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Antispasmodics. I. Bicyclic Basic Alcohols*

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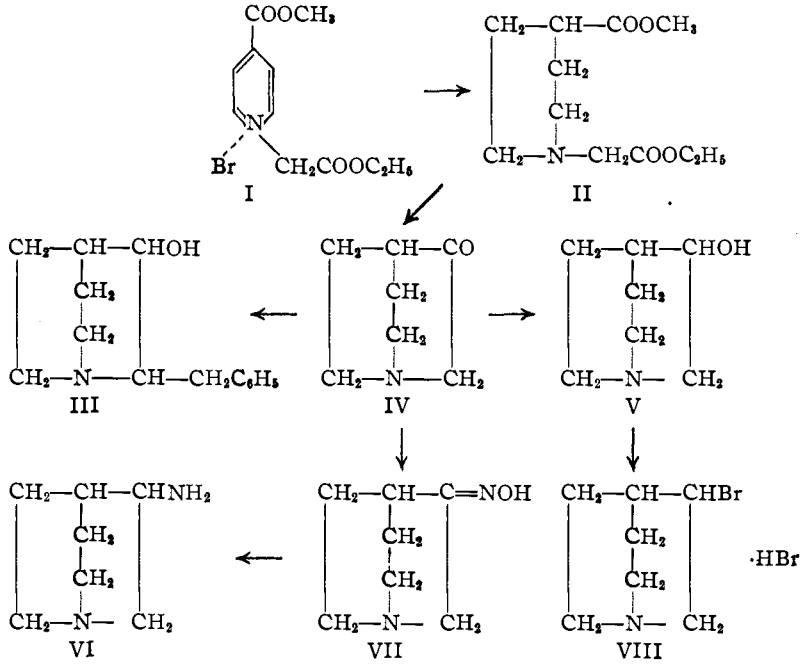
Several bicyclic ketones were prepared by Dieckmann condensations from dicarboxylic acid esters of the piperidine series, and were reduced to the corresponding alcohols. These alcohols, 3-quinuclidinol (V), 1-azabicyclo[3.2.1]6-octanol (XII), 1-azabicyclo[3.3.1]-4-nonanol (XVIa), octahydro-1-pyrrocolinol (XVII) and two alcohols derived from V and XVIa, were required as intermediates for the synthesis of antispasmodics. Levorotatory 3-quinuclidinol was obtained by resolution of the racemate and 3-aminoquinuclidine was made by the reduction of the oxime of 3-quinuclidone.

The present paper describes the synthesis of several basic bicyclic alcohols. These alcohols were used for the preparation of spasmolytically active esters, as shown in Paper II.[1]

The first alcohol to be prepared in this series was 3-quinuclidinol, which was obtained by reduction of the known 3-quinuclidone.[2] The procedures used in its preparation and the method of isolation of the ketone differ somewhat from the published ones[2] and are, therefore, briefly discussed.



Methyl isonicotinate was treated with ethyl bromoacetate to yield the crystalline quaternary salt (I) which, without further purification, was hydrogenated to the diester (II). This diester was then cyclized with potassium metal[3] as described by Clemo and Metcalfe[2] for the diethyl ester.[4] The keto-ester was saponified and decarboxylated in the usual way and 3-quinuclidone (IV) was isolated in about 40% yield in form of its readily crystallizing hydrochloride.

3-Quinuclidinol (V) was prepared from the ketone by catalytic hydrogenation of its hydrochloride or acetate, in the presence of platinum oxide, or by hydrogenation of the free base with Raney nickel as catalyst. Chemical methods were also used, such as the Bouveault–Blanc reduction with sodium in alcohol, and the reduction with lithium aluminum hydride in ether. The basic alcohol forms white prisms or needles with the remarkably high melting point of 221–223°. It is very soluble in water, sublimes readily and forms a crystalline hydrochloride and picrate.

In order to study the influence of the configuration of 3-quinuclidinol on the pharmacological activity of its esters, it was resolved into the optical antipodes by fractional crystallization of its *d*-camphor sulfonates. This resulted in the isolation of pure *l*-3-quinuclidinol *d*-camphor sulfonate, which gave *l*-quinuclidinol melting at 220–222°; it has a specific rotation of −43.8° in 1 *N* hydrochloric acid and of only −2° in water. The dextrorotatory 3-quinuclidinol was not isolated, but its diphenylacetic acid ester has been prepared in pure form[1] and proved to have an equal and opposite rotation to that of the corresponding ester prepared from *l*-3-quinuclidinol.

As possible intermediates for further syntheses, 3-bromoquinuclidine (VIII) hydrobromide was prepared from 3-quinuclidinol with hydrobromic acid at 180°, and 3-aminoquinuclidine by catalytic hydrogenation of 3-quinuclidone oxime (VII).

A substituted 3-quinuclidinol was obtained by hydrogenation of the known 2-benzal-3-quinuclidone[5] with Raney nickel as catalyst. Only one of two possible isomeric 2-benzyl-3-quinuclidinols (III) was isolated from the hydrogenation mixture.

The second bicyclic basic alcohol studied in this series was 1-azabicyclo[3.2.1]-6-octanol (XII). It was prepared from ethyl nicotinate in essentially the same way as 3-quinuclidinol from methyl isonicotinate. The quaternary compound IX was catalytically hydrogenated to the known diester (X)[6] in 60–75% yield (calculated on ethyl nicotinate). Cyclization with potassium metal in

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(1) L. H. Sternbach and S. Kaiser, THIS JOURNAL, 74, 2219 (1952).

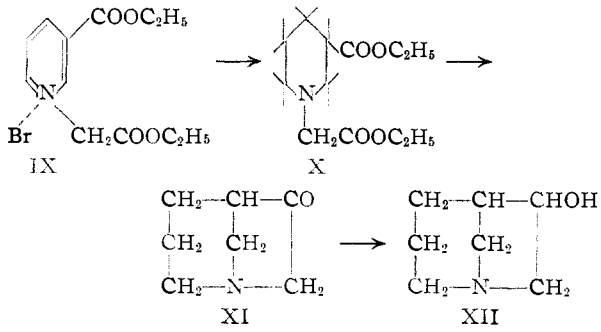
(2) G. R. Clemo and T. D. Metcalfe, *J. Chem. Soc.*, 1989 (1937).

(3) Sodium metal or sodium methylate gave inferior yields.

(4) Clemo and Metcalfe[2] prepared the diester from ethyl 4-piperidinecarboxylate and ethyl chloroacetate.

(5) G. R. Clemo and E. Hoggarth, *J. Chem. Soc.*, 1241 (1939).

(6) S. M. McElvain and Roger Adams, THIS JOURNAL, 45, 2783 (1923); G. R. Clemo, J. Ormston and G. R. Ramage, *J. Chem. Soc.*, 3185 (1931). Both groups made the diethyl ester of 3-carboxypiperidine-1-acetic acid by treating ethyl nipecotate with ethyl chloroacetate. They attempted without success its cyclization with sodium or sodium amide. We also obtained a considerably lower yield (7.5%) when sodium, instead of potassium, was used for the condensation.



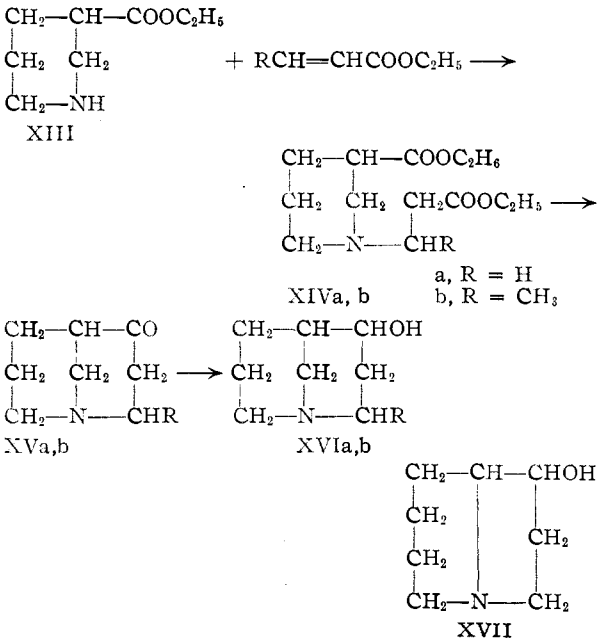
IX X

XI XII

boiling toluene yielded the corresponding keto ester, which was directly saponified and decarboxylated to 1-azabicyclo[3.2.1]-6-octanone (XI). The latter was isolated as the hydrochloride in a yield of 31–36%.

The free ketone obtained from the hydrochloride forms wax-like crystals, which sublime readily and turn yellow after prolonged exposure to air. The hydrochloride was hydrogenated to 1-azabicyclo-[3.2.1]-6-octanol (XII), using platinum oxide as catalyst. Only one of the two possible isomeric alcohols was formed and was isolated as the picrate or as free base (m.p. 177–179°).

Two bicyclic azanonanols (XVIa, b) were synthesized as



XIII XIVa, b (a, R = H; b, R = CH_3) XVa,b XVIa,b XVII

The diesters (XIVa,b)[7] were prepared in good yield by treating ethyl nipecotate with ethyl acrylate and ethyl crotonate, respectively. The Dieckmann condensation and saponification were carried out in the standard way and the new basic ketones (XVa,b) were again isolated as the hydrochlorides. These hydrochlorides were hydrogenated in aqueous solution using platinum oxide as catalyst. Like their analogs, the two free basic alcohols, which were liberated from their salts with alkali, are high melting wax-like, readily subliming, crystalline substances. In both cases, only one of the possible isomers was obtained. Very small amounts, if any, of the other isomers were formed, despite the presence of two asymmetric carbons in XVIa and of three in the methyl homolog XVIb.

1-Octahydropyrrocolinol (XVII) was prepared as an example of an alcohol derived from a bicyclic ring system without endocyclic carbon atom. It was obtained by hydrogenation of the corresponding crude ketone made by a Dieckmann condensation, as reported by Clemo and Ramage.[8] The new alcohol was isolated and characterized as the picrate.

Experimental[9]

Derivatives of Quinuclidine. 1-Carbethoxymethyl-4-carbomethoxypyridinium Bromide (I).—A mixture of 274 g. (2 moles) of methyl isonicotinate and 367 g. (2.2 moles) of ethyl bromoacetate in 125 cc. of dry ethanol was stirred until it became a solid crystalline mass. The reaction was exothermic and the mixture was cooled to 70°. It was then kept at room temperature for 16 hours, and used as such for the following reaction. A part of the crystalline quaternary product was filtered off and was recrystallized from a mixture of isopropyl alcohol and acetone. It forms prisms melting at 154–155° with decomposition.

Anal. Calcd. for $C_{11}H_{14}O_4NBr$: C, 43.44; H, 4.64. Found: C, 43.27; H, 4.52.

Mixture of Methyl and Ethyl Ester (II) of 1-Carbethoxymethylpiperidine-4-carboxylic Acid.—The crude reaction mixture containing 1-carbethoxymethyl-4-carbomethoxypyridinium bromide, obtained in the preceding experiment, was diluted with 1 liter of warm ethanol. This solution was hydrogenated at 70 atm. pressure and room temperature in the presence of 1 g. of platinum oxide. After the calculated amount of hydrogen had been absorbed (6 hours), the mixture was filtered and the solution concentrated *in vacuo*. The residue was dissolved in ice-water and made alkaline with ice-cold potassium carbonate solution. The diester was extracted with benzene, dried with sodium sulfate and distilled *in vacuo;* b.p. 110° (0.6 mm.), 30 mm. 175–182°; $[n]^{25}D$ 1.4613–1.4628. The yield was 338 g. (75%). The product was most probably a mixture of the methyl–ethyl and the diethyl esters, transesterification having taken place in the presence of ethyl alcohol.

Anal. Calcd. for $C_{11}H_{19}O_4N$ (methyl, ethyl): C, 57.62; H, 8.35. Calcd. for $C_{12}H_{21}O_4N$ (diethyl): C, 59.23; H, 8.70. Found: C, 58.45; H, 8.34.

3-Quinuclidone (IV) Hydrochloride[10] (Procedure A).—To a well-stirred suspension of 100 g. (2.5 atoms) of pulverized potassium in 200 cc. of boiling toluene were added in small portions within 1 hour 243 g. (1 mole) of 1-carbethoxymethylpiperidine-4-carboxylic acid methyl (or ethyl) ester and 500–700 cc. of toluene. Care was exercised during the addition, because the onset of the exothermic reaction was sometimes delayed. The refluxing and stirring were continued for 4 or 5 hours. The reaction mixture was then cooled and unreacted potassium decomposed with isopropyl alcohol. Two and one-half liters of concentrated hydrochloric acid was added, the mixture refluxed for 15 hours and then concentrated *in vacuo* to dryness. An excess of 50% potassium hydroxide was added with cooling to the residue and the precipitated potassium chloride was filtered off. The precipitate was washed with some ice-water and benzene, and the combined filtrates were extracted 5 times with 400-cc. portions of benzene. The combined extracts were dried with sodium sulfate and concentrated *in vacuo*. The residue, containing the crude ketone (75–90 g.), was acidified with 150–250 cc. of 3 *N* hydrochloric acid. The solution was decolorized with activated carbon, filtered and concentrated *in vacuo* to dryness. The residue was treated with

(7) Compound XIVa has been previously prepared by S. M. McElvain and Roger Adams[6] by treating ethyl β-chloropropionate with ethyl nipecotate in the presence of silver oxide. The same authors cyclized the diester to 1-azabicyclo[3.3.1]-3-carbethoxy-4-nonanone but did not prepare the decarboxylated ketone.

(8) G. R. Clemo and G. R. Ramage, *J. Chem. Soc.*, 2969 (1932).

(9) All melting points are corrected.

(10) The method of Clemo and Metcalfe[4] was adapted to the preparation of large batches. The isolation of the reaction product was carried out *via* the hydrochloride.

isopropyl alcohol, and the crystalline reaction product was filtered off.

The mother liquor, after concentration and treatment with isopropyl alcohol yielded an additional amount of the hydrochloride. The yields obtained in different batches varied between 60 and 72 g. (37–44%). The product was recrystallized from dilute isopropyl alcohol. It formed prisms melting at 311–313° (dec.).

Anal. Calcd. for $C_7H_{12}ONCl$: C, 52.01; H, 7.48. Found: C, 51.83; H, 7.59.

3-Quinuclidinol Hydrochloride (Procedure B).—A solution of 50 g. 3-quinuclidone hydrochloride in 200 cc. of water was hydrogenated at room temperature and 50–100 atm. pressure with 1 g. of platinum oxide as catalyst. After the calculated amount of hydrogen was absorbed (5 hours), the mixture was filtered and concentrated *in vacuo* to dryness. The yield was practically quantitative. The hydrochloride was recrystallized for analysis from a mixture of methanol and acetone. It formed prisms melting above 300°.

Anal. Calcd. for $C_7H_{14}ONCl$: C, 51.37; H, 8.62. Found: C, 51.53; H, 8.62.

Crude or pure 3-quinuclidone could also be hydrogenated in aqueous solution with Raney nickel as catalyst, or in acetic acid in the presence of platinum oxide (20°, 50–100 atm. pressure). The 3-quinuclidinol was isolated as the hydrochloride.

3-Quinuclidinol Base (V) (Procedure C).—A solution of 50 g. of 3-quinuclidinol hydrochloride in 30 cc. of water was made alkaline by the addition of 30 g. of potassium hydroxide. After the alkali was dissolved, 35 g. of granular potassium carbonate was added. The free basic alcohol was then extracted from the viscous mixture by shaking with several portions of 300 cc. of hot benzene each. The benzene extracts were decanted, filtered and concentrated *in vacuo* to a small volume.

The product obtained was filtered off and recrystallized from benzene or acetone. It formed needles or prisms melting at 221–223°. It sublimed readily at 120° and 20 mm.

Anal. Calcd. for $C_7H_{13}ON$: C, 66.10; H, 10.30. Found: C, 66.25; H, 10.41.

3-Quinuclidinol was also obtained from 3-quinuclidone by the following chemical reduction methods.

(1) To a refluxing solution of 3.32 g. (20 millimoles) of 3-quinuclidone hydrochloride in 100 cc. of absolute alcohol was rapidly added 4.6 g. (200 millimoles) of sodium. When all the sodium had dissolved, the mixture was diluted with water and concentrated *in vacuo*. The viscous residue was extracted with boiling benzene. The benzene solution was concentrated *in vacuo* and the residue recrystallized from benzene or acetone.

(2) A solution of 5 g. of 3-quinuclidone in 25 cc. of dry ether was added dropwise to a stirred solution of 1 g. lithium aluminum hydride in 100 cc. of dry ether. The mixture was refluxed for an additional hour, decomposed with water and concentrated *in vacuo* to a small volume. Potassium hydroxide was added and the basic alcohol extracted with hot benzene. The yield was almost quantitative.

The picrate was prepared by combining alcoholic solutions of 0.5 g. of 3-quinuclidinol and 1.4 g. of picric acid (containing 10% water). The precipitated picrate was recrystallized from alcohol. Yellow prisms formed melting at 212–214°.

Anal. Calcd. for $C_{13}H_{16}N_4O_8$: C, 43.82; H, 4.53. Found: C, 43.97; H, 4.85.

***l*-3-Quinuclidinol *d*-Camphor Sulfonate.**—10.2 g. (0.08 mole) of *d,l*-3-quinuclidinol and 19 g. (0.082 mole) of *d*-camphorsulfonic acid were dissolved in a hot mixture of 40 cc. of isopropyl alcohol and 150 cc. of acetone. The solution was left at room temperature for 60 hours; the crystals (8.5 g.) which had formed were filtered off and recrystallized from a hot mixture of 40 cc. of isopropyl alcohol and 50 cc. of acetone. The precipitate, weighing 4.4 g., $[\alpha]^{25}D$ +0.65° (water, *c* 7), was again recrystallized from 35 cc. of isopropyl alcohol and 70 cc. of acetone, yielding 1.6 g. of rhombic plates, $[\alpha]^{25}D$ −0.3° (water, *c* 7), melting with decomposition around 260°. The specific rotation and the melting point did not change upon further recrystallizations.

Anal. Calcd. for $C_{17}H_{29}O_5NS$: C, 56.80; H, 8.13. Found: C, 57.01; H, 8.11.

The mother liquor, obtained after the separation of the 8.5 g. of crystals, gave upon concentration large irregular thin plates decomposing around 260°, $[\alpha]^{25}D$ +20.0° (water *c* 7). These crystals consisted of a mixture of the two isomeric *d*-camphor sulfonates, which could not be separated by crystallization from a mixture of isopropyl alcohol and acetone or from ethanol and ethyl acetate. Fractional crystallization from these solvent mixtures consistently gave large irregular plates, each fraction showing the same rotation of +20.0° which corresponds to a content of 72% *d*-3-quinuclidinol *d*-camphor sulfonate.

Anal. Calcd. for $C_{17}H_{29}O_5NS$: H, 8.13. Found: C, 57.03; H, 8.33.

***l*-3-Quinuclidinol.**—The basic alcohol was obtained from its *d*-camphor sulfonate, $[\alpha]^{25}D$ −0.3°, by using procedure C. It was recrystallized from acetone, forming prisms melting at 220–222°. The compound showed no melting point depression when mixed with *d,l*-3-quinuclidinol; $[\alpha]^{25}D$ −2.0° (water, *c* 6.5); $[\alpha]^{25}D$ −43.8° (1 *N* hydrochloric acid, *c* 3).

Anal. Calcd. for $C_7H_{13}ON$: C, 66.10; H, 10.30. Found: C, 66.27; H, 10.32.

3-Bromoquinuclidine Hydrobromide (VIII).—A solution of 6 g. of quinuclidinol in 50 cc. of concentrated hydrobromic acid (48% hydrobromic acid saturated with hydrogen bromide at 0°) was heated in a closed tube for 18 hours at 180°. The mixture was concentrated *in vacuo*, the residue dissolved in water and purified with activated carbon. The filtered solution was concentrated and the residue crystallized from isopropyl alcohol, or a mixture of isopropyl alcohol and ether. The yield was 89%. The analytical sample was recrystallized from a mixture of methanol and isopropyl alcohol. Prisms melting at 243–245°.

Anal. Calcd. for $C_7H_{13}NBr_2$: C, 31.02; H, 4.84. Found: C, 30.91; H, 4.58.

3-Quinuclidone Oxime (VII) Hydrochloride.—A mixture of 25 g. of 3-quinuclidone hydrochloride, 25 g. of hydroxylamine hydrochloride, 130 cc. of dry pyridine and 500 cc. of dry alcohol was refluxed for 40 hours. It was then concentrated *in vacuo* and the residue heated with a small volume of methanol. The mixture, containing a considerable amount of undissolved material, was cooled and the crude reaction product filtered off. The yield was about 95%. The product was purified by recrystallization from methanol with the addition of isopropyl alcohol; prisms melting at 233–236°.

Anal. Calcd. for $C_7H_{13}ON_2Cl$: C, 47.59; H, 7.42. Found: C, 47.87; H, 7.22.

Free Oxime.—The calculated amount of an aqueous or a methanol solution of barium hydroxide was added to a saturated aqueous solution of the oxime hydrochloride. The mixture was concentrated *in vacuo* to dryness and the free oxime extracted with acetone. It was recrystallized from isopropyl alcohol, forming long prisms melting at 213–217°.

Anal. Calcd. for $C_7H_{12}ON_2$: C, 59.97; H, 8.63. Found: C, 59.97; H, 8.57.

3-Aminoquinuclidine (VI) and Its Dihydrochloride.—Three grams of crude 3-quinuclidone oxime hydrochloride, dissolved in 50 cc. of water, was hydrogenated at room temperature and atmospheric pressure in the presence of 0.5 g. of prehydrogenated platinum oxide and 3 cc. of concentrated hydrochloric acid. After the calculated amount of hydrogen was absorbed, the mixture was filtered and the solution concentrated *in vacuo*. The free diamine was obtained from the hydrochloride as described above for the oxime and was recrystallized from a mixture of methanol and petroleum ether. It could be sublimed at 120° in a vacuum of 14 mm. and formed prisms melting at 218–220°. This diamine was difficult to obtain in analytically pure form and was therefore reconverted to the dihydrochloride, forming prisms, from ethanol, melting above 280°.

Anal. Calcd. for $C_7H_{16}N_2Cl_2$: C, 42.22; H, 8.10. Found: C, 42.32; H, 8.00.

2-Benzyl-3-quinuclidinol (III).—A methanol suspension of 2-benzalquinuclidone[9] was hydrogenated at room temperature and atmospheric pressure in the presence of Raney nickel. After the calculated amount of hydrogen was absorbed, the mixture was filtered and concentrated *in vacuo*. The residue was purified by recrystallization from a mixture of ether and petroleum ether. One of the possible isomers was isolated in 50–60% yield. It formed needles or prisms melting at 154–156°. The hydrochloride formed needles melting at 201–205°. The residual mixture was not further investigated.

Anal. Calcd. for $C_{14}H_{19}ON$: C, 77.38; H, 8.81. Found: C, 77.09; H, 8.70.

Derivatives of 1-Azabicyclo[3.2.1]octane. Diethyl Ester of 3-Carboxypiperidine-1-acetic Acid (IX).[6]—A mixture of 302 g. (2 moles) of ethyl nicotinate, 367 g. (2.2 moles) of ethyl bromoacetate and 125 cc. of alcohol was stirred at room temperature. The initial reaction was exothermic and the mixture was cooled when the temperature rose above 70°. The brown viscous mixture, containing the quaternary compound (IX), was hydrogenated and the product isolated as described for the isomer derived from isonicotinic acid. The boiling point was 147–149° (5 mm.)[6] as reported in the literature; $n^{25}D$ 1.4580, yield 75%.

1-Azabicyclo[3.2.1]-6-octanone (XI) Hydrochloride.—This compound was prepared according to procedure A from the diethyl ester of 3-carboxypiperidine-1-acetic acid. The yield was 30–36%. The product was recrystallized from dilute acetone, forming prisms melting above 270°.

Anal. Calcd. for $C_7H_{12}ONCl$: C, 52.01; H, 7.48. Found: C, 52.32; H, 7.33.

The ketone base was liberated from the hydrochloride according to procedure C. The product could be purified by sublimation (50–70° (0.5 mm.)), or by crystallization from petroleum ether feathery crystals melting at 129–130°. The substance turned yellow after prolonged exposure to air.

Anal. Calcd. for $C_7H_{11}ON$: C, 67.16; H, 8.86. Found: C, 66.60; H, 8.55.

The picrate was prepared in the standard way and recrystallized from acetone or a mixture of acetone and ethanol. It formed yellow prisms melting at 202–204°.

Anal. Calcd. for $C_{13}H_{14}O_8N_4$: C, 44.07; H, 3.98. Found: C, 44.22; H, 3.81.

1-Azabicyclo[3.2.1]-6-octanol (XII) Hydrochloride.—1-Azabicyclo[3.2.1]-6-octanone hydrochloride was hydrogenated catalytically according to procedure B. The product could be recrystallized from a mixture of methanol and acetone, forming prisms melting above 300°.

Anal. Calcd. for $C_7H_{14}ONCl$: C, 51.37; H, 8.62. Found: C, 51.48; H, 8.77.

The free **basic alcohol** was liberated from the hydrochloride according to procedure C. It could be sublimed *in vacuo* (120°, 20 mm.), or recrystallized from petroleum ether. It formed prisms melting at 177–179°.

Anal. Calcd. for $C_7H_{13}ON$: C, 66.10; H, 10.30. Found: C, 65.74; H, 10.33.

The picrate was prepared in the usual way and was recrystallized from a mixture of acetone and alcohol. It formed thin yellow plates melting at 224–226°.

Anal. Calcd. for $C_{13}H_{16}N_4O_8$: C, 43.82; H, 4.53. Found: C, 44.03; H, 4.37.

Derivatives of 1-Azabicyclo[3.3.1]nonane. Diethyl Ester of 3-Carboxypiperidine-1-propionic Acid (XIV).[7]—A mixture of 109 g. (0.7 mole) of ethyl nipecotate and 82 g. (90 cc. = 0.82 mole) of ethyl acrylate was heated on the steam-bath for 3 hours and then distilled *in vacuo* (100–104°, 0.1 mm.), yielding 168.6 g. (94%) of the diester; $n^{25}D$ 1.4583.

1-Azabicyclo[3.3.1]-4-nonanone (XVa) Hydrochloride.—This product was prepared according to procedure A. The yield was about 23%. After crystallization from isopropyl alcohol it formed prisms melting at 248–249°.

Anal. Calcd. for $C_8H_{14}ONCl$: C, 54.70; H, 8.00. Found: C, 54.60; H, 8.16.

The ketone base was prepared according to procedure C. It crystallized from petroleum ether in feathery crystals melting at 95–98°. It was difficult to obtain in analytically pure form.

The picrate prepared in the usual way from the crude ketone was recrystallized from a mixture of acetone, ethanol and ether and formed flat yellow needles melting at 225–226°. The yield was almost quantitative.

Anal. Calcd. for $C_{14}H_{16}O_8N_4$: C, 45.65; H, 4.38. Found: C, 45.67; H, 4.37.

1-Azabicyclo[3.3.1]-4-nonanol (XVIa) Hydrochloride.—This compound was prepared according to procedure B from the ketone hydrochloride. It formed long prisms from methanol melting above 300°.

Anal. Calcd. for $C_8H_{16}ONCl$: C, 54.07; H, 9.08. Found: C, 53.93; H, 8.73.

The free **basic alcohol** was prepared according to procedure C. It crystallized from petroleum ether in wax-like prisms or needles, melting at 169–170°.

Anal. Calcd. for $C_8H_{15}ON$: C, 68.04; H, 10.71. Found: C, 68.36; H, 10.54.

Diethyl Ester of 3-Carboxy-1-piperidine-β-methylpropionic Acid (XIVb).—A mixture of 100 g. (0.64 mole) of ethyl nipecotate and 91.2 g. (0.8 mole) of ethyl crotonate was heated for 48 hours to 90° and then for 3 hours to 160°. The mixture was distilled *in vacuo* (129°, 0.15 mm.), yielding 113 g. (65%) of the diester; $n^{20}D$ 1.4603.

Anal. Calcd. for $C_{14}H_{25}O_4N$: C, 61.82; H, 9.27. Found: C, 62.07; H, 8.85.

1-Azabicyclo[3.3.1]-2-methyl-4-nonanone (XVb) Hydrochloride.—This compound was prepared according to procedure A. The yield was 27.5%. It formed prisms from methanol at 206–207°.

Anal. Calcd. for $C_9H_{16}ONCl$: C, 56.98; H, 8.50. Found: C, 56.77; H, 8.38.

1-Azabicyclo[3.3.1]-2-methyl-4-nonanol (XVIb) Hydrochloride.—This compound was prepared from the ketone hydrochloride according to procedure B. It was recrystallized from methanol with the addition of ether. Prisms melting at 250–254°.

Anal. Calcd. for $C_9H_{18}ONCl$: C, 56.38; H, 9.47. Found: C, 56.07; H, 9.55.

The free basic alcohol was prepared in very good yield from the crude hydrochloride according to procedure C. It was recrystallized from petroleum ether, forming needles or hygroscopic short prisms melting at 70–73°.

The two kinds of crystals gave no mixed melting point depression and were interconvertible by recrystallization from solutions of varying concentrations.

Anal. Calcd. for $C_9H_{17}ON$: H, 11.04. Found: C, 69.59. H, 10.67.

Picrate.—Crude samples and both pure crystalline forms reacted with picric acid in the usual way. They all yielded the same picrate, which crystallized from a mixture of acetone and alcohol as yellow needles melting at 262–263°.

This indicates that the alcohol consists of *one* homogeneous racemate or racemic mixture only, containing at the most, very small quantities of other isomers.

Anal. Calcd. for $C_{15}H_{20}O_8N_4$: C, 46.87; H, 5.24. Found: C, 46.83; H, 5.13.

Picrate of Octahydro-1-pyrrocolinol (XVII).—Fourteen grams of undistilled crude octahydro-1-keto-pyrrocoline prepared as described by G. R. Clemo and G. R. Ramage[11] was hydrogenated in acetic acid solution at room temperature and 50 atm. pressure, in the presence of 1 g. of platinum oxide. After the calculated amount of hydrogen had been taken up, the mixture was filtered, acidified with hydrochloric acid and concentrated *in vacuo*. The residue was dissolved in water and purified with activated carbon. The aqueous solution was again concentrated and the free basic alcohol (9 g.) liberated from the residue according to procedure C. To 6.9 g. of the crude basic alcohol was added a solution of 12.5 g. of picric acid in 300 cc. of alcohol. After 5 hours the solution was decanted from a dark oily precipitate. The solution was partially concentrated and left at room temperature for 24 hours, yielding yellow prisms melting between 160–170°. A further amount was obtained from the mother liquors. The total yield of crystalline picrate was around 7 g. After crystallization from a mixture of acetone and ether, yellow prisms were obtained melting at 176–178°.

Anal. Calcd. for $C_{14}H_{18}O_8N_4$: C, 45.40; H, 4.90. Found: C, 45.67; H, 5.13.

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(11) G. R. Clemo and G. R. Ramage, *J. Chem. Soc.*, 2969 (1932).