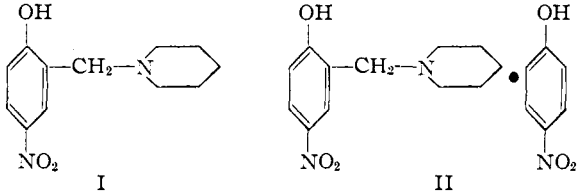
[CONTRIBUTION FROM THE RESEARCH LABORATORIES, PARKE, DAVIS & CO., AND THE DEPARTMENT OF PHARMACEUTICAL CHEMISTRY, UNIVERSITY OF KANSAS SCHOOL OF PHARMACY]

The Mannich Reaction with *p*-Nitrophenol

BY J. H. BURCKHALTER

During a reinvestigation of the Mannich reaction with *p*-nitrophenol, we have found that the product of the interaction of this phenol, paraformaldehyde and piperidine is a complex (II) or salt of the expected product (I) with *p*-nitrophenol.[1]



I II

Complex compound II (m. p. 139°) is probably identical with the product (m. p. 134°) obtained by Yang and erroneously assigned structure I.[2]

I, whose structure has been confirmed by an alternate synthesis from α-chloro-4-nitro-*o*-cresol and piperidine, readily forms II with *p*-nitrophenol. The diethylamino analog of II has also been prepared both by the Mannich reaction and from α-diethylamino-4-nitro-*p*-cresol and *p*-nitrophenol.

That some free I (m. p. 103°) also results in the Mannich reaction is shown by a 68% yield of I hydrochloride which was obtained in an earlier experiment by treatment of the reaction mixture with hydrochloric acid.[3] In that experiment the yield of I hydrochloride calculated on the basis of two moles of *p*-nitrophenol per mole of intermediate complex becomes an impossible 136%. Thus, it is apparent that much free I exists in the reaction mixture along with II.

Experimental

Addition Compound of 4-Nitro-α-1-piperidyl-*o*-cresol and *p*-Nitrophenol (II). (a) By the Mannich Reaction.—A mixture of 5.56 g. (0.04 mole) of *p*-nitrophenol, 1.26 g. (0.04 mole) of paraformaldehyde, 3.4 g. (0.04 mole) of piperidine and 15 cc. of isopropyl alcohol was heated at refluxing temperature for two hours. When no product separated upon cooling, the solvent was removed by evaporation, and the remaining oil was triturated with petroleum ether. After standing for several days, the mixture yielded a yellow crystalline material and an amber-colored oil. The solvent was decanted. Ether was added to dissolve the oil, and the insoluble yellow crystals were collected on a funnel; yield 2.32 g. (30% based on 0.02 mole theory); m. p. 138–139°. Recrystallization from alcohol did not change the melting point.

Anal. Calcd. for $C_{18}H_{21}N_3O_6$: C, 57.59; H, 5.64. Found: C, 57.60; H, 5.75.

From 6.95 g. (0.05 mole) of *p*-nitrophenol, 0.79 g. (0.025 mole) of paraformaldehyde and 2.5 g. (0.025 mole) of piperidine by the same procedure, 6.5 g. (70% yield) of the same addition product was obtained.

(b) By the Addition of *p*-Nitrophenol to I.—A solution of 1.39 g. (0.01 mole) of *p*-nitrophenol, 2.36 g. (0.01 mole) of 4-nitro-α-1-piperidyl-*o*-cresol (I) and 25 cc. of alcohol was heated in an open Erlenmeyer flask for about two hours, during which time most of the solvent evaporated and a yellow crystalline material separated. Collected on a funnel, 3.53 g. (94% yield) of product was obtained; m. p. 138–139°. A mixed melting point determination with a sample prepared by the Mannich reaction showed no depression.

4-Nitro-α-1-piperidyl-*o*-cresol (I): (a) From the Hydrochloride of I.—Treatment with excess ammonia of 15.7 g. (0.058 mole) of the hydrochloride of I, obtained by means of the Mannich reaction,[3] yielded the yellow crystalline base (I). After recrystallization of the product from alcohol, 8.3 g. (61% yield) was obtained; m. p. 103–104°.

Anal. Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.01; H, 6.83. Found: C, 60.96; H, 6.55.

(b) From α-Chloro-4-nitro-*o*-cresol.—A mixture of 5.63 g. (0.03 mole) of α-chloro-4-nitro-*o*-cresol,[4] 5.1 g. (0.06 mole) of piperidine and 50 cc. of absolute alcohol was heated at refluxing temperature for three hours. Volatile materials were removed at steam-bath temperature, and the residue triturated with 50 cc. of an acetone–ether mixture. The insoluble crystalline piperidine hydrochloride, weighing 3.5 g. and representing 96% yield, was removed by filtration. The amber-colored filtrate was treated with excess anhydrous hydrogen chloride to precipitate 7.57 g. (93% yield) of crude light yellow colored 4-nitro-α-1-piperidyl-*o*-cresol hydrochloride; m. p. 255° (dec.). When recrystallized from methanol, the compound melted at 260° (dec.), and was shown to be identical by a mixed melting point with the product obtained by means of the Mannich reaction.[3]

A small sample of the hydrochloride was converted to the free base in a manner already described. It proved to be identical by a mixed melting point determination with the base obtained from the Mannich reaction.

O-Acetyl-4-nitro-α-1-piperidyl-*o*-cresol.[5]—To 30 cc. of acetic anhydride and 11.8 g. (0.05 mole) of 4-nitro-α-1-piperidyl-*o*-cresol, two drops of concd. sulfuric acid was added. After warming for ten minutes on a steam-bath, the mixture was cooled and then neutralized with alcoholic hydrogen chloride. By precipitation with ether, 9.5 g. (61% yield) of desired product was obtained; m. p. 169–173°. Recrystallization from alcohol changed the melting point to 179–180°.

Anal. Calcd. for $C_{14}H_{18}N_2O_4 \cdot HCl$: C, 53.42; H, 6.10. Found: C, 53.99; H, 6.23.

Addition Compound of α-Diethylamino-4-nitro-*o*-cresol and *p*-Nitrophenol: (a) By the Mannich Reaction.—A mixture of 69.6 g. (0.5 mole) of *p*-nitrophenol, 125 cc. (0.5

(1) *p*-Nitrophenol is known to form complexes or salts with aniline and with aliphatic amines. *Cf.* Kremann and Rodinis, *Monatsh.*, **27**, 134 (1906), and Peters, *Ber.*, **39**, 2783 (1906). II possesses salt-like properties, and it is more water soluble than either of its components.

(2) Yang, *J. Org. Chem.*, **10**, 67 (1945). Certain other errors were noted in this article. The correct molecular weight of 4-nitro-α-1-piperidyl-*o*-cresol (I) is 236.26 instead of 212.2 as reported, while the calculated percentage of nitrogen is 11.86 and not 13.19. Present knowledge of the Mannich reaction (F. F. Blicke, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, 1942) would hardly allow 4-chloro-α-1-piperidyl-*m*-cresol to represent the structure of the compound derived from *p*-chlorophenol. The product formed is undoubtedly an *o*-cresol.

(3) Burckhalter, Tendick, Jones, Jones, Holcomb and Rawlins, THIS JOURNAL, **70**, 1365 (1948).

(4) *Org. Syntheses*, **20**, 59 (1940).

(5) This compound was prepared by Mr. L. M. Montibeller, Research Laboratories, Parke, Davis & Co., Detroit, Michigan.

mole) of paraformaldehyde–diethylamine reagent[6] and 100 cc. of alcohol was heated in a distilling apparatus until most of the alcohol had been removed. Upon standing, the solution yielded 56.2 g. (62% based on 0.25 mole) of the yellow addition compound; m. p. 130–131°. Recrystallization from isopropyl alcohol gave 43.3 g. of product with no change in melting point.

Anal. Calcd. for $C_{17}H_{21}N_3O_6$: C, 56.19; H, 5.83. Found: C, 56.54; H, 5.81.

(b) **By the Addition of *p*-Nitrophenol to α-Diethylamino-4-nitro-*o*-cresol.**—A solution of 0.62 g. (0.00446 mole) of the former and 1 g. (0.00446 mole) of the latter in 20 cc. of alcohol was reduced in volume by evaporation. By cooling the residue, 1.46 g. (90% yield) of the addition compound resulted. Melting point and mixed melting point determinations proved its identity with a sample prepared by the Mannich reaction.

Recovery of *p*-Nitrophenol and α-Diethylamino-4-nitro-*o*-cresol from their Addition Compound.—The treatment of 7.25 g. (0.02 mole) of the yellow addition compound with 25 cc. of dilute hydrochloric acid caused a disappearance of color and a momentary solution of reactants. The white insoluble α-diethylamino-4-nitro-*o*-cresol hydrochloride soon separated. It was collected on a funnel and triturated with ether to remove *p*-nitrophenol. After recollecting and drying the material for two days at 60°, 5.27 g. (theory 5.20 g.) of crude salt was obtained; m. p. 175–215° (dec.). Recrystallized from methanol, the off-white product melted at 223–224° (dec.). The melting point was not depressed by admixture with a previously prepared sample.[3]

The ether washings were shaken in a separatory funnel with the acidic filtrate. The ether layer was washed with water and dried by washing with a saturated solution of sodium chloride. Final drying was over anhydrous magnesium sulfate. From the evaporation of the filtered ether solution, 2.5 g. (theory 2.8 g.) of *p*-nitrophenol was isolated; m. p. 109–112°. Recrystallization from benzene gave crystals which melted at 113–104°. A mixed melting point determination with recrystallized Eastman Kodak Co. white label *p*-nitrophenol indicated no depression.

α-**Diethylamino-4-nitro-*o*-cresol:** (a) **From its Hydrochloride.**—Treatment with excess ammonia of 5.2 g. (0.02 mole) of the hydrochloride, obtained by means of the Mannich reaction,[3] yielded 4.35 g. (98%) of yellow crystalline base; m. p. 88–89°. Recrystallization from isopropyl alcohol failed to change the melting point.

Anal. Calcd. for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19. Found: C, 59.20; H, 7.30.

(b) **From α-Chloro-4-nitro-*o*-cresol.**—By following the same procedure outlined for I, 6.26 g. (80% yield) of the crude hydrochloride was obtained from 5.63 g. (0.03 mole) of α-chloro-4-nitro-*o*-cresol and 4.39 g. (0.06 mole) of diethylamine; m. p. 212–217° (dec.). Recrystallized from methanol, it melted at 224–225° (dec.)[7] and proved to be identical with the product obtained by means of the Mannich reaction.[3] Upon conversion to the free base, the compound melted at 88–90°.[8] A mixed melting point determination confirmed its identity with the Mannich base.

(6) Burckhalter, Tendick, Jones, Holcomb and Rawlins, THIS JOURNAL, **68**, 1894 (1946).

(7) Einhorn, *Ann.*, **343**, 247 (1905), using essentially the same procedure, found 197° (dec.), but failed to analyze his product.

(8) Einhorn found 68–69°.

LAWRENCE, KANSAS RECEIVED APRIL 30, 1949

Summary

The Mannich reaction with *p*-nitrophenol and piperidine or diethylamine has been shown to lead directly to a *p*-nitrophenol addition compound of the expected α-dialkylamino-4-nitro-*o*-cresol.

p-Nitro-α-1-piperidyl-*o*-cresol and α-diethylamino-4-nitro-*o*-cresol have been prepared, and their structures have been established.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF GIVAUDAN-DELAWANNA, INC.]

Adrenergic Blocking Agents. I. N-(2-Chloroethyl)-dibenzylamine Series

BY WILLIAM S. GUMP AND EDWARD J. NIKAWITZ

N-(2-Haloethyl)-dialkylamines and their salts have been described in the literature[1] and frequently used for organic syntheses. On the other hand, no information can be found in regard to the chemistry of N-(2-chloroethyl)-dibenzylamine (with the exception of a brief reference to its hydrochloride[2]) and to substituted N-(2-chloroethyl)-dibenzylamines.

In view of the known reactivity of the chlorine in the 2-chloroethyl group when the latter is attached to sulfur and nitrogen (mustard gases), it was thought that N-(2-chloroethyl)-dibenzylamine might be physiologically active and perhaps be useful therapeutically. For that reason, the hydrochloride of this amine was prepared according to the method given in Eisleb's patent. 2-Aminoethanol was condensed with benzyl chloride and the resulting 2-dibenzylaminoethanol converted into N-(2-chloroethyl)-dibenzylamine hydrochloride by means of thionyl chloride. N-(2-Bromoethyl)-dibenzylamine hydrobromide was also prepared by treatment of 2-dibenzylaminoethanol with hydrobromic acid.

The pharmacological study of N-(2-chloroethyl)-dibenzylamine (Dibenamine[3]) hydrochloride by Nickerson and Goodman[4] led to the important discovery that this compound is a potent and specific adrenergic blocking agent which inhibits and reverses the excitatory effects of epinephrine. Nickerson and Goodman's reports on Dibenamine stimulated the syntheses and

(1) Gough and King, *J. Chem. Soc.*, 2426 (1928); Slotta and Benisch, *Ber.*, **68**, 754 (1935); Amundsen and Krantz, THIS JOURNAL, **63**, 305 (1941); Huber, *et al.*, *ibid.*, **67**, 1618 (1945).

(2) Eisleb, U. S. Patent 1,949,247 (Feb. 27, 1934); see *C. A.*, **28**, 2850 (1934).

(3) Trade-mark of Smith, Kline & French Laboratories.

(4) Nickerson and Goodman, *Federation Proc.*, **5**, 194 (1946); *J. Pharmacol. Exp. Therap.*, **89**, 167 (1947).