CCCCXLII.—*Ring Closure Studies in the Piperidine Series.*

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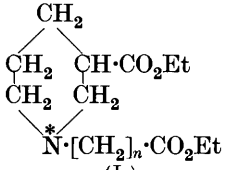
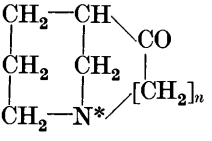
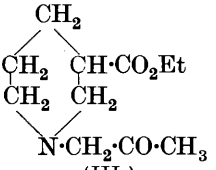
The development of synthetical work in these laboratories (see succeeding paper) made it necessary to investigate the possibility of *ethyl* 3-*carbethoxypiperidinoacetate* (I; $n = 1$) undergoing the Dieckmann reaction to give the dicyclic system (II).



(I.)



(II.)



(III.)

In view of the ready formation, for example, of tropinonedicarboxylic acid (Robinson, J., 1917, **111**, 762), ecgonine (Willstätter and Bommer, *Annalen*, 1921, **422**, 15), and fenchone (Ruzicka, *Ber.*, 1917, **50**, 1362), it was expected that structures such as (II) would form easily. The ester (I; $n = 1$) was prepared by condensing ethyl piperidine-3-carboxylate with chloroacetic ester (compare Clemo and Ramage, this vol., p. 437): it was refluxed in toluene with either powdered sodium or sodamide, but no trace of the desired ketone could be isolated from the reaction product. Attempts were also made to prepare ring system (II) in which $n = 2$ or 3, and in which the ring to be closed would be six- or seven-membered respectively. The *propionic* ester (I; $n = 2$) was best prepared from ethyl piperidine-3-carboxylate and β-chloropropionic ester in the presence of sodium acetate, and the corresponding *butyric* ester ($n = 3$) was prepared from ethyl piperidine-3-carboxylate and γ-bromobutyronitrile. In neither case, however, could the Dieckmann reaction be brought about in the above sense. In the case where $n = 3$, however, a small amount of a high-boiling oil was obtained, probably the result of a Claisen condensation between the butyric side chains of two molecules. These results are in marked contrast to the ease of formation of keto-octahydropyridocoline (Clemo and Ramage, *loc. cit.*).

The successful ring closures effected by Ruzicka (*Helv. Chim. Acta*, 1926, **9**, 499) by distilling the thorium salts of polymethylene αω-dicarboxylic acids made it of interest to try this method of ring closure in the present case. Ethyl 3-carbethoxypiperidinoacetate was hydrolysed, and the crystalline *acid* isolated by the action of hydrogen sulphide on the *copper* salt, but its thorium salt gave no ketone on distillation, and a similar result was obtained from the thorium salt of the corresponding crystalline propionic acid. In the case of the acid from (I; $n = 3$), which, however, could not be obtained crystalline, distillation of the thorium salt gave a reasonable amount of base, but analytical data and failure to give a semicarbazone show that it is not the ketone (II; $n = 3$).

The action of ammonia on ethyl 3-carbethoxypiperidinoacetate gave a crystalline *diamide*, but this distilled unchanged without forming a dicyclic imide, and the action of hydrazine hydrate on each of the three dicarboxylic esters gave only monocyclic dihydrazides.

In order further to activate the hydrogen atoms taking part in the Dieckmann reaction, (III) was prepared from ethyl piperidine-3-carboxylate and bromoacetone, but here again ring closure could not be effected with sodium, sodium ethoxide, or calcium chloride.

In all these compounds, however, we are dealing with tervalent nitrogen compounds, in which the bonds of the nitrogen atom are

presumably all in one plane (compare Meisenheimer, *Ber.*, 1924, **57**, 1744; Jackson and Kenner, J., 1928, 573), and the steric factors entering into the attempted ring closures will be different from those involved when the atom in (I) and (II) marked with an asterisk is carbon. With a view to overcoming this steric factor we decided to attempt the Dieckmann reaction with quaternary salts of substances of type (I) in which the bonds of the quadricovalent nitrogen are tetrahedrally disposed as in carbon (Mills and Warren, J., 1925, **127**, 2507; Mills, Parkin, and Ward, J., 1927, 2613). We used for this purpose the methyl *p*-toluenesulphonate of (I; $n = 3$), as this quaternary salt is slightly soluble in hot toluene. After carrying out the Dieckmann reaction and working up the product as described in the experimental part, we obtained a small amount of a low-boiling base. Analysis and failure to form a semicarbazone indicate that it is not (II; $n = 3$). Further, it does not form a crystalline picrate. This question is still being investigated.

Experimental.

Ethyl Piperidine-3-carboxylate.—A solution of pyridine-3-carboxylic acid (10 g.) in dry amyl alcohol (400 c.c.) was kept just boiling while sodium (32 g.) dissolved in it. The resulting solution was worked up as for ethyl piperidine-2-carboxylate (this vol., p. 440), but the esterification was effected by refluxing the residue from the alcoholic extract with ethyl-alcoholic hydrogen chloride (25 c.c.) for 12 hours. After removal of the alcohol, addition of excess of a saturated potassium carbonate solution, and extraction with ether, fractionation gave ethyl piperidine-3-carboxylate (6·0 g.), b. p. 109°/20 mm. (Found: N, 8·7. Calc.: N, 8·9%). The residue from the ethereal extraction was acidified and mixed with the next preparation.

Ethyl 3-Carbethoxypiperidinoacetate.—Ethyl piperidine-3-carboxylate (1·6 g.), ethyl chloroacetate (1·25 g.), and anhydrous potassium carbonate (1·5 g.) were heated in the water-bath for 1 hour with occasional stirring. Water was added, and the resulting oil extracted with ether; fractionation gave *ethyl 3-carbethoxypiperidinoacetate* (1·7 g.), b. p. 125°/0·1 mm. (Found: N, 5·6. $C_{12}H_{21}O_4N$ requires N, 5·75%).

The ester and hydrazine hydrate were allowed to stand with occasional shaking until homogeneous. The *dihydrazide* solidified in a vacuum desiccator and crystallised from alcohol in colourless microcrystalline aggregates, m. p. 162° (Found: N, 32·2. $C_8H_{17}O_2N_5$ requires N, 32·6%).

The *diamide* was prepared from the ester and aqueous ammonia by several days' standing with occasional shaking, and crystallised

from absolute alcohol by addition of light petroleum; m. p. 213° (Found : N, 22·8. $C_8H_{15}O_2N_3$ requires N, 22·7%).

3-*Carboxypiperidinoacetic Acid.*—The above ester (3 g.), concentrated hydrochloric acid (15 c.c.), and water (30 c.c.) were refluxed over-night. The hydrochloric acid was then completely removed under reduced pressure, the residue dissolved in water (100 c.c.), heated to boiling, and excess of copper carbonate slowly added. After filtration, the precipitate was washed with hot water, and the filtrate concentrated until a thick crust formed, and allowed to cool. The *copper* salt, which is very soluble in dilute acids, was collected, washed, and air-dried (2·7 g.) (Found : H_2O, 11·7; N, 5·1. $C_8H_{11}O_4NCu,2H_2O$ requires H_2O, 12·6; N, 4·9%. Found for the dried salt : Cu, 25·6. $C_8H_{11}O_4NCu$ requires Cu, 25·6%). A hot aqueous solution was decomposed with hydrogen sulphide, filtered, and the charcoaled filtrate taken to dryness under reduced pressure. 3-*Carboxypiperidinoacetic acid* (1·6 g.) crystallised from hot water, on addition of alcohol and cooling, in colourless granular aggregates, m. p. 270° (Found : C, 51·3; H, 6·8; N, 7·6. $C_8H_{13}O_4N$ requires C, 51·3; H, 7·0; N, 7·5%). The acid sublimes unchanged under 0·1 mm. pressure, and its thorium salt is insoluble in hot water.

β-*Piperidinopropionitrile.*—Piperidine (1·7 g.) and β-cyanoethyl toluene-*p*-sulphonate (2·3 g.) were heated in a sealed tube at 130° for 3 hours. The resulting oil was made alkaline with sodium hydroxide and extracted with ether, and the dried extract distilled, giving β-*piperidinopropionitrile* (1 g.), b. p. 116°/18 mm. (Found : N, 20·0. $C_8H_{14}N_2$ requires N, 20·3%). The *methiodide* formed colourless irregular plates, m. p. 155°, from alcohol (Found : C, 38·65; H, 6·3. $C_9H_{17}N_2I$ requires C, 38·6; H, 6·1%).

Ethyl β-3-*Carbethoxypiperidinopropionitrile.*—Ethyl piperidine-3-carboxylate (3·2 g.) and β-cyanoethyl toluene-*p*-sulphonate (2·25 g.) were condensed as for the above propionitrile and on fractionation ethyl piperidine-3-carboxylate (1 g.) was recovered, and *ethyl* β-3-*carbethoxypiperidinopropionitrile* (1·5 g.), b. p. 133°/0·1 mm., obtained (Found : N, 13·4. $C_{11}H_{18}O_2N_2$ requires N, 13·3%). With alcoholic hydrogen chloride it gave the dicarboxylic ester mentioned below.

Ethyl β-3-*Carbethoxypiperidinopropionate.*—Ethyl piperidine-3-carboxylate (1·6 g.), ethyl β-chloropropionate (1·4 g.), and anhydrous sodium acetate (1·5 g.) were condensed as for the acetate above. Water and excess of potassium carbonate were added, and *ethyl* β-3-*carbethoxypiperidinopropionate* (2 g.), b. p. 130°/0·1 mm., isolated as before (Found : C, 60·3; H, 9·0; N, 5·5. $C_{13}H_{23}O_4N$ requires C, 60·7 : H, 9·0; N, 5·5%). The *dihydrazide* crystallised from alcohol; m. p. 152° (Found : N, 30·6. $C_9H_{19}O_2N_5$ requires N, 30·6%).

β-3-*Carboxypiperidinopropionic Acid.*—The above ester (1·5 g.), concentrated sulphuric acid (3 g.), and water (15 c.c.) were refluxed over-night, and a hot aqueous solution containing the equivalent amount of barium hydroxide added. The barium sulphate was removed, and the filtrate evaporated to dryness. The residue (1·2 g.) was crystallised by dissolving it in the minimum amount of hot water, adding alcohol, and allowing the solution to stand; β-3-*carboxypiperidinopropionic acid* then separated as colourless irregular aggregates, m. p. 195—196° (Found: C, 53·7; H, 7·6; N, 7·2. $C_9H_{15}O_4N$ requires C, 53·7; H, 7·5; N, 7·0%).

γ-3-*Carbethoxypiperidinobutyronitrile.*—Ethyl piperidine-3-carboxylate (1·6 g.), γ-bromobutyronitrile (1·5 g.), and anhydrous potassium carbonate (1·5 g.) were condensed and worked up as for the acetate above, giving γ-3-*carbethoxypiperidinobutyronitrile* as a colourless oil (2·0 g.), b. p. 135°/0·1 mm. (Found: C, 64·1; H, 9·2; N, 12·4. $C_{12}H_{20}O_2N_2$ requires C, 64·3; H, 8·9; N, 12·5%).

Ethyl γ-3-*Carbethoxypiperidinobutyrate.*—The above nitrile (6·0 g.) was warmed with ethyl-alcoholic hydrogen chloride (30 c.c., saturated at 0°) until precipitation occurred, and then refluxed for 2 hours. After filtration from the ammonium chloride (1·5 g.), the alcohol was removed from the filtrate, and the residue made alkaline with a saturated solution of potassium carbonate and extracted with ether. Fractionation gave *ethyl* γ-3-*carbethoxypiperidinobutyrate* (6·4 g.) as a colourless oil, b. p. 133°/0·1 mm. (Found: N, 5·1. $C_{14}H_{25}O_4N$ requires N, 5·2%). The *dihydrazide* crystallised in colourless micro-crystalline aggregates, m. p. 165° (Found: N, 28·6. $C_{10}H_{21}O_2N_5$ requires N, 28·8%).

The thorium salt was prepared by hydrolysing the ester (5 g.) with hydrochloric acid, taking the solution to dryness, diluting the residue with aqueous alcohol, just neutralising it, and adding a hot aqueous solution of thorium nitrate. Distillation of the thorium salt (7 g.) gave a strongly basic oil, which, taken up in ether and fractionated, gave 0·17 g., b. p. 98—110°/20 mm. This redistilled at 105—110°/20 mm. (Found: C, 62·7, 62·1; H, 8·7, 8·6. $C_9H_{15}ON$ requires C, 70·6; H, 9·8%).

3-*Carbethoxypiperidinoacetone.*—Ethyl piperidine-3-carboxylate (1·6 g.), bromoacetone (1·4 g.), and anhydrous potassium carbonate (1·5 g.) were mixed together with ice-cooling and then slowly heated on the water-bath with occasional stirring. After being heated for ½ hour in the water-bath, the mixture was worked up and gave 3-*carbethoxypiperidinoacetone* (1·3 g.), b. p. 110°/0·1 mm. (Found: C, 62·0; H, 9·2; N, 6·8. $C_{11}H_{19}O_3N$ requires C, 62·0; H, 8·9; N, 6·6%). Hydrolysis with sulphuric acid gave a deliquescent acid.

Methyl p-*Toluenesulphonate of Ethyl* γ-3-*Carbethoxypiperidino-*

butyrate.—Methyl *p*-toluenesulphonate (7·5 g.) and ethyl γ-3-carbethoxypiperidinobutyrate (10·4 g.), heated on the water-bath with frequent stirring for ½ hour, became very viscous. The product, cooled and rubbed with ether, solidified; it was then crystallised thrice from ether–acetone; m. p. 139° (Found : N, 3·5. $C_{22}H_{35}O_7NS$ requires N, 3·1%).

Sodium (2·4 g.) was powdered in toluene (80 c.c.), and the above quaternary salt added in small portions, the toluene being gently boiled. After 4 hours, alcohol was added to dissolve the residual sodium, the liquid neutralised with 50% hydrochloric acid, hydrochloric acid (20 c.c. conc.) added, and the whole heated on the water-bath until the very vigorous gas evolution ceased. The aqueous layer was separated and evaporated, and the residue dissolved in a little water and treated with a hot saturated solution of lead chloride. After cooling, the precipitate was removed, and the filtrate evaporated to dryness. The residue was extracted with alcohol, the alcohol removed, and the brown deliquescent residue distilled in a high vacuum; there was then a vigorous evolution of gas and a basic-smelling oil was obtained. This was dissolved in dilute hydrochloric acid and treated with charcoal; after evaporation to dryness, the residue was dissolved in a little water, made alkaline, and extracted with ether. The extract was dried, and, on fractionation, a colourless oil was obtained (0·3 g.), b. p. 70°/0·3 mm. (Found : C, 62·3; H, 9·5; N, 11·4. $C_9H_{15}ON$ requires C, 70·6; H, 9·8; N, 9·1%).

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