Ureide Ring Scission of Phenobarbital by Sodium Borohydride

Keyphrases ☐ Phenobarbital—ureide ring scission by sodium borohydride ☐ Sodium borohydride—used in ureide ring scission of phenobarbital ☐ Ureide ring scission—reaction of phenobarbital with sodium borohydride

Sir:

Phenobarbital was found to react with sodium borohydride in aqueous and organic media, with ultimate formation of 2-phenyl-1-butanol. This finding was unexpected in view of the report by Smissman *et al.* (1) that phenobarbital was not reduced by sodium borohydride in absolute alcohol, tetrahydrofuran, or diglyme.

Solutions (0.1–1 mg./ml.) of phenobarbital in aqueous alkali, methanol, or methanol–ether mixtures were treated with excess sodium borohydride, added as the solid, and the mixtures were monitored at intervals by TLC. When using 0.25-mm. silica gel GF thin-layer plates with chloroform–methanol (4:1) for development and UV light and iodine vapor for detection, all reaction mixtures showed qualitatively identical patterns with time. At first, shrinkage of the phenobarbital spot at about R_f 0.8 was evident with the appearance of two more polar spots, at R_f's about 0.5 and 0.7. After no more phenobarbital was detected on the plates, a new spot became evident at about R_f 0.9, increasing in size and intensity with concomitant disappearance of the lower mobility spots until, finally, only this spot was visible. The reaction proceeded most rapidly in 0.1 *N* alkali and least in methanol–ether mixtures. Heating a solution of phenobarbital with excess sodium borohydride in 0.1 *N* sodium hydroxide for 20 min. was sufficient to effect complete conversion to R_f 0.9 material.

A quantity of the ultimate reaction product was prepared by dissolving 1.06 g. of phenobarbital in 40 ml. of 0.05 *N* sodium hydroxide, adding 4 g. of sodium borohydride in portions, and allowing the mixture to stand for 22 hr. at room temperature. TLC of the reaction mixture showed a single spot at R_f 0.9. Extraction of the mixture with two 50-ml. portions of hexane, washing the extracts with 10 ml. of water, and evaporation under a stream of nitrogen afforded 0.505 g. of faintly yellow liquid (73.6% yield based on phenobarbital). The product was characterized by NMR[1] spectroscopy in deuterochloroform. The signals obtained and their interpretation are summarized in Table I.

Elemental analysis showed no nitrogen, and the carbon–hydrogen values confirmed the structure of 2-phenyl-1-butanol.

[1] Using a Varian A-60 instrument.

Table I—Summary of NMR Spectrum of Phenobarbital Reduction Product

δ, p.p.m.	Multiplicity	Protons	Assignment
0.80	Triplet	3	$-CH_2-CH_3$
1.65	Multiplet	2	$CH_3-CH_2-C(-H)-$
2.05	Singlet	1	—OH (exchanges in D_2O)
2.6	Multiplet	1	$C_6H_5-CH(-)-CH_2$
3.7	Doublet	2	$-CH(-)-CH_2OH$
7.25	"Singlet"	5	$C_6H_5-CH(-)-$

Anal.—Calc. for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.30; H, 9.50.

Although the mechanism or reaction route was not investigated, we considered that the first step of the reaction might involve hydrolysis of phenobarbital. This hypothesis appears untenable, however, because no spot corresponding to the primary phenobarbital hydrolysis product, phenylethylacetylurea, was seen in chromatograms of the reaction mixtures. Moreover, phenobarbital was demonstrated to be stable when added to reaction mixtures in which the borohydride had been allowed to decompose to borate.

(1) E. E. Smissman, A. J. Matuszak, and C. N. Corder, *J. Pharm. Sci.*, **53**, 1541(1964).

LESTER CHAFETZ*▲
TSUN-MING CHEN*
R. CLIVE GREENOUGH†

* Pharmaceutical Research and Development Laboratories and †Department of Analytical and Physical Chemistry
Warner-Lambert Research Institute
Morris Plains, NJ 07950

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▲ To whom inquiries should be directed.

1,5-Diphenyl-3-dimethylaminopyrrolidine: A Long-Acting Histamine Antagonist

Keyphrases ☐ 1,5-Diphenyl-3-dimethylaminopyrrolidine—evaluation as potent, long-acting histamine antagonist ☐ Antihistamines, potential—1,5-diphenyl-3-dimethylaminopyrrolidine

Sir:

Antagonism of histamine-induced smooth muscle contraction by antihistamines is assumed to occur as a result of competitive occupation of tissue receptors by