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The Preparation and Analgesic Activity of 4-Carbethoxy-4-phenyl-1-(2-phenylethyl)piperidine and Related Compounds

THEODORE D. PERRINE AND NATHAN B. EDDY

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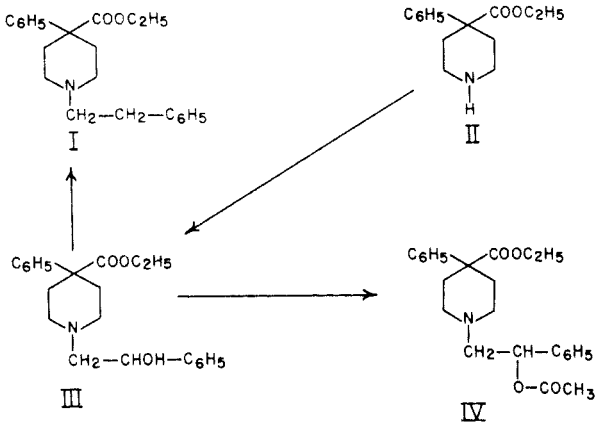
4-Carbethoxy-4-phenyl-1-(2-phenylethyl)piperidine (I) was obtained in good yield by reduction of 4-carbethoxy-1-(2-hydroxy-2-phenylethyl)-4-phenylpiperidine (III) which had been prepared by heating normeperidine with phenylethylene oxide. When phenylethyl or phenylethanol was substituted for N-methyl without other change in the meperidine structure, analgesic effectiveness was materially increased, but for subcutaneous administration only. The phenylethyl compound was less toxic, the phenylethanol derivative slightly more toxic than meperidine.

The synthesis of 4-carbethoxy-4-phenyl-1-(2-phenylethyl)piperidine (I) was effected by condensing 4-carbethoxy-4-phenylpiperidine with phenylethylene oxide,[1] with subsequent hydrogenolysis of the hydroxyl group. The latter step was expected to be difficult, and was, indeed, found to go rather slowly. Infrared spectra indicate that the hydroxyl group of 4-carbethoxy-1-(2-hydroxy-2-phenylethyl)-4-phenylpiperidine (III) is strongly associated, which would be predicted from a study of the molecular model.



EXPERIMENTAL

All melting points were determined on the Koffler hot stage unless otherwise noted.

4-Carbethoxy-4-phenylpiperidine (II). N-Benzyl-4-carbethoxy-4-phenylpiperidine[2] (10 g.) was converted to II by catalytic hydrogenolysis approximately by the method of Eisleb.[3] It was found that the reduction was facilitated by the use of 5% palladium-charcoal catalyst to which 10% of solid palladium chloride had been added. The product was isolated through the carbonate (6.05 g.) by the method of Thorp and Walton.[4] The hydrochloride had the m.p. 133–134° (lit. m.p. 133–134°), and the picrate had the m.p. 160–161° (lit. m.p. 157–158°).

4-Carbethoxy-1-(2-hydroxy-2-phenylethyl)-4-phenylpiperidine (III). 4-Carbethoxy-4-phenylpiperidine (II) (1.0 g.) was warmed overnight on the steam-bath with 0.5 g. of phenylethylene oxide (Eastman Kodak) in an atmosphere of nitrogen. The crystalline addition product was purified by crystallizing its *hydrochloride* from water, this salt having the m.p. 180–193°; yield, 60%.

Anal. Calc'd for $C_{22}H_{28}ClNO_3$ (389.91): C, 67.8; H, 7.24; N, 3.59. Found: C, 67.8; H, 7.24; N, 3.53.

The *base* was liberated from the hydrochloride, and was purified by vacuum sublimation at 125°/10^{-4} mm., m.p. 126–127°.

Anal. Calc'd for $C_{22}H_{27}NO_3$ (353.45): C, 74.7; H, 7.70; N, 3.96. Found: C, 74.6; H, 7.86; N, 3.98.

4-Carbethoxy-4-phenyl-1-(2-phenylethyl)piperidine (I). The hydrochloride of III (3.9 g., 0.01 mole) in ethanol, was hydrogenated at atmospheric pressure using 4 g. of 10% palladium-charcoal catalyst, to which 0.5 g. of $PdCl_2$ had been added. The reduction required about 2.5 hours. The hydrochloride of I (3.4 g.) was recrystallized from water. The m.p. was 175–190°, yield 2.4 g. After a further recrystallization from ethanol-ether, it showed the m.p. 186–190°. It was not possible to obtain this salt analytically pure.

The *perchlorate*, from the hydrochloride and $NaClO_4$ in water, had the m.p. 219–221° (from ethanol).

Anal. Calc'd for $C_{22}H_{28}ClNO_6$ (437.91): C, 60.3; H, 6.44; N, 3.20. Found: C, 60.3; H, 6.71; N, 3.13.

The *base* (I), liberated from either the hydrochloride or the perchlorate, had the m.p. 55–56° (capillary tube) after sublimation at 80°/10^{-4} mm., and was hygroscopic.

Anal. Calc'd for $C_{22}H_{27}NO_2 + {}^1/_4\ H_2O$ (341.47): C, 77.3; H, 8.11; N, 4.10. Found: C, 77.4, 77.4; H, 8.34, 8.26; N, 4.05, 4.09.

The infrared spectrum of III showed a strong band at 3390 cm.$^{-1}$, indicative of an associated hydroxyl group. This band was absent in the infrared spectrum of I, which showed no OH absorption.

1-(2-Acetoxy-2-phenylethyl)-4-carbethoxy-4-phenylpiperidine (IV). When 4-carbethoxy-4-phenyl-1-(2-hydroxy-2-phenylethyl)piperidine (III) was allowed to stand 48 hours with freshly distilled acetyl chloride, the initially-formed white precipitate was transformed into an oily hydrochloride, which could not be induced to crystallize. After washing this salt with ether, it was dissolved in water, the base liberated with ammonia and extracted with ether. The oily base was purified by distillation at 130°/10^{-4} mm. and had n_D^{20} 1.5453.

Anal. Calc'd for $C_{24}H_{29}NO_4$ (395.48): C, 72.9; H, 7.39; N, 3.54. Found: C, 72.7; H, 7.55; N, 3.50.

The infrared spectrum showed two carbonyl absorption bands at 1725 cm^{-1} and and 1740 cm^{-1}.

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(1) Emerson, *J. Am. Chem. Soc.*, **67**, 516 (1945).

(2) A generous gift of this material was received from the Winthrop-Stearns Chemical Co.

(3) Eisleb, *Ber.*, **74**, 1447 (1941).

(4) Thorp and Walton, *J. Chem. Soc.*, 559 (1948).

(5) Deceased.

ANALGESIC ACTIVITY

Heretofore, substitution of other groups for methyl on the nitrogen of meperidine has been reported to decrease analgesic activity.[6] It was surprising, therefore, to find that phenylethyl or phenylethanol in the place of N-methyl had the opposite effect. Analgesic activity has been determined in mice by our modification of the hot-plate method, and the ED_{50} in each case has been calculated by probit analysis of the data.[7] Doses are expressed in mg./kg. of base. For subcutaneous administration the ED_{50} of 4-carbethoxy-4-phenyl-1-(2-phenylethyl)piperidine (I) was 4.3 mg./kg., and that of 4-carbethoxy-1-(2-hydroxy-2-phenylethyl)-4-phenylpiperidine (III) was 3.0 mg./kg. The ED_{50} of meperidine for comparison was 8.6 mg./kg. and that of morphine was 1.6 mg./kg. Acetylation of the hydroxyl to form compound IV, reduced analgesic activity markedly to an ED_{50} of about 200 mg./kg. By oral administration I and III were much less effective, the ED_{50} of these two compounds being 93 and 128 mg./kg., respectively. Corresponding figures for oral administration of meperidine and morphine were 48 and 2.9 mg./kg. There was no significant difference in the duration of effect of the phenylethyl and phenylethanol derivatives, and that of meperidine orally or subcutaneously. Each of the three compounds had a slightly shorter duration of action than morphine. The toxicity of phenylethylnormeperidine (I) was much less than that of meperidine, while the toxicity of the phenylethanol compound (III) was slightly more. The LD_{50} subcutaneously for I was more than 500, for meperidine was 135, and for III was 116 mg./kg.

BETHESDA 14, MARYLAND

(6) Braenden, Eddy, and Halbach, *Bull. World Health Org.*, in press.

(7) Eddy and Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953).