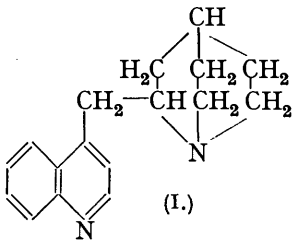
261. *Synthesis of 5-Substituted Rubans.*

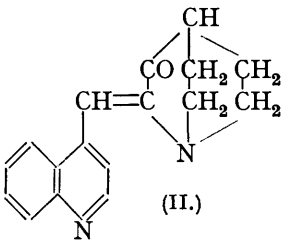
By G. R. Clemo and E. Hoggarth.

A new synthesis of the ruban skeleton (I) has been achieved by the condensation of 3-*ketoquinuclidine* with quinoline-4-aldehyde, and a number of 5-substituted derivatives are described.

3-Ketoquinuclidine (Clemo and Metcalfe, J., 1937, 1989 *) condensed very readily with benzaldehyde in the presence of alkalis giving 2-*benzylidene*-3-*ketoquinuclidine*, and in the presence of acids or, better, by means of piperidine acetate (Kuhn and Morris, *Ber.*, 1937, **70**, 857) a similar condensation was effected with quinoline-4-aldehyde, the product being 5-*keto*-6 : 9-*rubanene* (II). Hydrogenation of this compound in methyl-alcoholic solution



(I.)



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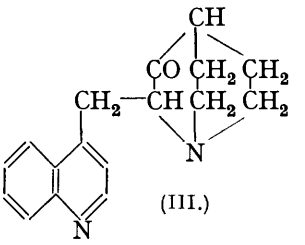


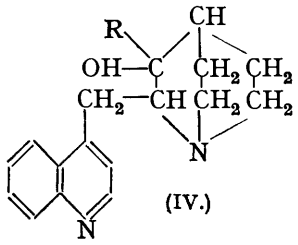
(III.)

by hydrogen at ordinary pressure and palladised charcoal gave 5-ketoruban (III), which, on reduction with aluminium *iso*propoxide afforded *ruban*-5-*ol* (IV; R = H), and on reaction with ethylmagnesium iodide yielded 5-*ethylruban*-5-*ol* (IV; R = Et).

A crystalline *compound*, $C_{19}H_{22}ON_2$, was obtained by the action of ethylmagnesium iodide on 5-keto-6 : 9-rubanene, and in view of the extended work by Kohler and his co-workers since 1904 upon addition of Grignard reagents to αβ-unsaturated ketones, this should have one or other of the constitutions (V, A or B). The attempt to decide between these alternatives has not yet yielded definite results. No crystalline compounds were obtained with hydrazine hydrate, phenylhydrazine, semicarbazide, or hydroxylamine, although 5-ketoruban gives a normal phenylhydrazone. No acetone was detected in attempted reductions with aluminium *iso*propoxide, and in all cases the material was recovered unchanged. On the other hand, we failed to induce anionotropy or dehydration

* In this paper, the compound was termed 2-ketoquinuclidine.

by boiling with formic acid or acetic anhydride, the compound being unaffected even by prolonged treatment with these reagents, and in addition, attempted hydrogenation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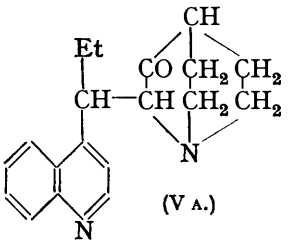
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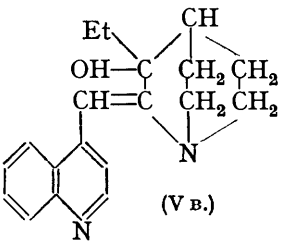
(V B.)

under conditions suitable for reduction of the 6 : 9 double bond of 5-keto-6 : 9-rubanene (II) failed to give 5-ethylruban-5-ol.

Experimental.

The quinoline-4-aldehyde was obtained from lepidine by way of the chloral condensation product, γ-trichloro-β-hydroxy-α-(4-quinolyl)propane in overall yields of 38—40%. This yield is much higher than could be attained by repetition of the direct oxidation method of Kwartler and Linwall (*J. Amer. Chem. Soc.*, 1937, **59**, 524), who report a yield of 61% of quinoline-4-aldehyde hydrate from lepidine by use of selenium dioxide. Improvement in the original method of Miller and Spady (*Ber.*, 1886, **19**, 130) for the intermediate trichloropropane was made by using pyridine as a solvent and, as in the case of "quinaldine-chloral" (Alberts and Bachman, *J. Amer. Chem. Soc.*, 1935, **57**, 1284), the product was much cleaner and required far fewer crystallisations than when zinc chloride or acetic anhydride was used as a condensing agent. The β-4-quinolylacrylic acid obtained by hydrolysis with alcoholic potash had m. p. 270°; Koenigs and Müller (*Ber.*, 1904, **37**, 1337) give m. p. 250—255° (decomp.). Although the same workers state (*loc. cit.*) that they were unable to oxidise their β-4-quinolylacrylic acid to quinoline-4-aldehyde, we succeeded by means of the action of ice-cold saturated permanganate solution upon an alkaline solution of the acid at — 10° in the presence of a suitable organic solvent (see Cohen and Cooper, **J.**, 1932, 723; D.R.P. 421,088, Chemische Fabrik auf Aktien, vorm. E. Schering).

γ-Trichloro-β-hydroxy-α-(4-quinolyl)propane.—Freshly distilled lepidine (40 g.) was dissolved in pure dry pyridine (100 c.c.), and chloral (44 g.) quickly added. The faintly yellow liquid was warmed at 85—90° on the water-bath (2 hours), the light brown viscous product poured into cold water (500 c.c.) with vigorous stirring, and the resulting fine powder collected, washed with water, and dried on the water-bath. The pale yellow γ-trichloro-β-hydroxy-α-(4-quinolyl)-propane, crystallised once from alcohol, had m. p. 177—178° (65 g.; 80%), raised to 178° (colourless rectangular prisms) by further recrystallisations (Found: C, 49·9; H, 3·7. Calc. for $C_{12}H_{10}ONCl_3$: C, 49·6; H, 3·5%).

β-4-*Quinolylacrylic Acid.*—Potassium hydroxide (65 g.) was dissolved in absolute alcohol (300 c.c.) on the water-bath and the above trichloropropane (65 g.) cautiously added during 2 hours with effective stirring. After a further hour's heating on the water-bath, the separated potassium chloride was collected and well washed with absolute alcohol. The combined filtrates were diluted with an equal volume of water, and the alcohol removed under reduced pressure. The residual solution was decolorised by charcoal, the β-4-quinolylacrylic acid precipitated with 50% acetic acid (40 c.c.), coagulated by boiling, collected, and washed with water. The compound was purified by boiling its solution in sodium carbonate (10%) with charcoal and precipitating it as previously; 36 g. (80%), m. p. 268—269°. Although this material was pure enough for the next operation, recrystallisation from glacial acetic acid gave slender needles, m. p. 270° (slight decomp.) (Found: C, 72·4; H, 4·7. Calc. for $C_{12}H_9O_2N$: C, 72·3; H, 4·6%).

Quinoline-4-aldehyde.—β-4-Quinolylacrylic acid (36 g.) was dissolved in a solution of sodium carbonate (14 g. in 500 c.c. water) and placed in a large, wide-necked flask with a mixture of ether and chloroform (1 l.; 1 : 1). The whole was stirred vigorously, cooled to — 10°, and an ice-cold solution of potassium permanganate (60 g. in 1½ l. of water) added during 4 hours. The stirring was continued for a further hour and the sludge rapidly filtered. The separated aqueous layer was extracted three times with small amounts of chloroform, the residue of manganese dioxide was washed with the same solvent, and the combined ether–chloroform extracts

were then shaken with three small amounts of 50% hydrochloric acid (15 c.c.). The combined acid extracts were evaporated to dryness, the hydrochloride decomposed with a small amount of saturated sodium carbonate solution, and the quinoline-4-aldehyde extracted with ether. Distillation of the dried extract gave 16·5 g. of the free base (58% of theory), b. p. 122—123°/4 mm., crystallising to a solid, m. p. 51°.

Recrystallisation from light petroleum (b. p. 60—80°) gave needles, very soluble in benzene and alcohol m. p. 52° (Found : C, 76·3; H, 4·6. Calc. for $C_{10}H_7ON$: C, 76·4; H, 4·5%). Its *picrate*, formed in absolute alcohol and crystallised from the same solvent, gave yellow needles sintering at 170°, m. p. 179°, which appear to contain one molecule of solvent (Found : C, 50·2; H, 3·9. $C_{10}H_7ON,C_6H_3O_7N_3$ requires C, 49·7; H, 2·6. $C_{10}H_7ON,C_6H_3O_7N_3,C_2H_5OH$ requires C, 50·0; H, 3·7%). The phenylhydrazone was obtained from alcohol as large yellow prisms, m. p. 176°. The hydrochloride crystallises from alcohol–acetic acid mixtures in small colourless prisms, m. p. 206°.

2-Benzylidene-3-ketoquinuclidine.—3-Ketoquinuclidine (0·3 g.; b. p. 110°/14 mm.) was dissolved in absolute alcohol (2 c.c.), freshly distilled benzaldehyde (0·5 g.) and 1 drop of piperidine or potassium hydroxide (0·1 g.) added, and the mixture refluxed for 8—10 hours. The yellow solution was poured into water (10—20 c.c.), alcohol and excess benzaldehyde removed in a current of steam, a little saturated potassium carbonate solution added, and the liquid extracted with ether. The oil remaining after removal of the ether solidified on rubbing with aqueous methyl alcohol (75%). It was kept in the refrigerator overnight, and the solid crystallised from light petroleum (b. p. 60—80°), *2-benzylidene-3-ketoquinuclidine* being obtained in stout, light yellow needles, m. p. 133°, soluble in alcohol and benzene, insoluble in water (Found : C, 78·6; H, 6·9. $C_{14}H_{15}ON$ requires C, 78·8; H, 7·1%). The *phenylhydrazone*, prepared in and crystallised from absolute alcohol, formed light yellow rectangular plates, m. p. 184° (Found : C, 79·5; H, 6·7. $C_{20}H_{21}N_3$ requires C, 79·2; H, 7·0%).

5-Keto-6 : 9-rubanene (II).—(a) *Condensation by hydrogen chloride in acetic acid.* Pure 3-ketoquinuclidine (0·5 g.) and quinoline-4-aldehyde hydrochloride (0·8 g.) were separately dissolved in glacial acetic acid (10 c.c. each), mixed, and saturated with dry hydrogen chloride at 0°. The yellow liquid was kept for 2—3 hours, then warmed at 80—85° for 8 hours, poured into water (50 c.c.), and the greater part of the acetic acid together with excess aldehyde removed on the water-bath under reduced pressure. The oil which separated upon basifying with saturated potassium carbonate solution was taken up in ether, the solvent removed from the dried extracts, and the residue repeatedly extracted with light petroleum (b. p. 60—80°). The united extracts were reduced to 20 c.c., decanted from a small amount of red oil which separated during the concentration, and allowed to crystallise. The *5-keto-6 : 9-rubanene* (0·2 g.) was collected and recrystallised from the same solvent, forming small, deep yellow prisms, m. p. 153°, very soluble in alcohol and benzene, sparingly soluble in ether (Found : C, 77·35; H, 5·8; N, 10·7. $C_{17}H_{16}ON_2$ requires C, 77·25; H, 6·1; N, 10·6%).

(b) *Condensation with piperidine acetate.* 3-Ketoquinuclidine (0·5 g.) and quinoline-4-aldehyde (0·65 g.) were dissolved in absolute alcohol (2 c.c.), and piperidine (0·1 g.) and glacial acetic acid (0·1 g.) added. The mixture was kept for at least 60 hours in the cold, heated momentarily to boiling, and poured into water (10—20 c.c.). The liquid was basified with a little potassium carbonate, and alcohol, excess aldehyde, and piperidine removed in steam. The oil remaining in the flask was taken up in ether, the extracts dried, and the solvent removed. The residual oil solidified on scratching, and was crystallised from light petroleum (b. p. 60—80°). The compound (0·4—0·5 g.) was identical with that obtained by the previous method, m. p. 153° (Found, C, 77·5; H, 5·8%). The *picrate* of 5-keto-6 : 9-rubanene crystallised from alcohol–acetone in small red needles, m. p. 209°, slightly soluble in alcohol (Found : C, 56·2; H, 4·3. $C_{17}H_{16}ON_2,C_6H_3O_7N_3$ requires C, 56·0; H, 3·9%). The *platinichloride* crystallised in orange needles from dilute alcohol, and decomposed above 260° without melting. For analysis it was dried for 10 hours at 120° in a vacuum (Found : C, 30·4; H, 2·4; Pt, 29·2. $C_{17}H_{16}ON_2,H_2PtCl_6$ requires C, 30·3; H, 2·7; Pt, 29·0%).

5-Ketoruban (III).—5-Keto-6 : 9-rubanene (0·5 g.) was dissolved in methyl alcohol (10 c.c.), palladised charcoal (20 mg.) added, and the mixture shaken for 10 hours with hydrogen at the ordinary pressure. Fresh catalyst (10 mg.) was then added, and the shaking continued for a further 2 hours. The charcoal was filtered off, washed with a little hot methyl alcohol, the solvent evaporated, and the residual oil crystallised from light petroleum (b. p. 60—80°). *5-Ketoruban* separates in colourless needles, m. p. 125—126° (0·3 g.), very soluble in alcohol, benzene, and ether (Found : C, 76·8; H, 6·6. $C_{17}H_{18}ON_2$ requires C, 76·7; H, 6·8%). Its *phenylhydrazone*, formed by boiling with phenylhydrazine in alcohol, separated from the same

solvent in yellow prisms, m. p. 198° (Found: N, 16·0. $C_{23}H_{24}N_4$ requires N, 15·7%); and its *picrate* gave deep yellow needles from alcohol–acetone, m. p. 168°, almost insoluble in alcohol but quite soluble in acetone (Found: C, 48·2; H, 3·5. $C_{17}H_{18}ON_2,2C_6H_3O_7N_3$ requires C, 48·0; H. 3·3%).

Ruban-5-ol (IV; R = H).—5-Ketoruban (0·5 g.) was dissolved in dry *iso*propyl alcohol (5 c.c.), and aluminium *iso*propoxide (1·0 g.) added. The solution was gently refluxed under a short fractionating column so that in the course of 2 hours about 5 c.c. of *iso*propyl alcohol distilled over, the volume of solution in the flask being maintained by dropping in dry *iso*propyl alcohol at the same rate. Excess of reagent was then decomposed by water (20 c.c.), and the *iso*propyl alcohol removed in steam. The *ruban-5-ol* was extracted from the gelatinous residue with ether–chloroform (1 : 1), the solvents removed from the dried extracts, and the residual oil crystallised from ethyl acetate; it formed small, pointed needles, m. p. 198° (0·3 g.), soluble in alcohol and benzene, sparingly soluble in ether (Found: C, 76·4; H, 7·4. $C_{17}H_{20}ON_2$ requires C, 76·1; H, 7·5%). Its *picrate* is very sparingly soluble in alcohol, and crystallised from alcohol–acetone in yellow needles, m. p. 188—189° (Found: C, 48·3; H, 3·8. $C_{17}H_{20}ON_2,2C_6H_3O_7N_3$ requires C, 47·9; H, 3·6%).

5-Ethylruban-5-ol (IV; R = Et).—The Grignard reagent from magnesium (1·5 g.), ethyl iodide (4 c.c.), and ether (25 c.c.) was taken to dryness on the water-bath under reduced pressure to remove excess of ethyl iodide, the gelatinous residue dissolved in ether (25 c.c.) and filtered through fritted glass with suitable protection from the atmosphere, cooled to − 10°, and poured slowly into a solution of 5-ketoruban (0·3 g.) in ether (30 c.c.) also at − 10°. After standing for 1 hour at this temperature, the yellow addition compound was decomposed with ice and acetic acid, the solution basified with potassium carbonate solution, and extracted with chloroform. The gum remaining when the solvent was removed was taken up in acetic acid (10 c.c. of 30%), boiled with charcoal, and the filtered solution basified with potassium carbonate. The *5-ethylruban-5-ol*, which separated as a gummy precipitate, solidified on standing for several days in the refrigerator; it was collected, washed with water, dried in a vacuum desiccator, and crystallised from ethyl acetate–light petroleum. The compound (0·03—0·05 g.), white prisms, m. p. 139°, is soluble in alcohol and benzene, sparingly soluble in ether (Found: C, 77·3; H, 8·3; N, 9·6. $C_{19}H_{24}ON_2$ requires C, 77·0; H, 8·2; N, 9·5%). Its *picrate*, formed in alcohol, crystallises from this solvent in yellow prisms, m. p. 161°, very soluble in acetone (Found: C, 49·2; H, 3·7. $C_{19}H_{24}ON_2,2C_6H_3O_7N_3$ requires C, 49·3; H, 4·0%).

Reaction of 5-Keto-6 : 9-rubanene with Ethylmagnesium Iodide.—A Grignard solution from magnesium (2·6 g.) and ethyl iodide (6·4 c.c.) was freed from excess ethyl iodide, cooled to 0°, and a solution of 5-keto-6 : 9-rubanene (0·8 g.) in ether (30 c.c.), also at 0°, added slowly with stirring. After standing for 1 hour in ice, the mixture was warmed for 5 minutes on the water-bath, and the deep yellow addition product decomposed with ice and acetic acid. The solution was basified with saturated potassium carbonate solution and extracted with ether–chloroform (1 : 1). The united extracts were dried, the solvent removed, the residual gum taken up in absolute alcohol (5 c.c.), and precipitated with a solution of picric acid (0·5 g.) in absolute alcohol (10 c.c.). The yellow picrate was collected, crystallised from absolute alcohol, and decomposed with hydrochloric acid (1 : 1). The acid filtrate was basified with potassium carbonate solution, the gummy precipitate allowed to harden, collected, and crystallised from light petroleum (b. p. 60—80°). After several recrystallisations, colourless prisms, soluble in alcohol and benzene, sparingly soluble in ether (0·05 g., m. p. 164°), were obtained (Found: C, 77·8; H, 7·5. $C_{19}H_{22}ON_2$ requires C, 77·5; H, 7·55%). The *compound* gave a *picrate* crystallising from alcohol in slender, deep yellow needles, m. p. 150° (Found: C, 49·4; H, 3·9. $C_{19}H_{22}ON_2,2C_6H_3O_7N_3$ requires C, 49·4; H, 3·7%).

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