. From these data the product isolated was 3-phenyl-3-allophanyl-2-piperidone (**10**).



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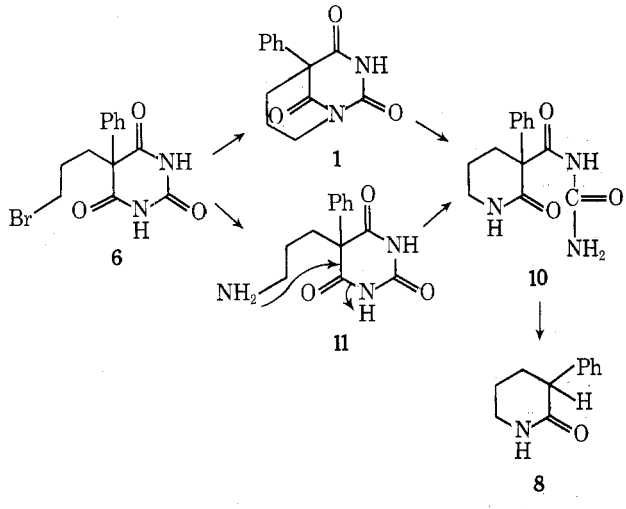
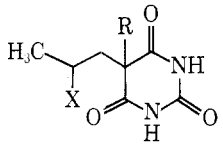
Therefore, the formation of **8** from **6** can be envisioned to occur by either of two pathways.

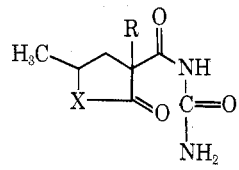
Pathway 1. Treatment of **6** with ammonium hydroxide leads to the abstraction of the imide proton followed by N-alkylation to give **1**. Compound **1** is then opened to **10**, which is further hydrolyzed to **8**.

Pathway 2. Alternatively, treatment of **6** with ammonium hydroxide leads, not to proton abstraction, but to the ammonolysis of **6** to yield the primary amine **11**. The primary amino function attacks the C-6 (C-4) carbonyl of the barbiturate ring in a neighboring group with ring opening to yield **10**, which is further hydrolyzed to **8**.



Bobranski and coworkers[6] have reported that 5-allyl-5-(2-hydroxypropyl)barbituric acid (**12**) undergoes a similar type of intramolecular isomerization to yield α-allyl-α-allophanyl-γ-valerolactone (**15**).

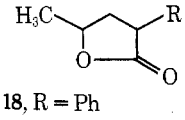




	X	R
12	OH	$CH_2CH{=}CH_2$
13	NH_2	$CH_2CH{=}CH_2$
14	OH	Ph

	X	R
15	O	$CH_2CH{=}CH_2$
16	NH	$CH_2CH{=}CH_2$
17	O	Ph

We similarly found that treatment of 5-phenyl-5-(2-hydroxypropyl)barbituric acid (**14**) with a catalytic amount of ammonium hydroxide yielded α-phenyl-α-allophanyl-γ-valerolactone (**17**). Hydrolysis of **17** under acidic conditions afforded α-phenyl-γ-valerolactone (**18**).

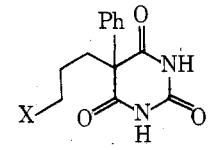


18, R = Ph

19, R = $CH_2CH{=}CH_2$

The amino derivative, 5-allyl-5-(2-aminopropyl)barbituric acid (**13**), however, failed to undergo such an isomerization to α-allophanyl-α-allyl-γ-valerolactam (**16**) and only α-allyl-γ-valerolactone (**19**) was formed.[7]

An attempt was made to obtain 5-phenyl-5-(3-aminopropyl)barbituric acid (**11**) by the reaction of **6** with gaseous ammonia under various conditions;[8] however, no identifiable products were obtained. An alternate approach to **11** involved the conversion of **6** to 5-phenyl-5-(3-azidopropyl)barbituric acid (**20**). Hydrogenation of **20** yielded the primary amine **11**. Treatment of **11** with ammonium hydroxide led to the formation of **10**.



20, X = N_3

21, X = $N(C_2H_5)_2$

In a similar manner, treatment of **6** with diethylamine afforded 5-phenyl-5-(3-diethylaminopropyl)barbituric acid (**21**), whereas addition of aqueous methylamine to **6** yielded a mixture of oils.

These results, although not eliminating pathway 1, suggest that treatment of **6** with ammonium hydroxide leads to the formation of **11**, which then isomerizes to **10** (pathway 2).

Experimental Section[9]

Treatment of 5-Phenyl-5-(3-bromopropyl)barbituric Acid (6) with Ammonium Hydroxide in the Autoclave. A suspension of 5-phenyl-5-(3-bromopropyl)barbituric acid (**6**, 5.0 g, 0.0154 mol) in 50 ml of concentrated NH_4OH (58%) was heated in a steel autoclave at 160° for 24 hr. The autoclave was allowed to cool to room temperature and opened, and the contents were filtered. Recrystallization of the solids from acetone yielded 2.0 g (0.0114 mol, 74%) of 3-phenyl-2-piperidone (**8**) as white needles, mp 169–171° (lit.[10] mp 170.0–170.5°). The ir spectrum of **8** was completely superimposable on the ir spectrum of an authentic sample of 3-phenyl-2-piperidone prepared by an alternate route.[10] Anal. Calcd for $C_{11}H_{13}NO$: C, 75.39; H, 7.47; N, 7.99. Found: C, 75.67; H, 7.62; N, 7.83.

3-Phenyl-3-allophanyl-2-piperidone (10). A suspension of 5-phenyl-5-(3-bromopropyl)barbituric acid (**6**, 15.0 g, 0.046 mol) in 150 ml of concentrated NH_4OH (58%) was heated on a steam bath for 1 hr. The reaction mixture was cooled to room temperature and filtered to yield 7.10 g (0.027 mol, 59%) of a white, crystalline solid. Recrystallization from CH_3OH yielded **10** as pure white needles: mp 220–221°; NMR (trifluoroacetic acid, 1% TMS) (detection of imide and lactam nitrogen H was made in DMSO-d_6) δ 1.40–1.80 (m, 2, $-CH_2CH_2CH_2-$), 2.20–2.60 (m, 2, $-CH_2-$), 3.20–3.60 (m, 2, $-CH_2NH$), 7.16 (singlet superimposed and broad singlet, 7, aromatic and $-NH_2$), 8.43 (br s, 1, $-CH_2CONH-$), 10.04 (s, 1, $-CONHCO-$).

Anal. Calcd for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.78; N, 16.08. Found: C, 59.97; H, 5.74; N, 16.25.

5-Phenyl-5-(3-azidopropyl)barbituric Acid (20). Sodium azide (19.5 g, 0.30 mol) and 5-phenyl-5-(3-bromopropyl)barbituric acid (**6**, 52.0 g, 0.16 mol) were dissolved in a mixture of 600 ml of acetone and 400 ml of H_2O. The reaction mixture was heated at reflux for 18 hr, cooled to room temperature, and filtered. The filtrate was concentrated in vacuo to yield a slightly yellow solid. The solid was filtered, washed with water, and air dried to yield 43.2 g (0.15 mol, 94%) of the desired product **20**. Recrystallization from 95% EtOH yielded small, white crystals: mp 183–184°; NMR (DMSO-d_6–$CDCl_3$, 1% TMS) δ 1.30–1.83 (m, 2, $-CH_2-$), 2.16–2.60 (m, 2, $-CH_2-$), 3.13–3.37 (t, 2, $-CH_2CH_2N_3$), 7.33 (s, 5, aromatic), 10.00–10.60 (br s, 2, imide H); ir (KBr) 3230, 3110, 2110, 1700, 1425, 1360, 830 cm^{-1}.

Anal. Calcd for $C_{13}H_{13}N_5O_3$: C, 54.35; H, 4.56; N, 24.38. Found: C, 54.70; H, 4.65; N, 24.31.

5-Phenyl-5-(3-aminopropyl)barbituric Acid Hydrochloride (11). A solution of 5-phenyl-5-(3-azidopropyl)barbituric acid (**20**,

21.3 g, 0.074 mol) in 160 ml of glacial acetic acid and 40 ml of dimethoxyethane (DME) was added to a suspension of 2 g of prereduced platinum oxide (Pt_2O) in 20 ml of HOAc in a Parr shaker hydrogenation apparatus. The azide was hydrogenated at an initial pressure of 50 psi at room temperature for 12 hr. The catalyst was filtered and the solvents were removed in vacuo to leave a clear, viscous oil. The oil was dissolved in 150 ml of anhydrous CH_3OH and saturated with gaseous HCl at 0–10°. Concentration of the solvents in vacuo yielded a pale, amorphous solid which was filtered, washed with Et_2O, and dried to yield 17.0 g (0.057 mol, 77%) of **11**. Recrystallization from CH_3OH–$CHCl_3$ yielded a white, amorphous powder: mp 262–263° dec; NMR (DMSO-d_6–$CDCl_3$, 1% TMS) δ 1.32–2.01 (m, 2, $-CH_2-$), 2.08–2.52 (m, 2, $-CH_2-$), 2.65–3.41 (m, 2, $-CH_2N^+$), 3.95 (s, 2.2, $-NH_3^+$, disappears with addition of D_2O), 7.32 (s, 5, aromatic), 11.42 (s, 2, imide H); ir (KBr) 3300–2900, 1710, 1405, 1345 cm^{-1}.

Treatment of 3-Phenyl-3-allophanyl-2-piperidone (10) with Nitrous Acid. Sodium nitrite (5 g) in 50 ml of water was added in a dropwise manner to a cooled solution (0–10°) of **10** (2.0 g, 0.0076 mol) in 200 ml of CH_3OH and 75 ml of concentrated HCl. With each addition a fine white precipitate formed in addition to the copious evolution of gas. After addition had been completed the reaction mixture was warmed to 80° for 15 min, cooled to room temperature, and filtered. A white, crystalline solid (0.8 g), mp 218–220°, was obtained whose ir spectrum was identical with that of the starting material **10**. Concentration of the CH_3OH solution in vacuo yielded a solid residue. This solid was dissolved in hot acetone and the solvent was allowed to slowly evaporate to yield an additional 0.7 g of **10**. Further evaporation of the solvent yielded 0.20 g (0.0011 mol, 15%), mp 170–171°, of a white, crystalline solid whose NMR and ir spectra were completely superimposable on those of an authentic sample of 3-phenyl-2-piperidone (**8**).

α-Allophanyl-α-phenyl-γ-valerolactone (17). To a solution of 5-phenyl-5-(2-hydroxypropyl)barbituric acid (**14**, 10.0 g, 0.038 mol) in 100 ml of CH_3OH was added 1 ml of concentrated NH_4OH (58%) and the resulting solution was heated at reflux for 2 hr. Removal of the solvent in vacuo yielded a white, crystalline solid. Recrystallization from CH_3OH yielded 5.10 g (0.019 mol, 51%) of **17** as pure white cubes: mp 167–169°; NMR (DMSO-d_6–$CDCl_3$, 1% TMS) δ 1.40–1.50 (d, 3, J = 6 Hz, CH_3CHO-), 2.70–2.90 (m, 2, $-CH_2-$), 4.13–4.80 (m, 1, CH_3CHO-), 7.43 (s, 7, aromatic and NH_2), 9.10 (s, 1, $-CONHCO-$); ir (KBr) 3420, 3230, 1755, 1725, 1700, 1590, 1375, 1190, 1215 cm^{-1}.

Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.64; H, 5.55; N, 10.78.

α-Phenyl-γ-valerolactone (18). To 50 ml of aqueous 5% hydrochloric acid (HCl) was added 5.1 g (0.019 mol) of α-allophanyl-α-phenyl-γ-valerolactone (**17**). The reaction mixture was heated to reflux for 4 hr, cooled to room temperature, extracted with 3 × 50 ml of diethyl ether, and dried ($MgSO_4$), and the solvent was removed in vacuo to yield 3.5 g of an oil–solid mixture. Filtration and distillation of the oil under reduced pressure yielded 2.30 g (0.013 mol, 68%) of **18** as a clear, colorless liquid: bp 146–147° (2 mm); NMR ($CDCl_3$, 1% TMS) δ 1.43–1.53 (dd, 3, J = 6 Hz, CH_3CHOCH_2-), 1.90–3.00 (m, 2, $-CH_2-$), 3.55–4.03 (m, 1, $-CH_2-CHPh$), 4.33–4.97 (m, 1, CH_3CHO), 7.33 (s, 5, aromatic); ir (neat) 1770, 1170 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.73; H, 7.25.

Treatment of 5-Phenyl-5-(3-aminopropyl)barbituric Acid Hydrochloride (11) with Ammonium Hydroxide. A solution of 2.0 g (0.0067 mol) of 5-phenyl-5-(3-aminopropyl)barbituric acid hydrochloride (**11**) in 10 ml of concentrated NH_4OH (58%) was heated on a steam bath for 1 hr. The reaction mixture was allowed to cool to room temperature, during which time a gummy residue formed. The aqueous phase was made acidic with 10% HCl and decanted, and the solids were collected. Recrystallization of the solids from CH_3OH yielded 0.85 g (0.0032 mol, 48%) of 3-phenyl-3-allophanyl-2-piperidone (**10**) as pure white needles, mp 219–221°. The ir spectrum of the product was completely superimposable on the ir spectrum of an authentic sample of **10** prepared by an alternate route.

5-Phenyl-5-(3-diethylaminopropyl)barbituric Acid (21). A solution of 5-phenyl-5-(3-bromopropyl)barbituric acid (**6**, 6.50 g, 0.020 mol) in 200 ml of 50% aqueous diethylamine was heated to reflux for 1 hr. Removal of excess volatile components yielded a milky white solution. Careful acidification (aqueous 10% HCl) of the aqueous solution to pH 6–7 yielded 2.70 g (0.012 mol, 60%) of a white solid. Recrystallization from CH_3OH yielded **21** as very fine, white needles: mp 256–257° dec; NMR (trifluoroacetic acid, 1% TMS) δ 1.30–1.60 (t, 6, $-NCH_2CH_3$). 1.73–2.23 (m, 2, $-CH_2-$), 3.10–3.60 (m, 6, $-NCH_2-$) 7.37 (s, 5, aromatic); ir (KBr) 3250, 3450, 1690, 1600, 1410, 1380, 1445, 1290, 1260 cm^{-1}.

Anal. Calcd for $C_{17}H_{23}N_3O_3$: C, 64.33; H, 7.30; N, 13.24. Found: C, 64.13; H, 7.30; N, 13.37.

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Registry No.—**6**, 25860-47-3; **8**, 51551-56-5; **10**, 54832-99-4; **11**, 54833-00-0; **14**, 25860-53-1; **17**, 54833-01-1; **18**, 40923-67-9; **20**, 54833-02-2; **21**, 54833-03-3; ammonium hydroxide, 1336-21-6; sodium nitrite, 7632-00-0; diethylamine, 109-89-7; sodium azide, 26628-22-8.

References and Notes

(1) Taken in part from the dissertation presented by P. J. Wirth, Aug 1974, 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, J. B. Carr, and A. J. Matuszak, *J. Org. Chem.*, **35**, 3821 (1970).
(3) E. E. Smissman, R. A. Robinson, and A. J. Matuszak, *J. Org. Chem.*, **35**, 3822 (1970).
(4) E. C. Taylor and A. McKillop, *Acc. Chem. Res.*, **3**, 338 (1970).
(5) N. Kornblum, P. J. Berrigan, and W. J. LeNoble, *J. Am. Chem. Soc.*, **85**, 1141 (1963).
(6) (a) B. Bobranski, D. Prelicz, L. Syper, and R. Wojtowski, *Rocz. Chem.*, **37**, 395 (1963); (b) *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **8**, 475 (1960).
(7) M. Konieczny, *Arch. Immunol. Ther. Exp.*, **15**, 920 (1967).
(8) G. S. Skinner, A. Stoker, and G. Spiller, *J. Am. Chem. Soc.*, **69**, 3083 (1947).
(9) Infrared spectra were obtained on a Beckman IR-33 spectrophotometer. Nuclear magnetic resonance spectra were obtained using Varian A-60A and T-60 spectrometers. Elemental analyses were determined on a Hewlett-Packard 185 C, H, N analyzer at the University of Kansas. Melting points were obtained on a calibrated Thomas-Hoover Unimelt and are corrected.
(10) R. K. Hill, C. E. Glassick, and L. J. Fliedner, *J. Am. Chem. Soc.*, **81**, 737 (1959).