

THE CONFIGURATION OF ALPHAPRODINE AND BETAPRODINE

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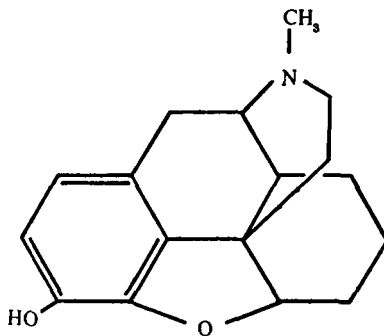
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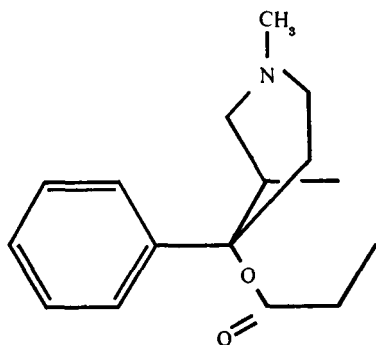
Two diastereoisomeric forms (α and β) of 1:3-dimethyl-4-phenyl-4-propionoxypiperidine have been isolated¹ and shown to possess high analgesic activities, the β -isomer racemate possessing 5 to 6 times the activity of the α -isomer racemate². The approved names of alphaprodine and betaprodine have been given to the hydrochlorides of the α - and β -isomers respectively.

The *trans* [*trans* Me/Ph \equiv *cis* Me/propionoxy (see Beckett and Casy³)] configuration has been assigned to the β -isomer and the *cis* (Me/Ph) configuration to the α -isomer^{1,2}, but these assignments were not rigidly established. They are stated to be dependent upon the easier breakdown of the α -isomer under hydrolytic conditions and upon the pharmacological results presuming that the more active β -isomer was more closely related to the analgesically active dihydrodeoxymorphine-D than the α -isomer as shown in Figure 1.

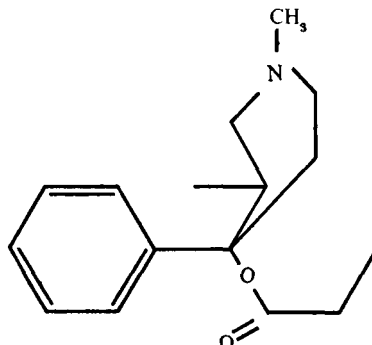
In an earlier communication Beckett and Casy³, although presenting diagrams indicating that both isomers could fit their proposed "analgesic



(I) Dihydrodeoxymorphine



(II) *trans*(β -isomer?)



(III) *cis*(α -isomer?)

FIG. 1.

receptor site," stated that if these provisional configurational assignments were incorrect, then the most probable conformation of the more active β -isomer (IX) would represent a 3-dimensional arrangement closer to that of morphine (VII) than the most probable conformation of the α -isomer (VIII) (see Fig. 2.).

In the absence of strong electrostatic effects between groups, the most stable conformations of substituted *cyclohexanes* are chair forms with the maximum number of equatorial substituents^{4,5,6}. If one axial and one equatorial substituent be present, the molecule will assume the chair form in which the larger group is equatorial. Ignoring the conformation of the methyl group on the nitrogen atom, four possible chair forms of 1:3-dimethyl-4-phenyl-4-propionoxypiperidine are possible as shown in Table I, and applying the above generalisations to a piperidine ring leads to 1 and 3 as the most probable conformations of the *cis*- and *trans*-isomer respectively. This is even more likely as the phenyl and propionoxy groups do not differ greatly in size. The *cis*-isomer will thus possess an equatorial and the *trans*-isomer an axial propionoxy group.

TABLE I

	Configuration	4-Propionoxy	3-Methyl	4-Phenyl
1	<i>cis</i> (Me/Ph)	e	e	a
2	<i>cis</i> (Me/Ph)	a	a	e
3	<i>trans</i> (Me/Ph)	a	e	e
4	<i>trans</i> (Me/Ph)	e	a	a

It is known that carboxy esters of equatorial hydroxyl groups are more readily hydrolysed than the corresponding axial esters^{4,5,6}, and consequently the *cis* (Me/Ph) isomer would be expected to hydrolyse more readily than the *trans*-isomer.

The hydrolysis of alphaprodine and betaprodine in aqueous ethanolic alkaline solutions was examined under comparable conditions at a number of concentrations. Some of the results are presented in Table II.

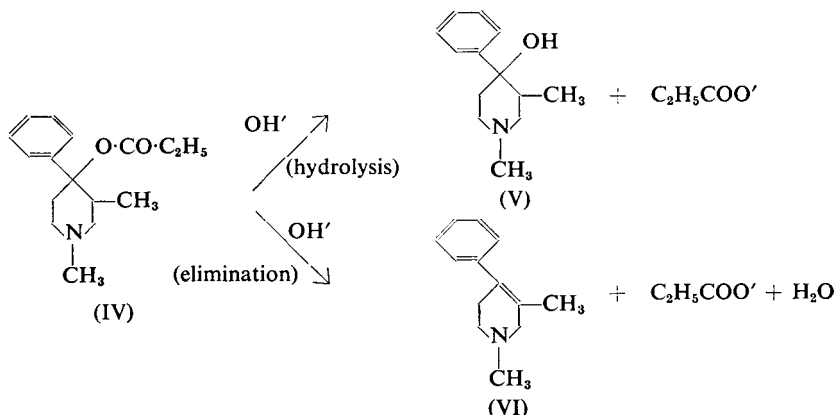
TABLE II

COMPARATIVE HYDROLYSIS STUDIES OF ALPHAPRODINE AND BETAPRODINE

Initial concn. of alphaprodine and betaprodine (in g. mol.)	Initial concn. of NaOH (in g. mol.)	Time after mixing	Percentage hydrolysis	
			Alphaprodine	Betaprodine
0.023	0.036	20 hours	11.5	16.5
0.023	0.036	79 hours	21.0	32.0
0.067	0.450	12.5 hours	54.5	62.0
0.067	0.450	44 hours	80.5	98.0

There is a possibility that the determination of the acid liberated in the reaction might not be a true measure of the hydrolysis because of the possibility of the occurrence of the competing elimination reaction also removing hydroxyl ions as outlined below. That the latter reaction does not constitute a serious complicating factor under the conditions used for the hydrolysis experiments was shown in the following manner. The ultra-violet absorption spectra of the α - and β -alcohols (V) will approximate roughly to the spectra of the parent esters (i.e., ϵ_{max} . ca 220 to 250

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at λ_{max} . ca 260 $\text{m}\mu$ e.g., ethylbenzene has ϵ_{max} . 220 at λ_{max} . 261⁷) whereas compound VI in which the double bond is conjugated with the aromatic ring would exhibit an intense band (K band) (ϵ_{max} . ca 10,000 to 12,000 at λ_{max} . ca 245 $\text{m}\mu$ e.g., β -methylstyrene has ϵ_{max} . 12,600 at λ_{max} . 244 $\text{m}\mu$ ⁸) in addition to the B band (ϵ_{max} . ca 500 at λ_{max} . ca 280). Ultra-violet absorption curves of the alkaline aqueous-ethanolic solutions of alphaprodine and betaprodine after standing and then neutralisation, although exhibiting an increased intensity of absorption in some of the solutions in the region 240 to 250 $\text{m}\mu$ (e.g., two-fold at 245 $\text{m}\mu$ in one run of betaprodine) showed the general pattern exhibited by the parent esters in freshly made solutions of comparable concentration, indicating the presence of negligible quantities of (VI) as compared with (V) in the hydrolysing solutions. An alcohol (V), identical in melting point with the α -isomer obtained by Ziering and Lee¹ from the mixture resulting from the reaction of 1:3-dimethyl-4-piperidone with phenyllithium, was also isolated in good yield from an hydrolysis experiment involving alphaprodine; an isomeric alcohol m. pt. 77 to 78° C. was isolated from experiments involving betaprodine.

The results quoted in Table I can therefore be regarded as a measure of the hydrolysis of the isomers. They show that betaprodine hydrolyses more readily than alphaprodine and indicate that the former possesses an equatorial and the latter an axial propionoxy group. Betaprodine should therefore be allocated the *cis* (Me/Ph) configuration and alphaprodine the *trans* (Me/Ph) configuration, i.e., the reverse of the previous provisional assignments.

These new configurational assignments result in the thermodynamically most stable conformation of betaprodine (IX) showing a closer relationship than alphaprodine (VIII) to the 3 dimensional structure of morphine (VII) (see Fig. 2 for diagrammatic representation). The pharmacological results² show that, at least in rats, alphaprodine is as active, and betaprodine 5 to 6 times as active, as morphine. It is possible to explain these results in terms of the analgesic receptor site (X) being fitted less closely by morphine than by IX, in which the projecting portion of the

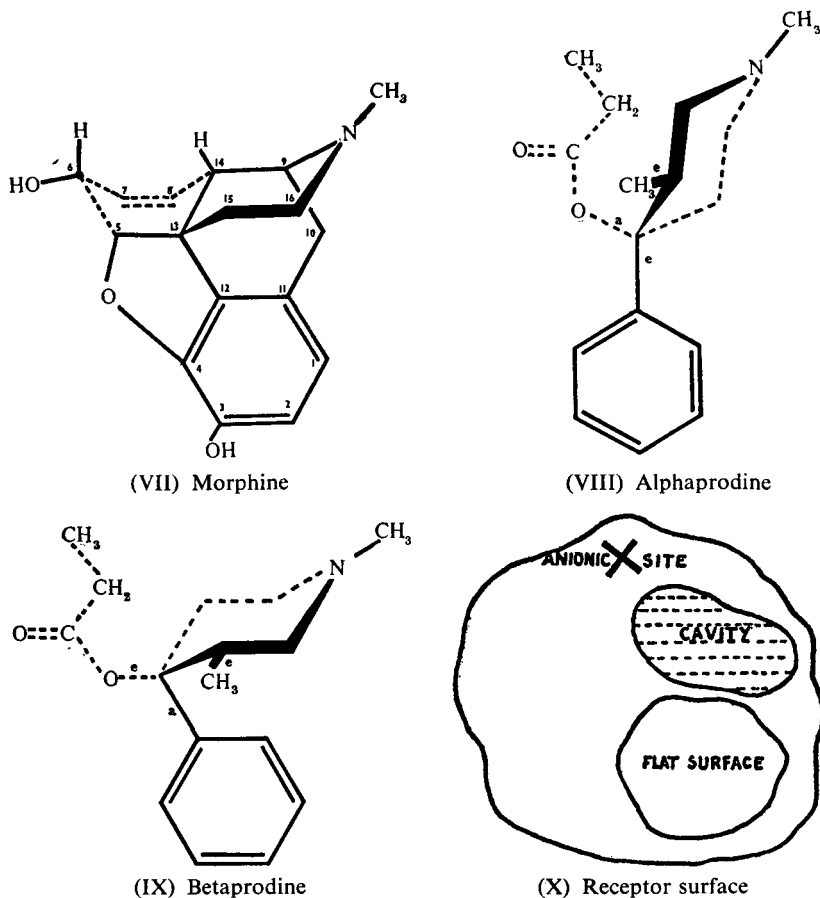


FIG. 2. Diagrammatic representation of the relationship of alphaprodine and betaprodine to morphine and the "analgesic receptor surface". The diagrams represent the lower surface of the drug and the upper surface of the receptor, i.e. complementary surfaces. In front of, behind, and in the plane of the paper are represented by , - - - - -, and respectively.

piperidine ring and the equatorial methyl group constitute a more bulky hydrocarbon moiety than that present in morphine. Alphaprodine will also "fit" the receptor site, but the distance between the centre of the aromatic ring and the basic group is greater than that in morphine or betaprodine.

EXPERIMENTAL

Hydrolysis Experiments

Reagents. Carbonate-free 0.1N sodium hydroxide solutions, prepared using the ion exchange resin IRA 400 (OH) by the method described by Davies and Nancollus⁹. The solution was stored in an automatic burette protected against entry of carbon dioxide. Ethanol (70 per cent. w/w), freshly boiled and cooled under reflux, the condenser being closed with a

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soda-lime tube. *Ethanolic sodium hydroxide solutions* 0.05N and N solutions were prepared by dissolving freshly cut sodium in 70 per cent. w/w ethanol freshly boiled as described above. The solutions were stored in automatic burettes protected against entry of carbon dioxide.

Method. A typical hydrolysis experiment is described below. Other determinations were also performed in which the relative concentrations of alkali and samples were varied.

1 ml. portions of solutions of alphaprodine and betaprodine (4.004 g. per 100 ml. 70 per cent. w/w ethanol solution) were pipetted into Pyrex tubes fitted with ground-glass stoppers, the tubes being previously swept out with carbon dioxide free nitrogen. To each tube was added 1 ml. of N ethanolic sodium hydroxide, taking precautions against entry of carbon dioxide.

To the contents of 1 tube (for each isomer), 10 ml. of 0.1N hydrochloric acid was added, carbon dioxide free nitrogen bubbled through the solution for 10 minutes, 4 ml. of chloroform added to remove the organic base liberated in the subsequent titration, and the contents titrated with carbonate-free 0.1N sodium hydroxide solution using phenolphthalein as indicator.

The remaining tubes with their contents were immediately stoppered, the stoppers well sealed in position with Picien Wax to prevent entry of carbon dioxide, and placed in a water bath thermostatically controlled at $55^{\circ}\text{C.} \pm 0.1^{\circ}\text{C.}$ Tubes were removed after the stated periods (Table II), the hydrolysis terminated by the addition of 10 ml. 0.1N hydrochloric acid and the procedure completed as described above. In all determinations, parallel sets of blank titrations were carried out, the contents of the tubes consisting of 1 ml. of N-ethanolic sodium hydroxide solution and 1 ml. of 70 per cent. ethanol containing hydrochloric acid equivalent to that present in the hydrolysis determinations due to the fact that alphaprodine and betaprodine are hydrochlorides.

(Preliminary experiments performed by dissolving known weights of alphaprodine and betaprodine in 70 per cent. ethanol, adding known volumes of standard 0.1N hydrochloric acid, and then back-titrating with carbonate-free 0.1N sodium hydroxide solution using conditions described above gave correct and reproducible equivalent weights.)

Examination of the reaction products. The hydrolysis was carried out using the precautions stated above. Samples (0.25 g.) of alphaprodine and betaprodine were dissolved in 6 ml. of 70 per cent. w/w ethanol and 6 ml. of N ethanolic sodium hydroxide solution added. The tubes were placed in the thermostatically controlled water bath for 70 hours to ensure complete hydrolysis. (After 20 hours, 1 ml. was withdrawn to check the course of the hydrolysis by the manner reported above.) The remaining solution was diluted to 20 ml. with 70 per cent. ethanol (Dilution A).

Ultra-violet measurements. 1 ml. of Dilution A (of both alphaprodine and betaprodine) was neutralised with 0.1N hydrochloric acid and diluted to 20 ml. with 70 per cent. ethanol and the ultra-violet absorption measured (1 cm. cell in a Unicam S.P. 500 spectrophotometer). The solvent cell

contained a solution prepared in a similar manner but omitting the ester samples.

The measurement was compared with those obtained by dissolving samples of the two esters in 70 per cent. ethanol.

Isolation of the products. 10 ml. of Dilution A was diluted to approximately 20 ml. with water and extracted with 3×5 ml. portions of chloroform. The combined chloroform extracts were washed with water, dried (anhyd. MgSO_4), and the chloroform removed under reduced pressure.

The alphaprodine solution yielded a solid product (53 mg. \equiv 70 per cent. yield calc. as alcohol V). Recrystallisation from *n*-hexane gave α -1 : 3-dimethyl-4-phenyl-4-hydroxypiperidine (42 mg.) as white prisms, m.pt 101 to 102° C. (Found: C, 76.3; H, 9.3; N, 6.9 per cent. Equiv. 203. Calc. for $\text{C}_{13}\text{H}_{19}\text{ON}$: C, 76.0; H, 9.3; N, 6.8 per cent. Equiv. 205). (Ziering and Lee¹ report m.pt. 103° C.)

The betaprodine solution yielded a gum (61.5 mg. \equiv 80 per cent. yield calc. as alcohol (V)) (Found: Equiv. 203. $\text{C}_{13}\text{H}_{19}\text{ON}$ requires Equiv. 205). The gum slowly solidified and recrystallisation from *n*-hexane gave β -1 : 3-dimethyl-4-phenyl-4-hydroxypiperidine as white needles, m.pt. 77 to 78° C. (Found: C, 76.2; H, 9.3; N, 6.95. $\text{C}_{13}\text{H}_{19}\text{ON}$ requires C, 76.0; H, 9.3; N, 6.8 per cent.) (Equivalent weights of the bases were determined by dissolving the samples in glacial acetic acid and titrating with 0.02N perchloric acid in glacial acetic acid using crystal violet as indicator.)

The authors thank Roche Products Ltd. for samples of alphaprodine and betaprodine.

SUMMARY

1. A study of the reactions of alphaprodine and betaprodine in alkaline solutions under comparable conditions has been made.

2. As a result of experimental observations and conformational considerations, alphaprodine is now allocated the *trans* (Me/Ph) and betaprodine the *cis* (Me/Ph) configuration, (i.e., the reverse of the previous provisional assignments).

3. The new assignments result in the observed differences in analgesic potencies of the isomers being more readily explicable in terms of the receptor theory proposed by Beckett and Casy³.

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DISCUSSION

The paper was presented by DR. A. H. BECKETT.

MR. A. R. ROGERS (Brighton) asked whether the authors had made absorption measurements on the purified alcohols which were isolated and, if so, whether the data could be included in the published paper.

DR. J. B. STENLAKE (Glasgow) said that the paper provided definite evidence on rates of hydrolysis, and was another example of the successful application of configurational assignments to ring systems. The relation of configuration and resistance was fraught with several hazards. There was in addition to normal non-bonded interactions the possibility of electrostatic interactions between the basic group and other groups present. It was a pity that the differences in rates of hydrolysis which the authors had been able to establish were not more marked, and they might consider the use of dissociation constant measurements.

DR. A. H. BECKETT, in reply, said that the ultra-violet analysis of the purified alcohols had been carried out, and since the submission of the paper one of the alcohols had crystallised, so it would be possible to insert the actual analysis at a later stage. Dissociation constants had been considered, but a more suitable method would be that of elimination experiments which would give a cross-link with hydrolysis.