419. 2-*Ketoquinuclidine and a New Synthesis of Quinuclidine.**

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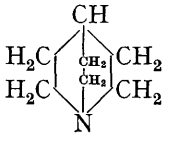
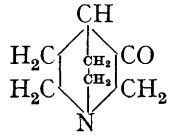
2-*Ketoquinuclidine* (II) has been prepared through the Dieckmann condensation of *ethyl piperidine-1-acetate-4-carboxylate*. Reduction by both the Wolff and the Clemmensen method gives quinuclidine (I).

Although the quinuclidine ring system only occurs naturally in the cinchona alkaloids, it is nevertheless of much interest. Quinuclidine (I) was first prepared by Löffler and Stietzel (*Ber.*, 1909, **42**, 124), who employed the same series of reactions previously used by Koenigs and Bernhardt (*Ber.*, 1904, **37**, 3244; 1905, **38**, 3049) for the preparation of 2-ethylquinuclidine from 4-methyl-3-ethylpyridine: γ-picoline was condensed with formaldehyde, and the resulting β-4-pyridylethyl alcohol reduced with sodium and alcohol; treatment of the product with hydriodic acid gave β-4-piperidylethyl iodide, which underwent an intramolecular rearrangement to quinuclidine hydriodide, the yield in the last process being only 10%.

Meisenheimer (*Annalen*, 1920, **420**, 190) repeated this synthesis; he increased the yield in the intramolecular rearrangement to 70% and described the base as a volatile crystalline solid with the surprisingly high m. p. 158°, whereas Löffler and Stietzel had described it as a liquid, b. p. 141°, and 2-ethylquinuclidine, according to Koenigs and Bernhardt, has b. p. 190°/720 mm.

In the preparation of quinuclidine, the rather inaccessible γ-picoline, obtainable from commercial β-picoline by fractional crystallisation of the mercuric chloride double salts, was employed and furthermore, the yield from the condensation with formaldehyde to give 4-pyridylethyl alcohol was very poor, being only about 1% in Meisenheimer's work. It is not surprising, therefore, that the chemistry of (I) has been little investigated.

(I.) 

 (II.)

A much better method for the preparation of quinuclidine has now been found. Ethyl piperidine-4-carboxylate (this vol., p. 1523) was condensed with ethyl chloroacetate to give *ethyl piperidine-1-acetate-4-carboxylate* and the Dieckmann reaction, followed by hydrolysis and decarboxylation, gave 2-*ketoquinuclidine* (II) as a crystalline deliquescent solid.

The Clemmensen and the Wolff reduction of this ketone were of special interest [the ketone being comparable with 1-keto-octahydropyridocoline, from which octahydropyridocoline and *nor*lupinane have been obtained by these two reduction methods (J., 1936, 1429)], but, as anticipated, quinuclidine, which theoretically can only exist in one form, was obtained in each case. Further work on 2-ketoquinuclidine is in progress.

Experimental.

Ethyl Piperidine-1-acetate-4-carboxylate.—Ethyl piperidine-4-carboxylate (8·2 g.), ethyl chloroacetate (8 g.), and anhydrous potassium carbonate (8 g.) were mixed and heated at 110—115° for 4 hours. Water was added, and the *oil* taken up in ether and fractionated (9·35 g., b. p. 134—136°/1 mm.) (Found: C, 58·8; H, 8·8. $C_{12}H_{21}O_4N$ requires C, 59·2; H, 8·7%).

2-*Ketoquinuclidine.*—The above di-ester (4·4 c.c.) in toluene (5 c.c.) was added to a warm suspension of very finely powdered potassium (2 g.) in toluene (8 c.c.); the mixture, heated

* This paper was written some time before the *Annalen*, 1937, **32**, came to hand with the description (p. 69) by Prelog of a synthesis of quinuclidine by a modification of the method he used for *bicyclo*[1 : 2 : 2]aza-1-heptane (*Annalen*, 1936, **525**, 292).

at 120° for 10 minutes, solidified, and was then heated at 110° for 3 hours. After cooling, alcohol was added to remove the excess of potassium, followed by water (2 c.c.) and concentrated hydrochloric acid (50 c.c.), and the solution was heated in the water-bath for 14 hours. After evaporation to dryness, the residue was basified with potassium hydroxide solution (50%), and the product extracted with ether. The pale yellow extract, dried over potassium carbonate, was added to a warm alcoholic solution of picric acid (3 g.). The ketone picrate which separated (2·2 g., m. p. 188—190°), after one crystallisation from alcohol, was decomposed with a slight excess of potassium hydroxide solution. The product, extracted and dried (solid potassium hydroxide) in ether, gave on distillation the *ketone* (1 g., b. p. 110°/12 mm.) as a colourless crystalline solid. It readily sublimed in a vacuum (1 mm.) in colourless deliquescent prisms, was easily soluble in light petroleum (b. p. 60—80°) at the ordinary temperature and separated at 0° in colourless dendrites, m. p. 138° (Found: C, 67·1; H, 9·3. $C_7H_{11}ON$ requires C, 67·2; H, 8·9%). The *methiodide*, formed in acetone, crystallised from alcohol in colourless prisms, m. p. 310° (decomp.) (Found: C, 36·0; H, 5·9. $C_8H_{14}ONI$ requires C, 35·95; H, 5·2%). The *picrate* was difficultly soluble in alcohol and crystallised from alcohol–acetone in golden-yellow rectangular prisms, m. p. 210° (Found: C, 44·0, 44·1; H, 3·75, 4·2. $C_7H_{11}ON,C_6H_3O_7N_3$ requires C, 44·1; H, 4·0%).

Quinuclidine.—(1) *Wolff reduction.* The ketone (0·3 g.), regenerated from 1 g. of its picrate, and hydrazine hydrate (0·5 g. of 95%) were refluxed for 24 hours, the hydrazone extracted with ether, the extract dried over sodium sulphate, and the ether removed. The residual viscous liquid (0·35 g.), sodium ethoxide (from sodium, 0·2 g.), and alcohol (4 c.c.) were heated in a sealed tube at 175° for 5 hours. Water was added, followed by excess of hydrochloric acid, and the solution was evaporated to dryness. The residue was basified, the base extracted with ether, and the dried extract added to an alcoholic solution of picric acid (0·2 g.); 0·2 g. of a picrate, m. p. 270°, separated at once. The picrate formed rosettes of bright yellow, acicular prisms, m. p. 275° (decomp.), from alcohol; Meisenheimer gives m. p. 275—276° (Found: C, 45·5; H, 4·9. Calc. for $C_7H_{13}N,C_6H_3O_7N_3$: C, 45·9; H, 4·7%).

(2) *Clemmensen reduction.* The ketone (0·3 g.) was refluxed for 24 hours with amalgamated zinc (10 g.) and concentrated hydrochloric acid (15 c.c.). More amalgamated zinc (5 g.) and hydrochloric acid (10 c.c.) were then added and the refluxing was continued for a further 20 hours. The acid solution was decanted, basified with concentrated sodium hydroxide solution, and steam-distilled until the distillate was no longer alkaline to litmus (about 100 c.c.). It was then acidified with hydrochloric acid and taken to dryness, the residue basified with potassium hydroxide solution (50%) and thoroughly extracted with ether, and the extract dried over potassium carbonate and added to an alcoholic solution of picric acid (0·3 g.); 0·25 g. of a picrate separated at once (m. p. 250° approx.). One recrystallisation from alcohol raised the m. p. to 268—270° (decomp.) and a second gave yellow prisms, m. p. 275° (decomp.), identical with the picrate obtained in the Wolff reduction.

The above picrate (0·5 g.) was decomposed by grinding with dilute hydrochloric acid (1 : 1), the filtered solution taken to dryness, and the residue basified with potassium hydroxide solution (50%) and thoroughly extracted with ether. The extract was dried over potassium carbonate and then solid potassium hydroxide and distilled in a vacuum over the latter reagent, the receiver being cooled in solid carbon dioxide. The quinuclidine was thus obtained in colourless prisms; on recrystallisation from light petroleum (b. p. 40—50°) at 0° it formed dendrites which sublimed so easily in a sealed tube that its accurate melting point has not been found. It gave the ethiodide in colourless prisms, m. p. 270° as claimed by Meisenheimer.

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