XI in 100 ml. of methanol was hydrogenated over Raney nickel for 2 hours at room temperature under an initial gauge reading of 50 lb./sq. in. The catalyst was filtered and the methanol was evaporated. The white crystalline residue was recrystallized from 20 ml. of boiling water to give 1.2 g. of a solid (51% yield), m.p. 140°, which did not depress the melting point of authentic salicylamide. The infrared spectrum was identical with the spectrum obtained from salicylamide.

N-(9-Xanthyl)-tetracycline (X).—To 500 ml. of glacial acetic acid contained in a 1-liter erlenmeyer flask was added slowly with stirring 60 g. (0.135 mole) of anhydrous tetracycline. After nearly all of the tetracycline had dissolved 29.8 g. (0.150 mole) of 9-xanthenol (xanthydrol, Eastman) was added and the mixture was heated and stirred on the steam-bath at 45–50° for 15–20 minutes. The resulting solution was poured into 2 liters of water to form a milky precipitate which was extracted with 2 liters of ethyl acetate in 3 portions. The combined extracts were washed with 500 ml. of water. The organic layer was concentrated under reduced pressure on the steam-bath to a volume of approximately 400 ml. Dilution with 500 ml. of methanol and chilling caused 50.2 g. of product to crystallize. Recrystallization was accomplished by dissolving the material in 300 ml. of warm ethyl acetate and diluting the solution with 300 ml. of methanol. After drying for two days *in vacuo* over phosphorus pentoxide, the yellow crystals weighed 36.9 g. (40% yield), m.p. 178–180° dec. (with previous darkening and shrinking commencing at about 154° when the temperature was raised 3° per minute). For analysis a sample was dried *in vacuo* at 110° over phosphorus pentoxide for two hours.

Anal. Calcd. for $C_{35}H_{32}N_2O_9$: C, 67.30; H, 5.17; N, 4.49. Found: C, 67.4; H, 4.86; N, 4.45.

Because the solubility of X in water is less than 0.1 mg./ml., a suspension for bioassay was prepared by weighing 100 mg. of a micronized sample into 50 ml. of distilled water, adding 6 drops of Tween 40 and 6 drops of acetone and finally diluting to a volume of 100 ml. with water. The *in vitro* biological activity is about 315 μg./mg.[16] As in the infrared spectrum of VI, the 6 μ infrared band for X is split into 3 peaks at 6.1, 6.2 and 6.3 μ and shows a doublet at 6.53 and 6.58 μ. There is no alteration of the 3 μ region. The ultraviolet absorption spectrum is reported in Table I.

Acknowledgments.—We are indebted to R. M. Downing for the microanalyses, to Professor John C. Sheehan for interpretation of the spectral data and to Dr. F. M. Palermiti and D. L. Evans for the spectral data.

SYRACUSE, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACEUTICAL CHEMISTRY, UNIVERSITY OF WISCONSIN]

The Quasi-Favorskii Rearrangement. I. The Preparation of Demerol and β-Pethidine

BY EDWARD E. SMISSMAN AND GILBERT HITE

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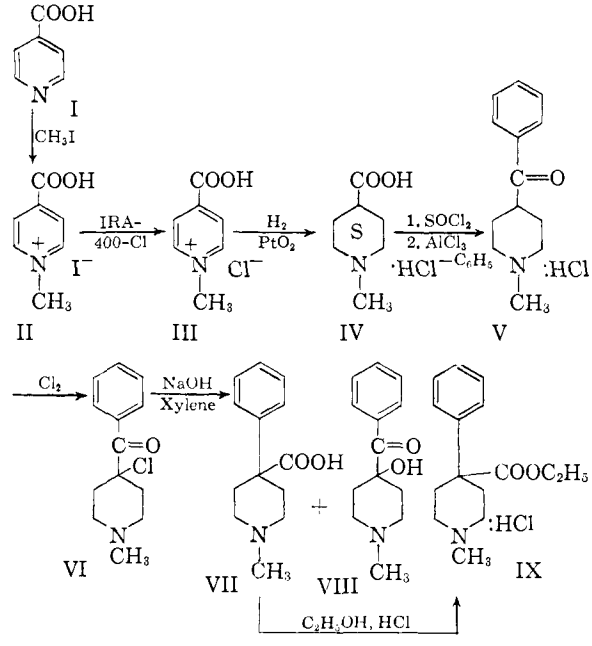
The use of the alkaline rearrangement of α-haloketones in the preparation of two analgesics, Demerol (ethyl 1-methyl-4-phenyl-4-piperidinecarboxylate, IX) and β-Pethidine (ethyl 1-methyl-3-piperidinecarboxylate, X) is reported. This constitutes a novel synthesis for analogs of Demerol-type compounds.

In 1939, Tchoubar and Sackur[1] reported the base-catalyzed rearrangement of α-chlorocyclohexyl phenyl ketone to 1-phenyl-cyclohexanecarboxylic acid. Later Stevens and Farkas[2] investigated the conditions for this reaction and were able to modify the procedure to secure higher yields of the acid.

Since the mechanism of the alkaline rearrangement of α-haloketones having no α-hydrogens has not been elucidated, and because the above rearrangement would give an excellent method for the preparation of Demerol-type compounds, it was decided to synthesize Demerol by a modification of the Favorskii rearrangement.[3] Isonicotinic acid (I) was methylated using methyl iodide, and the resulting methiodide II was converted to the methochloride III with Amberlite IRA-400 (chloride) resin. This compound was then reduced to 1-methyl-4-piperidinecarboxylic acid hydrochloride (IV) which was converted to the acid chloride hydrochloride by allowing it to react with thionyl chloride. The acid chloride hydrochloride was then condensed with benzene under Friedel–Crafts conditions to give 1-methyl-4-benzoylpiperidine hydrochloride (V). Chlorination of the ketone V gave the mono-chloroketone hydrochloride VI in excellent yields. When subjected to alkaline treatment the products obtained were 1-methyl-4-phenyl-4-piperidinecarboxylic acid (VII)



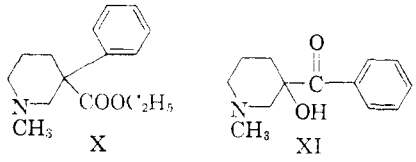
and 1-methyl-4-hydroxy-4-benzoylpiperidine (VIII). Esterification of VII gave the desired

(1) B. Tchoubar and O. Sackur, *Compt. rend.*, **208**, 1020 (1939).

(2) C. L. Stevens and E. Farkas, THIS JOURNAL, **74**, 5352 (1952).

(3) Excellent general papers on the Favorskii reaction: R. Jacquier, *Bull. soc. chim.*, D35 (1950) and R. B. Loftfield, THIS JOURNAL, **73**, 4707 (1951).

compound Demerol, ethyl 1-methyl-4-phenyl-4-piperidinecarboxylate hydrochloride (IX). Then β-pethidine (X) was prepared by the same sequence of reactions utilizing nicotinic acid as the starting material. The major products isolated from the



attempted rearrangements in each case were the 1-methylhydroxybenzoylpiperidines VIII and XI.

The optically active 1-methyl-3-chloro-3-benzoylpiperidine and its *p*-substituted analogs afford an excellent series for the mechanism study of the quasi-Favorskiĭ rearrangement involving α-haloketones containing no α-hydrogens. The mechanism and stereochemistry of this reaction now are under investigation.

Acknowledgment.—We are indebted to Parke-Davis and Co. for financial support of this project.

Experimental

All melting points reported were obtained in a Hershberg-type, silicone-filled melting point apparatus equipped with Anschutz immersion thermometers. The samples were placed in the circulating silicone bath 10° below the reported melting points and heated at the rate of 1–2° per minute.

Isonicotinic Acid Methochloride (III).—To a slurry of 246.0 g. (2.00 moles) of isonicotinic acid in 3.2 liters of methanol and 300 ml. of water containing 88.0 g. (2.20 moles) of sodium hydroxide was added 355.0 g. (2.5 moles 156 ml.) of methyl iodide. The mixture was stirred and refluxed for 60 hours and the methanol removed under vacuum. Sodium thiosulfate was used to reduce iodine present to iodide and sufficient water and concentrated hydrochloric acid were added to give a volume of 1.5 liters at *p*H 2.0.

An ion exchange column was prepared by placing a slurry of Amberlite IRA-400 (6.30 equivalents) in a tube 10 cm. in diameter and 100 cm. in height. The resin was washed with 20 l. of 5% hydrochloric acid followed by 40 l. of distilled water. The yellow aqueous solution was passed through the column and the effluent, which was iodine-free, was collected at the flow rate of 50 ml./minute. Three and one-half liters of effluent was concentrated and the residue was dried and extracted with acetic acid. Xylene was added to the hot acetic acid solution. The solution was cooled and saturated with dry hydrogen chloride to give 336.0 g. (1.94 moles) of crude product, m.p. 260–265°. Recrystallization from acetic acid gave the pure product, m.p. 265° dec. (lit.[4] m.p. 265°).

1-Methyl-4-carboxypiperidine Hydrochloride (IV).—Isonicotinic acid methochloride was quantitatively reduced in a steel reaction vessel in the presence of platinum oxide at 1000 p.s.i. in methanol solution, m.p. 231–232° dec. (lit.[5] m.p. 223–225°).

Anal. Calcd. for $C_7H_{13}NO_2 \cdot HCl$: C, 46.81; H, 7.87; N, 7.80; Cl, 19.74. Found: C, 46.86; H, 7.78; N, 7.83; Cl, 20.00.

1-Methyl-4-benzoylpiperidine (V).—A mixture of 1-methyl-4-carboxypiperidine hydrochloride (135.0 g. 0.75 mole) and 200 ml. of thionyl chloride was refluxed for 6 hours. After the excess thionyl chloride was removed, 800 ml. of dry benzene was introduced to form a slurry. Sublimed, anhydrous aluminum chloride (267.0 g., 2.00 moles) was added with constant stirring over a period of 15 minutes. The deep brown mixture was stirred for an additional 0.5 hour and was then poured onto 2.50 l. of crushed ice. Enough 50% sodium hydroxide solution was added with cooling and agitation to give a basic solution of aluminates. The benzene phase was separated and the aqueous phase was extracted with ether. The benzene and ether solutions were combined and extracted with six 300-ml. portions of 5% hydrochloric acid. The acid extract was adjusted to *p*H 11 with sodium hydroxide and re-extracted with ether. The ether solution was dried over sodium sulfate, filtered, and evaporated to a dark, reddish-brown oil. On fractional distillation 135.0 g. (0.66 mole, 88%) of a light yellow oil, b.p. 122° (0.5 mm.), lit.[6] b. p. 130–135°, (2 mm.), was obtained). On crystallization from Skelly A pure crystals were obtained, m.p. 40–40.5°.

The hydrochloride salt was prepared by passing dry hydrogen chloride through an ether solution of the amine. The salt was recrystallized from acetone, m.p. 208–209° dec.

Anal. Calcd. for $C_{13}H_{17}NO \cdot HCl$: C, 65.13; H, 7.57; N, 5.84; Cl, 14.79. Found: C, 65.37; H, 7.57; N, 5.74; Cl, 14.70.

The methyl p-toluenesulfonate was prepared and recrystallized from ethanol, m.p. 224.5–225° dec.

1-Methyl-4-chloro-4-benzoylpiperidine Hydrochloride (VI).—Chlorine gas was slowly bubbled into a solution of 48.0 g. (0.20 mole) of 1-methyl-4-benzoylpiperidine hydrochloride in 500 ml. of glacial acetic acid at 70° for 8 hours. The volume was reduced to 150 ml. and 1 liter of anhydrous ether was added. The resulting white powder was recrystallized from chloroform, yielding 49.5 g. (0.18 mole, 90%) of the hydrochloride salt, m.p. 181–182° dec. The free amine, m.p. 48–49°, was recrystallized from Skelly A.

Anal. Calcd. for $C_{13}H_{16}NOCl \cdot HCl$: C, 56.94; H, 6.25; N, 5.11; Cl, 25.86. Found: C, 56.78; H, 6.53; N, 5.18; Cl, 25.80.

Rearrangement of 1-Methyl-4-chloro-4-benzoylpiperidine (VI).—To a refluxing mixture containing 200 ml. of dried xylene and 18.00 g. (0.45 mole) of finely powdered, dried sodium hydroxide was added 50 ml. of xylene containing 3.57 g. (0.015 mole) of 1-methyl-4-chloro-4-benzoylpiperidine with stirring during a 30-minute period. The mixture was cooled and extracted with 25-ml. portions of water until the *p*H of the extracts approached neutrality.

The combined aqueous extract was washed with three 25-ml. portions of ether and then adjusted to *p*H 8.0 with hydrochloric acid. The aqueous solution was concentrated to 50 ml., the solution filtered, and acidified to *p*H 6.45 with hydrochloric acid. The solution was cooled and the crystals were washed with water, acetone, ether and then dried. Recrystallization from water gave fine, white needles of 1-methyl-4-phenyl-4-carboxypiperidine (VII), 0.81 g. (0.0037 mole, 25%), m.p. 309–310° dec. (lit.[7] m.p. 308°).

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.81; N, 6.39. Found: C, 71.16; H, 8.21; N, 6.22.

The hydrochloride salt was prepared and recrystallized from acetic acid-benzene, m.p. 225.5–227° dec.

Anal. Calcd. for $C_{13}H_{17}NO_2 \cdot HCl$: C, 61.05; H, 7.09; N, 5.48; Cl, 13.86. Found: C, 61.04; H, 7.28; N, 5.78; Cl, 13.71.

The ethyl ester hydrochloride of this compound was prepared by refluxing with ethanolic hydrogen chloride. The resulting product was identical with Demerol in all respects and did not depress the melting point on admixture with Demerol hydrochloride (IX).

1-Methyl-4-hydroxy-4-benzoylpiperidine (VIII).—The organic phase from the above rearrangement was extracted with hydrochloric acid. The acidic aqueous solution was made basic and extracted with chloroform. On evaporation of the chloroform a yellowish powder weighing 2.11 g. (64%) was obtained. Recrystallization from acetone gave a white crystalline product, m.p. 134–135°.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.81; N, 6.39. Found: C, 71.06; H, 7.78; N, 6.44.

The hydrochloride salt was prepared and recrystallized from chloroform, m.p. 174.5–175.5° dec. when placed in the silicone bath at 145° and heated at the rate of 2.5° per minute. The compound melts at 165° dec. if placed in the bath at 165° directly.

The methyl *p*-toluenesulfonate was prepared and recrystallized from ethanol–ethyl acetate, m.p. 185–186° dec.

(4) H. Meyer, *Monatsh.*, **24**, 201 (1903).

(5) R. L. Clarke, A. Mooradian, P. Lucas and T. J. Slauson, THIS JOURNAL, **71**, 2821 (1949).

(6) N. Sperber, F. J. Villani, M. Sherlock and D. Papa, *ibid.*, **73**, 5010 (1951).

(7) F. Bergel, *et al.* (to Roche Products Ltd.), U. S. Patent 2,398,575, April 16 (1946); *cf. C. A.*, **40**, 4397 (1946).

Anal. Calcd. $C_{21}H_{27}NO_5S$: C, 62.20; H, 6.71; N, 3.45; S, 7.91. Found: C, 62.38; H, 6.69; N, 3.53; S, 7.78.

Nicotinic Acid Methochloride.—The synthesis was performed in the same manner as that reported above for isonicotinic acid methochloride. A 92% yield of product, m.p. 258–259° dec., was obtained (lit.[8] m.p. 245–250° dec.)

Anal. Calcd. for $C_7H_7NO_2 \cdot HCl$: C, 48.53; H, 4.65; N, 8.07; Cl, 20.42. Found: C, 48.72; H, 4.47; N, 7.80; Cl, 19.95.

***dl*-1-Methyl-3-carboxypiperidine Hydrochloride.**—The reduction of nicotinic acid methochloride by the procedure reported above for the reduction of isonicotinic acid methochloride gave a quantitative yield of a product, m.p. 201.5–202.5° dec.

Anal. Calcd. $C_7H_{13}NO_2 \cdot HCl$: C, 46.81; H, 7.86; N, 7.80; Cl, 19.74. Found: C, 46.81; H, 735; N, 7.70; Cl, 19.69.

***dl*-1-Methyl-3-benzoylpiperidine.**—The acyl chloride of *dl*-1-methyl-3-carboxypiperidine hydrochloride was allowed to react under the Friedel–Crafts conditions described above for the 4-isomer to give an 89% yield of the desired product, b.p. 119–120° (0.2 mm.). The material was crystallized from Skelly A, m.p. 34–35°. The hydrochloride salt was recrystallized from acetone, m.p. 176–177° dec.

Anal. Calcd. for $C_{13}H_{17}NO \cdot HCl$: C, 65.13; H, 7.57; N, 5.84; Cl, 14.79. Found: C, 65.67; H, 7.68; N, 6.04; Cl, 14.50.

The methyl *p*-toluenesulfonate was recrystallized from ethanol–ethyl acetate, m.p. 225–226° dec.

Anal. Calcd. $C_{21}H_{27}NO_4S$: C, 64.75; H, 6.99; N, 3.60; S, 8.23. Found: C, 64.63; H, 6.94; N, 3.52; S, 8.20.

***dl*-1-Methyl-3-benzoyl-3-chloropiperidine.**—The chlorination procedure used for the preparation of the 4-isomer gave a 93% yield of the 3-isomer, m.p. 169.5–170.5° dec. when recrystallized from chloroform.

Anal. Calcd. for $C_{13}H_{16}NOCl$; C, 56.94; H, 6.25; N, 5.11; Cl, 25.86. Found: C, 57.16; H, 6.37; N, 5.40; Cl, 26.00.

The free amine had m.p. 25–25.5° when recrystallized from Skelly A.

Rearrangement of *dl*-1-Methyl-3-chloro-3-benzoylpiperidine.—The conditions described above for the rearrangement of 1-methyl-4-chloro-4-benzoylpiperidine (VI) were modified in the following manner. To a refluxing mixture of 4.80 g. (0.120 mole) of finely powdered, dry sodium hydroxide in 200 ml. of dry xylene was added 50 ml. of a xylene solution containing 5.94 g. (0.025 mole) of *dl*-1-methyl-3-chloro-3-benzoylpiperidine. The mixture was cooled and the volume reduced to 50 ml.; 100 ml. of ether was added and the organic phase was extracted with 10-ml. portions of water until the aqueous washings were nearly neutral. The combined aqueous extract was acidified to *p*H 2.0 with hydrochloric acid and extracted with ether. The aqueous acidic solution was concentrated under vacuum and the dried residue extracted in a Soxhlet extractor with glacial acetic acid. The extract was concentrated to 15 ml. and 100 ml. of ether was added. A buff powder precipitated, m.p. 267–270° dec. This material was dissolved in 4 ml. of 2% sodium hydroxide. After adding 1 ml. of acetic acid, the solution was evaporated to dryness. The residue was sublimed under reduced pressure at 210° and the sublimate recrystallized from chloroform to give 420 mg. (7.7%) of 1-methyl-3-phenyl-3-carboxypiperidine, m.p. 250–250.5° dec.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.81; N, 6.39. Found: C, 71.19; H, 7.79; N, 6.37.

***dl*-1-Methyl-3-hydroxy-3-benzoylpiperidine.**—The organic phase from the above rearrangement was treated as previously outlined for the 4-isomer. The resulting viscous oil was crystallized from Skelly A to give 4.16 g. (0.19 mole, 76%) of a white crystalline product, m.p. 53–53.5°.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.81; N, 6.39. Found: C, 71.19; H, 8.33; N, 6.26.

The methyl *p*-toluenesulfonate was prepared and crystallized from ethanol–ethyl acetate, m.p. 192–193° dec.

Anal. Calcd. for $C_{21}H_{27}NO_5S$: C, 62.20; H, 6.71; N, 3.45; S, 7.91. Found: C, 62.54; H, 6.60; N, 3.87; S, 8.23.

The hydrochloride, m.p. 162–163° dec., was crystallized from ethanol–ethyl acetate.

Anal. Calcd. for $C_{13}H_{17}NO_2 \cdot HCl$: C, 61.05; H, 7.09; N, 5.48; Cl, 13.86. Found: C, 60.51; H, 6.99; N, 5.78; Cl, 14.12.

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(8) R. Turneau, *Monatsh.*, **26**, 552 (1905).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA]

The Nitroethylation of Indoles. III.[1-3] A Synthetic Route to Substituted Tryptamines

BY WAYLAND E. NOLAND AND RONALD F. LANGE[4]

RECEIVED JULY 28, 1958

The previously described nitroethylation of indole has been extended successfully to four readily available substituted indoles: 2-methylindole, 1,2-dimethylindole, 1-methylindole and 2-phenylindole. As had been the case with indole, the best yields of adducts were obtained with β-nitrostyrene, with good yields of adducts also often obtainable from β-methyl-β-nitrostyrene, and lesser yields from the other nitroölefins tried. Catalytic hydrogenation of the adducts yielded the corresponding tryptamines, which were converted to phthalimide derivatives. Indole–nitroölefin addition appears to be a quite general synthetic route to tryptamines from substituted indoles, as well as from indole itself.

The addition of unsubstituted indole to the nitroolefins, nitroethylene, 1-nitropropene, β-nitrostyrene and β-methyl-β-nitrostyrene, forming the adducts Ia–Id, has been described previously.[1,2] The nitroethylene adduct Ia also has been prepared by other methods[5-7] and has been proposed

(1) Paper I, W. E. Noland and P. J. Hartman, THIS JOURNAL, **76**, 3227 (1954).

(2) Paper II, W. E. Noland, G. M. Christensen, G. L. Sauer and G. G. S. Dutton, *ibid.*, **77**, 456 (1955).

(3) Presented in part as Paper 10 before the Organic Division at the 132nd National Meeting of the Am. Chem. Soc., New York, N. Y., Sept. 9, 1957, Abstracts p. 6P.

(4) Taken in part from the Ph.D. thesis of Ronald F. Lange, University of Minnesota, June, 1958. We gratefully acknowledge the financial support provided R. F. L. through academic year fellowships by the Ethyl Corporation and the Monsanto Chemical Co., and through summer fellowships provided by the Procter and Gamble Co. and the Hercules Powder Co. A part of the work described here was carried out by students in the advanced organic chemistry laboratory course at the University of Minnesota. Particular credit is due to: (a) Richard E. Duvall, (b) Kenneth J. Krost, (c) Kathleen E. Jongedyk, (d) Arnold A. Liebman, (e) Donald C. Johnson, (f) Elmer W. Lippmann, Jr., (g) Lois R. Kelley. We are also indebted to Donald N. Robinson and James A. Elberling for carrying out several reactions.

(5) D. I. Weisblat and D. A. Lyttle (to the Upjohn Co.), U. S. Patent 2,616,896, Nov. 4, 1952.

(6) D. A. Lyttle and D. I. Weisblat, THIS JOURNAL, **77**, 5747 (1955).

(7) D. W. Henry and E. Leete, *ibid.*, **79**, 5254 (1957).