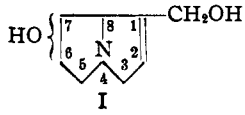
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Structure of Monocrotaline. XI. Proof of the Structure of Retronecine[1]

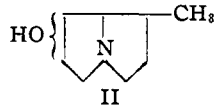
BY ROGER ADAMS AND N. J. LEONARD

Retronecine, the base obtained along with carbon dioxide and monocrotic acid upon alkaline hydrolysis of monocrotaline, has been postulated[2,3] as having structure I. The presence of the

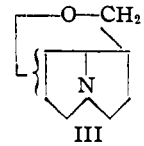


I

—CH_2OH group in the 1-position of the pyrrolizidine nucleus[3] and the location of the double bond in the 1,2-position[4] have been proved conclusively. The location of the secondary hydroxyl group in retronecine (I) or in retronecanol (II)[3] has been in doubt. The experimental evidence favors either the 6- or the 7-position. The degradation of retronecanol by bromocyanogen indicates that the 7-position is the more likely.[2] Corroborative evidence for the 7-position is obtained by construction of models representing anhydroplatynecine (III). When the secondary



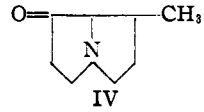
II



III

hydroxyl group is in the 7-position, the structural model of anhydroplatynecine involves somewhat less strain.

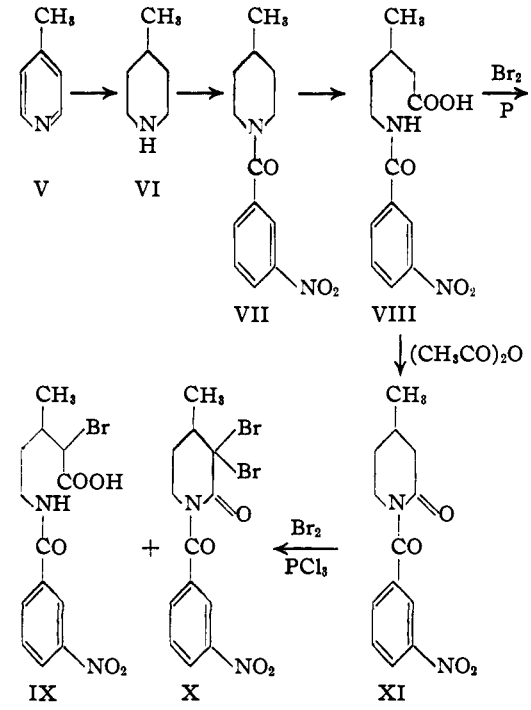
An optically active form of 1-methyl-7-ketopyrrolizidine has now been synthesized by an unequivocal method and found to be identical with the retronecanone (IV)[3] obtained by oxidation of



IV

retronecanol with aluminum *t*-butoxide. It has thus been proved that retronecine and its derivatives have the secondary hydroxyl group in the 7-position.

4-Methylpyridine (V) was reduced catalytically to 4-methylpiperidine (VI), which was converted into 1-*m*-nitrobenzoyl-4-methyl-piperidine (VII) by a Schotten–Baumann reaction with *m*-nitrobenzoyl chloride. Oxidation of compound VII with potassium permanganate according to the method of Schotten[5,6] and Fischer and Zemplén[7]



gave β-methyl-δ-*m*-nitrobenzoylaminovaleric acid (VIII), which would be formed by cleavage of either ring carbon–nitrogen bond. Bromination of this acid (VIII) in the presence of red phosphorus resulted in the formation of two products IX and X. Compound X was identified as N-*m*-nitrobenzoyl-γ-methyl-β,β-dibromo-α-piperidone by bromination of N-*m*-nitrobenzoyl-γ-methyl-α-piperidone (XI).[8] The structure of compound IX was accepted on the basis of the results of the researches of Fischer and Zemplén,[7] who prepared the analogous compound through a similar series of reactions from pyridine.

α-Bromo-β-methyl-δ-*m*-nitrobenzoylaminovaleric acid (IX) was not obtained in a pure state but the crude product was converted to ethyl 3-methylpyrrolidine-2-carboxylate (XIV) through the intermediates XII and XIII. The formation of 1-*m*-nitrobenzoyl-3-methylpyrrolidine-2-carboxylic acid (XII) resulted from the reaction of alkali upon IX, and 3-methylpyrrolidine-2-carboxylic acid hydrochloride (XIII) was obtained by the hydrolysis of XII with hydrochloric acid. Owing to the difficulty in purifying either XII or XIII, compound XIII was esterified directly to XIV, which was obtained readily in pure form by distillation. The physical properties and analyses of XIV and its picrate indicated conclusively that the compound was ethyl 3-methylpyrrolidine-2-

(1) For previous paper see Adams and Wilkinson, THIS JOURNAL, 65, 2203 (1943).

(2) Adams, Carmack and Mahan, *ibid.*, 64, 2593 (1942).

(3) Adams and Hamlin, *ibid.*, 64, 2597 (1942).

(4) Adams and Mahan, *ibid.*, 65, 2009 (1943).

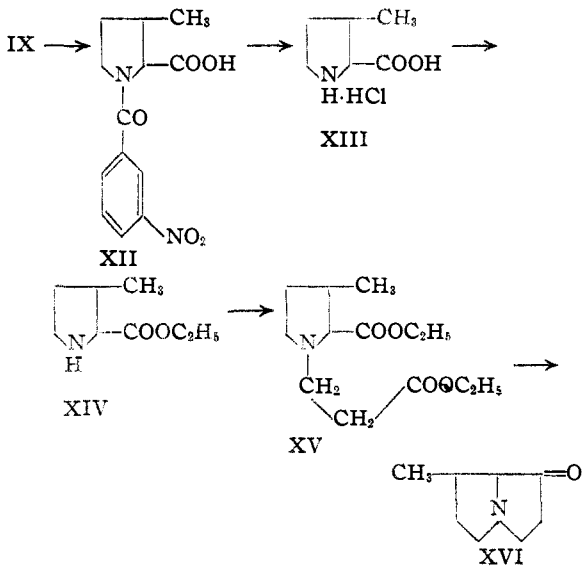
(5) Schotten, *Ber.*, 17, 2544 (1884).

(6) Schotten, *ibid.*, 21, 2235 (1888).

(7) Fischer and Zemplén, *ibid.*, 42, 2989 (1909).

(8) Schniepp and Marvel, THIS JOURNAL, 61, 2822 (1939).

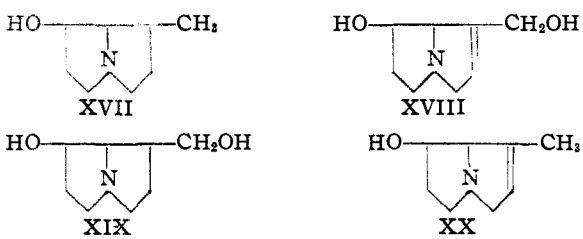
carboxylate. Proline has been made previously by a similar series of reactions.[7] Ethyl 3-methylpyrrolidine-2-carboxylate underwent practically quantitative addition to ethyl acrylate to give ethyl β-N-(3-methyl-2-carbethoxypyrrolidyl)-propionate (XV), which was cyclized with powdered potassium. The intermediate keto-ester was not



isolated but was hydrolyzed and decarboxylated to 1-methyl-7-ketopyrrolizidine (XVI). There may be formed in the ring closure two keto-esters depending upon which ethoxy group is eliminated as ethanol. Both of these, however, on hydrolysis and decarboxylation would yield the same ketone.

The picrate, methiodide and oxime of compound XVI were prepared. Although theoretically two racemic modifications might be present in the liquid XVI as synthesized only single derivatives were isolated in each case. An attempt was made to isolate an optically active 1-methyl-7-ketopyrrolizidine from the possible mixture of four forms by the use of *l*-menthydrazide. A pure *l*-menthydrazone was obtained but it proved to have a different melting point and specific rotation from the *l*-menthydrazone of retronecanone. Moreover, hydrolysis of the 1-methyl-7-ketopyrrolizidine *l*-menthydrazone and conversion of the ketone to the oxime gave an optically inactive product.

In order to decrease the stereochemical possibilities in the final product as a result of working with racemic modifications, a similar series of reactions was carried out using *l*-β-methyl-δ-*m*-nitrobenzoylaminovaleric acid. This optically active acid was obtained by resolution through the quinidine salt of the racemic acid (VIII). There was thus obtained optically active 1-methyl-7-ketopyrrolizidine (XVI) which could not consist of a mixture of more than two forms. Like the product from the racemic acid this was an oil. When treated with hydroxylamine, however, a single, pure, optically active oxime was isolated. This proved to be identical in melting point, crystalline form as observed under the microscope, and specific rotation with retronecanone oxime, and the melting points of mixtures of the two compounds showed no depression. The picrates of the aminoketoximes obtained from natural and synthetic sources were also found to be identical and showed no depression of melting-decomposition point when mixed. Likewise, the picrolonates of the oximes were identical. Since the keto group in retronecanone occupies the same position as the secondary hydroxyl group in its parent, retronecanol, this hydroxyl group has been located definitely at the 7-position, and the precise structure of retronecanol may now be represented by XVII. Retronecine, therefore, has structure XVIII; platynecine,[9] structure XIX; and desoxyretronecine,[10] structure XX. Owing



to the fact that heliotridine and oxyheliotridane[11] are merely stereoisomers, respectively, of retronecine and retronecanol, it is also established that these molecules have the secondary hydroxyl group in the 7-position.

Monocrotaline, the acetyl and benzoyl esters of retronecine, and retronecine itself have been reduced to retronecanol.[10,12,13] These reductions have been carried out in solutions of widely different *p*H over palladium or platinum oxide catalysts, and retronecanol is the only 1-methyl-7-hydroxypyrrolizidine isomer which has been obtained, always in essentially quantitative yield. Likewise, the catalytic reduction of desoxyretronecine in hydrochloric acid resulted in almost quantitative production of retronecanol,[10] and isoheliotridene was reduced in ethanol over platinum oxide to heliotridane,[4] which is related to retronecanol through chlororetronecane,[14]

Reduction of all of these $\Delta^{1,2}$-unsaturated pyrrolizidines makes carbon atom-1 asymmetrical. There is the possibility of reduction proceeding to give a mixture of isomers in which the C_1-CH_3 would be both *cis* and *trans* with respect to the C_8-H; the other possibility would be asymmetric reduction proceeding to give *either* the *cis*- or the *trans*-C_1-CH_3 configuration. Asymmetric reduction is indicated because of the fact that synthetic (and, therefore, naturally-obtained) retronecanone possesses the C_1-CH_3 fixed in one stereo-

(9) Orekhov and Tiedebel, *Ber.*, **68**, 650 (1935).
(10) Adams and Rogers, THIS JOURNAL, **63**, 537 (1941).
(11) Menshikov, *Ber.*, **68**, 1051 (1935).
(12) Barger, Seshadri, Watt and Yabuta, *J. Chem. Soc.*, 11 (1935).
(13) Adams and Rogers, THIS JOURNAL, **61**, 2815 (1939).
(14) Adams and Rogers, *ibid.*, **63**, 228 (1941).

chemical configuration. This may be deduced from the fact that the starting material for its preparation was *l*-β-methyl-δ-*m*-nitrobenzoylaminovaleric acid, in which the C_β-CH_3 had a fixed configuration.

Reduction of retronecanone could yield a mixture of a maximum of four stereoisomeric 1-methyl-7-hydroxypyrrolizidines if C-8 were racemized in the aluminum *t*-butoxide oxidation of retronecanol to retronecanone. A maximum of two isomers, of which one would be retronecanol, could result on reduction of retronecanone if the latter possessed only one stereochemical configuration about C-8. Neither retronecanol nor its derivatives could be obtained by reduction of retronecanone over platinum oxide in ethanol or in ethanolic hydrochloric acid solution. The reaction products from reductions carried out both in neutral and acid solution were mixtures. In each of the two experiments it was possible to isolate a pure compound as a picrate, but these were not identical with each other or with retronecanol picrate. Upon acetylation of each reduction product mixture and then treatment with methyl iodide, the same pure acetyl methiodide was isolated in small yield. This methiodide was not identical but stereoisomeric with acetylretronecanol methiodide. As a consequence of these results no attempt was made to synthesize natural retronecanol from synthetic optically active 1-methyl-7-ketopyrrolizidine.

Experimental

4-Methylpiperidine (VI).—Hydrogenation of 482 g. (5.18 moles) of redistilled 4-methylpyridine (V) (b. p. 142–144°) was concluded after twenty-four hours at 210° and 150–300 atm. with 50 g. of Raney nickel catalyst. The product was fractionally distilled and the fraction boiling at 126–129° was collected[15]; $n^{20}D$ 1.4487; yield 283 g. (55%, or 90% on the basis of unrecovered 4-methylpyridine).

1-*m*-Nitrobenzoyl-4-methylpiperidine (VII).—To a well-stirred mixture of 265 g. (2.67 moles) of 4-methylpiperidine and 120 g. (3.00 moles) of sodium hydroxide in 630 cc. of water was added slowly, during the course of two hours, 500 g. (2.69 moles) of molten *m*-nitrobenzoyl chloride.[6] The temperature was maintained at 35–40°. When addition was complete the mixture was stirred for an additional hour and then cooled in ice. The yellow crystals were filtered, washed with water and dried; yield of crude product, 582 g. (88%). After recrystallization from aqueous ethanol, 550 g. of large colorless prisms was obtained, m. p. 72–73°. The compound may be recrystallized also from benzene–ligroin (b. p. 90–110°).

Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.49. Found: C, 63.00; H, 6.50.

***dl*-β-Methyl-δ-*m*-nitrobenzoylaminovaleric Acid (VIII).**—A total of 520 g. (2.1 moles) of 1-*m*-nitrobenzoyl-4-methylpiperidine was oxidized in thirteen batches of 40 g. each. The amide (40 g.) was dissolved in 2.5 liters of boiling water and a solution of 60 g. of potassium permanganate in 500 cc. of hot water was added during one hour, while stirring vigorously and refluxing. The reaction mixture was filtered hot and the alkaline filtrate was cooled and extracted with ether. The combined ether extracts of thirteen runs furnished 88 g. of crude starting material which again was subjected to permanganate oxidation. The aqueous solution (above) was acidified with dilute sulfuric acid and cooled in ice. The colorless crystalline product which separated was collected on a filter; extraction of the acidic filtrate with ether furnished additional product. The total combined yield was 340 g. (57%) which was purified by recrystallization from dilute acetic acid or aqueous ethanol; colorless elongated prisms, m. p. 103–105°.

Anal. Calcd. for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99. Found: C, 55.78; H, 5.93; N, 9.84.

Resolution of *dl*-β-Methyl-δ-*m*-nitrobenzoylaminovaleric Acid.—A mixture of 100 g. of the *dl*-acid and 116 g. of anhydrous quinidine was dissolved in hot absolute ethanol, boiled with Darco and Norite and filtered. The ethanolic filtrate, which amounted to 450 cc., was diluted with 1300 cc. of anhydrous ether and allowed to stand at room temperature for several days. Rosets of colorless elongated prisms separated and these were isolated by filtration, washed with anhydrous ether and dried (Fraction 1); m. p., 125.0–126.5° (cor.); yield 77 g. (36% of total).

Rotation. 0.2286 g. made up to 5 cc. with absolute ethanol at 28° gave αD +5.10°; *l*, 1; $[\alpha]^{28}D$ +111.5° (±0.5°). Further recrystallization from absolute ethanol–anhydrous ether altered neither the melting point nor the rotation.

After removal of 77 g. of the most insoluble quinidine salt (Fraction 1), the filtrate was diluted further with anhydrous ether and allowed to stand in the cold. A further 48 g. (22%) of yellow, semicrystalline material separated, leaving approximately 42% of the total salt in solution (Fraction 2). The more soluble salt could not be obtained crystalline.

***l*-β-Methyl-δ-*m*-nitrobenzoylaminovaleric Acid.**—Fraction 1 (75 g.) was shaken thoroughly with 500 cc. of 2 *N* sulfuric acid and 200 cc. of ether, then separated. The mixture of dilute acid and undissolved quinidine salt was shaken with 200-cc. portions of ether until no more solid material remained. The ethereal extracts were combined, dried over anhydrous magnesium sulfate, and evaporated to give 30 g. of crystalline *l*-acid. This was purified by recrystallization from aqueous ethanol: colorless rods, m. p. 113–114°.

Anal. Calcd. for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99. Found: C, 55.96; H, 6.02; N, 9.92.

Rotation. 0.2040 g. made up to 5 cc. with absolute ethanol at 30° gave αD −0.205°; *l*, 1; $[\alpha]^{30}D$ −5.0° (±0.2°).

***d*-β-Methyl-δ-*m*-nitrobenzoylaminovaleric Acid.**—The ethereal solution containing Fraction 2 was shaken with 2 *N* sulfuric acid, and 34 g. of the *d*-acid was obtained by the same procedure as that outlined above. Purification was accomplished by recrystallization from chloroform–ligroin (b. p. 90–110°): colorless elongated prisms, m. p., 113–114°.

Anal. Calcd. for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99. Found: C, 55.94; H, 5.84; N, 10.09.

Rotation. 0.2164 g. made up to 5 cc. with absolute ethanol at 25° gave αD +0.23°; *l*, 1; $[\alpha]^{25}D$ +5.3° (±0.2°).

Bromination of *dl*-β-Methyl-δ-*m*-nitrobenzoylaminovaleric Acid.—An intimate mixture of 50 g. (0.18 mole) of *dl*-β-methyl-δ-*m*-nitrobenzoylaminovaleric acid and 8 g. of red phosphorus was protected from moisture, cooled in ice, and stirred manually during the thirty-minute addition of 51.5 cc. (*ca.* 0.94 mole) of dry bromine. When addition was complete the mixture was stirred at room temperature for thirty minutes, warmed to 90° during ten minutes, and kept at 90° for a further ten minutes. The reaction mixture was cooled in ice and ice-water was added gradually. Excess bromine was reduced by passing a slow stream of sulfur dioxide into the cold solution. After addition of excess sodium carbonate solution the mixture was stirred vigorously and filtered. The sodium carbonate-insoluble material weighed 15 g. It was purified by recrystallization from ethanol, from which it separated in leaf-like aggregates of colorless elongated prisms, m. p. 152–153° (cor.). It proved to be N-*m*-nitrobenzoyl-γ-methyl-β,β-dibromo-α-piperidone (X).

(15) Ladenburg, *Ann.*, **247**, 1 (1888).

Anal. Calcd. for $C_{18}H_{12}Br_2N_2O_4$: C, 37.17; H, 2.88; N, 6.67. Found: C, 37.36; H, 3.08; N, 6.62.

After removal of the alkali-insoluble material the filtrate was cooled, acidified with 1 *N* sulfuric acid and extracted thoroughly with ether. The ethereal solution was dried over anhydrous magnesium sulfate, and the ether was removed to leave a residue of 42 g. of straw-colored oil which could not be crystallized. The crude α-bromo-β-methyl-δ-*m*-nitrobenzoylaminovaleric acid (IX) was not purified but was used directly in the next step (ring-closure).

N-*m*-Nitrobenzoyl-γ-methyl-α-piperidone (XI).—A solution of 2 g. of *dl*-β-methyl-δ-*m*-nitrobenzoylaminovaleric acid (VIII)[6] in 25 cc. of acetic anhydride was refluxed for two and one-half hours in all-glass apparatus. The acetic anhydride was removed *in vacuo* and the residue was recrystallized from aqueous ethanol: colorless elongated prisms, m. p. 102–103°. The melting point of a mixture of this product and the starting material (m. p. 103–104°) was depressed to 85–95°.

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.71; H, 5.44; N, 10.82.

N-*m*-Nitrobenzoyl-γ-methyl-β,β-dibromo-α-piperidone (X).—To 0.25 g. of N-*m*-nitrobenzoyl-γ-methyl-α-piperidone in 5 cc. of dry chloroform were added three drops of phosphorus trichloride and 0.6 g. of bromine.[8] The solution was illuminated by a bright electric light for forty-eight hours, then the reaction mixture was treated with water and sufficient sodium bisulfite to decompose the excess bromine. The chloroform layer was separated and evaporated to dryness, leaving 0.10 g. of product which was recrystallized from ethanol: colorless elongated prisms, m. p., 152–153° (cor.). When this product was mixed with the alkali-insoluble material obtained in brominating *dl*-β-methyl-δ-*m*-nitrobenzoylaminovaleric acid, there was no depression of melting point.

Bromination of *l*-β-Methyl-δ-*m*-nitrobenzoylaminovaleric Acid.—The bromination was carried out in a manner identical with that used for the *dl*-acid. The quantities employed were 25 g. (0.09 mole) of *l*-acid, 3.5 g. of red phosphorus, and 20 cc. of bromine (*ca.* 0.36 mole), and two products were obtained. The alkali-insoluble bromination product was recrystallized from ethanol: colorless prisms, m. p., 167–168° (cor.). This was *l*-N-*m*-nitrobenzoyl-γ-methyl-β,β-dibromo-α-piperidone.

Anal. Calcd. for $C_{13}H_{12}Br_2N_2O_4$: C, 37.17; H, 2.88; N, 6.67. Found: C, 37.33; H, 3.05; N, 6.54.

Rotation. 0.1211 g. made up to 5 cc. with pyridine at 30° gave α_D −0.49°; *l*, 1; $[\alpha]^{30}_D$ −20.2° (±0.2°).

The alkali-soluble product of bromination weighed 19 g. but was not obtained crystalline. It was crude optically active α-bromo-β-methyl-δ-*m*-nitrobenzoylaminovaleric acid and was used directly in the next step.

1-*m*-Nitrobenzoyl-3-methylpyrrolidine-2-carboxylic Acid (XII).—A solution of 42 g. of crude α-bromo-β-methyl-δ-*m*-nitrobenzoylaminovaleric acid (IX) in 350 cc. of 1 *N* sodium hydroxide was kept at 37° for forty-eight hours. The red solution was nearly neutralized with 1 *N* sulfuric acid and concentrated *in vacuo* to 100 cc. The solution was cooled, acidified strongly with sulfuric acid and extracted with five 100-cc. portions of ether. The combined ether extracts were washed with a small quantity of water, dried over anhydrous magnesium sulfate, and the ether was removed. The residue amounted to 29 g. of thick yellow oil which could not be induced to crystallize.

The crude 1-*m*-nitrobenzoyl-3-methylpyrrolidine-2-carboxylic acid was esterified directly.

Optically Active 1-*m*-Nitrobenzoyl-3-methylpyrrolidine-2-carboxylic Acid.—This compound was prepared in the same manner as the above acid, starting with a solution of 19 g. of crude optically active α-bromo-β-methyl-δ-*m*-nitrobenzoylaminovaleric acid in 160 cc. of 1 *N* sodium hydroxide. The product was obtained as 14 g. of yellow oil which was used directly in the next step in the synthesis.

Ethyl 3-Methylpyrrolidine-2-carboxylate (XIV).—A solution of 27.5 g. of crude 1-*m*-nitrobenzoyl-3-methylpyrrolidine-2-carboxylic acid in 1 l. of 3 *N* hydrochloric acid was refluxed for four hours. The solution was cooled, and the *m*-nitrobenzoic acid was removed by filtration. The filtrate was concentrated to small volume *in vacuo*, cooled and filtered free of additional precipitated *m*-nitrobenzoic acid. This filtrate was extracted with three portions of ether and evaporated to dryness *in vacuo* to yield 9 g. of crude 3-methylpyrrolidine-2-carboxylic acid hydrochloride (XIII) as a viscous oil. This amino acid hydrochloride was esterified by a method analogous to that used for preparing the ethyl ester of *l*-proline.[16] The crude material was suspended in 150 cc. of freshly distilled absolute ethanol. The suspension was saturated with dry hydrogen chloride which brought about complete solution. The solution was refluxed gently for ten minutes, allowed to stand for several hours protected from moisture, and then evaporated *in vacuo*. The residue was redissolved in 100 cc. of absolute ethanol and again saturated with dry hydrogen chloride, with natural refluxing. After standing overnight the solution was evaporated to dryness *in vacuo*. The brown viscous residue was dissolved in 25 cc. of warm absolute ethanol and 175 cc. of anhydrous ether was added. The solution was cooled in an ice–salt-bath and dry ammonia was passed through, slowly at first, then in a rapid stream until the solution was saturated. It was allowed to stand overnight and, after filtration and removal of the ether, the residue was distilled under diminished pressure; b. p. 90–91.5° (17.5 mm.), 96–97° (21 mm.); n^{20}_D 1.4470; d^{20}_4 0.993. The yield was 4 g., or an over-all yield of 14% of the theoretical amount, based upon 50 g. (0.18 mole) of *dl*-β-methyl-δ-*m*-nitrobenzoylaminovaleric acid (VIII).

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.13; H, 9.61; N, 8.91; MR_D, 42.36. Found: C, 61.18; H, 9.60; N, 8.92; MR_D, 42.31.

Picrate.—Prepared in and recrystallized from dry benzene, the picrate formed long yellow prisms, m. p. 112.5–114°.

Anal. Calcd. for $C_{14}H_{18}N_4O_9$: C, 43.53; H, 4.69. Found: C, 43.67; H, 4.81.

Optically Active Ethyl 3-Methylpyrrolidine-2-carboxylate.—The same procedure was followed as for the optically inactive compound. The hydrolysis was carried out by refluxing a solution of 14 g. of crude optically active 1-*m*-nitrobenzoyl-3-methylpyrrolidine-2-carboxylic acid in 400 cc. of 3 *N* hydrochloric acid for five hours. The crude optically active 3-methylpyrrolidine-2-carboxylic acid hydrochloride weighed 4.7 g. and was esterified with absolute ethanol saturated with dry hydrogen chloride as described above. The ethyl ester boiled at 97–98° (23 mm.); n^{20}_D 1.4458; yield, 1.2 g.

Anal. Calcd. for $C_8H_{15}NO_2$: N, 8.91. Found: N, 8.76.

Rotation. 0.0686 g. made up to 5 cc. with absolute ethanol at 28° showed no measurable rotation.

Ethyl β-N-(3-Methyl-2-carbethoxypyrrolidyl)-propionate (XV).[17]—A solution of 3.8 g. (24 millimoles) of ethyl 3-methylpyrrolidine-2-carboxylate and 8 cc. (*ca.* 70 millimoles) of ethyl acrylate containing a trace of hydroquinone was heated under reflux for twenty-four hours on the steam-bath, protected from moisture. The clear yellow solution was fractionally distilled *in vacuo*. The boiling point of the colorless product was 163.5–165.5° (18 mm.), 126–127° (4 mm.); n^{20}_D 1.4523; d^{20}_4 1.032; yield, 6.0 g. (97%).

Anal. Calcd. for $C_{13}H_{23}NO_4$: C, 60.69; H, 8.98; N, 5.44; MR_D, 67.46. Found: C, 60.73; H, 8.96; N, 5.36; MR_D, 67.27.

Picrate.—Prepared in anhydrous ether and recrystallized from dry benzene, the picrate formed glistening yellow platelets, m. p., 98–99°.

Anal. Calcd. for $C_{19}H_{26}N_4O_{11}$: C, 46.92; H, 5.39. Found: C, 47.07; H, 5.50.

(16) Kapfhammer and Matthes, *Z. physiol. Chem.*, **222**, 43 (1933).

(17) The procedure used here is similar to that followed by Dr. M. Carmack in the addition of ethyl *l*-pyrrolidine-2-carboxylate to ethyl acrylate.

Optically Active Ethyl β-N-(3-Methyl-2-carbethoxypyrrolidyl)-propionate.—A solution of 1.2 g. of the ethyl 3-methylpyrrolidine-2-carboxylate prepared from optically active starting material and 4 cc. of ethyl acrylate was refluxed on a steam-bath for twenty hours, protected from moisture. The product boiled at 170–171° (25 mm.); $n^{20}D$ 1.4512; yield, 1.5 g.

Anal. Calcd. for $C_{13}H_{23}NO_4$: C, 60.69; H, 8.98; N, 5.44. Found: C, 60.88; H, 9.16; N, 5.69.

Rotation. 0.1038 g. in 2.5 cc. of absolute ethanol at 30° gave αD −1.45°; *l*, 1; $[\alpha]^{30}D$ −34.9° (±0.5°).

1-Methyl-7-ketopyrrolizidine (XVI).—Metallic potassium (2.5 g.) was finely powdered under 20 cc. of dry xylene. The mixture was cooled and 10 cc. of dry benzene was added. With vigorous stirring, a solution of 6 g. (23 millimoles) of optically inactive ethyl β-N-(3-methyl-2-carbethoxypyrrolidyl)-propionate and 10 cc. of dry benzene was added dropwise over a period of thirty-five minutes. The residual diester solution was washed in with an additional 10 cc. of dry benzene and the reaction mixture was heated under reflux on the steam-bath for four and one-half hours, protected from moisture. The mixture was cooled and the excess potassium was decomposed by the addition of 8 cc. of ethanol, followed by 20 cc. of distilled water. The mixture was separated and the benzene–xylene solution was extracted with four 5-cc. portions of water. To the combined aqueous extracts was added 30 cc. of concentrated hydrochloric acid, and the solution was heated under reflux for two and one-half hours on the steam-bath. After the hydrochloric acid had been removed by distillation *in vacuo*, the dark reddish residue was taken up in 20 cc. of water, basified with saturated sodium hydroxide solution, and extracted five times with ether. The ethereal solution was dried, the ether removed, and the residue distilled under reduced pressure. The optically inactive 1-methyl-7-ketopyrrolizidine was obtained as a colorless mobile liquid which rapidly darkened; b. p. 96.5–98° (18 mm.), 79–80° (8 mm.); $n^{20}D$ 1.4770; yield, 1.9 g. (59%).

Anal. Calcd. for $C_8H_{13}NO$: C, 69.03; H, 9.41. Found: C, 68.91; H, 9.33.

Picrate.—Prepared in anhydrous ether and recrystallized from absolute ethanol, the picrate formed yellow, feathery elongated prisms which melted, with decomposition, at 189–190° (cor.).

Anal. Calcd. for $C_{14}H_{16}N_4O_8$: C, 45.65; H, 4.37. Found: C, 45.73; H, 4.49.

Methiodide.—Prepared in and recrystallized from dry benzene the methiodide formed colorless prisms, m. p. 149.5–150.5° (cor.).

Anal. Calcd. for $C_9H_{16}INO$: C, 38.46; H, 5.73. Found: C, 38.33; H, 5.94.

***l*-Menthydrazone.**—A solution of 1.9 g. of optically inactive 1-methyl-7-ketopyrrolizidine and 2.25 g. of *l*-menthydrazide[18] in the minimum amount of absolute ethanol (containing 2 g. of fused sodium acetate and 1 g. of glacial acetic acid per 100 cc. of absolute ethanol) was heated under reflux on the steam-bath for twenty-five hours, protected from moisture. After standing at room temperature, crystals separated. These were collected on a filter, washed with a little absolute ethanol, and recrystallized from ligroin (b. p. 90–110°). After the first recrystallization, 160 mg. of colorless elongated prisms was obtained; these melted at 169.5–171° (cor.) and the melting point was unchanged after three more recrystallizations from ligroin.

Anal. Calcd. for $C_{19}H_{33}N_3O_2$: C, 68.02; H, 9.92; N, 12.53. Found: C, 68.09; H, 9.79; N, 12.64.

Rotation. 0.0658 g. made up to 5 cc. with absolute ethanol at 27° gave αD −0.52°; *l*, 1; $[\alpha]^{27}D$ −39.5° (±0.5°).

After the above crystals had been removed by filtration, the ethanolic filtrate was heated and diluted with water. When the solution was allowed to cool slowly, 2.7 g. of crystals was obtained and submitted to a systematic six-stage fractionation from ligroin. The melting points of all of the fractions remained nearly identical and the specific rotations of widely separated fractions also were identical within the precision of measurement. Chromatographic adsorption of a dilute ligroin solution of the *l*-menthydrazone on activated alumina brought about no recognizable separation of the diastereoisomers. In order to check the assumption that no resolution was being accomplished through this derivative, the most insoluble fraction of *l*-menthydrazone obtained at the sixth fractional recrystallization stage was converted to the oxime.

Oxime.—Approximately 0.6 g. of the most insoluble portion of *l*-menthydrazone was refluxed for one hour in 20 cc. of 2 *N* sulfuric acid. The solution was cooled, extracted with ether and the ether extract discarded. The aqueous solution was made strongly basic with sodium hydroxide and extracted again with ether. The combined ether extracts of the alkaline solution were dried over anhydrous magnesium sulfate and evaporated to small volume. Addition of excess picric acid in dry ether resulted in the precipitation of yellow crystals. This picrate, after one recrystallization from absolute ethanol, melted at 189–190° (cor.) and gave no depression of melting point when mixed with the picrate of optically inactive 1-methyl-7-ketopyrrolizidine. The picrate was decomposed in hydrochloric acid solution, and the picric acid was removed by extraction with ether. The aqueous solution was evaporated to dryness *in vacuo*. The residue was redissolved in 3 cc. of water and treated with 3 cc. of 5 *N* sodium hydroxide and 0.25 g. of hydroxylamine hydrochloride. The oxime was formed and isolated in the same manner as described for the oxime of retronecanone.[3] Recrystallization from chloroform–petroleum ether (b. p. 40–60°) gave colorless prisms, m. p. 128–130° (cor.). The compound showed no optical activity.

Anal. Calcd. for $C_8H_{14}N_2O$: C, 62.31; H, 9.15; N, 18.17. Found: C, 62.54; H, 9.16; N, 18.26.

Optically Active 1-Methyl-7-ketopyrrolizidine.—Cyclization of levorotatory ethyl β-N-(3-methyl-2-carbethoxypyrrolidyl)-propionate was carried out under the same conditions employed in the formation of the optically inactive 1-methyl-7-ketopyrrolizidine (XVI). A suspension of 0.6 g. of finely powdered potassium in 6 cc. of dry xylene and 3 cc. of dry benzene was treated with a solution of 1.3 g. of the levorotatory diester and 6 cc. of benzene added dropwise during one-half hour. The aminoketone was obtained as 0.4 g. of light amber-colored oil which was not distilled but was converted directly to the oxime in the usual manner, by treating with 0.6 g. of hydroxylamine hydrochloride in 6 cc. of 2.5 *N* sodium hydroxide. The oxime was purified by recrystallization from chloroform–petroleum ether (b. p. 40–60°), from which it separated as colorless elongated prisms, m. p. 166–167° (cor.).

Anal. Calcd. for $C_8H_{14}N_2O$: C, 62.31; H, 9.15; N, 18.17. Found: C, 62.44; H, 9.06; N, 18.08.

Rotation. 0.0659 g. made up to 5 cc. with absolute ethanol at 32° gave αD −1.02°; *l*, 1; $[\alpha]^{32}D$ −77.3° (±1.5°).

The melting point was not depressed when the oxime was mixed with varying proportions of authentic retronecanone oxime (reported m. p. 167–168° (cor.)). The crystalline form of the synthetic oxime was identical with that of retronecanone oxime as observed under the microscope. Furthermore, the specific rotation of this synthetic oxime was identical, within the precision of measurement, with that recorded for retronecanone oxime ($[\alpha]^{26}D$ −76.0° ±2.5°).

Picrate of Optically Active 1-Methyl-7-ketopyrolizidine Oxime.—Prepared in anhydrous ether, from the oxime of optically active 1-methyl-7-ketopyrrolizidine and dry picric acid, and recrystallized from absolute ethanol, the picrate formed yellow elongated prisms which melted, with decomposition, at 188–190° (cor.).

Anal. Calcd. for $C_{14}H_{17}N_5O_8$: C, 43.86; H, 4.47; N, 18.27. Found: C, 43.97; H, 4.66; N, 18.23.

(18) Woodward, Kohman and Harris, THIS JOURNAL, 63, 120 (1941).

The melting-decomposition point was not depressed when the synthetic picrate was mixed with the picrate of retronecanone oxime.

Picrolonate of Optically Active 1-Methyl-7-ketopyrrolizidine Oxime.—Prepared in absolute ethanol and recrystallized from ethanol-benzene solution, the picrolonate formed clusters of yellow elongated prisms which melted, with decomposition, at 209–211° (cor.).

Anal. Calcd. for $C_{18}H_{22}N_8O_8$: C, 51.67; H, 5.30; N, 20.09. Found: C, 51.83; H, 5.48; N, 20.02.

The melting-decomposition point was not depressed when the picrolonate was mixed with the picrolonate of retronecanone oxime.

Retronecanone Picrolonate.—Prepared in and recrystallized from absolute ethanol, the picrolonate formed yellow elongated prisms which melted, with decomposition and foaming, at 195–196° (cor.).

Retronecanone Methiodide.—Formed by warming retronecanone with excess methyl iodide in benzene solution and recrystallized from absolute ethanol, the methiodide formed colorless elongated prisms, m. p. 160–161° (cor.).

Retronecanone *l*-Menthydrazone.—An absolute ethanol solution of 0.8 g. of retronecanone and 0.95 g. of *l*-menthydrazide was heated on the steam-bath for twenty-four hours under reflux. When the reaction mixture was cooled and diluted with water, 0.8 g. of fine elongated prisms separated in a closely adhering mass. After seven recrystallizations from ligroin (b. p. 90–110°) the product melted at 175.5–176.5° (cor.).

Anal. Calcd. for $C_{19}H_{33}N_3O_2$: C, 68.02; H, 9.92; N, 12.53. Found: C, 68.20; H, 9.95; N, 12.65.

Rotation. 0.0655 g. made up to 5 cc. with absolute ethanol at 28° gave α_D −1.09°; *l*, 1; $[\alpha]^{28}D$ −83.2° (±0.5°); $[M]^{28}D$ −279°.

Hydrolysis of Retronecanone *l*-Menthydrazone.—A representative sample was boiled with 20 cc. of 1 *N* sulfuric acid for one hour. The solution was cooled and extracted with ether, which removed most of the coloration. After the aqueous solution had been made strongly basic, it was thoroughly extracted with ether, the combined ether extracts dried, and the ether solution concentrated to 10 cc. Picric acid in anhydrous ether was added until there was no further yellow precipitation. The solid picrate was collected on a filter and recrystallized from ethanol, from which it separated as fine elongated prisms, m. p. 195° (cor.), with decomposition. There was no depression of melting point when the sample was mixed with retronecanone picrate.

Picrate of Retronecanone Oxime.—Formed in anhydrous ether from picric acid and retronecanone oxime[3] and recrystallized from absolute ethanol, the picrate formed yellow elongated prisms which melted, with decomposition, at 188–190° (cor.).

Picrolonate of Retronecanone Oxime.—Prepared in absolute ethanol and recrystallized from ethanol-benzene, the picrolonate formed clusters of yellow elongated prisms which melted, with decomposition, at 209–211° (cor.).

Acetylretronecanol Methiodide.—This derivative of retronecanol was prepared according to the method of Barger, Seshadri, Watt and Yabuta,[12] but the stout colorless prisms from acetone were found to melt at 215–216° (cor.) instead of 207–208° as reported.

Rotation. 0.0709 g. made up to 5 cc. with absolute methanol at 28° gave α_D −1.24°; *l*, 1; $[\alpha]^{28}D$ −87.4° (±1.0°).

Reduction of Retronecanone

(a) **Neutral Solution.**—A solution of 366 mg. of retronecanone in 20 cc. of absolute ethanol was hydrogenated at normal pressure over 50 mg. of platinum oxide catalyst. The theoretical volume of hydrogen was absorbed in one hour. The reduction product was not obtained crystalline but the impure oil obtained exhibited a specific rotation in absolute ethanol of $[\alpha]^{33}D$ −9.5° (c = 1.266). This differs widely from that reported for retronecanol (−91.1°).[13]

The **methiodide,** obtained crystalline at first from acetone solution, was extremely hygroscopic (unlike retronecanol methiodide) and could not be recrystallized.

The **picrate,** formed in ether solution and recrystallized from absolute ethanol, separated as yellow elongated prisms which melted, with decomposition, at 218–219° (cor.). Retronecanol picrate melts, with decomposition, at 210° (cor.).[13]

Anal. Calcd. for $C_{14}H_{18}N_4O_8$: C, 45.41; H, 4.89. Found: C, 45.51; H, 4.96.

The reduction product of retronecanone was acetylated by heating under reflux on the steam-bath for four hours with excess acetyl chloride. The acetyl chloride was removed *in vacuo*, leaving a brown semicrystalline residue which was dissolved in 5 cc. of water. The aqueous solution was made alkaline with potassium carbonate and the acetylated base was extracted with ether. The ethereal solution was dried, decolorized and the ether removed. The residue did not crystallize, but the **methiodide** was obtained crystalline from benzene. After repeated fractional crystallization from acetone, the least-soluble fraction, obtained as colorless elongated prisms, possessed a maximum constant melting point of 210–212° (cor.). No other methiodide was obtained pure in the fractional crystallization process.

Anal. Calcd. for $C_{11}H_{20}INO_2$: C, 40.62; H, 6.20. Found: C, 40.79; H, 6.37.

Rotation. 0.0234 g. made up to 2.5 cc. with absolute methanol at 28° gave α_D +0.07°; *l*, 1; $[\alpha]^{28}D$ +7.5° (±1.5°).

The rotation differs widely from that of acetylretronecanol methiodide (−87.4°), and a melting point of a mixture of the two methiodides is depressed to 135–190°.

(b) **Acid Solution.**—Reduction of retronecanone over platinum oxide catalyst was carried out in 20 cc. of absolute ethanol containing 1 cc. of concentrated hydrochloric acid. The reduction was complete after nine hours. The reduced free base was liberated but was not obtained crystalline.

The **methiodide,** obtained crystalline at first from acetone solution, was hygroscopic and could not be recrystallized.

The **picrate,** formed in and recrystallized from absolute ethanol, separated as yellow platelets which melted, with decomposition, at 230–232° (cor.). The picrate differed from the picrate of the reduction product of retronecanone in neutral solution, and also from retronecanol picrate and oxyheliotridane picrate.[11]

Anal. Calcd. for $C_{14}H_{18}N_4O_8$: N, 15.13. Found: N, 15.23. Carbon and hydrogen values are not reported since the analytical sample exploded.

Acetylation of the reduced product was carried out as before and the **picrate** of the acetylated reduction product was formed in anhydrous ether and recrystallized from absolute ethanol: yellow elongated prisms, m. p. 178.5–179.5° (cor.).

Anal. Calcd. for $C_{16}H_{20}N_4O_9$: C, 46.60; H, 4.89. Found: C, 46.64; H, 4.91.

The **methiodide** of the acetylated reduction product was formed in benzene and subjected to repeated fractional crystallization from acetone. The least-soluble methiodide fraction was finally obtained as colorless elongated prisms, m. p. 210.5–211.5° (cor.). This was identical with the methiodide of the acetylated reduction product of retronecanone in neutral solution and gave no melting point depression when mixed with it. Mixing with acetylretronecanol methiodide again produced a sharp depression of melting point. No other methiodide could be obtained pure in the fractional crystallization process.

Reduction of 1-Methyl-7-ketopyrrolizidine: 1-Methyl-7-hydroxypyrrolizidine.—Hydrogenation of 520 mg. of optically inactive 1-methyl-7-ketopyrrolizidine in 20 cc. of absolute ethanol was carried out at atmospheric pressure in the presence of 50 mg. of platinum oxide catalyst. The theoretical volume of hydrogen was taken up in one-half hour, after which the ethanol solution was filtered free of catalyst and used directly for the formation of derivatives. Neither the hydrochloride nor the methiodide was ob-

tained pure because both were very hygroscopic. The picrate and picrolonate were obtained as well-characterized crystalline salts.

Picrate.—Prepared in and recrystallized from absolute ethanol, the picrate formed yellow elongated prisms which softened at 210° and melted, with decomposition, at 218.5–219.5° (cor.).

Anal. Calcd. for $C_{14}H_{18}N_4O_8$: C, 45.41; H, 4.89. Found: C, 45.57; H, 5.06.

Picrolonate.—Prepared in and recrystallized from absolute ethanol, the picrolonate formed yellow elongated prisms, m. p. 182.5–183.5° (cor.). It is interesting that the melting point of the racemic 1-methyl-7-hydroxypyrrolizidine picrolonate is almost the same as that of retronecanol picrolonate, m. p. 184–185°.[19] These picrolonates, of course, are not identical.

Anal. Calcd. for $C_{18}H_{23}N_5O_6$: C, 53.33; H, 5.72; N, 17.28. Found: C, 53.26; H, 5.71; N, 17.32.

Summary

1. 1-Methyl-7-ketopyrrolizidine has been synthesized through ethyl 3-methylpyrrolidine-2-carboxylate (obtained from γ-picoline) by addition to ethyl acrylate followed by a Dieckmann cyclization and hydrolysis. The final product probably was a mixture of two racemates. By condensation with *l*-menthydrazide a single pure 1 - methyl - 7 - ketopyrrolizidine - *l* - menthydrazone was isolated. This was different from the *l*-menthydrazone of retronecanone in melting point and rotation.

2. Optically active ethyl 3-methylpyrrolidine-2-carboxylate was converted to the corresponding optically active 1-methyl-7-ketopyrrolizidine by a similar series of reactions. By treatment of the reaction mixture with hydroxylamine, a pure optically-active 1 - methyl - 7 - ketopyrrolizidine oxime resulted, which was identical with retronecanone oxime in melting point and rotation. The identity was verified further by the preparation of identical picrates and picrolonates.

3. It has been proved that the keto group in retronecanone is in the 7-position. From this it may be deduced that the secondary hydroxyl group in retronecanol, retronecine, platynecine, desoxyretronecine, heliotridine, and oxyheliotridane is in the 7-position.

4. It has been shown that in the reduction of desoxyretronecine, retronecine, and esters of retronecine to give retronecanol, asymmetric reduction has taken plaec with the exclusive formation of one stereochemical configuration of the C_1-CH_3.

5. Reduction of retronecanone in neutral and acid solutions gave a mixture of corresponding hydroxy compounds, from which retronecanol could not be isolated.

(19) Konovalova and Orekhov, *Bull. soc. chim.*, [5] **4**, 1285 (1937).

URBANA, ILLINOIS RECEIVED NOVEMBER 8, 1943

[CONTRIBUTION FROM THE BURROUGHS WELLCOME & CO. U. S. A. EXPERIMENTAL RESEARCH LABORATORIES]

The Preparation of N-Mono-substituted and Unsymmetrically Disubstituted Piperazines

BY RICHARD BALTZLY, JOHANNES S. BUCK, EMIL LORZ AND WILLIAM SCHÖN

The direct alkylation of piperazine produces a mixture of substitution products from which the isolation of mono-substituted compounds is difficult or impossible when the substituting group is relatively small. Because of this the belief has arisen that mono-substitution products are not formed, although examination of reported experiments shows only that they were not isolated. A similar situation has prevailed in regard to acylation, although even mono-acetylpiperazine can be obtained easily by logical manipulation.

In Table I are shown the yields of mono- and di-substituted piperazines from a number of reactions, together with the reaction conditions. It seems indicated that in the ideal case where the entire reaction takes place in one homogeneous phase, equimolecular proportions of reactants result in the 1:2:1 proportions of piperazine, mono-substituted piperazine and di-substitution product predicted on general considerations.

Major deviations from these proportions would be expected if a salt of piperazine itself (such as the dihydrochloride which is sparingly soluble in absolute ethanol) were to precipitate during the reaction, or if the acylating or alkylating agent were to form a second liquid phase, thus tending to extract preferentially mono-substituted piperazine already present.

The yields here recorded compare favorably with those claimed for more involved procedures.[1] The argument by which Moore[1a] was led to operate at low *p*H is probably valid. The second benzylation recorded in Table I, run at *p*H about 3.5 gave a proportion of mono-benzyl to dibenzyl piperazine of about 5–1. Similarly a proportion of 2.7–1 was observed in the carbethoxylation, where a low *p*H must have existed toward the end of the reaction. As a preparative method with moderately priced chemicals, however, the buffering procedures seem unprofitable.

From the mono-substituted piperazines that were thus rendered available a number of unsymmetrically disubstituted derivatives have been prepared. These are characterized in Table II.

(1) (a) Moore, Boyle and Thorn, *J. Chem. Soc.*, 39 (1929); (b) Jacobi, *Ber.*, **66**, 113 (1933). The methods described in these papers are two-phase acylations at low *p*H. The conditions are difficult to reproduce exactly and it is doubtful if yields significantly above 50% should be expected from them.