*Short Communication*

# POTENTIAL ANALGESICS. THE STEREOCHEMISTRY OF SOME ISOMERIC PIPERIDINOL DERIVATIVES

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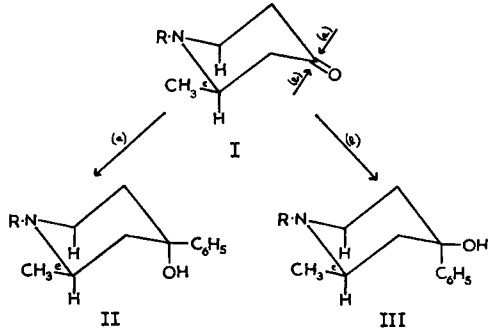
DURING continued investigations of structure-activity relationships in synthetic analgesics, some compounds related to the reversed esters of pethidine, namely isomers of *N*-(2′-phenylethyl)-2-methyl-4-phenyl-4-piperidinol, *N*-(2′-phenylethyl)-2,6-dimethyl-4-phenyl-4-piperidinol, *cis*-2,6-dimethyl-4-phenyl-4-piperidinol and some of their esters were prepared by routes involving the addition of lithium phenyl to the appropriate ketone. These compounds are of interest in view of the recent introduction by the Russians of the potent analgesic Promedol[1,2].

Treatment of *N*-(2′-phenylethyl)-2-methyl-4-piperidone (I) with lithium phenyl gave two isomeric piperidinols (Type A and B) which were separated by fractional crystallisation of the hydrochlorides. These isomers A and B (II and III) obtained in a ratio of 2:1 were assigned *cis*-$CH_3/C_6H_5$ and *trans*-$CH_3/C_6H_5$ configurations respectively on the basis of the following evidence.

(*a*) The steric course of addition of organometallic derivatives to ketones is controlled by steric hindrance involved in the approach to the carbon atom of the carbonyl group, and by an energy factor which influences the ease with which a group may be forced into an unfavoured position[3]. With *N*-(2′-phenylethyl)-2-methyl-4-piperidone, attack from side "b" is sterically hindered, and causes a preferential formation of the type A isomer (II), with an equatorial phenyl group.




R=$CH_2CH_2C_6H_5$

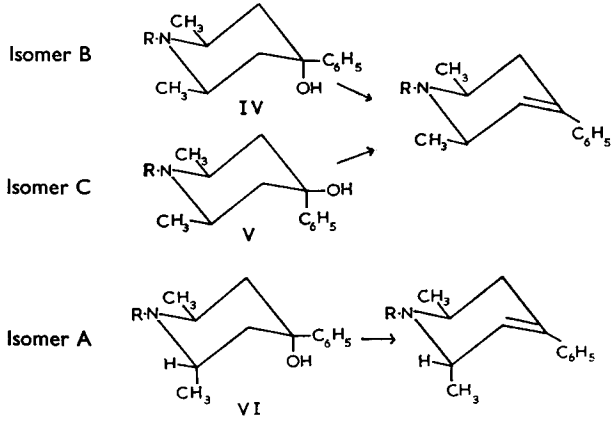
(*b*) The infra-red spectra of $\alpha$ and $\beta$-prodine type compounds show two regions[4,5] (Region A, 990–1010 cm.$^{-1}$ and Region B, 1350–1385 cm.$^{-1}$) which are isomerically characteristic. The infra-red spectrum of the A isomer substantially resembles those of $\alpha$-prodine type compounds and that of the B isomer the spectra of $\beta$-prodine type compounds; an axial and an equatorial conformation of the hydroxyl group for the A and the B isomers respectively is indicated.

(*c*) The isomer B is more readily esterified than is A; an equatorial hydroxyl group in the former isomer is indicated.

*N*-(2′-Phenylethyl)-2,6-dimethyl-4-piperidone was prepared by the interaction of acetaldehyde, 2-phenylethylamine and diethyl acetonedicarboxylate. The addition of lithium phenyl to isomerically impure *N*-(2′-phenylethyl)-2,6-dimethyl-4-piperidone gave the three theoretically possible piperidinols in the ratio 9:2:1 designated Types A, B and C respectively; these were separated by fractional crystallisation of the free base.

The following configurations have been assigned. A isomer, *trans*-$CH_3/CH_3$ (VI); B, *cis*-$CH_3/CH_3$, *cis*-$CH_3/C_6H_5$ (IV) and C, *cis*-$CH_3/CH_3$, *trans*-$CH_3/C_6H_5$ (V), the evidence for the assignation being as follows.

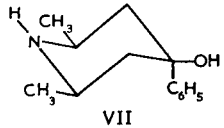
(*a*) Elimination of B and C isomers gave identical eliminated products which indicated their derivation from the *cis*-$CH_3/CH_3$ ketone, while isomer A gave a different eliminated product indicating its formation from *trans*-$CH_3/CH_3$ ketone.



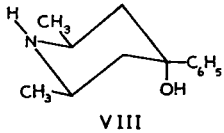

(*b*) The dissociation constants[6] of isomers B and C were 8·4 and 8·57 respectively but that of A was greatly dissimilar at 9·06; the similar geometry of the methyl groups in isomers B and C which differ from that obtaining in isomer A is indicated. An axial methyl group on a carbon adjacent to a basic nitrogen atom would be predicted to have a greater base strengthening effect than a corresponding equatorial methyl group; the *e*, *e* arrangement of the two methyl groups in isomers B and C and the *a*, *e* conformation in isomer A advanced above is therefore supported.

(*c*) Infra-red spectra demonstrated intermolecular hydrogen bonding in A and B isomers but not in C; similar arrangement of the hydroxyl groups in A and B but not in C is indicated. Isomer A with the *trans* dimethyl groups would be expected to have the $CH_3$ (*e*), $CH_3$ (*a*), $C_6H_5$ (*e*) and OH (*a*) conformation (VI) and isomer B is therefore given the *cis*-$CH_3/CH_3$, *cis*-$CH_3C_6H_5$ configuration (IV).

The reaction of *cis*-2,6-dimethyl-4-piperidone[7] with lithium phenyl gave two isomeric piperidinols, A and B, which were separated chromatographically in a ratio of 12: 13 respectively. Upon attempting to prepare hydrobromides, isomer A gave the piperidinol salt but isomer B eliminated to the tetrahydropyridine salt. Therefore the *e* and *a* conformation of the hydroxyl group in isomers A (VII) and B (VIII) respectively is indicated. This assignment is supported by esterification studies in which, using identical conditions, A but not B could be esterified. The infra-red spectra of isomer A in the 1000 to 1200 cm.$^{-1}$ region showed the strongest peak at 1141 cm.$^{-1}$, the strongest absorption of isomer B being at 1013 cm.$^{-1}$. These peak locations are in close agreement with those of isomer C (V) (1143 cm.$^{-1}$) and isomer B (IV) (1018 cm.$^{-1}$) of *N*-(2′-phenylethyl)-2,6-dimethyl-4-phenyl-4-piperidinol; the conformational similarities of isomer A (VII) to (V) and of isomer B (VIII) to (IV) is thus indicated and supports the above conclusions.




VII




VIII

The compounds and their esters are being tested as potential analgesics.

## References

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After Dr. Harper presented the communication there was a DISCUSSION. The following points were made.

The acetoxy and propinoxy esters of the Isomer A of *N*-2-phenylethyl-2,6-dimethyl-4-phenyl-4-piperidinol were about four times as active as morphine when assessed by the hot plate method. In the compounds tested the various types of morphine-like activity had been clearly separated.