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).

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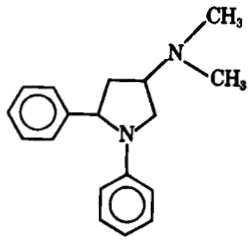
1,5-Diphenyl-3-dimethylaminopyrrolidine: A Long-Acting Histamine Antagonist

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



I

the antagonist drugs (1, 2). We now report pharmacological data demonstrating that 1,5-diphenyl-3-dimethylaminopyrrolidine (I) is a potent histamine antagonist which exhibits a remarkably long duration of action. Compound I is a cyclic analog of the ethylenediamine antihistamine phenbenzamine. It was synthesized as a single racemic diastereoisomer in which the 3-dimethylamino and 5-phenyl substituents have been tentatively assigned the *trans*-configuration. The synthesis of I and related compounds will be the subject of a future paper.

When I was studied for antihistaminic activity *in vitro* using the isolated guinea pig ileum (3), it was found that concentrations as low as 2×10^{-9} *M* inhibited the contractile response to histamine. However, the antagonistic effect of I could not be readily reversed by washing the tissue. Therefore, experiments were undertaken to compare the duration of action of I with that of the potent ethylenediamine antihistamine tripelennamine. The antagonists (as the hydrochloride salts) were kept in contact with the ileal tissue for 15 min. prior to the addition of agonists. The tissue was then washed at 5-min. intervals with fresh Tyrode's solution, and after each wash either histamine (4×10^{-6} *M*) or acetylcholine (4×10^{-7} *M*) was added. The concentration of histamine employed in these experiments produced a near maximal contraction prior to the introduction of antagonists. Figure 1 shows the recovery of the response to histamine with time after a single exposure of the tissues to the antagonists

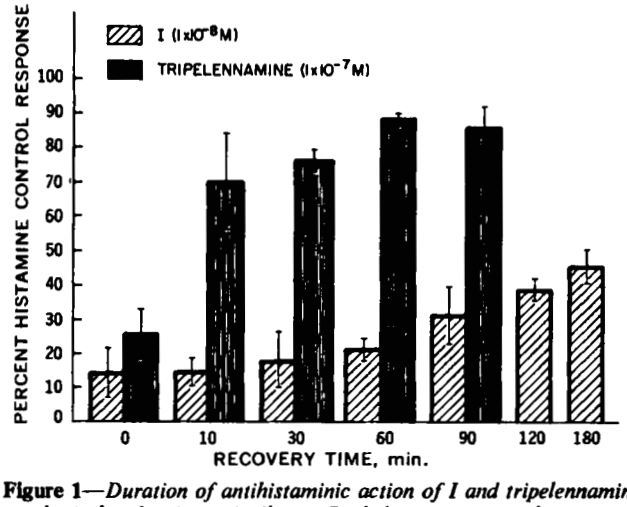


Figure 1—*Duration of antihistaminic action of I and tripelennamine on the isolated guinea pig ileum. Each bar represents the mean of three experiments with I or two experiments with tripelennamine. Vertical lines represent standard error (I) and range (tripelennamine). The 100% control response is defined as the mean response to 4 × 10^{-6} M histamine in these experiments.*

Table I—Percent Decrease in Hind-Limb Perfusion Pressure Produced by Close Intraarterial Injections of Histamine and Methacholine before and after Close Intraarterial Infusion of 5 mg. of I

	Histamine			
	Control			
Experiment	Dose 1 (1–2 mcg.)	Dose 2 (2–4 mcg.)	After Infusion of I[a] Dose 1	Dose 2
1	35	44	4	8
2	14	27	0	3
	Methacholine			
	Control			
Experiment	Dose 1 (0.025–0.1 mcg.)	Dose 2 (0.1–0.4 mcg.)	After Infusion of I[a] Dose 1	Dose 2
1	37	43	35	40
2	15	23	13	18

[a] Agonists were administered in 0.9% saline solution 20–30 min. after infusion of I.

followed by repeated washing. The response to histamine did not exceed 45% of control 3 hr. after exposure to I (1×10^{-8} *M* final bath concentration), whereas recovery after treatment with tripelennamine (1×10^{-7} *M* final bath concentration) reached 70% of control within 10 min. The response to acetylcholine was not inhibited by I or by tripelennamine, and the response to acetylcholine did not fall below control levels during the experiments.

In other studies with the guinea pig ileum, a concentration of 4×10^{-6} *M* of I produced an 85% inhibition of the contractile response to acetylcholine (4×10^{-7} *M*). The response to acetylcholine returned to near control levels within 30 min. after exposure of the tissue to this concentration of I. These experiments demonstrate that I is a much more effective inhibitor of histamine than of acetylcholine on the guinea pig ileum.

Experiments were also conducted on the perfused innervated dog's hind limb, employing the preparation described by Zimmerman (4) to examine the relative effectiveness of I in blocking the direct vasodilator responses to close intraarterial injections of histamine and methacholine. The results, expressing the vasodilator responses as percent decreases in perfusion pressure, obtained in two dogs are shown in Table I. The direct vasodilator effect of histamine was greatly reduced, while the perfusion pressure response resulting from the direct vasodilator action of methacholine was only slightly inhibited.

The results of the experiments reported in this communication demonstrate that I is a potent and selective histamine antagonist which inhibits both the contractile response in guinea pig ileum *in vitro* and the vasodilator response in the dog's hind limb *in vivo*. The very long duration of action of I appears to be unique among selective histamine antagonists and may be an important finding with respect to this new antihistamine. We also prepared the other diastereoisomer of I and found it to be a reversible histamine antagonist, having a pA_2 value of 7.97.

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Prediction of Dissolution Rates of Drugs

Keyphrases □ Dissolution rates, slightly water-soluble powders—prediction from simple mathematics □ Powders, slightly water soluble—dissolution rates predicted from simple mathematics □ Powders, volume surface diameter—calculation of surface area

Sir:

Hussain (1) recently showed that, by making certain assumptions and using simple mathematics, it was possible to predict the dissolution rates of slightly water-soluble powders using the formula:

$$Q = \frac{A \cdot S \cdot D \cdot t}{h} \qquad \text{(Eq. 1)}$$

where:

Q = amount of drug (in grams) dissolved in time, t
A = surface area occupied by the total weight of the sample
S = solubility of the drug (in grams per milliliter) in the dissolution medium
D = diffusion coefficient of the drug (in square centimeters per second)
h = thickness of diffusional layer (in centimeters)

By assuming that the diffusion coefficient, D, and the thickness of the diffusional layer, h, are constant at 9×10^{-6} cm.²/sec. and 50×10^{-4} cm., respectively, knowledge of only the surface area exposed, A, and the solubility, S, of the drug enables the dissolution rate Q/t to be calculated.

Despite the remarkable correlation between the experimental and calculated results for the dissolution rates of hydrocortisone, benzoic acid, levodopa, and griseofulvin, there appears to be a considerable argument against the use of such predicted results as a routine measure.

Hussain's Eq. 3 is in error by a density factor (ρ):

$$\text{number of particles in } W \text{ grams of powder} = \frac{W}{4/3\pi r^3 \rho} \qquad \text{(Eq. 2)}$$

assuming spherical particles:

$$V = 4/3\pi r^3 \qquad \text{(Eq. 3)}$$

Since the density for benzoic acid is 1.32 (2), the area would be overestimated without this correction by 32%, with a corresponding overestimation in the calculated dissolution rate.

Hussain also used the average particle size on an arithmetic basis, using the two extremes of the mesh fraction in his calculation of the surface area. While this may not lead to gross errors for the comparatively narrow size ranges considered by Hussain, for larger particle-size distributions a better mean size would be the volume–surface mean diameter, d_{vs} (3):

$$d_{vs} = \frac{\Sigma n d^3}{\Sigma n d^2} \qquad \text{(Eq. 4)}$$

and the surface area computed from:

$$A = \frac{W \times 6}{d_{vs}\rho} \qquad \text{(Eq. 5)}$$

Since the volume–surface mean diameter will also be larger than the arithmetic mean diameter, this will add further to the overestimation of the dissolution rate.

To explain Hussain's apparent correlation requires a compensating decrease in the value of the area used in Eq. 1. This may be due to assuming that the particles are spherical, while deviations from either spherical or cubical shape will lead to an increase in the constant value of 6 given in Eq. 5.

Due to the complexity of these compensating mechanisms, it would be rash to adopt Hussain's method for the prediction of the dissolution rate of sparingly soluble drugs without further evidence. Hussain's article dealt with particles in powder form only. However, for solid dose formulations, where it is known that the total area available may not come into contact with the dissolution medium due to failures of disintegration (4), or where the ingredients may invalidate the diffusion assumptions made by Hussain, we must be prepared to continue to determine experimentally the dissolution rate of the drug.

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