

SYNTHESIS OF PIPERIDINE DERIVATIVES. PART III

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Nine new substituted γ -piperidones have been synthesised by the Mannich condensation of ethyl acetone-dicarboxylate with different aldehydes and primary amines.

In two previous communications (Zaheer, Sen and Sidhu, this *Journal*, 1947, 24, 293; Sen and Sidhu, *ibid.*, 1948, 25, 433) the synthesis of some substituted *N*-alkyl- γ -piperidinols by the action of alkyl- and arylmagnesium halides on ethyl 1-methyl (or ethyl)-2:6-phenyl-4-piperidone-3:5-dicarboxylate has been described. The pharmacological interest attaching to the piperidone derivatives, specially in the field of analgesics and antispasmodics, has led to much work being done towards the synthesis of substituted piperidines (Plati *et al.*, *J. Org. Chem.*, 1949, 14, 1873; Kagi and Mi scher, *Helv. Chim. Acta*, 1949, 32, 2589; Badger, Cook and Donald, *J. Chem. Soc.*, 1950, 197; Lespagrol and Bertrand, *Compt. rend.*, 1950, 230, 658; British Patents, 595, 631; 614, 567; 629, 196; U. S. Patents, 2,476,913; 2, 489, 546; 2,496,555 2, 496,556; 2, 496, 558; 2, 500, 714; Swiss Patents, 252, 958; 253, 175; 259, 422; 295, 120)

In this paper the Mannich reaction between ethyl acetone-dicarboxylate, an aldehyde and a primary amine has been extended to the synthesis of nine new γ -piperidones, following, in general, the method of Petrenko-Kritschenko (*Ber.*, 1907, 40, 2884; 1909, 42, 3683, 3689)

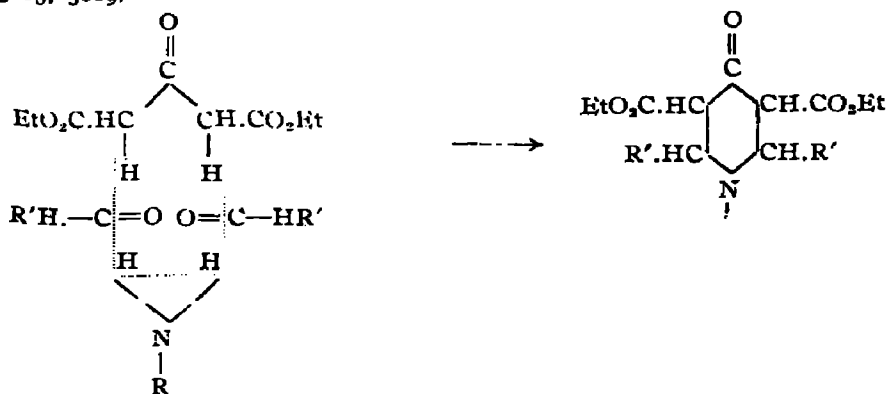


TABLE I

R =	R =
1. + * Phenyl	γ -Propyl
2. + * β -Hydroxyethyl	Phenyl
3. * Allyl	"
4. * Propyl	"
5. * Butyl	"
6. * Amyl	"
7. * <i>iso</i> Amyl	"
8. * Benzyl	"
9. * β -Phenylethyl	"

The condensation of ethyl acetone-dicarboxylate with benzaldehyde and β -amino-*n*-acetane, however, yielded, surprisingly enough, a nitrogen-free crystalline product, the nature of which is being investigated.

These piperidones appear to be dimorphic, as already observed by Petrenko-Kritschenko in the case of analogous ethyl 1-methyl- and 1-ethyl-2:6-diphenyl-4-piperidone-3:5-dicarboxylates (*loc.cit.* Cf. also Sen and Sidhu, *loc.cit.*). Higher and lower melting crystalline forms have been obtained in the case of piperidones marked with an asterisk in the above table. The lower melting forms, in cold alcoholic solution, give a deep red coloration with ferric chloride and also immediately decolorise bromine water and are thus probably the enol forms. The higher melting forms, on the contrary, in cold alcoholic solution do not give a colour with ferric chloride and do not decolorise bromine water, and are thus probably the keto isomers. Free bases could not be obtained in the case of piperidones marked + which have been isolated only as crystalline hydrochlorides.

EXPERIMENTAL*

Ethyl 1-Phenyl-2:6-diphenyl-4-piperidone-3:5-dicarboxylate Hydrochloride.—A mixture of ethyl acetone-dicarboxylate (5 g., 0.024 mole) and *n*-butyric aldehyde (3.6 g., 0.048 mole) was thoroughly cooled in ice-salt mixture and 2.4 g. (0.026 mole) of aniline, freshly distilled over zinc dust, was added to it dropwise. The reaction mixture was allowed to stand overnight in a refrigerator and after a further twelve hours' standing at room temperature and cooling again in ice, when no solid separated, the viscous yellow liquid was dissolved in ether-benzene, cooled in ice and saturated with dry hydrogen chloride. The precipitated hydrochloride was collected at the pump and recrystallised from methanol-ethyl acetate as white leaflets, m.p. 192-93°, yield 2.3 g. (21% of theory). (Found: N, 3.438. $C_{23}H_{24}O_5NCl$ requires N, 3.474 per cent).

The mother-liquor on slow evaporation deposited crystals of another hydrochloride, m.p. 109°.

Attempts to convert the hydrochlorides into bases by treatment with ice and dilute ammonia yielded in both cases a viscous oil.

Ethyl 1-(2'-Hydroxyethyl)-2:6-diphenyl-4-piperidone-3:5-dicarboxylate hydrochloride was prepared in the same manner from ethyl acetone-dicarboxylate (5 g., 0.025 mole), benzaldehyde (5.3 g., 0.05 mole) and ethanolamine (1.6 g., 0.026 mole). The benzaldehyde used in this and in the subsequent preparations was washed with sodium carbonate solution, dried and distilled in an atmosphere of nitrogen to ensure its being free of benzoic acid. The hydrochloride on recrystallisation from ethanol melted at 158-59°, yield 7.5 g. (62% of theory). (Found: N, 3.0. $C_{23}H_{26}O_6NCl$ requires N, 2.94 per cent).

Ethyl 1-Allyl-2:6-diphenyl-4-piperidone-3:5-dicarboxylate.—Allylamine (2.85 g., 0.05 mole) was added dropwise to a mixture of ethyl acetone-dicarboxylate (10.1 g., 0.059 mole) and benzaldehyde (10.6 g., 0.10 mole), cooled in ice and salt. The reaction mixture was left overnight in a refrigerator and the resulting pasty mass was rubbed up with a little chilled alcohol, filtered, dried, and recrystallised from ethanol, m.p.

* All melting points are uncorrected.

129-31°, yield 12.4 g. (59% of theory). (Found: N, 2.40. $C_{22}H_{23}O_3N$ requires N, 3.22 per cent)

The hydrochloride was prepared by passing dry hydrogen chloride in an ether-benzene solution of the base, m.p. 151-53°. The mother-liquor on standing leposited crystals of another hydrochloride which after recrystallisation from ethanol melted at 132-33°. It was thought that this might be a part of the piperidone itself recovered unchanged but it gave a positive test for chlorine and a mixed melting point determination with piperidone lowered the m.p. to 109-111°.

Ethyl 1-propyl-2:6-diphenyl-4-piperidone-3:5-dicarboxylate was obtained in the same manner from ethyl acetone-dicarboxylate (10.1 g., 0.059 mole), benzaldehyde (10.6 g., 0.059 mole) and *n*-propylamine (2.95 g., 0.05 mole). The reaction mixture solidified immediately. It was crystallised from ethanol as white leaflets, m.p. 123-25°, yield 18 g. (82.5% of theory). (Found: N, 2.80. $C_{28}H_{31}O_5N$ requires N, 3.31 per cent).

The alcoholic mother liquor from the recrystallisation of the base was left over for slow evaporation and deposited crystals of lower melting form which after recrystallisation from ethanol melted at 80°.

The hydrochloride from higher melting form melted at 146-49°.

Ethyl 1-butyl-2:6-diphenyl-4-piperidone-3:5-dicarboxylate was prepared in the same manner from ethyl acetone-dicarboxylate (5 g., 0.025 mole), benzaldehyde (5.3 g., 0.05 mole) and *n*-butylamine (1.82 g., 0.026 mole), m.p. 143-44° (from ethanol), yield 4.3 g. (38 % of theory). (Found: N, 2.76. $C_{27}H_{31}O_5N$ requires N, 3.10 per cent).

Lower-melting form from alcoholic mother-liquor by slow evaporation melted at 82-83° (from ethanol). Hydrochloride from higher base, m.p. 127-28°. Hydrochloride from lower melting base, m.p. 142-43°.

Ethyl 1-amyl-2:6-diphenyl-4-piperidone-3:5-dicarboxylate was prepared in the same manner from ethyl acetone-dicarboxylate (5 g., 0.025 mole), benzaldehyde (5.3 g., 0.05 mole) and *n*-amylamine (2.2 g., 0.026 mole). The reaction mass crystallised only after three days' standing in a refrigerator and was then filtered after rubbing up with a little chilled alcohol. It melted at 147-48° after recrystallisation from isopropyl alcohol, yield 6.6 g. (57 % of theory). (Found: N, 2.59. $C_{28}H_{33}O_5N$ requires N, 3.01 per cent).

Lower melting form on standing of the mother-liquor melted at 98-99°; the hydrochloride of higher melting form melted at 138-39°.

Ethyl 1-(3' methylbutyl)-2:6-diphenyl-4-piperidone-3:5-dicarboxylate was prepared in the same manner from ethyl acetone-dicarboxylate (5 g., 0.025 mole), benzaldehyde (5.3 g., 0.050 mole) and isoamylamine (2.2 g.), m.p. 132-34° from methanol, yield 3.1 g. (29 % of theory). (Found: N, 3.62. $C_{28}H_{33}O_5N$ requires N, 3.01 per cent).

Lower melting form by slow evaporation of the mother-liquor melted at 90-92° (from methanol).

A hydrochloride was prepared from the higher melting form but it had a long melting range, 130°-180°. Recrystallisation from alcohol and washing with ether failed to yield a purer product. Presumably it may be a mixture of two dimorphic hydrochlorides.

Ethyl 1-Benzyl-2:6-diphenyl-4-piperidone-3:5-dicarboxylate.—Ethyl acetone-dicarboxylate (10.1 g., 0.059 mole), benzaldehyde (10.6 g.) and benzylamine (5.35 g., 0.05

mole) were reacted as in the previous cases. When reaction mixture did not crystallise after keeping in a refrigerator for two days, it was dissolved in benzene and the hydrochloride precipitated by passing HCl gas, m.p. 160-63° (from methanol), yield 12.6 g. (50 % of theory). (Found: N, 2.64. $C_{30}H_{22}O_6NCl$ requires N, 2.68 per cent). Crystals of another hydrochloride (m.p. 243-48°) could be obtained from the mother-liquor on standing.

This hydrochloride was converted into the piperidone by treatment with ice and dilute ammonia. The crude piperidone could not be crystallised. After washing with alcohol and petroleum ether it melted at 172-73°.

Ethyl 1-(2'-phenylethyl)-2:6-diphenyl-4-piperidone-3:5-dicarboxylate was obtained in the usual manner from ethyl acetone-dicarboxylate (10.1 g., 0.059 mole), benzaldehyde (10.6 g., 0.10 mole) and β -phenylethylamine (6 g., 0.05 mole), m.p. 133.5° from ethanol, yield 21.2 g. (85% of theory). (Found: N, 2.24. $C_{31}H_{28}O_6N$ requires N, 2.8 per cent). Hydrochloride, m.p. 216-18°.

Condensation of Ethyl Acetone-dicarboxylate with Benzaldehyde and β -Amino-n-octane.—The condensation was carried out in the usual manner using ethyl acetone-dicarboxylate (5 g., 0.025 mole), benzaldehyde (5.3 g., 0.05 mole) and β -amino-n-octane (3.23 g., 0.025 mole). The reaction product after recrystallisation from ethanol melted at 149-50°. Surprisingly enough this reaction product does not contain nitrogen and does not form a hydrochloride or hydrobromide.

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