315. bicyclo[1 : 2 : 2]*Aza*-1-*heptane.*

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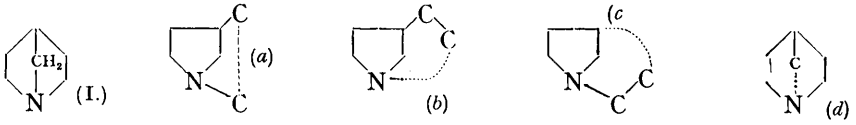
Whereas attempts to prepare derivatives of *bicyclo*[1 : 2 : 2]aza-1-heptane by bridging the 1 : 3-positions of the pyrrolidine ring by each of the three possible routes (see *a*, *b*, *c*, below) have been unsuccessful, we find that the piperidine ring can be easily bridged in the 1 : 4-positions by a single methylene group. An examination of the models, the pyrrolidine ring being assumed to be planar, and the piperidine ring to

react in the " boat " form, shows that ring closure in the first three cases would involve a much greater distortion than in the last case. The synthesis of *bicyclo*[1 : 2 : 2]aza-1-heptane, now described, is simple and gives excellent yields at each stage, and is superior to that recorded by Prelog and Cerkovnikov (*Annalen*, 1936, **525**, 292). Whereas, however, these authors describe the base as a crystalline solid, m. p. 71°, we find it is a colourless, water-like liquid which has not yet shown any sign of crystallising.

FOR a considerable time we have been working on methods for the synthesis of the bicyclic system (I) and of its derivatives. Many attempts have been made to prepare such compounds by bridging the 1 : 3-positions of the pyrrolidine ring by each of the three possible routes (*a*), (*b*), and (*c*), but all have ended in failure (compare J., 1931, 3185 for similar attempts to bridge the piperidine ring in the *m*-position). The preparation of simple



substituted pyrrolidines of the types (*a*), (*b*), and (*c*) is rendered difficult because of the great stability of the pyrrole nucleus to hydrogenation; for instance, we were unable to hydrogenate ethyl 2-methylpyrrole-3-carboxylate (*Ber.*, 1911, **44**, 493) by platinum and hydrogen in acetic acid solution, or by Rupe's nickel catalyst (*Helv. Chim. Acta*, 1918, **1**, 452) at 140° or 180°.

Ethyl 2 : 2 : 5 : 5-*tetramethylpyrrolidine*-3-*carboxylate*-1-*acetate* has been prepared from ethyl 2 : 2 : 5 : 5-tetramethylpyrrolidine-3-carboxylate (Pauly, *Ber.*, 1903, **36**, 3351) by condensation with ethyl chloroacetate, but it could not be ring-closed by the Dieckmann reaction; neither could a ketone be obtained by distillation of the calcium or thorium salt. Ethyl 2-pyrrolidone-3-oxalate has been prepared from 2-pyrrolidone and ethyl oxalate, but the compound could not be ring-closed (route *b*). Further, ethyl 2-pyrrolidone-1-acetate (Tafel and Wassmuth, *Ber.*, 1907, **40**, 2831) could not be cyclised by the Claisen reaction (route *c*).

Prelog and Cerkovnikov (*Annalen*, 1936, **525**, 292), however, have recently described the preparation of *bicyclo*[1 : 2 : 2]aza-1-heptane from ethyl tetrahydropyrone-4-carboxylate, which was subjected to the Bouveault reaction (33% yield), followed by treatment with hydrobromic acid, giving 1 : 5-dibromo-3-bromomethylpentane (84% yield), and finally with methyl-alcoholic ammonia to give the compound (I) (31% yield). The base was found to melt at 71° and boil at 121°, but it is curious that, although these authors prepared the hydrochloride, picrate, picrolonate, methiodide, aurichloride, and the platinichloride, no m. p.'s are recorded for these derivatives.

Although the systems (*a*), (*b*), and (*c*) could not be cyclised, we have found that the piperidine ring can be easily bridged in the 1 : 4-positions to give system (I). An examination of the models, the pyrrolidine ring being assumed planar, the nitrogen valencies tetrahedral, and the piperidine ring to react in the " boat " form, shows that the ring closure in the first three cases would involve a distortion of about 84° 30′, whereas in the last case the value is only 70° 30′.

The following synthesis of (I) is simple and gives consistently good yields at each stage. 2 : 4-Lutidinic acid, obtained from 2 : 4-lutidine by oxidation, on heating gave pyridine-4-carboxylic acid (Ladenburg, *Annalen*, 1888, **247**, 38), which was reduced with sodium and amyl alcohol and esterified, giving the hitherto unrecorded *ethyl piperidine*-4-*carboxylate*. Reduction of this ester by the Bouveault reaction gave 4-*piperidylcarbinol* (in 64% yield), which was treated with phosphorus pentabromide, and the resulting 4-piperidylmethyl bromide, when warmed in dilute alkaline solution, readily gave the bicyclic base (I) (in 60% yield calculated from the carbinol). The base was separated from a small amount of the unchanged carbinol by conversion into the picrate. The recovered base, after distillation over sodium in a vacuum, was, however, a colourless, water-like liquid which has not yet shown any sign of crystallising. The facts that it is unchanged by treatment with

p-toluenesulphonyl chloride in alkaline solution, is stable to cold acidified permanganate solution, is unchanged by treatment with hydrogen and platinum in acetic acid, and readily gives a crystalline methiodide exclude the possibility of its being 4-methylenepiperidine. We have repeated Prelog and Cerkovnikov's synthesis, and the picrate, picrolonate, and methiodide made from the liquid base thus obtained correspond in every way with the same derivatives made from our base. Prelog and Cerkovnikov record their hydrochloride as liquefying on exposure to moist air, but we find it to be stable and non-hygroscopic.

Experimental.

Ethyl 2 : 2 : 5 : 5-*Tetramethylpyrrolidine*-3-*carboxylate*-1-*acetate.*—Ethyl 2 : 2 : 5 : 5-tetramethylpyrrolidine-3-carboxylate (9 g.), ethyl chloroacetate (11 g.), and anhydrous potassium carbonate (15 g.) were well mixed and heated for 18 hours at 115°. Water (20 c.c.) was added, and the oil extracted with ether and fractionated, giving the *ester* as a colourless mobile liquid (7·2 g., b. p. 169°/16 mm.) (Found : C, 63·2; H, 9·5. $C_{15}H_{27}O_4N$ requires C, 63·2; H, 9·5%), together with unchanged mono-ester (3·2 g.).

3-*Carboxy*-2 : 2 : 5 : 5-*tetramethylpyrrolidine*-1-*acetic Acid.*—The above diethyl ester (4·8 g.), water (45 c.c.), and concentrated hydrochloric acid (32 c.c.) were refluxed gently for 12 hours. The solution was evaporated to dryness, the residue taken up in hot water and treated with copper carbonate (12 g.), and the filtrate evaporated to 4 c.c., whereupon the deep blue copper salt crystallised (3·6 g.). It was taken up in a little cold water, filtered from a small residue of cuprous chloride, diluted to 100 c.c., warmed, and decomposed with hydrogen sulphide, and the filtrate from the copper sulphide evaporated to dryness. The above *acid* crystallised from hot water in colourless prisms, m. p. 261° (Found : C, 55·65; H, 8·4. $C_{11}H_{19}O_4N,\frac{1}{2}H_2O$ requires C, 55·5; H, 8·4%).

Ethyl 2-*Pyrrolidone*-3-*oxalate.*—A mixture of ethyl oxalate (2 g.) and alcohol-free sodium ethoxide (from sodium, 0·6 g.) in benzene (10 c.c.) was treated with 2-pyrrolidone (1 g.). The pale yellow solution was heated on the water-bath for 10 hours, acidified with dilute acetic acid, and extracted with ether. The pyrrolidone *ester* separated from the concentrated ethereal extract in colourless needles, m. p. 132° (Found : C, 52·6; H, 6·6. $C_8H_{11}O_4N$ requires C, 52·9; H, 6·9%); it was soluble in hot water, the solution being neutral to litmus, and giving a deep red coloration with ferric chloride solution.

Pyridine-4-*carboxylic Acid.*—2 : 4-Lutidine (10 g.) was heated on the water-bath with a solution of potassium permanganate (30 g.) in water (1 l.) till the colour disappeared (8 hours); a further equal amount of potassium permanganate in water (500 c.c.) was added, and the heating continued till the liquid was again decolorised (16 hours). The filtrate from the manganese dioxide was evaporated to 1 litre, acidified to litmus with dilute sulphuric acid, and evaporated to 50 c.c. An equal volume of alcohol was added, the filtrate from the potassium sulphate diluted with water (500 c.c.) and warmed, and 2 : 4-lutidinic acid precipitated as the silver salt by addition of dilute silver nitrate solution. The precipitate, well washed with warm water, was suspended in hot water (250 c.c.) and decomposed with hydrogen sulphide. The 2 : 4-lutidinic acid separated from the filtrate on cooling, and the anhydrous acid (8·0 g.) was obtained by heating at 100° for 2 hours. When heated above its m. p. under diminished pressure (250 mm.), this acid (8·7 g.) evolved carbon dioxide, and the pyridine-4-carboxylic acid (6·4 g.) readily sublimed.

Ethyl Piperidine-4-*carboxylate.*—The mono-acid (5·0 g.) was dissolved in boiling amyl alcohol (300 c.c.) and treated during one hour with sodium (22 g.). The clear solution was cooled somewhat, poured into water (1 l.), and the amyl alcohol distilled off in steam. The residual solution was acidified with hydrochloric acid and evaporated to dryness, the completely dry residue extracted five times with boiling ethyl alcohol (300 c.c. of 95%), and the extract evaporated to dryness. Alcohol (30 c.c.), saturated at 0° with hydrogen chloride, was added to the residue, and, after standing at room temperature for 12 hours, the solution was refluxed gently for 5 hours and evaporated to dryness; the residue was basified with saturated potassium carbonate solution and extracted with ether. The extract, dried over sodium sulphate, gave on fractionation *ethyl piperidine*-4-*carboxylate* as a colourless mobile liquid (4·4 g., b. p. 74°/1 mm.) (Found : C, 61·1; H, 9·7. $C_8H_{15}O_2N$ requires C, 61·15; H, 9·6%). The *picrate* formed bright yellow needles, m. p. 172°, from alcohol (Found : C, 44·3; H, 4·9. $C_8H_{15}O_2N,C_6H_3O_7N_3$ requires C, 44·5; H, 4·7%). A fraction (b. p. 80°/13 mm.) was also obtained but was not identified. It crystallised from light petroleum (b. p. 40—60°) in rosettes of colourless, deliquescent needles, m. p. 97° (Found : C, 60·7; H, 12·1%).

4-*Piperidylcarbinol.*—A solution of the above ester (3·3 g.) in anhydrous ethyl alcohol (35 c.c.) was boiled vigorously, and sodium (3·4 g.) added in one piece, the heating being continued until all the sodium had dissolved. The solution was cooled, water (15 c.c.) added, and the ethyl alcohol distilled off under diminished pressure (32 c.c. being collected). The residual, strongly alkaline liquid was extracted with ether; the extract, dried over potassium carbonate and distilled, gave the *carbinol* as a colourless viscous liquid (1·55 g., b. p. 122°/12 mm.) (Found : C, 63·0; H, 11·5. $C_6H_{13}ON$ requires C, 62·6; H, 11·3%). It solidified after several days and was hygroscopic. The *picrate* formed bright yellow, rectangular prisms, m. p. 120°, from alcohol (Found : C, 42·2; H, 4·75. $C_6H_{13}ON,C_6H_3O_7N_3$ requires C, 41·9; H, 4·7%).

bicyclo[1 : 2 : 2]*Aza*-1-*heptane.*—A solution of the carbinol (1·55 g.) in benzene (10 c.c.) was treated with phosphorus pentabromide (8·0 g.), and the mixture heated on the water-bath under reflux for 3 hours. The reddish-brown mixture was cooled, and a little crushed ice added, followed by excess of a suspension of sodium bicarbonate. The mixture was diluted with water (90 c.c.) and left at room temperature for several hours; potassium hydroxide solution (10 c.c. of 50%) was then added, and the solution warmed at 40° for 2 hours. It was steam-distilled, the distillate (50 c.c.) acidified with hydrochloric acid and evaporated to dryness, and the residue basified with potassium hydroxide solution (50%) and extracted several times with ether (30 c.c.). The ethereal extract, dried over potassium carbonate, was added to an alcoholic solution of picric acid (3 g.), whereupon the bright yellow, insoluble picrate of the bicyclic base separated, m. p. 271° (2·7 g.). The *picrate* was difficultly soluble in ethyl alcohol, easily soluble in warm acetone, and crystallised from alcohol–acetone in lemon-yellow needles, m. p. 274° (decomp.) (Found : C, 44·5; H, 4·4. $C_6H_{11}N,C_6H_3O_7N_3$ requires C, 44·2; H, 4·3%). The yield of the bicyclic base calculated from the amount of picrate obtained is 60% of the theoretical. The picrate was treated with a slight excess of potassium hydroxide solution (10%) and steam-distilled; the distillate (20 c.c.) was acidified with hydrochloric acid and evaporated to dryness, absolute alcohol (10 c.c.) added, and the solution again evaporated to dryness. The residue of the hydrochloride of the base was easily soluble in water, and crystallised from methyl alcohol in white rectangular prisms, which sublimed at 310° and decomposed at 350°.

The free base was obtained by dissolving the hydrochloride in a little water and treating it with an excess of solid potassium hydroxide with cooling. The oil which separated was taken up in ether and dried over solid potassium hydroxide, the ether removed in a vacuum at 10°, and the residual liquid distilled in a vacuum over sodium; a colourless, mobile liquid having a very penetrating, basic, herring-like odour was obtained (b. p. 130°/755 mm.) (Found : N, 14·3, 14·6. Calc. for $C_6H_{11}N$: N, 14·4%).

The *methiodide* crystallised from ethyl alcohol in white rectangular prisms, m. p. 320° (decomp.) (Found : C, 34·9; H, 5·9. $C_6H_{11}N,CH_3I$ requires C, 35·1; H, 6·0%). The *aurichloride* was difficultly soluble in water, and crystallised from aqueous alcohol in yellow prisms, m. p. 280° (decomp.) (Found : Au, 45·3; C, 17·1; H, 3·0. $C_6H_{11}N,HAuCl_4$ requires Au, 45·1; C, 16·5; H, 2·8%), and the *picrolonate* crystallised from acetone–alcohol in pale yellow rosettes of needles, m. p. 255° (decomp.) (Found : C, 53·1; H, 5·0. $C_6H_{11}N,C_{10}H_8O_5N_4$ requires C, 53·2; H, 5·3%).

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