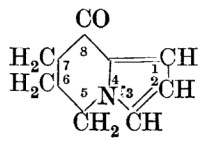
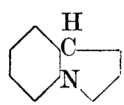
456. *Octahydropyrrocoline.*

By G. R. Clemo and G. R. Ramage.

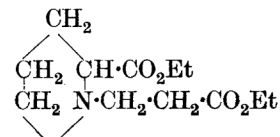
In the J., 1931, 49 the synthesis of 8-keto-5 : 6 : 7 : 8-tetrahydropyrrocoline (I) was described, and the chemistry of the fully reduced ring system (II) would appear to have been adequately discussed by Löffler and co-workers under the name of piperolidine (or inactive δ-coniceine). In view of the interest attaching to the possible existence of two stereoisomeric forms of (II) (compare preceding paper) we have investigated the question afresh, and, as shown in the sequel, obtained two isomeric picrates from (II) as prepared by the Dieckmann and subsequent reactions on *ethyl* β-2-*carbethoxypiperidinopropionate* (III). This is in contrast with the corresponding formation of only one octahydropyridocoline.



(I.)



(II.)



(III.)

Löffler and Kaim (*Ber.*, 1909, **42**, 94) prepared 2-pyridylacrylic acid by the hydrolysis of the readily obtainable aldol condensation product from α-picoline and chloral. This acid was reduced by

sodium and alcohol to β-2-piperidylpropionic acid, which underwent ring closure on distillation. Further reduction with sodium and alcohol gave piperolidine, and a series of well-defined derivatives are described. The same base was obtained by Löffler and Flugel (*Ber.*, 1909, **42**, 3420) in a pure condition by carrying out a Bouveault reduction on ethyl 2-pyridylacrylate, the resulting 2-ω-hydroxypropylpiperidine being converted into a ring compound by iodination with hydriodic acid and red phosphorus and treatment with alkali.

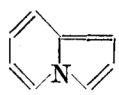
In view of the poor yields resulting from sodium and alcohol reductions, and the ease of production of the analogous octahydropyridocoline (Clemo and Ramage, J., 1931, 307) it was thought that the ring system (II) would be more readily obtained by the Dieckmann reaction on (III). This ester was prepared by condensing ethyl piperidine-2-carboxylate with ethyl β-chloropropionate in the presence of anhydrous sodium acetate, although possibly steric influences account for the much lower yield than with the corresponding ethyl piperidine-3-carboxylate (Clemo, Ormston, and Ramage, J., 1931, 3185). Further, as the yield in the Dieckmann reaction is lower than that in the same reaction leading to octahydropyridocoline, it would appear that the 6 : 6 ring system of the latter is more readily formed than that of (II).

The octahydropyrrocoline as obtained by Clemmensen reduction of the 1-*keto-compound* was treated with an equivalent amount of picric acid and fractional crystallisation of the product gave two analytically pure picrates, m. p. 135° and 226° respectively. The latter compound can be more readily obtained by allowing (II) to stand : the base giving rise to the picrate of m. p. 135° decomposes first. On repeating Löffler's synthesis through 3-keto-octahydropyrrocoline, only the picrate, m. p. 226° after one crystallisation, was isolated. It has been found, however, that the 3-keto-compound is far more readily obtained by catalytically reducing ethyl 2-pyridineacrylate with the Adams and Shriner platinum oxide catalyst to ethyl β-2-piperidylpropionate, which is difficult to isolate in a pure condition, as it undergoes ring closure on distillation under ordinary pressure. An attempt to reduce the resulting amide group electrolytically in only 20% (volume) aqueous sulphuric acid was not successful.

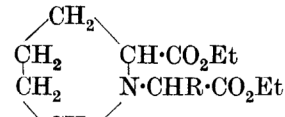
It is difficult to imagine that the Dieckmann reaction on (III) can lead to a mixture of two structural isomerides, one of which would have a 6 : 4 ring system, and the occurrence of two picrates with widely different melting points suggests that the octahydropyrrocoline ring system occurs in *cis*- and *trans*-forms as in the case of octahydropyridocoline, in which other possible explanations have

been excluded. In the recent work by Diels and Alder referred to in the previous paper, it is claimed that, by the action of dilute nitric acid on (VII of previous paper), followed by decarboxylation and reduction of (IV), octahydropyrrocoline (termed indolizidine) (II) is formed. The derived picrate melts at 226°, and so, if it is derived from (II), only one form of the base is thus produced.

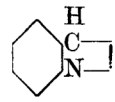
Although the Dieckmann reaction has hitherto failed to lead to the formation of a four-membered ring, it was nevertheless thought that conidine (VI), or more particularly a substituted conidine, might be thus prepared from (V; R = H or, say, Me). No simple ketone could be isolated, however, by the action of sodium in toluene on either *ethyl 2-carbethoxypiperidinoacetate* (V; R = H) or its *methyl* derivative (R = Me). The high-boiling base resulting from the latter was apparently formed by a Claisen condensation between two molecules.



(IV.)



(V.)



(VI.)

Löffler and co-workers also failed to obtain (VI) (*Ber.*, 1907, **40**, 1336), but they have described various substituted conidines prepared by ring closure from the appropriate iodo-piperidine (*Ber.*, 1907, **40**, 1310; 1909, **42**, 948; 1910, **43**, 2048).

Experimental.

Ethyl β-2-Carbethoxypiperidinopropionate.—Ethyl piperidine-2-carboxylate (1·6 g.), ethyl β-chloropropionate (1·4 g.), and anhyd. NaOAc (1·5 g.) were heated for 1½ hr. in the water-bath with occasional stirring. H_2O and excess of K_2CO_3 were added to four similar expts. and the liberated ester was extracted by Et_2O and fractionated, giving *ethyl β-2-carbethoxypiperidinopropionate* (6·0 g.), b. p. 116—118°/0·2 mm., as a colourless oil (Found: N, 5·6. $C_{13}H_{23}O_4N$ requires N, 5·45%).

β-2-Carboxypiperidinopropionic Acid.—The above ester (2·0 g.), conc. HCl (10 c.c.), and H_2O (20 c.c.) were refluxed for 5 hr. The excess acid was completely removed under reduced press., and the residue dissolved in H_2O and heated to boiling while $CuCO_3$ was slowly added. After filtration the ppt. was washed with hot H_2O, and the filtrate concentrated to small bulk and allowed to cool. The Cu salt which separated was washed with acetone and air-dried (2·0 g.). A hot aq. solution was decomposed with H_2S and filtered, and the filtrate (charcoal) taken to dryness under reduced press., giving *β-2-carboxypiperidinopropionic acid* (1·0 g.). This crystallised from hot H_2O, after addition of an equal vol. of EtOH, in colourless granular aggregates, m. p. 210° (Found: C, 54·3; H, 7·4; N, 7·2. $C_9H_{15}O_4N$ requires C, 53·7; H, 7·5; N, 7·0%).

1-Keto-octahydropyrrocoline.—Na (1·0 g.) was powdered under xylene (40 c.c.) and gently refluxed while ethyl β-2-carbethoxypiperidinopropionate

(6·3 g.) in xylene (6 c.c.) was gradually added; when the mixture was heated for 2 hr. on the water-bath, the Na salt separated. H_2O (10 c.c.) was added, followed by conc. HCl (15 c.c.), and the heating continued for 6 hr., CO_2 evolution then ceasing. After evaporation, the residue was made alkaline with NaOH aq. (10%) and extracted with Et_2O. Fractionation gave 1-*keto-octahydropyrrocoline* as a colourless basic oil (2·3 g.), b. p. 93°/18 mm., with a characteristic smell; it slowly decomposed on standing (Found: C, 69·2; H, 9·5; N, 10·2. $C_8H_{13}ON$ requires C, 69·1; H, 9·35; N, 10·1%).

Octahydropyrrocoline (II).—A mixture of the above ketone (2·0 g.), amalgamated Zn (15 g.), and conc. HCl (15 c.c.) was refluxed for 6 hr., and for a further period after addition of more HCl aq. (10 c.c.). The decanted solution was evaporated to dryness, and the residue made strongly alkaline with NaOH aq. (10%) and steam-distilled. The distillate was extracted with Et_2O, and the dried extract gave a colourless oil (0·6 g.), b. p. 65—67°/18 mm. (Found: N, 11·0. Calc.: N, 11·2%). The compound turns yellow on standing and partly decomposes. It is slightly sol. in cold H_2O, giving a solution markedly alkaline to litmus. The picrate from the freshly prepared base (0·2 g.), cryst. from EtOH, m. p. 164—166° (Found: C, 47·25; H, 5·15. Calc.: C, 47·5; H, 5·1%), was twice extracted with C_6H_6 (7 c.c.). The yellow elongated plates obtained from the first extract on cooling had m. p. 195°, raised by recrystn. from EtOH (m. p.'s 215°, 224°, 226°, all with decomp.). The residue after C_6H_6 extraction gave yellow needles from EtOH, m. p.'s 139—140°, 135—136° (a C_6H_6 extract also gave picrate, m. p. 135—136°) and 135° (Found: C, 47·5; H, 4·8%). On distilling the base after considerable decomp. had occurred through standing for several days, the picrate obtained had m. p. 196°, raised to 226° (decomp.) (Found: C, 47·7; H, 5·0; N, 16·0%), and not depressed by admixture with Löffler's picrate (below).

Ethyl 2-Pyridylacrylate.—Pyridyl-ω-trichloro-β-hydroxypropane hydrochloride (*Ber.*, 1909, **42**, 96) (30 g.) [the free base, isolated by Et_2O extraction, solidified on removal of solvent and crystallised from petroleum (b. p. 100—120°) in stout colourless prisms, m. p. 82° (Found: N, 5·9. Calc. for $C_8H_8ONCl_3$: N, 5·8%)] was hydrolysed by KOH as described, the residue from the EtOH extract esterified by refluxing with EtOH–HCl, the solvent removed, and the residue (and K_2CO_3) extracted with Et_2O. A pale yellow oil (12·5 g.), b. p. 153°/16 mm., was obtained (Found: N, 7·8. Calc.: N, 7·9%).

3-*Keto-octahydropyrrocoline.*—(1) The above ester (5·0 g.) was hydrolysed by boiling for 5 hr. with conc. HCl (15 c.c.) and H_2O (30 c.c.), the solution evaporated to dryness, and the residue reduced with Na (20 g.) in EtOH. The free piperidylpropionic acid was isolated by means of Ag_2CO_3 (see *Ber.*, 1909, **42**, 97) and on distillation gave 3-keto-octahydropyrrocoline (1·1 g.).

(2) Ethyl 2-pyridylacrylate (10 g.) in EtOH (50 c.c.) containing equiv. amounts of HCl and catalyst (0·2 g.) was shaken in H (55 lb./sq. inch) for 9 hr. After decanting (the catalyst can be used again with the further addition of 0·1 g.), the EtOH was removed, and the residue made alkaline with K_2CO_3; an Et_2O extract on distillation gave ethyl β-2-piperidylpropionate (7·5 g.) almost pure (Found: N, 8·3. Calc.: N, 7·6%). This material, heated to its b. p. 258°/750 mm., underwent ring closure: the product was purified by just acidifying it with HCl aq. (50%) to Congo-paper and extraction with $CHCl_3$, which gave the non-basic 3-keto-octahydropyrrocoline (5·0 g.), b. p. 135°/18 mm. (Found: N, 10·0. Calc.: N, 10·1%).

Octahydropyrrocoline.—A Bouveault reduction on the above amide (1·5 g.) gave octahydropyrrocoline (0·25 g.) and recovered compound (0·6 g.). The base, which was relatively stable on standing, gave a picrate, m. p. 220°, which, recrystallised from EtOH, formed yellow elongated plates, m. p. 226° (decomp.) (Found: N, 16·0. Calc.: N, 15·85%).

Ethyl 2-Carbethoxypiperidinoacetate.—Ethyl piperidine-2-carboxylate (1·6 g.) ethyl chloroacetate (1·25 g.), and anhyd. K_2CO_3 (1·5 g.) were heated in the water-bath for 1 hr. with occasional stirring. The oil resulting from the addition of H_2O was collected in Et_2O and fractionated, giving *ethyl 2-carbethoxypiperidinoacetate* (1·5 g.), b. p. 149°/17 mm., as a colourless oil (Found: N, 5·9. $C_{12}H_{21}O_4N$ requires N, 5·75%).

Ethyl α-2-Carbethoxypiperidinopropionate.—Ethyl α-bromopropionate (1·8 g.) was used in the above preparation, and *ethyl α-2-carbethoxypiperidinopropionate* (2·1 g.), b. p. 151°/17 mm., 110°/0·2 mm., obtained (Found: N, 5·6. $C_{13}H_{23}O_4N$ requires N, 5·45%).

Our thanks are due to Imperial Chemical Industries for a grant.

UNIVERSITY OF DURHAM, ARMSTRONG COLLEGE,
NEWCASTLE-UPON-TYNE. [*Received, November 29th*, 1932.]