

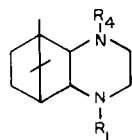
Some *dl*-5,9,9-Trimethyldecahydro-5,8-methanoquinolines

Edgar A. Steck (1) and John T. Suh

Johnson & Johnson Research Center, New Brunswick, New Jersey 08902
and McNeil Laboratories, Inc., Fort Washington, Pennsylvania 19034

Received June 16, 1975

Our prior work on terpenoid types (2-4) led to interest in derivatives of the readily accessible (5) *dl*-5,9,9-trimethyldecahydro-5,8-methanoquinoline, I. A short series of compounds was prepared (6) [II and III]. Lack of appreciable biological activity failed to justify further work, either in synthesis or establishing the structure of type II. It was assumed that the 5-methyl grouping exerted steric hindrance for reaction at position 4. Thus, the Eschweiler-Clarke methylation of II-f was unsuccessful.



- I $R_1 = R_4 = H$
 II $R_4 = H; R_1 = a) -CO_2C_2H_5;$
 b) $-CO_2N(CH_3)_2;$ c) $-CH_2CH_2N(CH_3)_2;$
 d) $-CH_2CH_2OH;$ e) $-COC_6H_4NH_2(4-);$
 f) $-CH(C_6H_5)[C_6H_4Cl(4-)]$
 III $R_1 = R_4 = -CH_2CH_2OH$

EXPERIMENTAL (7)

dl-5,9,9-Trimethyldecahydro-5,8-methanoquinoline.

dl-Camphorquinone (8) was converted into I in 45% yield (5). It separated from aqueous acetone as shimmering platelets, m.p. 113-116° [lit. (5), m.p. 116-118°]; ir (chloroform): 6.24 μ . It formed a hydrogen fumarate, which separated from 2-propanol and ether as fine needles, m.p. 140-143° dec.; ir (potassium chloride): 5.32, 6.10 μ .

Anal. Calcd. for $C_{12}H_{22}N_2 \cdot C_4H_4O_2$: C, 61.91; H, 8.44; N, 9.02; N.E. 155.2. Found: C, 62.02; H, 8.58; N, 8.99; N.E. 155.5.

dl-1-Carboethoxy-5,9,9-trimethyldecahydro-5,8-methanoquinoline.

Ethyl chloroformate (8.2 g., 0.76 mole) was added to a solution of 14.72 g. (0.076 mole) of I in 100 ml. of 85% ethanol during 1 hour, keeping the temperature below 45°. The mixture was held at room temperature for a day, then the solvents were removed and the residue crystallized from ethanol-ether. A 70% yield of hydrochloride resulted; m.p. 238-240.5° dec.; ir (potassium chloride): 5.85 μ .

Anal. Calcd. for $C_{15}H_{26}N_2O_2 \cdot HCl$: C, 59.47; H, 8.66; N, 9.26. Found: C, 59.22; H, 8.81; N, 9.19.

dl-1-Dimethylcarbanyl-5,9,9-trimethyldecahydro-5,8-methanoquinoline.

This compound was prepared from I and dimethylcarbanyl chloride after the method used above. Following crystallization from ethanol-ether, the hydrochloride was obtained in 70.5% yield. It was a white solid, m.p. 272-274° dec.; ir (potassium chloride): 6.08 μ .

Anal. Calcd. for $C_{15}H_{22}N_3O \cdot HCl$: C, 59.67; H, 9.51; N, 13.93. Found: C, 59.05; H, 9.51; N, 13.67.

dl-1-(2-Dimethylaminoethyl)-5,9,9-trimethyldecahydro-5,8-methanoquinoline.

A mixture of 9.46 g. (0.048 mole) of I, 7.0 g. (0.049 mole) of 2-dimethylaminoethyl chloride hydrochloride, and 5.3 g. (0.05 mole) of sodium carbonate in 120 ml. of 95% ethanol was refluxed for a day, filtered in the hot, and concentrated *in vacuo*. The residue was dried by azeotropic distillation, then converted into the tris-hydrochloride, and crystallized from ethanol-ether. A 49.5% yield (9.1 g.) of cryptocrystalline solid resulted; m.p. 206-210° dec.

Anal. Calcd. for $C_{16}H_{31}N_3 \cdot 3HCl$: C, 51.27; H, 9.14; N, 11.21. Found: C, 50.91; H, 9.32; N, 11.15.

dl-1-(2-Hydroxyethyl)- and *dl*-1,4-bis-(2-Hydroxyethyl)-5,9,9-trimethyldecahydro-5,8-methanoquinoline.

Thirteen g. (0.067 mole) of I, 5.4 g. (0.067 mole) of ethylene chlorohydrin, and 7.1 g. (0.067 mole) of sodium carbonate were stirred well in 100 ml. of anhydrous xylene and refluxed 7 hours. The hot mixture was filtered, cooled, diluted with 100 ml. of anhydrous ether, and saturated with dry hydrogen chloride. There resulted a mixture of dihydrochlorides of the mono- and di-substituted compounds, of which the former was more readily soluble in boiling ethanol. The less soluble fraction was recrystallized from ethanol-ether to give 3.5 g. (14.5% yield) of bis compound as fine white needles, m.p. 208-210° dec.; ir (potassium chloride): 3.02, 9.30, 9.35 μ .

Anal. Calcd. for $C_{16}H_{30}N_2O_2 \cdot 2HCl$: C, 54.09; H, 9.08; N, 7.89. Found: C, 53.95; H, 9.20; N, 7.81.

The ethanol extracts and first liquors of crystallization from above were concentrated to obtain crude mono-substituted compound. Following multiple crystallizations from ethanol-ether, 10.5 g. (50% yield) of white cryptocrystalline solid resulted; m.p. 259-261° dec.; ir (potassium chloride): 3.07, 9.40 μ .

Anal. Calcd. for $C_{14}H_{26}N_2O \cdot 2HCl$: N, 9.00. Found: N, 9.00.

When the reaction was carried out with 2 equivalents of ethylene chlorohydrin, the yields of mono- and bis-compounds were 32% and 38%, respectively.

dl-2-(4-Aminobenzoyl)-5,9,9-trimethyldecahydro-5,8-methanoquinoline.

A solution of 9.87 g. (0.05 mole) of I in 150 ml. of absolute ether was gradually added to a solution of 9.30 g. (0.05 mole) of 4-nitrobenzoyl chloride in 150 ml. cold benzene which contained 4.0 g. (0.05 mole) of pyridine. The mixture was stirred at ambient temperature for one day, then heated at 50-60° for 1 hour, and chilled. There resulted 17.5 g. (91.5% yield) of hydrochloride, m.p. 287-288.5° dec. The nitrobenzoyl compound was crystallized from methanol-ether, whence it separated as an hygroscopic, yellowish microcrystalline solid, m.p. 287-289° dec.; ir (potassium chloride): 6.08, 6.54, 7.37 μ .

Anal. Calcd. for $C_{19}H_{25}N_3O_3 \cdot HCl$: N, 11.06. Found: N, 10.87.

The above nitro compound was reduced catalytically in ethanol solution in the presence of 10% palladium-charcoal, then the product crystallized from ethanol-ether to give 73% yield of fine needles of desired hydrochloride; m.p. 253-255° dec.; ir (potassium chloride): 2.97, 6.09, 6.23 μ .

Anal. Calcd. for $C_{19}H_{27}N_3O \cdot HCl$: C, 65.22; H, 8.06; N, 12.01. Found: C, 64.97; H, 8.35; N, 11.89.

dl-1-(4-Chlorobenzhydryl)-5,9,9-trimethyldecahydro-5,8-methanoquinoline.

A well stirred mixture of 25.7 g. (0.13 mole) of I, 10.6 g. of sodium carbonate, and 65 ml. of anhydrous xylene was treated with 23.5 g. (0.1 mole) of 4-chlorobenzhydryl chloride (9,10), then refluxed for 3 days, filtered while hot, and allowed to cool. Unchanged I separated from the liquors, and more was obtained by extraction with water (total recovery, 26.6%). The xylene was extracted with 150 ml. of 4 N hydrochloric acid to isolate the product, which was then crystallized from chloroform-ethyl acetate to give 38.0 g. (80% yield, based on I consumed) of hygroscopic needles, m.p. 283.5-284.5° dec.; ir (potassium chloride): 6.40, 14.15 μ .

Anal. Calcd. for $C_{25}H_{31}ClN_2 \cdot 2HCl$: N, 5.99; Cl (total), 22.74. Found: N, 6.04; Cl (total), 23.10.

Acknowledgments.

The authors are indebted to Mrs. M. Christie, Mr. J. Weinberger, and Mr. P. D. Carp for the analyses and spectra here reported. We further wish to thank Dr. W. M. Govier and his staff for the multiple biological screening tests to which the compounds were subjected.

REFERENCES

- (1) Present address: Division of Medicinal Chemistry, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D.C. 20012.
- (2) E. A. Steck and R. P. Brundage, *J. Org. Chem.*, **24**, 2021 (1959).
- (3) E. A. Steck and S. T. Ross, *J. Med. Chem.*, **6**, 820 (1963).
- (4) L. Wei and E. A. Steck, *Can. J. Chem.*, **42**, 2623 (1964).
- (5) T. Pavolini, F. Gambarin, and A. Paliaga, *Farmaco Ed. Sci.*, **5**, 3 (1950).
- (6) This contribution is based upon work completed during 1960. There have been no publications in this area since then.
- (7) All melting points were determined in Pyrex capillary tubes in an electrically heated bath. These were immersed about 5° below the apparent melting point, and heated at 1° per minute thereafter. No appreciable difference was found when sealed capillary tubes were used. All compounds had camphoraceous odors.
- (8) H. Rupe and A. T. Tommasi di Vignano, *Helv. Chim. Acta*, **20**, 1079 (1937).
- (9) K. E. Hamlin, A. W. Weston, F. E. Fischer, and R. J. Michaels, Jr., *J. Am. Chem. Soc.*, **71**, 2731 (1949).
- (10) J. F. Norris and J. T. Blake, *ibid.*, **50**, 1811 (1928).