# ALPHA- AND BETA-PRODINE TYPE COMPOUNDS: CONFIGURATIONAL STUDIES

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The addition of various lithium aryl compounds to 1:3-dimethyl-4-piperidone is investigated. Those stereoisomers present as the major proportion of the respective stereoisomeric mixtures are shown to have similar infra-red absorption characteristics which are different from those exhibited by those isomers formed in minor amount. The stereochemistry of addition to 6-membered alicyclic and heterocyclic ketones is discussed; on the basis of these discussions, and the rates of hydrolysis of appropriate esters, the above isomers formed in major amount are allocated the *trans* (Me/Ar) configuration. The analgesic activities in mice of various stereoisomeric amino-alcohols and esters are given.

The addition of phenyl lithium to 1:3-dimethyl-4-piperidone yields two diastereoisomeric alcohols from which two analgesically active propionoxy esters, alphaprodine and betaprodine have been prepared[1]. In animals, betaprodine is much more active than alphaprodine[2] although the differences in observed potencies are less in man[3]. Results of hydrolysis studies which indicate that betaprodine should be allocated the *cis* (Me/Ph) and alphaprodine the *trans* (Me/Ph) configuration have previously been presented[4].

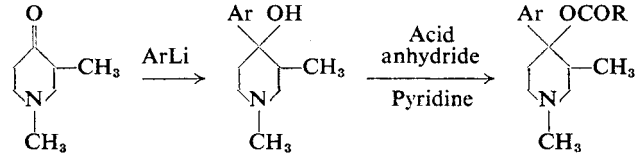
The stereochemical compositions of the products of addition of certain lithium aryl compounds to 1:3-dimethyl-4-piperidone are now considered. Information of isomeric composition is of value in assigning configurations to various stereoisomers and also supplements information from hydrolysis experiments with stereoisomeric esters. There is the additional object of producing compounds of known configuration for analgesic tests to provide further information about the stereochemical requirements of analgesics[5–7] and the analgesic receptor site[8,9].

*Preparation of Compounds and Separation of Isomers*

The key intermediate, 1:3-dimethyl-4-piperidone (I), was prepared by cyclisation of β-carbomethoxyethyl-β-carbomethoxypropylmethylamine and subsequent decarboxylation[10]. Treatment of the ketone with a lithium aryl gave a mixture of tertiary alcohols (II) which was esterified by refluxing with an acid anhydride in the presence of pyridine. Attempts to separate the diastereoisomers involved fractional crystallisation of the free alcohols from hydrocarbon solvents, or the ester hydrochlorides from ether-ethanol.

Separation of the alcohols derived from phenyl lithium was achieved by crystallisation of the propionoxy ester hydrochlorides; alphaprodine was obtained from the first four, and betaprodine from the fifth crop.

Adsorption chromatographic separations were unsuccessful. The infra-red absorption spectra of the derived isomeric alcohols (alpha- and beta-prodine alcohols) showed distinct differences in three regions (see Table II).

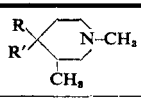



(I) (II) (III)

The *m*-tolyl alcohols (II, Ar = *m*-$CH_3 \cdot C_6H_4$) were separated by crystallisation from *n*-hexane; 15 recrystallisations were necessary to separate the pure isomers. The infra-red absorption spectrum of one isomer (A) resembled that of alphaprodine alcohol; that of the other isomer (B) resembled that of betaprodine alcohol.

TABLE I

CHARACTERISTICS AND PROPORTIONS OF ISOMERS OBTAINED BY THE ADDITION OF LITHIUM ARYLS TO 1:3-DIMETHYL-4-PIPERIDONE




| | | Reaction product | | Isomer A | | Isomer B | | |
|---|---|---|---|---|---|---|---|---|
| R | R' | Wt. in g. | m.p. ° C. | Wt. in g. | m.p. ° C. | Wt. in g. | m.p. ° C. | Ratio A:B |
| $C_6H_5$ | $OCOC_2H_5$ | 11·0 | 181–197 | 7·6 | 218–220 | 2·6 | 181–185 | 3:1 |
| *o*-$CH_3 \cdot C_6H_4$ | OH | 6·5 | 83–85 | 4·96 | 86–87 | 0 | — | mainly one isomer (A) |
| *m*-$CH_3 \cdot C_6H_4$ | OH | 14·7 | 104–108 | 10·58 | 88·5–89·5 | 1·28 | 114–115 | 9:1 |
| *p*-$CH_3 \cdot C_6H_4$ | OH | 6·3 | softened 85 m.p. 122–133 | 4·21 | 135–136 | 0·04* | 103–104 | A > B |
| *o*-$OCH_3 \cdot C_6H_4$ | OH | 7·3 | 109 | 7·18 | 111·5 | 0 | — | mainly one isomer (A) |

* Isolated by hand picking from a weight of 1·8 g., m.p. 81–91°; the latter was examined spectroscopically for infra-red absorption and exhibited characteristics of both isomers.

The first three crops obtained by crystallisation of the *p*-tolyl alcohols (II, Ar=*p*-$CH_3 \cdot C_6H_4$) from *n*-hexane gave one pure isomer (A) with a sharp melting point, little changed upon recrystallisation, and an infra-red absorption spectrum resembling that of alphaprodine alcohol. Further crops gave material melting over a wide range 40° or so below the melting point of the initial crops. Crystallisation of the corresponding propionoxy ester hydrochlorides from ether-ethanol again gave sharp melting point initial crops; further crops melted at similar temperatures but showed softening 40° or so below the final melting point. A small quantity of a second isomer (B) was obtained by hand-picking crystals from the tenth recrystallisation of the free alcohols; the infra-red absorption spectrum of this isomer resembled that of betaprodine alcohol, while that of a powdered sample of the tenth fraction showed characteristics of both isomers.

Treatment of the piperidone (I) with *o*-tolyl lithium gave a product which, upon recrystallisation, was recovered in high yield with little change in melting point; the infra-red absorption spectrum of this alcohol resembled that of alphaprodine alcohol. A similar result was found upon treatment of the piperidone (I) with *o*-methoxyphenyl lithium. These last two additions result in virtually single products and isomeric forms, if they occur, represent only a small proportion of the reaction products.

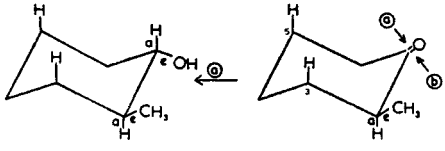
An estimate of the ratio of isomer weights is summarised in Table I. The weights of the isolated isomers accounted for the major portion of the reaction product, and their relative proportions may therefore be used as a basis for a discussion of the isomeric composition of the products of addition of lithium aryl compounds to 1:3-dimethyl-4-piperidone.

## Discussion

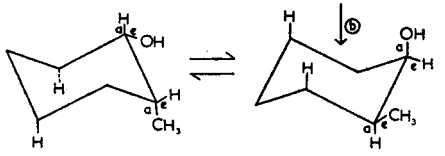
### *Stereochemistry of Addition to Ketones*

The stereochemical composition of the products of addition to the carbonyl group of cyclic ketones will be mainly dependent upon two factors. The first is the difference in the steric environment about the two directions of approach to the C atom of the carbonyl group and the second, the relative thermodynamic stability of the isomers. This will influence the rate of formation of the isomers from the transition complexes. The importance of these factors may be shown by the following examples.

In the reduction, other than hydrogenation, of 2-methyl*cyclo*hexanone, which exists mainly in the conformation IV, attack from side (*a*) to yield the *trans* isomer (V) will be more hindered, mainly from the 3 and 5



(V) *trans* isomer (IV)



(VI) *cis* isomer

axial H-atoms, than that from side (*b*) to yield the *cis* isomer (VI). But the *trans* isomer (V) is thermodynamically more stable than the *cis* isomer. For example, equilibration of the alcohols yields 99 per cent of the *trans* isomer[11]. The two effects are in opposition, and the yields of 58 and 31 per cent of the *cis* isomer, upon reduction of the ketone by

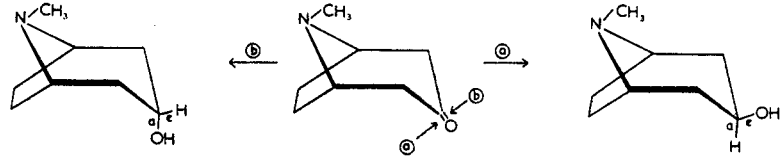
aluminium isopropoxide and sodium borohydride in methanol[11] respectively, are explicable in terms of the larger reducing species of the former reagent. [Dauben and others[11] explain these results by assuming that attack from side (*a*) and (*b*) in IV are equally favoured; the high proportion of *cis* isomers in the product is explained by these authors as resulting from the contributions of the less stable conformation of 2-methyl*cyclo*hexanone in which the axial methyl group hinders attack from its side of the carbonyl group.]

The equatorial 2-methyl group of IV constitutes a small steric factor operating on the same side as the 3 and 5 axial H-atoms. The following predictions may therefore be made about the isomeric composition of the products of reduction of 2 (or 4) monoalkyl*cyclo*hexanones.

The product will contain more of the *cis* isomer than the product of equilibration; the proportion of this isomer will increase with increasing size of reducing reagent species. Increase in bulk of the 2-alkyl substituent will increase the relative proportion of the *cis* isomer. Reduction of the 4-alkyl derivatives will give relatively less, compared with equilibrated mixtures, of the *cis* isomer than reduction of the corresponding 2-alkyl derivatives.

The recorded values[11–13] for the stereochemical composition of the reduction product of various alkyl*cyclo*hexanones supports these predictions, although some values are only of a semi-quantitative character.

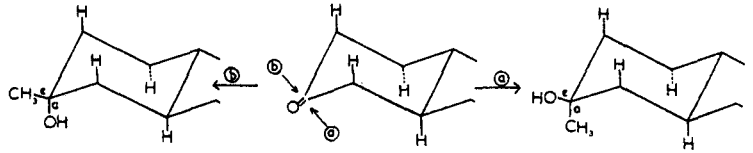
Reduction of heterocyclic ketones may be considered similarly. Beckett and others[14] have shown that reduction of tropinone (VII), by various reducing agents, yielded much more of the thermodynamically less stable tropine (VIII) than was present in "equilibrated" tropine or




$\psi$-tropine (IX). This was expected, since approach from side (*a*) is less favoured sterically than that from side (*b*); changes in the reducing species yielded larger proportions of tropine under conditions in which larger species would be expected.

The formation of isomers by addition of Grignard reagents, or lithium derivatives, to alicyclic or heterocyclic ketones will be also influenced by the factors governing the stereochemistry of addition to ketones. Cyclic transition states will be involved but the rate-controlling step of such reactions involves addition of the R of the reagent to the C atom of the carbonyl group. Equilibration of these tertiary alcohols to give a measure of the relative thermodynamic stabilities of the isomers is usually precluded. However, examination of isomeric compositions (the isomer formed in larger amounts will be derived from attack from the least hindered side of the molecule, if the energy contents of the isomers are not

too dissimilar) and the effect of an increase in the size of the hydrocarbon portion of the addendum (increase will favour more the attack from the least hindered side) may be used for tentative configurational assignment to the isomers. Few examples of such additions are available in which quantitative results of isomeric composition have been obtained. Barton and others[15] reported that the addition of methylmagnesium bromide to 5·2 g. cholestanone (X) gave 2·9 g. of the α-OH isomer (XI) and 2·2 g. of the β-OH isomer (XII); thus the isomer resulting from attack from the

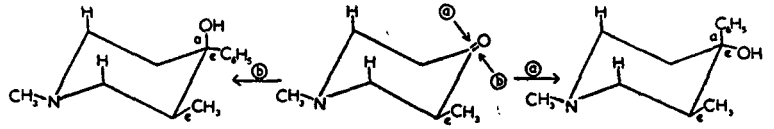


(XI) (X) (XII)

least hindered side of the carbonyl group is formed in major amount. We find that the addition of phenyl lithium to tropinone gives a tertiary alcohol in 97 per cent yield with the OH in the same configuration as that of tropine, showing predominant attack from the least hindered side.

*Configurational Assignments to Prodine-type Compounds*

Beckett and Walker[4], from hydrolysis experiments, have allocated the *trans* (Me/Ph) configuration to alphaprodine (propionoxy ester of XIV) and the *cis* (Me/Ph) configuration to betaprodine (propionoxy ester of



(XIV) (XIII) (XV)

XV). The preceding arguments indicate that the *trans* (Me/Ph) isomer should be formed in larger amount upon addition of phenyl lithium to 1:3-dimethyl-4-piperidone (XIII) since attack from the least hindered side (*b*) would be favoured. Careful fractional crystallisation of the propionoxy ester hydrochlorides derived from the reaction product yielded the ratio of 3:1 of alphaprodine to betaprodine, thus supporting the previous assignments.

Addition of *m*-tolyl and *p*-tolyl lithium gave isomeric pairs of compounds; the isomers were not present in equal amounts (see Table I). The predominant isomer would be expected to have the same configuration as the alcohol (XIV) from alphaprodine. Even higher proportions of the isomers configurationally related to XIV would be expected by using an *o*-methyl or *o*-methoxy group substituted in phenyl lithium. These substitutions will increase the bulk of the addendum in the vicinity of the centre which itself will form a bond with the carbonyl group on addition. The results (Table I) indicated that increases in the size of the

addendum led to the formation of one isomer almost exclusively. Evidence was therefore sought for the configurational identity of the isomers (Type A, see Table II) formed in major amount on the addition of phenyl lithium and *m*- and *p*-tolyl lithium to 1:3-dimethyl-4-piperidone (XIII) and the single isomers (Type A, see Table II) formed upon addition of

TABLE II

CHARACTERISTICS OF INFRA-RED ABSORPTION SPECTRA OF 1:3-DIMETHYL-4-ARYL-4-SUBSTITUTED PIPERIDINES

| R | R′ | Isomer | Absorption peaks of characteristic frequency (cm.$^{-1}$) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Region A (990–1020 cm.$^{-1}$) | Region B (1350–1385 cm.$^{-1}$) | | | Region C (2670–2780 cm.$^{-1}$) | | |
| $C_6H_5$ | OH | A* | 1000 | 1355 | | 1383 | 2670 (w) | 2735 (s.sh.) | 2760 |
| *o*-$OCH_3{\cdot}C_6H_4$ | OH | A | 1001 | 1357 | | 1380 | 2675 (w) | 2730 (w) | 2760 |
| *o*-$OCH_3{\cdot}C_6H_4$ | $OCOCH_3$ | A | 1001 | 1365 | | 1380 | 2675 | 2725 (w) | 2760 |
| *o*-$CH_3{\cdot}C_6H_4$ | OH | A | 1001 | 1352 | | 1376 | 2680 (s.sh.) | 2740 (w) | 2775 |
| *m*-$CH_3{\cdot}C_6H_4$ | OH | A | 1000 | 1355 | | 1383 | 2680 (w) | 2745 (s.sh.) | 2770 |
| *p*-$CH_3{\cdot}C_6H_4$ | OH | A | 1002 | 1354 | | 1382 | 2675 (w) | 2730 (s.sh.) | 2755 |
| $C_6H_5$ | OH | B† | no peak | | 1372 | 1380 | | 2740 | 2775 |
| *m*-$CH_3{\cdot}C_6H_4$ | OH | B | no peak | | 1376 | 1383 | | 2740 | 2780 |
| *p*-$CH_3{\cdot}C_6H_4$ | OH | B | no peak | | 1372 | 1383 | | 2725 | 2760 |

w = Weak peak; s.sh. = Slight shoulder; * Alcohol from alphaprodine
A = Isomer in major amount; B = Isomer in minor amount; † Alcohol from betaprodine

*o*-tolyl and *o*-methoxyphenyl lithium to this ketone. Infra-red absorption measurements (see Table II) revealed a consistent pattern for these isomers in the regions, 990 to 1020 cm.$^{-1}$, 1350 to 1385 cm.$^{-1}$ and 2670 to 2780 cm.$^{-1}$, which was completely different from that shown by the isomers (Type B, see Table II) formed in lesser amount upon the addition of phenyl lithium and *m*- and *p*-tolyl lithium to the piperidone (XIII). Our own hydrolysis experiments show that esters of the isomers exhibiting the infra-red pattern of Type B (betaprodine type) hydrolyse more readily than the corresponding esters of their stereoisomeric alcohols with the Type A infra-red pattern.

It is therefore concluded that Type A isomers (Table II) have the *trans* (Me/Ar) configuration (configurationally related to XIV) whereas Type B isomers have the *cis* (Me/Ar) configuration as shown in XV.

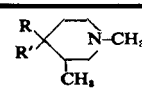
## ANALGESIC COMPARISONS IN MICE

The analgesic activities of certain of the compounds reported in this paper are summarised in Table III. Compounds 1, 3–9, and 12–14 all have been assigned a *trans* configuration and must therefore be compared with alphaprodine, *trans* Me/Ph configuration, in any assessment of structure-activity relationships. The results are summarised as follows:— Replacement of the 4-phenyl group of alphaprodine by a 4-tolyl group results in a fall in activity; replacement by *p*-tolyl, *o*-tolyl and *m*-tolyl gives progressively less active compounds.

In the 4-tolyl series, replacement of the 4-propionoxy by a 4-acetoxy group results in a fall in activity; this fall is greatest in the *p*- and *m*-tolyl compounds and least in the *o*-tolyl compound. The activity in the acetoxy

TABLE III

ANALGESIC ACTIVITIES* OF 1:3-DIMETHYL-4-ARYL-4-SUBSTITUTED PIPERIDINES



| | R | R′ | Configuration (Me/Ar) | Salt | Analgesic activity (morphine = 100) |
|---|---|---|---|---|---|
| 1 | OH | *o*-$CH_3$·$C_6H_4$ | *trans* | base | 20 |
| 2 | ,, | *m*-$CH_3$·$C_6H_4$ | *cis* | ,, | <20 |
| 3 | ,, | *m*-$CH_3$·$C_6H_4$ | *trans* | ,, | <20 |
| 4 | ,, | *p*-$CH_3$·$C_6H_4$ | ,, | ,, | <15 |
| 5 | ,, | *o*-$OCH_3$·$C_6H_4$ | ,, | ,, | <20 |
| 6 | $OCOCH_3$ | *o*-$CH_3$·$C_6H_4$ | ,, | HCl | 70 |
| 7 | ,, | *m*-$CH_3$·$C_6H_4$ | ,, | ,, | <20 |
| 8 | ,, | *p*-$CH_3$·$C_6H_4$ | ,, | ,, | 30 |
| 9 | ,, | *o*-$OCH_3$·$C_6H_4$ | ,, | base | 30 |
| 10 | $OCOC_2H_5$† | $C_6H_5$ | *cis* | HCl | 870 |
| 11 | ,, ‡ | $C_6H_5$ | *trans* | ,, | 200 |
| 12 | ,, | *o*-$CH_3$·$C_6H_4$ | ,, | ,, | 85 |
| 13 | ,, | *m*-$CH_3$·$C_6H_4$ | ,, | ,, | 50 |
| 14 | ,, | *p*-$CH_3$·$C_6H_4$ | ,, | ,, | 150 |
| 15 | Pethidine | | | | 40 |

* Determined in mice by subcutaneous injection, using adaptation of the "hot plate" method as described by Janssen and Jageneau [17].
† Betaprodine.
‡ Alphaprodine.

esters is *o*-tolyl > *p*-tolyl > *m*-tolyl. The free alcohols (Compounds 1–5) are less than one fifth as active as morphine.

## EXPERIMENTAL

All m.ps. are uncorrected. Microanalyses were by Mr. G. S. Crouch, School of Pharmacy, University of London.

Equivalent weights of the bases were determined by titration with 0·02N perchloric acid in glacial acetic acid using Oracet Blue B as indicator. Titration of the hydrochloride salts in non-aqueous media in the presence of mercuric acetate was by the method of Pifer and Wollish[16].

1:3-*Dimethyl*-4-*piperidone*. This was prepared by the method described by Howton[10]; equiv. wt. 124, theory 127, hydrochloride, needles from ether-ethanol, m.p. 195°; Howton[10] gives m.p. 194·9° to 195·3°.

1:3-*Dimethyl*-4-*phenyl*-4-*propionoxypiperidine hydrochloride isomers* (*alpha- and beta-prodine*). The piperidone (I) (15 g.) was added dropwise with stirring to a cooled, (ice-salt bath) solution of phenyl lithium in ether (200 ml.) prepared from lithium (3·05 g.) and bromobenzene (34 g.). The mixture was stirred for 2 hours at room temperature and then added to crushed ice and glacial acetic acid (26 ml.). The solid which separated was washed with ether, the base liberated with strong aqueous ammonia and extracted with ether. After drying with $Na_2SO_4$, the solvent was removed to give a mixture of the crude alcohols (21 g.). The crude alcohols (12 g.) were refluxed for 4 hours with propionic anhydride (20 g.) and pyridine (20 ml.), the solvents removed under reduced pressure, the residue made alkaline with strong aqueous ammonia and the free base extracted with ether. After drying with $Na_2SO_4$, the solvent was removed to give a mixture of the crude propionoxy esters (13·7 g.). A solution of the crude esters (11·7 g.) in ether (160 ml.) was saturated with dry hydrogen chloride, the solid which separated collected, washed

with ether and dried in a vacuum desiccator to give the crude ester hydrochlorides (11·9 g.). Fractional crystallisation of the latter mixture (11 g.) from ether-ethanol gave alphaprodine (7·6 g.), m.p. 218° to 220° and betaprodine (2·6 g.) m.p. 181° to 185°. Further crystallisation of alphaprodine from acetone raised its m.p. to 220° to 221°; crystallisation of betaprodine from methyl ethyl ketone gave material m.p. 195° to 196°. Ziering and Lee[1] give alphaprodine m.p. 212° to 214° and betaprodine 190° to 192°. A mixture of alphaprodine (2 g.), ethanol (5 ml.) and 5 per cent aqueous sodium hydroxide (20 ml.) was refluxed for 3 hours, saturated with $K_2CO_3$ and the free base extracted with ether. After drying with $MgSO_4$, the solvent was removed to give α-1:3-dimethyl-4-phenyl-4-piperidinol, m.p. 101° to 102° after recrystallisation from *n*-hexane. Ziering and Lee[1] give m.p. 103°. β-1:3-Dimethyl-4-phenyl-4-piperidinol was prepared in a similar way from betaprodine and had m.p. 118° to 119° after recrystallisation from *n*-hexane. Lee informs us that the m.p. is 116° to 117°.

1:3-*Dimethyl-4-o-methoxyphenyl-4-piperidinol and its acetoxy ester.* The piperidone (I) (6·35 g.) was added dropwise with stirring to a cooled (ice-salt bath) solution of *o*-methoxyphenyl lithium in ether (50 ml.) prepared from lithium (1·36 g.) and *o*-methoxybromobenzene (18·7 g.). The reaction mixture was treated as above, the free base liberated with strong aqueous ammonia and extracted with chloroform. After drying with $Na_2SO_4$ the solvent was removed to give a solid (7·3 g.) m.p. 109°. Fractional crystallisation of this solid from light petroleum (b.p. 60° to 80°) gave needles of 1:3-*dimethyl-4-o-methoxyphenyl-4-piperidinol* (7·18 g.) m.p. 111·5°. Found: C, 71·2; H, 8·6; N, 6·0 per cent; equiv. wt. 235. $C_{14}H_{21}O_2N$ requires C, 71·4; H, 8·9; N, 5·95 per cent; equiv. wt. 235. A mixture of the alcohol (2 g.), acetic anhydride (2 ml.) and pyridine (2 ml.) was refluxed for 3 hours, the solvents removed under reduced pressure, the residue made alkaline with strong aqueous ammonia and the free base extracted with ether. After drying with $Na_2SO_4$, the solvent was removed to give 1:3-*dimethyl-4-o-methoxyphenyl-4-acetoxypiperidine* (2 g.) m.p. 112° to 113° after recrystallisation from light petroleum (b.p. 60° to 80°). Found: C, 69·3; H, 8·4; N, 5·0 per cent; equiv. wt. 280. $C_{16}H_{23}O_3N$ requires C, 69·3; H, 8·4; N, 5·05 per cent; equiv. wt. 277.

1:3-*Dimethyl-4-o-tolyl-4-piperidinol and its esters.* The piperidone (I) (5·08 g.) was added dropwise with stirring to a cooled solution of *o*-tolyl lithium in ether (50 ml.) prepared from lithium (0·7 g.) and *o*-bromotoluene (8·55 g.). The reaction mixture was treated as above, the free base liberated with strong aqueous ammonia and extracted with ether. After drying with $Na_2SO_4$, the solvent was removed to give a pale yellow oil (6·5 g.) which solidified on storing in a vacuum desiccator. Fractional crystallisation of the solid m.p. 83° to 85° from *n*-hexane gave the *piperidinol* (II, Ar = *o*–$CH_3$·$C_6H_4$) (4·96 g.) needles m.p. 86° to 87°. Found: C, 76·7; H, 9·4; N, 6·35 per cent; equiv. wt. 223. $C_{14}H_{21}ON$ require C, 76·65; H, 9·7; N, 6·4 per cent; equiv. wt. 219. The alcohol was esterified with acetic anhydride as above; the *acetoxy ester* (III,

Ar = *o*–$CH_3 \cdot C_6H_4$; R = $CH_3$) gave a *hydrochloride*, needles from ether-ethanol, m.p. 222° to 223°. Found: C, 64·5; H, 8·1; N, 4·65 per cent; equiv. wt. 301. $C_{16}H_{24}O_2NCl$ requires C, 64·5; H, 8·1; N, 4·7 per cent; equiv. wt. 298. The *propionoxy ester* (III, Ar = *o*–$CH_3 \cdot C_6H_4$; R = Et), prepared in an analogous manner using propionic anhydride, gave a *hydrochloride*, needles, m.p. 198° to 199°. Found: C, 65·5; H, 8·6; N, 4·3 per cent; equiv. wt. 314. $C_{17}H_{26}O_2NCl$ requires C, 65·5; H, 8·4; N, 4·5 per cent; equiv. wt. 312.

1 : 3-*Dimethyl*-4-*m-tolyl*-4-*piperidinol isomers and esters.* The piperidone (I) (12·7 g.) was added dropwise with stirring to a solution of *m*-tolyl lithium in ether (200 ml.) prepared from lithium (1·53 g.) and *m*-bromotoluene (18·8 g.). The reaction mixture was treated as above, the free base liberated with strong aqueous ammonia and extracted with ether. After drying with $Na_2SO_4$, the solvent was removed to give a solid (14·7 g.) m.p. 104° to 108° after softening at 80°. Fractional crystallisation of this solid from *n*-hexane gave the piperidinol (II, Ar = *m*–$CH_3 \cdot C_6H_4$) in two isomeric forms: *Isomer A*, needles (10·58 g.) m.p. 88·5° to 89·5°. Found: C, 76·4; H, 9·3; N, 6·3 per cent; equiv. wt. 221. $C_{14}H_{21}ON$ requires C, 76·65; H, 9·65; N, 6·4 per cent; equiv. wt. 220; *Isomer B*, prisms (1·28 g.) m.p. 114° to 115°. Found: C, 76·85; H, 9·5; N, 6·1 per cent; equiv. wt. 221. $C_{14}H_{21}ON$ requires C, 76·65; H, 9·65; N, 6·4 per cent; equiv. wt. 220. The *acetoxy ester* of Isomer A, prepared as above, gave a *hydrochloride*, platelets from ether-ethanol, m.p. 238·5°. Found: C, 64·1; H, 8·4; N, 4·7 per cent; equiv. wt. 300. $C_{16}H_{24}O_2NCl$ requires C, 64·5; H, 8·1; N, 4·7 per cent; equiv. wt. 298. The *propionoxy ester* of Isomer A, prepared as above, gave a *hydrochloride*, needles from ether-ethanol, m.p. 233°. Found: C, 65·5; H, 7·8; N, 4·5 per cent; equiv. wt. 314. $C_{17}H_{26}O_2NCl$ requires C, 65·5; H, 8·4; N, 4·5 per cent; equiv. wt. 312.

1 : 3-*Dimethyl*-4-p-*tolyl*-4-*piperidinol and esters.* The piperidone (I) (5·08 g.) was added dropwise with stirring to a cooled solution of *p*-tolyl lithium in ether (50 ml.) prepared from lithium (0·7 g.) and *p*-bromotoluene (8·55 g.). The reaction mixture was treated as above, the free base liberated with strong aqueous ammonia, and extracted with chloroform. After drying with $Na_2SO_4$, the solvent was removed to give a solid (6·3 g.) m.p. 128° to 133° after softening at 85°. Fractional crystallisation of this solid from *n*-hexane gave the *piperidinol* (II, Ar = *p*–$CH_3 \cdot C_6H_4$) (4·21 g.), needles, m.p. 135° to 136° (*Isomer A*). Found: C, 76·6; H, 9·3; N, 6·4 per cent; equiv. wt. 221·5. $C_{14}H_{21}ON$ requires C, 76·65; H, 9·7; N, 6·4 per cent; equiv. wt. 220. A final crop of crystals (1·8 g.) m.p. 81° to 91° equiv. wt. 222, theory 220, was obtained which could not be further purified by fractional crystallisation; these crystals were hand-picked to give a small quantity of *Isomer B*, m.p. 103° to 104°. *Isomer A* gave an *acetoxy ester hydrochloride*, prepared as above, plates from ether-ethanol, m.p. 218° to 219°. Found: C, 60·8; H, 8·2; N, 4·2 per cent; equiv. wt. 311. $C_{16}H_{24}O_2NClH_2O$ requires C, 60·8; H, 8·3; N, 4·4 per cent; equiv. wt. 316. The *propionoxy ester hydrochloride*, prepared as above, gave needles from ether-ethanol, m.p. 221° to 222°. Found: C, 65·1; H, 8·1;

N, 4·4 per cent; equiv. wt. 314. $C_{17}H_{26}O_2NCl$ requires C, 65·5; H, 8·4; N, 4·5 per cent; equiv. wt. 312.

*Infra-red Absorption Measurements*

Determinations were carried out in carbon disulphide solution, concentration range 0·3 to 0·9 per cent w/v. Calibration was accurate to $\pm 3$ cm.$^{-1}$ over the region 650 to 2000 cm.$^{-1}$ and $\pm 5$ cm.$^{-1}$ over the region 2000 to 5000 cm.$^{-1}$. Infra-red spectra were measured on a Hilger H.800 double-beam automatic recording spectrophotometer fitted with sodium chloride optics, run in cells of path length 0·75 mm. and compensated with carbon disulphide.

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REFERENCES

1. Ziering and Lee, *J. org. Chem.*, 1947, **12**, 911.
2. Randall and Lehman, *J. Pharmacol.*, 1948, **93**, 314.
3. Gross, Holland and Schueler, *J. Appl. Physiol.*, 1948, **1**, 298.
4. Beckett and Walker, *J. Pharm. Pharmacol.*, 1955, **7**, 1039.
5. Beckett and Casy, *J. chem. Soc.*, 1955, 900.
6. Beckett and Harper, *ibid.*, 1957, 858.
7. Beckett and Casy, *ibid.*, 1957, 3076.
8. Beckett and Casy, *J. Pharm. Pharmacol.*, 1954, **6**, 986.
9. Beckett, Casy, Harper and Phillips, *ibid.*, 1956, **8**, 860.
10. Howton, *J. org. Chem.*, 1945, **10**, 277.
11. Dauben, Fonken and Noyce, *J. Amer. chem. Soc.*, 1956, **78**, 2579.
12. Mitchovitch, *Bull. Soc. chim. Belgrade*, 1949, **14**, 181.
13. Goering, Reeves and Espy, *J. Amer. chem. Soc.*, 1956, **78**, 4927.
14. Beckett, Harper, Balon and Watts, *Chem. and Ind.*, 1957, 663.
15. Barton, Campos-Neves and Cookson, *J. chem. Soc.*, 1956, 3500.
16. Pifer and Wollish, *J. Amer. pharm. Ass., Sci. Ed.*, 1951, **40**, 609.
17. Janssen and Jageneau, *J. Pharm. Pharmacol.*, 1957, **9**, 381.

## DISCUSSION

The paper was presented by DR. A. F. CASY.

THE CHAIRMAN. It seemed that analgesic activity had been measured only by the hotplate method. The results required further consideration before one attempted to draw too close a deduction about the relative effects of ortho, meta and para substituents.

PROFESSOR K. BULLOCK (Manchester) also suggested that certain of the biological results were not sufficiently different to warrant conclusions being drawn from them.

DR. G. E. FOSTER (Dartford). It would seem that there were asymmetric carbon atoms present in the compounds. Had consideration been given to resolving them and testing the isomers?

DR. L. SAUNDERS (London). Did the active compounds confirm the authors' receptor site theory?

DR. J. B. STENLAKE (Glasgow). In the discussion of a previous paper on the receptor site theory he had put forward the view which was contrary to that held by the authors that the Randall and Lehman figure should be reversed. With regard to the infra-red results, particularly the region B (1380 to 1385 cm.$^{-1}$) was it to be understood that absorption in that region was C-methyl absorption? If so, he took it that the more or less constant band about 1380 was C-methyl. Doublets in that region were well known, and duality of those bands seemed to be correlated with configuration.

DR. A. F. CASY, in reply, agreed that not too much significance should be put on the biological results. The replacement of the phenyl by an aryl group brought about a reduction in activity. Resolution had been carried out in the case of the betaprodine, and one optical isomer was considerably more active than the other. The work described in the paper was confined to configuration, and at this stage he would prefer not to comment on the receptor site theory. No attempt had been made to relate the characteristics of infra-red absorption spectra to structural features.

DR. N. J. HARPER added that Dr. Janssen had shown the results which he obtained could be duplicated in a different laboratory. The original structures of alpha and betaprodine were assigned by Lee, but Beckett and Walker developed their structures as a result of hydrolysis studies, and it was significant that the results agreed with the idea of a receptor site.