Reduction of Barbiturates under Hydroboration Conditions

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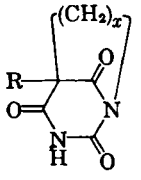
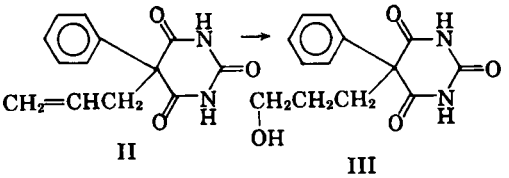
An attempt to utilize hydroboration conditions on 5-phenyl-5-allyl barbituric acid afforded unexpected reduction of the barbituric acid nucleus. Further investigation of this reaction indicated sodium borohydride-boron trifluoride etherate will reduce 5-phenyl-5-ethyl barbituric acid to 5-phenyl-5-ethyl-2,4-hexahydropyrimidinedione (V) and 5-phenyl-5-ethyl-2-hexahydropyrimidinone (VI) in a stepwise manner.

During the synthesis of bridged barbiturates of the type I as potential anticonvulsant agents, an attempt was made to prepare 5-phenyl-5-(3-hydroxypropyl) barbituric acid (III) from 5-phenyl-5-allyl barbituric acid (II) by the hydroboration procedure of Brown (1).



I R = alkyl, aryl; $x = 0, 1, 2$, etc.



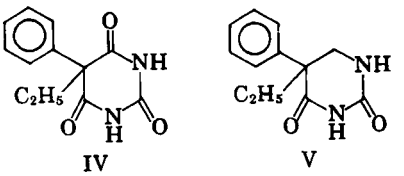
II III

The normal hydroboration procedure failed to give the desired product, and an investigation of this reaction was undertaken.

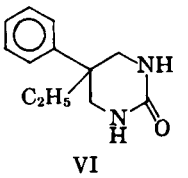
Phenobarbital (5-phenyl-5-ethylbarbituric acid) (IV) was subjected to hydroboration conditions and gave 5 - phenyl - 5 - ethyl - 2,4 - hexahydropyrimidinedione (V). The extension of this reduction to preparation of the mono- and diketo compounds from the corresponding barbiturates appeared feasible. The reduction of phenobarbital only proceeded using the conditions described by Brown (1). Sodium borohydride in absolute alcohol, tetrahydrofuran, or diglyme would not reduce the molecule, even though the liberation of hydrogen was observed. Sodium borohydride with hydrochloric acid in tetrahydrofuran was also ineffective (2). The possibility existed that diborane was the reducing agent; however, this agent in diglyme and tetrahydrofuran failed to reduce phenobarbital.

In the normal hydroboration procedure, oxidation to an alcohol is accomplished using sodium hydroxide and hydrogen peroxide. No reduction product was obtained until this procedure was invoked. If either sodium hydroxide or hydrogen peroxide was omitted, no product was obtained. If sodium phenobarbital rather than the acid was employed in the initial reaction, no reduction occurred. The application of heat to the reaction mixture had no effect on yield.

The stepwise reduction of phenobarbital proceeded smoothly to reduce two carbonyl groups but stopped with the formation of 5-phenyl-5-ethyl-2-hexahydropyrimidinone (VI). An excess of sodium borohydride and boron trifluoride-etherate did not increase the yield or result in the formation of the nonoxygenated product.



IV V

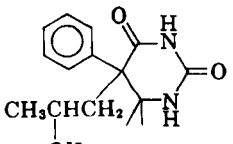


VI

Marshall (3) was able to prepare the 2-hexahydropyrimidinone (VI) utilizing lithium aluminum hydride.

The reaction was attempted on two barbiturates not containing a phenyl ring, 5,5-diethyl-1-methylbarbituric acid, and 5-ethyl-5-(1-methylbutyl) barbituric acid. Under a variety of conditions, including sodium borohydride in the presence of aluminum chloride (4), no reaction occurred.

The product obtained in the attempted hydroboration of allylphenylbarbituric acid (5-phenyl-5-allylbarbituric acid) (II) contained three atoms of oxygen rather than the predicted four atoms. The infrared spectrum of this compound showed a band at 7.27 μ attributable to C-methyl absorption, and the compound gave a positive iodoform test. It would be expected that side-chain hydroxylation and the reduction of the 6-keto function in the nucleus would give a compound capable of forming a dibenzoate. When the hydroboration product was treated with benzoyl chloride, a dibenzoate was obtained. Infrared analysis showed a band at 5.68 μ, which can be assigned to an ester carbonyl, and a band at 8.04 μ that could be due to the grouping C—O—C. This evidence leads to the conclusion that the product is 5-phenyl-5-(2-hydroxypropyl)-2,4-hexahydropyrimidinedione (VII).



VII

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The mechanism and unique specificity of this reaction will be investigated further.

EXPERIMENTAL[1]

5 - Phenyl - 5 - ethyl - 2,4 - hexahydropyrimidinedione (V).—To a stirred solution of 2.8 Gm. (0.073 mole) sodium borohydride in 85 ml. of diglyme maintained under nitrogen was added 23.2 Gm. (0.1 mole) of 5-phenyl-5-ethyl barbituric acid. Immediate effervescence was observed. A solution of 8.0 Gm. (0.056 mole) of boron trifluoride etherate in 15 ml. of diglyme was then added dropwise over a 40-minute period. The mixture was stirred 2.5 hours at room temperature and 0.5 hour at 100°. The clear solution was cooled and 20 ml. of water added in 5-ml. portions. Sodium hydroxide (4.8 Gm. in 40 ml. of water) was added to the frothing mixture as one portion. Hydrogen peroxide (30%, 40 ml.) was slowly added in a manner which caused gentle refluxing. The mixture was allowed to stand 12 hours at room temperature and crystals formed, m.p. 255–260°. The crystals were filtered, dissolved in 5% sodium hydroxide, and precipitated by the addition of 5% hydrochloric acid. The precipitate was recrystallized from ethanol to give 6.24 Gm. (28.6%) of a crystalline material, m.p. 268–269°. The product was identical to a known sample (5) as shown by infrared spectrum and mixed melting point.

Anal.—Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.81; H, 6.69; N, 12.72.

5 - Phenyl - 5 - ethyl - 2 - hexahydropyrimidinone (VI).—Using the general procedure described above, 5.6 Gm. (0.147 mole) of sodium borohydride and 32.0 Gm. (0.224 mole) of boron trifluoride etherate was allowed to react with 23.2 Gm. (0.1 mole) of 5-phenyl-5-ethyl barbituric acid. The cooled reaction mixture was treated with 40 ml. of water, sodium hydroxide (9.16 Gm. in 80 ml. of water), and hydrogen peroxide (30%, 80 ml.) and allowed to stand 12 hours at room temperature. The mixture separated into two layers. The upper layer was decanted, diluted with water to the cloud point, and allowed to stand 24 hours at room temperature. The resulting precipitate was crystallized from ethanol-skellysolve B to give 5.6 Gm. (27.4%) of the desired product, m.p. 195–197°.

Anal.—Calcd. for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.89; N, 13.71. Found: C, 70.34; H, 7.82; N, 13.28.

The product was identical in melting point and infrared spectrum to a sample prepared by the method of Marshall (3).

Hydroboration of 5-Phenyl-5-allylbarbituric Acid (II).—To a solution of 1.9 Gm. (0.05 mole) of sodium borohydride in 50 ml. of diglyme was added 2.62 Gm. (0.017 mole) of anhydrous aluminum chloride in 50 ml. of cold diglyme. A solution of 24.4 Gm. (0.1 mole) of allylphenylbarbituric acid in 50 ml. of diglyme was added dropwise over a period of 1 hour, after nitrogen was allowed to sweep through the apparatus for 15 minutes. The reaction mixture was allowed to stir at room temperature for 1 additional hour, then heated at 100° for 1 hour. After the reaction cooled to room temperature, 10 ml. of water was added in small portions. A solution of 2.4 Gm. of sodium hydroxide in 20 ml. of water was added, followed by 16 Gm. of 30% hydrogen peroxide. After standing overnight, the solution was filtered and the filtrate acidified with 85% phosphoric acid to pH 2. Two layers separated, with crystals forming at the interface. After standing, 5.31 Gm. (19%) of white crystalline material was obtained, m.p. 310° dec. Recrystallization from absolute alcohol gave crystals, m.p. 316–317° dec.

Anal.—Calcd. for $C_{23}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 63.35; H, 6.34; N, 11.25.

Principal absorbance bands in the infrared occurred at 5.85 μ (broad, single) and at 7.27 μ.

The filtrate was concentrated until it became viscous, water was added, and the mixture extracted with ether. The ether solution was dried over magnesium sulfate and distilled to leave a residue, which on crystallization, afforded 9.4 Gm. (0.039 mole) of allylphenylbarbituric acid.

Reaction of Allylphenylbarbituric Acid Hydroboration Product with Benzoyl Chloride.—A mixture of 0.213 Gm. (8.0×10^{-4} mole) of the allylphenylhydroboration product, 24 drops of benzoyl chloride, and 5 ml. of pyridine was heated at 100° for 1 hour and allowed to stand overnight. Distillation of the solvent *in vacuo* left an orange oil residue. Treatment of the oil with 5% sodium bicarbonate solution, followed by ether extraction and evaporation of the ether, produced an oil. Treatment of the oil with concentrated hydrochloric acid and extraction with ether, followed by distillation of the ether, afforded a solid. This solid, on recrystallization from ethanol, yielded 0.196 Gm. (54%) of crystals, m.p. 173.5–174.5°.

Anal.—Calcd. for $C_{27}H_{24}N_2O_5$: C, 71.04; H, 5.30; N, 6.14. Found: C, 71.16; H, 4.85; N, 6.03.

Principal bands in the infrared (Nujol mull) were at 5.68 μ (sharp), 5.85 μ (broad with a shoulder), and at 8.2 μ.

[1] Melting points were determined on a Thomas-Hoover apparatus and were corrected. Analyses were performed by Weiler and Strauss Microanalytical Laboratory, Oxford, England. The barbituric acids were dried *in vacuo* for 12 hours. The solvents used were carefully dried and distilled prior to use. Sodium borohydride and boron trifluoride-etherate were used without treatment.

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