The di-tertiaryamino ester derivatives were transformed into dihydrochlorides and were quaternized by refluxing with the appropriate alkyl halides in alcohol solution. Isopropyl alcohol was most commonly used as the alkylation solvent to minimize any tendency toward reversal of the preparative ester exchange reaction. The physical properties and analytical data for the two series of aminoalkyl esters are compiled in Table I.

The intermediate methyl esters of N-methylnipecotic and isonipecotic acids were prepared by catalytic hydrogenation in methanol of the methyl chlorides of the methyl esters of nicotinic and isonicotinic acids using Adams catalyst at 25° and 3 atmospheres of hydrogen pressure. This reduction goes moderately rapidly and gives high yields of the reduced esters. The process seems deserving of comment only for reasons of comparison with certain other hydrogenations of pyridine rings performed in this Laboratory. Earlier an extensive series of 2- and 4-stilbazole *methiodides* was found to be reduced rapidly and completely to the stilbazolines[3] under the above stated reduction conditions. The ganglionic blocking agents derived from nicotine[1] were obtained by catalytic hydrogenation, under the same conditions, of nicotine *dialkiodides*. Yet the *methiodides* of methyl nicotinate or methyl isonicotinate were hydrogenated under the same conditions only very sluggishly and incompletely, if at all. In these cases, as in several others which will be reported on later in connection with other series of compounds, the methiodides of simple pyridine derivatives were resistant to reduction under the mild conditions used, and conversion to the methochlorides was necessary to permit a practical hydrogenation rate. It thus appears that iodide may be a weak or partial poison to these reductions with Adams catalyst, but the appearance of the deleterious effects is somewhat controlled by the inherent ease of reduction of the particular system under consideration.

(3) A. P. Phillips, THIS JOURNAL, **72**, 1850 (1950).

The aminoester derivatives I and II have been found, as expected, to be ganglionic blocking agents of short duration. The most potent compound seemed to be the isonipecotic ester II ($R' = CH_3$, $RX = CH_3I$, $n = 2$). This compound upon intravenous injection into anesthetized cats produced ganglionic block and lowering of blood pressure with a potency approximating that of hexamethonium chloride, although of much shorter duration. The hypotensive blood pressure effects lasted between 5–10 minutes.

Acknowledgments.—The author is indebted to Mr. Samuel W. Blackman for the microanalytical results included and to Dr. Kenneth Colville for the results of pharmacological testing.

Experimental

Preparation of N-Methylisonipecotic Acid Diethylaminoethyl Ester.—To a solution of about 0.1 g. of sodium in 25 cc. (theory 6 g.) of freshly distilled diethylaminoethanol (b.p. 162–164°), was added 7.9 g. (0.05 mole) of N-methylisonipecotic acid methyl ester (b.p. 100° at 22 mm.). This mixture was refluxed vigorously in a metal-bath at 170–180° for 20 hr. After removal of excess of diethylaminoethanol the product was distilled *in vacuo*, b.p. 154–155° at 11–12 mm., yield 9.5 g. (80%).

Dihydrochloride.—A sample of the base was treated with excess of ethanolic hydrogen chloride and the hydrochloride was precipitated with ether. After recrystallization from alcohol–ether mixtures the white crystals melted at 195–196°.

Dimethiodide.—A sample, 2.4 g. (0.01 mole), of the above-distilled base was dissolved in 20 cc. of isopropyl alcohol, 5 cc. of methyl iodide was added and the mixture was left for 2 hr. at 40–45°. A heavy white crystalline precipitate formed. After cooling, the product was collected and weighed 5.3 g. (100%). Recrystallization from mixtures of methanol–ethyl acetate gave white crystals, m.p. 262–263°.

See Table I for the details of these and the other compounds.

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[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, HARVARD MEDICAL SCHOOL]

The Preparation of Indanylpiperidinemethanol Derivatives

BY FREDERICK C. UHLE, JAMES E. KRUEGER AND ADRIANNE ELLEFSON ROGERS

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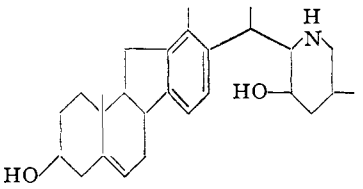
Indanylpiperidinemethanol derivatives formally related in skeletal structure to the alkaloid veratramine have been prepared. Condensation of 5-indanyl methyl ketone with 5-methylpicolinic acid, obtained by carbonation of 5-methyl-2-pyridyllithium, has afforded 1-(5-indanyl)-1-[2-(5-methylpyridyl)]-ethylene (III), reduction of which, with one mole of hydrogen, has given 1-(5-indanyl)-1-[2-(5-methylpyridyl)]-ethane (IV). Addition of 5-methyl-2-pyridyllithium to 5-indanyl methyl ketone has yielded α-(5-indanyl)-α-methyl-(5-methyl-2-pyridine)-methanol (V), catalytic hydrogenation of which has produced α-(5-indanyl)-α-methyl-(5-methyl-2-piperidine)-methanol (VIA). Sodium–alcohol reduction of V has afforded a diastereoisomeric carbinol, VIB. The isomers VIA and VIB have been found to exhibit antiaccelerator cardiac properties of the type characteristic of veratramine in molar quantities of the order of one hundred times those effective in the case of the naturally occurring alkaloid.

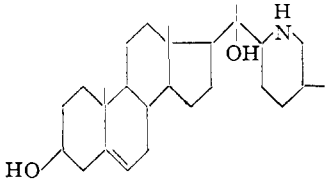
Veratramine (I), the pentacyclic, secondary 2-ethyl-5-methylpiperidine derivative native to *Veratrum viride*, has recently been demonstrated to be the prototype of a novel "modified steroid" skeletal arrangement characterized by the five- and six-membered nature of rings C and D, respectively.[1] The alkaloid has, furthermore, been shown to exhibit a marked pharmacodynamic specificity in its capacity to antagonize the consequences of accelerans stimulation as well as to annul the cardioaccelerator effects of epinephrine and related sympathomimetic amines without disturbing their positive inotropic and vasopressor properties.[2]

(1) J. Fried, O. Wintersteiner, M. Moore, B. M. Iselin and A. Klingsberg, THIS JOURNAL, **73**, 2970 (1951); C. Tamm and O. Wintersteiner, *ibid.*, **74**, 3842 (1952); O. Wintersteiner and N. Hosansky, *ibid.*, **74**, 4474 (1952).

(2) O. Krayer, *J. Pharmacol. Exptl. Therap.*, **96**, 492 (1949); **97**, 246 (1949).



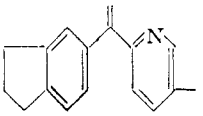
I



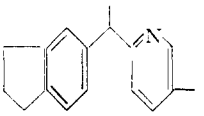
II

This "anti-accelerator" behavior of veratramine is shared by its closely related congener, jervine, and by the β-D-glucosides of the two alkaloids,[3] as well as by certain other steroid amines obtained by partial synthesis and by reductive transformation of members of the solanum group.[4] The synthetic alkaloid II, for example, derived by addition of 5-methyl-2-pyridyllithium to Δ^5-pregnen-3β-ol-20-one, followed by sodium–propanol reduction, was shown to be as active in this respect as was jervine.[5] In an endeavor to learn whether or not this specific epinephrine antagonism is a property limited solely to complex, polycyclic alkanolamines, as well as to appraise possible devices for the partial synthesis of alkaloids of the type of veratramine and jervine, simpler substances, characterized by formal structural relationships to the naturally occurring bases, have been prepared.

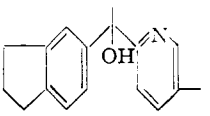
5-Indanyl methyl ketone was chosen as the starting material for the preparation of a series of tricyclic indanylpiperidinemethanol and indanylpiperidylethane derivatives of this class. In a first effort, 5-methylpicolinic acid, obtained by carbonation of 5-methyl-2-pyridyllithium, was allowed to react with the carbonyl compound at elevated temperature in the absence of solvent. While no appreciable change was observed under conditions developed by earlier workers with condensations of this type,[6] the evolution of carbon dioxide became apparent when the reaction was conducted in refluxing *p*-cymene in the presence of metallic copper. The product, which was isolated as the picrate in yields of the order of 10%, was shown to be an unsaturated compound, presumably derived by dehydration of a carbinol initially formed, and was assigned the ethylene formulation III. Catalytic hydrogenation of this labile styryl derivative, in the presence of palladium on carbon, gave rise to the indanylpyridylethane IV. Condensation of 5-indanyl methyl ketone with picolinic acid proceeded exactly as did the reaction with the substituted acid to give a related unsaturated derivative which, on absorption of one mole of hydrogen, afforded the 1-(5-indanyl)-1-(2-pyridyl)-ethane, homologous with IV.



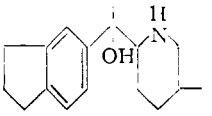
III



IV



V



VIA, m.p. 81–84°
B, m.p. 113–116°

According to a second scheme, analogous to that carried out earlier with steroid intermediates,[5] 5-methyl-2-pyridyllithium was allowed to react with 5-indanyl methyl ketone in ether solution to yield the indanylpyridylmethanol V. Hydrogenolysis, in the presence of palladium on carbon and 12 *N* hydrochloric acid, afforded the ethane derivative IV, identical with the hydrogenation product from the methylpicolinic acid sequence.

Catalytic hydrogenation of V in the presence of platinum gave, in 50% yield, a crystalline piperidinemethanol of the formulation VIA. Reduction of V with sodium and ethanol yielded a diastereoisomeric product VIB in an amount of 10–15% of the theory. The isomers were characterized as their picrates, as their benzamides and as their N-nitroso derivatives. Evidence for the stereochemical homogeneity of the two substances was provided by the constancy of their melting points, and of the melting points of their salts and their derivatives, following repeated recrystallization. The two alkanolamines exhibited identical ultraviolet absorption spectra, reconcilable with the absorption characteristic of polyalkylbenzenes. Their infrared spectra, measured in carbon disulfide solution, and the infrared spectra of the isomeric benzamides and N-nitroso derivatives, determined in potassium bromide, were comparable and exhibited the expected bands consistent with the assigned structures.[7]

Inasmuch as four racemates characterized by the structure VI are possible, the mother liquors from the separation of both isomers A and B were examined in detail. The filtrates from the picrate of isomer A, derived by hydrogenation, yielded successive fractions of crystalline material which were not resolved into components exhibiting sharp melting points. While the mother liquors from the sodium reduction isomer VIB yielded no solid product, benzoylation of the entire filtrate mixture, followed by chromatography on alumina, resulted in the separation, in 30% yield, of an oil whose infrared spectrum was notable for the absence of

(3) O. Krayer, *J. Pharmacol. Exptl. Therap.*, **98**, 427 (1950).

(4) O. Krayer, F. C. Uhle and P. Ourrisson, *ibid.*, **103**, 412 (1951); O. Krayer and L. H. Briggs, *Brit. J. Pharmacol.*, **5**, 118, 517 (1950).

(5) F. C. Uhle, THIS JOURNAL, **73**, 883 (1951).

(6) P. Dyson and D. Ll. Hammick, *J. Chem. Soc.*, 1724 (1937); M. R. F. Ashworth, R. P. Doffern and D. Ll. Hammick, *ibid.*, 809 (1939); B. R. Brown and D. Ll. Hammick, *ibid.*, 173, 659 (1949); N. H. Cantwell and E. V. Brown, THIS JOURNAL, **75**, 1489 (1953).

(7) The infrared spectra of the isomeric alkanolamines measured in potassium bromide exhibited divergencies in the 2–4μ region of greater magnitude than would ordinarily have been anticipated in the case of diastereoisomers. However, *cf.* R. J. Koegel, J. P. Greenstein, M. Winitz, S. M. Birnbaum and R. A. McCallum, THIS JOURNAL, **77**, 5708 (1955), who observed marked differences at these wave lengths in the case of the potassium bromide spectra of certain diastereoisomeric pairs of α-amino acids, *e.g.*, hydroxyproline and allohydroxyproline, β-phenylserine and β-allophenylserine, aminotricarballylic acid and alloaminotricarballylic acid, and pyrrolidonedicarboxylic acid and allopyrrolidonedicarboxylic acid.

a hydroxyl band at 2.6–3.2 μ. Attempts to characterize this fraction more precisely were not carried out. Further elution with solvents of increasing polarity afforded, in 46% yield, a nicely crystalline product which displayed a rather broad melting range (173–202°). Rechromatography on alumina, and fractional crystallization according to the triangular scheme, did not lead to the isolation of a precisely defined substance. However, the product resulting from four recrystallizations (m.p. 199–204°) gave correct analytical data and exhibited an infrared spectrum closely resembling those given by the benzamides of isomers VIA and VIB. This material is therefore regarded as representing the benzamide of a third diastereoisomeric modification of VI, VIC, still not entirely free of stereoisomers.

Attempts to secure indanylpiperidylethane derivatives devoid of the tertiary hydroxyl function of VI proved unrewarding. Hydrogenolysis, as well as chemical reduction, under various conditions, of the piperidinemethanols, led to the production of unpromising and intractable mixtures.

The indanylpiperidinemethanol isomers VIA and VIB were examined for antiaccelerator properties in the Starling heart-lung preparation of the dog under conditions of maximal cardioacceleration with 3 mg. of ephedrine in the presence, as well as in the absence, of atropine. In the case of both substances, reduction of heart rate was observed, leading to 50% inhibition of cardioacceleration with quantities of the order of 25 mg. On a comparative, molar basis, the compounds were found to be approximately one hundredth as potent as veratramine, as disclosed by the following relative values: veratramine, 100; dihydroveratramine, 57; synthetic alkaloid II, 3; jervine, 2; indanylpiperidinemethanol isomers VIA and VIB, 0.7.[8]

Experimental[9]

5-Indanyl Methyl Ketone.—A mixture of 23.6 g. (0.2 mole) of indan and 24.5 g. (0.24 mole) of acetic anhydride was added during a period of 3 hours to a stirred mixture of 64.0 g. (0.48 mole) of anhydrous aluminum chloride and 160 ml. of redistilled tetrachloroethane (b.p. 146°) which was immersed in an ice-bath. After stirring had been maintained for 15 hours at ordinary temperature, the mixture was added to hydrochloric acid and ice. The organic phase was separated and washed successively with 75 ml. quantities of 5 *N* hydrochloric acid, water and 10% aqueous sodium bicarbonate. The residue from the dried ether solution was distilled under reduced pressure through a Vigreux column; yield 28.8 g. (90%); b.p.[10] 90–97° (0.7–1.0 mm.); $n^{25}D$ 1.5593–1.5604; semicarbazone,[11] m.p. 222–225°.

5-Methylpicolinic Acid.—To a stirred mixture of 4.3 g. (0.625 mole) of lithium ribbon and 100 ml. of anhydrous ether at −40° under an atmosphere of nitrogen was added, drop by drop, over a period of 75 minutes, a solution of 34.25 g. (0.25 mole) of *n*-butyl bromide in 50 ml. of ether. After the mixture had been allowed to stir at 0° for a period of 2 hours, 35 g. (0.20 mole) of 2-bromo-5-methylpyridine was added during a period of 3 minutes. After 7 minutes at −30°, the reaction mixture was siphoned into a large excess of Dry Ice and the whole was allowed to approach room temperature. Water was added and the alkaline solution was extracted with several successive quantities of ether. The aqueous phase was neutralized to *p*H 4 with acetic acid and the solution was reduced in volume by concentration under diminished pressure. A saturated aqueous solution of cupric acetate was added to the filtered residue to yield a dark blue, crystalline deposit. After 48 hours at 0°, the copper salt was collected by filtration and was washed with water; yield 13.4 g. (40%).

A suspension of 3.35 g. (0.01 mole) of the copper salt in 100 ml. of water was treated with hydrogen sulfide. The filtrate from the copper sulfide was concentrated under diminished pressure and the residue was recrystallized from benzene; yield 2.4 g. (87%); m.p. 167–168°.[12]

Anal. Calcd. for $C_7H_7NO_2$ (137.14): C, 61.31; H, 5.15; N, 10.21. Found: C, 61.43; H, 4.95; N, 10.12.

1-(5-Indanyl)-1-[2-(5-methylpyridyl)]-ethylene Picrate (III).—A mixture of 8.0 g. (0.05 mole) of 5-indanyl methyl ketone, 1.37 g. (0.01 mole) of 5-methylpicolinic acid and 0.05 g. of copper powder in 8 ml. of *p*-cymene was maintained at reflux temperature for 3.5 hours. The carbon dioxide, which began to be evolved after an induction period of 35 minutes, was collected as barium carbonate; 1.25 g. (60%). Ether was added to the reaction mixture and the whole was extracted with 5 successive quantities of 1 *N* hydrochloric acid. Unchanged 5-indanyl methyl ketone was recovered from the ether solution by fractional distillation under diminished pressure. The acid solution was clarified by filtration, was treated with ammonium hydroxide solution and extracted with ether. The residual oil, 260 mg., from concentration of the washed and dried ether solution was titrated with a solution of picric acid in methanol. The crystalline solid was collected by filtration and was recrystallized from methanol; yield 280 mg. (6.0%); m.p. 181–183°.

Anal. Calcd. for $C_{23}H_{20}N_4O_7$ (464.42): C, 59.48; H, 4.34; N, 12.06. Found: C, 59.31; H, 4.28; N, 11.89.

Condensation of 5-indanyl methyl ketone with picolinic acid was carried out exactly as was the reaction with 5-methylpicolinic acid to yield, from methanol, 310 mg. (6.9%) of 1-(**5-indanyl**)-1-(**2-pyridyl**)-**ethylene picrate**, m.p. 187–189°.

Anal. Calcd. for $C_{22}H_{18}N_4O_7$ (450.40): C, 58.66; H, 4.03; N, 12.44. Found: C, 58.78; H, 3.90; N, 12.86.

1-(5-Indanyl)-1-[2-(5-methylpyridyl)]-ethane Picrate (IV).—A solution of 300 mg. (0.00067 mole) of III picrate in methanol was passed through a column of aluminum oxide (Merck). The column was washed with methanol to yield a final eluate volume of 100 ml. This solution was shaken with hydrogen in the presence of 0.05 g. of 10% palladium on carbon. After 17.2 ml. of hydrogen had been absorbed during a period of 15 minutes (theory 16 ml.), the catalyst was removed by filtration and the filtrate was titrated with a solution of picric acid in methanol. The solution was concentrated under diminished pressure and the remainder was recrystallized from ethanol; yield 150 mg. (50%); m.p. 131–133°.

Anal. Calcd. for $C_{23}H_{22}N_4O_7$ (466.44): C, 59.22; H, 4.76; N, 12.01. Found: C, 58.95; H, 5.20; N, 11.77.

The base from 294 mg. of 1-(5-indanyl)-1-(2-pyridyl)-ethylene picrate was hydrogenated as was the derivative from 5-methylpicolinic acid to yield, from ethanol, 50 mg. of 1-(**5-indanyl**)-1-(**2-pyridyl**)-**ethane picrate**, m.p. 111–113°.

Anal. Calcd. for $C_{22}H_{20}N_4O_7$ (452.41): C, 58.43; H, 4.46; N, 12.38. Found: C, 58.54; H, 4.35; N, 12.11.

The latter picrate was allowed to react with dilute lithium hydroxide solution and ether to yield, after treatment of the dried ether solution with anhydrous hydrogen chloride, 1-(**5-indanyl**)-(**2-pyridyl**)-**ethane hydrochloride**, m.p. 145–147°.

Anal. Calcd. for $C_{16}H_{18}NCl$ (259.77): C, 73.97; H, 6.98; N, 5.39. Found: C, 73.63; H, 6.85; N, 5.65.

(8) The pharmacological studies were carried out by Dr. Otto Krayer of this department.

(9) Microanalyses and spectroscopic determinations by Dr. S. M. Nagy and associates of the Massachusetts Institute of Technology, Cambridge, Massachusetts. Melting points were observed on the micro hot stage and are corrected. Boiling points are uncorrected.

(10) *Cf.* J. V. Braun, G. Kirschbaum and H. Schuhmann, *Ber.*, **53**, 1155 (1920), who obtained the ketone by the Friedel–Crafts procedure with acetyl chloride, and L. F. Fieser and E. B. Hershberg, THIS JOURNAL, **62**, 49 (1940), who effected the acylation with acetic acid and hydrogen fluoride.

(11) W. Borsche and M. Pommer, *Ber.*, **54**, 102 (1921).

(12) This substance has recently been obtained by processing of a commercial mixture of lutidines with benzaldehyde, separation of the resulting 2,4-distyrylpyridine and 2-styryl-5-methylpyridine, and oxidation of the latter with potassium permanganate; M. Haring, B. Prijs and H. Erlenmeyer, *Helv. Chim. Acta*, **37**, 147 (1953).

α-(5-Indanyl)-α-methyl-(5-methyl-2-pyridine)-methanol (V).—A solution of 52.1 g. (0.30 mole) of 2-bromo-5-methylpyridine[13] in 150 ml. of ether was added, under nitrogen, during 15 minutes to a solution of 0.30 mole of *n*-butyllithium[14] in 500 ml. of ether at an internal temperature of −40°. The orange solution was allowed to stir for an additional period of 15 minutes and a solution of 48.5 g. (0.30 mole) of 5-indanyl methyl ketone in 150 ml. of ether was added during 15 minutes. The solution was allowed to stir for 45 minutes during which time the temperature rose to −17°. After 15 hours at ordinary temperature, the mixture was extracted with 1500 ml. of 0.4 *N* sulfuric acid and with two successive quantities of water. The aqueous phase was basified with 10 *N* sodium hydroxide solution and was extracted with three 250-ml. quantities of ether. The residue from the washed and dried ether extract was crystallized from petroleum ether to yield 5 successive crops which were combined and sublimed at 0.01 mm. at a heating bath temperature of 100–150° to give 32.0 g. (42%); m.p. 78–80°.

Anal. Calcd. for $C_{17}H_{19}NO$ (253.33): C, 80.57; H, 7.56; N, 5.53. Found: C, 80.25; H, 7.60; N, 5.62.

Ultraviolet absorption spectrum: λ_{max} (log ϵ) 268.8 mμ (3.77); λ_{min} (log ϵ) 245 mμ (3.38).

The picrate was prepared in absolute ethanol and was recrystallized from the same solvent; m.p. 161–162°.

Anal. Calcd. for $C_{23}H_{22}N_4O_8$ (482.44): C, 57.26; H, 4.60; N, 11.61. Found: C, 57.11; H, 4.85; N, 11.60.

α-(5-Indanyl)-α-methyl-(5-methyl-2-piperidine)-methanol (VI). Isomer A, m.p. 81–84°.—Hydrogenation of a solution of 5.0 g. (0.02 mole) of V in 55 ml. of acetic acid in the presence of 5.0 g. of prereduced platinum oxide was complete (1600 ml., 106% of 3 molar equivalents) in 5.5 hours. The filtrate from the catalyst was concentrated under reduced pressure, was dissolved in ether and washed with aqueous potassium hydroxide. The residue from the washed and dried ether extract was titrated to congo red with 0.25 *N* picric acid in absolute ethanol. The crystalline deposit was collected by filtration; yield, from two crops, 5.48 g. (58%). The material was recrystallized from absolute ethanol to give 5.24 g. (56%); m.p. 207–208°. Subsequent crops were impure.

Anal. Calcd. for $C_{23}H_{28}N_4O_8$ (488.49): C, 56.55; H, 5.78; N, 11.47. Found: C, 56.41; H, 5.72; N, 11.39.

A quantity of 4.24 g. of the picrate was dissolved in 100 ml. of refluxing ethanol and was treated with 0.78 ml. of 12 *N* aqueous sodium hydroxide. The solvent was distilled under reduced pressure, the residue was triturated with water and twice extracted with ether. The ether solution was washed with dilute lithium hydroxide solution and with water. The residue from the washed and dried ether solution was recrystallized from petroleum ether; yield 1.93 g. (86%); m.p. 81–84°.

Anal. Calcd. for $C_{17}H_{25}NO$ (259.38): C, 78.71; H, 9.72; N, 5.40. Found: C, 78.71; H, 9.81; N, 5.23.

Ultraviolet absorption spectrum: λ_{max} (log ϵ): 269.4 mμ (3.06); 276.8 mμ (3.12); λ_{min} (log ϵ) 240 mμ (2.06); 274 mμ (2.89).

Nitrosamine.—A solution of 53 mg. of VIA in 2.5 ml. of 10% aqueous acetic acid was treated with 1.0 ml. of 10% aqueous sodium nitrite and, after 1 hour, with an additional 0.5 ml. of the same reagent. After 15 hours at ordinary temperature, 57 mg. of product was collected by filtration to yield, after 3 recrystallizations from methylcyclohexane, 36 mg.; m.p. 122–124°.

Anal. Calcd. for $C_{17}H_{24}N_2O_2$ (288.38): C, 70.80; H, 8.39; N, 9.72. Found: C, 70.58; H, 8.22; N, 9.51.

Benzamide.—To a solution of 100 mg. of VIA in 1.5 ml. of chloroform were added 0.06 ml. (1.35 equivalents) of benzoyl chloride, 2 ml. of 10 *N* aqueous sodium hydroxide and 10 ml. of water. After 15 hours at 0°, the chloroform was separated and the aqueous phase was washed with chloroform. The extract was washed with dilute sulfuric acid, aqueous sodium bicarbonate and water. The residue from the dried solution was recrystallized from a mixture of ethanol and water; yield 119 mg. (85%); m.p. 178–181°.

(13) F. H. Case, THIS JOURNAL, **68**, 2574 (1946).

(14) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn and L. S. Miller, *ibid.*, **71**, 1499 (1949).

Anal. Calcd. for $C_{24}H_{29}NO_2$ (363.48): C, 79.30; H, 8.04; N, 3.85. Found: C, 79.27; H, 8.00; N, 4.02.

Isomer VIB, m.p. 113–116°.—To a solution of 2.53 g. (0.01 mole) of V in 100 ml. of absolute ethanol, under nitrogen, was added, with occasional cooling, during a period of 5 minutes, 11.5 g. (0.5 mole) of sodium. After the sodium had entirely dissolved (1–2 hours under vigorous reflux), the mixture was cooled under nitrogen, 25 ml. of water was added and the solvents were concentrated under diminished pressure. Water was added and the mixture was extracted with ether. The residue from the washed and dried ether solution was treated with 10 ml. of petroleum ether to yield, after 15 hours at 0°, 0.30 g. (11%); m.p. 97–113°. The material was sublimed at 0.02 mm. (heating block temperature 90–140°) and the sublimate was recrystallized from petroleum ether; m.p. 113–116°.

Anal. Calcd. for $C_{17}H_{25}NO$ (259.38): C, 78.71; H, 9.72; N, 5.40. Found: C, 78.68; H, 9.87; N, 5.73.

Ultraviolet absorption spectrum: λ_{max} (log ϵ) 210 mμ (3.84); 270 mμ (3.01); 277 mμ (3.07); λ_{min} (log ϵ) 240 mμ (2.05); 264 mμ (2.84); 274 mμ (2.82).

The picrate was prepared in absolute ethanol and was recrystallized from the same solvent; m.p. 194–196°.

Anal. Calcd. for $C_{23}H_{28}N_4O_8$ (488.49): C, 56.55; H, 5.78; N, 11.47. Found: C, 56.64; H, 5.87; N, 11.36.

Nitrosamine.—By the method described for the preparation of the nitrosoamine of VIA, there was obtained, from 95 mg. of VIB, 95 mg. of VIB nitrosoamine which was recrystallized from methylcyclohexane and from ethanol–water to give 40 mg., m.p. 122–124°.

Anal. Calcd. for $C_{17}H_{24}N_2O_2$ (288.38): C, 70.80; H, 8.39; N, 9.72. Found: C, 70.84; H, 8.45; N, 9.36.

Benzamide.—Reaction of 100 mg. of VIB with benzoyl chloride as described for the preparation of VIA benzamide gave 78 mg.; m.p. 133–142°. Two recrystallizations from ethanol–water yielded 58 mg.; m.p. 147–149°.

Anal. Calcd. for $C_{24}H_{29}NO_2$ (363.48): C, 79.30; H, 8.04; N, 3.85. Found: C, 79.26; H, 8.10; N, 4.08.

Benzamide of VIC.—A quantity of 2.20 g. of the oil which remained after crystallization of VIB was treated with excess benzoyl chloride according to the Schotten–Baumann procedure. The non-basic product was dissolved in 20 ml. of benzene and was chromatographed on 100 g. of alumina (Woelm non-basic, activity grade 1). Elution with benzene and ether removed material (0.88 g., 30%) which was not obtained in crystalline form. The infrared spectrum of this oil displayed an amide carbonyl band at 6.17 μ, but did not exhibit a hydroxyl band in the 3 μ region.

Elution with ethyl acetate yielded 1.42 g. (46%) of material which crystallized from absolute ethanol; 0.74 g.; m.p. 173–202°. Four recrystallizations from ethanol gave 0.21 g.; m.p. 199–204°. The infrared spectrum of this substance was markedly similar to the spectra of the benzamides of VIA and VIB.

Anal. Calcd. for $C_{24}H_{29}NO_2$ (363.48): C, 79.30; H, 8.04; N, 3.85. Found: C, 79.17; H, 8.31; N, 3.90.

Hydrogenolysis of V. A.—A solution of 0.51 g. (0.002 mole) of V in 10 ml. of absolute ethanol was shaken with hydrogen in the presence of 0.42 ml. of 70% perchloric acid and 0.50 g. of 10% palladium on carbon. After 70.6 ml. (117% of 1 molar equivalent) of hydrogen had been absorbed during a period of 60 hours, the uptake of hydrogen ceased. The catalyst was removed by filtration and was washed with water. The filtrate was diluted with 75 ml. of water, aqueous sodium hydroxide was added and the whole was extracted with ether. The residue from the washed and dried ether solution was titrated to congo red with ethanolic picric acid. After 15 hours at 0°, the crystalline deposit was collected by filtration; yield 0.68 g.; m.p. 125–131°. Two recrystallizations from absolute ethanol yielded 0.45 g. (48%); m.p. and mixed m.p. with IV 131–133°.

B.—A solution of 0.10 g. of V in 5 ml. of concentrated hydrochloric acid solution was shaken with hydrogen in the presence of 0.10 g. of 10% palladium-on-carbon. After 2 hours, the uptake of hydrogen ceased. The catalyst was removed by filtration and the hydrochloric acid was distilled under diminished pressure. The residue was treated with aqueous sodium hydroxide and extracted with ether. The residue from the washed and dried ether solution gave 0.135 g. (73%); m.p. 131–133°.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY]

The 2-Pyridyl Analog of Demerol

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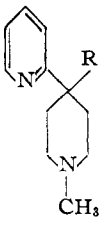
2-Pyridylacetonitrile has been converted by established procedures *via* the intermediate nitrile I and amide II to 1-methyl-4-(2-pyridyl)-4-carbomethoxypiperidine (III), the 2-pyridyl analog of Demerol.

The replacement of a benzene ring of a physiologically active compound by an isosteric system such as the pyridine nucleus is a process which has led to many interesting compounds and some useful drugs.[2] We have made use of this principle in the preparation of the 2-pyridyl analog of the known analgesic Demerol (Meperidine).[3] No previous report of the preparation of this compound or its 3- or 4-pyridyl isomers could be found in the literature.



I, R = CN
II, R = $CONH_2$
III, R = $COOCH_3$
IV, R = H

2-Pyridylacetonitrile was condensed with di-(2-chloroethyl)-methylamine in the presence of sodium amide according to the procedure of Eisleb[3] to give 1-methyl-4-(2-pyridyl)-4-cyanopiperidine (I) (48% yield). This was converted with concentrated sulfuric acid to the amide II (94% yield) which was treated with methanol and hydrogen chloride to give the ester III (34% yield), the desired analog.

Considerable difficulty was encountered in converting the nitrile I to the ester III. A series of attempts to prepare the ester III directly from the nitrile I in hydrogen chloride saturated methanol gave poor results, due in part at least to the insolubility of the nitrile hydrochloride in the reaction medium. Attempts to prepare the ethyl ester directly from the nitrile using ethanol and concentrated sulfuric acid gave 1-methyl-4-(2-pyridyl)-piperidine (IV), the product to be expected from hydrolysis and decarboxylation. Compounds I, II and III were submitted to Parke, Davis and Co. for pharmacological evaluation.

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Experimental

Methyl 2-Pyridylacetate.—This compound was prepared, with slight modification, according to the procedure of Woodward and Kornfeld[4] for the corresponding ethyl ester. 2-Picolyllithium prepared from 30 g. (4.3 gram-atoms) of lithium, 314 g. (2.00 moles) of bromobenzene and 186 g. (2.00 moles) of 2-picoline, under an atmosphere of dry natural gas, was added to an ether slurry of Dry Ice which had been powdered in a polyethylene bag. The resulting paste was dissolved in dry methanol, and saturated below 10° with hydrogen chloride gas. On standing, a crystalline precipitate formed. If this precipitate did not redissolve completely on standing at room temperature, more hydrogen chloride gas was introduced. After the solid had redissolved and the mixture had separated into two layers, the reaction mixture was evaporated under reduced pressure. The residue was treated with sodium carbonate-water paste, and extracted with dichloromethane. The extract was evaporated and distilled, b.p. 74–78° (2 mm.), $n^{24}D$ 1.5070–1.5092, 151 g. (1.00 mole), 50% yield. The picrate was prepared from ethanol; m.p. 141–142.5°.[5,6]

2-Pyridylacetamide. A.—Methyl 2-pyridylacetate (80.3 g., 0.531 mole) was dissolved in 125 ml. of concentrated ammonium hydroxide (28%, 2.28 moles). The solution was allowed to stand at room temperature for two days. After treatment with Norit and Celite, evaporation of the solution to near dryness at reduced pressure, and recrystallization of the residue from acetone, the amide, 59.2 g. (81.7% yield), was obtained, m.p. 120–122°.[7]

2-Pyridylacetamide. B.—This compound was also prepared by the Willgerodt reaction, according to the procedure of Carmack and DeTar.[7] Some modifications in details of this procedure were worked out. In each Pyrex combustion tube there was placed 15 g. (0.143 mole) of freshly distilled 2-vinylpyridine (Reilly Tar and Chemical Co.), 23 g. (0.719 gram-atom) of sifted sulfur, 28 ml. of concd. ammonium hydroxide (0.511 mole) and 25 ml. of purified dioxane. Each tube was sealed and heated for two hours at 150°. After cooling, the contents of several tubes were combined and evaporated under reduced pressure at 40–60°. Acetone was added to the tarry residue to precipitate solid sulfur. The evaporation was continued to near dryness, and the residue extracted with three portions of boiling methyl ethyl ketone. The extract was treated with Norit and Celite, and evaporated to a mass of yellow or brown crystals containing some sulfur. Recrystallization from acetone gave white needles, m.p. 120–122°.[7] The combined yield of fifteen tubes initially containing 225 g. (2.14 moles) of 2-vinylpyridine, was 119 g. (0.875 mole), 40.8% yield. The picrate was prepared from ethanol, m.p. 155–157°, and the hydrochloride, m.p. 185–186°.

2-Pyridylacetonitrile.—This compound was prepared according to procedure B used by Sperber, *et al.*,[8] for the preparation of the 3-isomer. From 75 g. of the amide was obtained 55.1 g. (79%) of the nitrile,[8] b.p. 76–77° (2 mm.), $n^{25}D$ 1.5224, m.p. 23–25.5°; picrate from ethanol, m.p. 155–157°.

(1) Taken in part from the M.S. Thesis of Robert J. Dummel, Stanford University, 1954.

(2) A. Burger, "Medicinal Chemistry," Vol. 1, Interscience Publishers, Inc., New York, N. Y., 1951, pp. 36–50.

(3) O. Eisleb, *Ber.*, **74B**, 1433 (1941).

(4) R. Woodward and E. Kornfeld, *Org. Syntheses*, **29**, 44 (1950).

(5) All melting points were taken on a calibrated Kofler hot-stage, equipped with polarization filters.

(6) Reported m.p. 142–144°; W. Gruber and K. Schlögl, *Monatsh.*, **81**, 473 (1950).

(7) Reported m.p. 120–121°; M. Carmack and D. DeTar, THIS JOURNAL, **68**, 2033 (1946).

(8) N. Sperber, D. Papa, E. Schwenk, M. Sherlock and R. Fricano, *et al.*, *ibid.*, **73**, 5752 (1951).