63. *The Constitution of Apocinchene and Syntheses of its Methyl and Ethyl Ethers.*

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IN the course of their investigations on the constitution of the cinchona alkaloids Comstock and Koenigs observed a remarkable reaction whereby cinchene and quinene were respectively converted by prolonged boiling with concentrated hydrobromic acid into apocinchene and apoquinene (*Ber.*, 1881, **14**, 1885; 1894, **27**, 900), but the matter has received no further attention. This is probably because Koenigs was able to show that these products represent fundamental departures in type from the alkaloids themselves. By progressive oxidation of its ethyl ether, Koenigs converted apocinchene into a 4-dicarboxyethoxyphenylquinoline, from which 4-*o*-hydroxyphenylquinoline was obtained and identified by comparison with a synthetic material, prepared by Besthorn and Jaeglé (*Ber.*, 1894, **27**, 3035). Since, further, the dicarboxylic acid yielded an anhydride, and its precursor was a quinolylethoxyacetophenonecarboxylic acid, it followed that apocinchene contained two ethyl groups and that these occupied either the 2 : 3- or the 3 : 4-position (IV) with respect to the phenolic hydroxyl group.

Of these alternatives Koenigs seemed to prefer the former, and it has been cited without qualification in the literature [compare Meyer and Jacobson, " Lehrbuch der organischen Chemie," II, (3), 1006; Brühl, " Die Pflanzenalkaloide," p. 197].

From an inspection of the formula (I) for cinchene (Koenigs, *J. pr. Chem.*, 1900, **61**, 146), however, it seemed to us highly probable that the two ethyl groups arise from the vinyl group and from the two bridge methylene groups respectively, and therefore that apocinchene should be represented by (IV). The detailed mechanism of the change remains

somewhat obscure, but in view of Lipp's work on the relationships of δ-amino-ketones and the corresponding tetrahydropyridines (*Ber.*, 1905, **38**, 2474; *Annalen*, 1915, **409**, 79) it would seem that the idea of conversion of cinchene into the ketone (II) could be entertained at the most for dilute acid solutions, in which the formation of lepidine and meroquinene is observed (Koenigs, *Ber.*, 1890, **23**, 2677; 1894, **27**, 900):
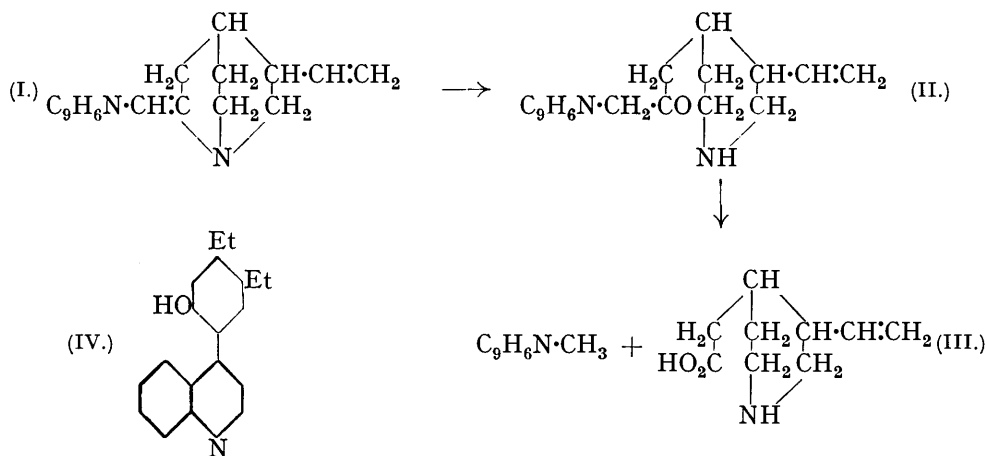
A different mechanism must be sought for strongly acid solutions, and is probably to be connected with the formation of olefins by decomposition of the salts of amines.

In order to test our views, we undertook the synthesis of (IV) and, as a preliminary, decided to examine the possibility of extending the method of Blaise and Maire (*Bull. Soc. chim.*, 1908, **3**, 658, 667) from aliphatic to aromatic β-chloroethyl ketones:
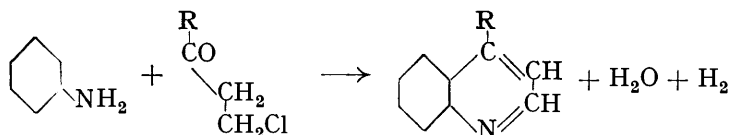
In this manner, 4-phenylquinoline was readily obtained, and although, as we had anticipated from the observations of Blaise and Maire in the aliphatic series, we only obtained a very moderate yield (10%), this was amply compensated by the directness of the method as contrasted with that employed by Besthorn and Jaeglé in their work.

Although the yields were still smaller in the cases of the phenolic ethers, it was clear that the application of the method to 3 : 4-*diethyl-anisole* and -*phenetole* was sufficiently practicable for our purpose. The identity of the solid ethyl ether, as well as of the *picrates* derived from each of the synthetic bases with the respective products prepared from authentic apocinchene, served to confirm our prediction. Although the preference of Koenigs is thus shown to have been wrong, it must in fairness be stated that he conceived the reaction as involving an olefinic intermediate product (*J. pr. Chem., loc. cit.*).

m-Ethylphenol, the starting material for the preparation of 3 : 4-diethylanisole, was prepared from *m*-hydroxyacetophenone by Clemmensen's method of reduction, and also by decomposition of its semicarbazone with potassium hydroxide. It has been isolated from coal tar by Kruber and Schmitt (*Ber.*, 1931, **64**, 2270). Conversion of the phenol through its acetate successively into 4-*hydroxy-2-ethylacetophenone* and 3 : 4-*diethylphenol* was carried out along familiar lines. The constitutions of the products follow by analogy with those prepared under the same conditions from *m*-cresol (Rosenmund and Schnurr, *Annalen*, 1928, **460**, 65), and we have independently confirmed that of the ketone by converting it, with the aid of hydrogen peroxide (compare Baker, *J.*, 1934, 1678), into 2-ethylquinol. *m*-Ethylphenyl acetate exhibits a much smaller tendency than *m*-tolyl acetate to yield a *p*-hydroxyacetophenone derivative.

<div align="center">EXPERIMENTAL.</div>

4-Phenylquinoline.—Hale and Britton (*J. Amer. Chem. Soc.*, 1919, **41**, 845) claim a 90% yield of β-chloropropiophenone, m. p. 57°. Conant and Kirner, however (*ibid.*, 1924, **46**, 240), record a melting point of 49—50° for the ketone, and a repetition of Hale and Britton's work has now yielded a mixture of products, m. p. 71—72° (obviously 1 : 3-diphenylpropan-1-one, for which Schneidewind, *Ber.*, 1888, **21**, 1325, gives m. p. 72—73°) and m. p. 49—50° respectively. In confirmation of Conant's work, the latter melting point could not be raised by crystallisation from light petroleum or alcohol. Hale and Britton's procedure was therefore modified by heating β-chloropropionic acid (20 g.) with phosphorus trichloride (18 g.) on the water-bath for 1 hour, treating the product with carbon disulphide (30 c.c.), and adding the filtered mixture slowly to a mixture of benzene (14 g.), carbon disulphide (30 c.c.), and aluminium chloride (24 g.). After being gently warmed for $\frac{1}{2}$ hour, the mixture was poured on ice. A crude product (30 g.), m. p. 30—40°, remaining after spontaneous evaporation of the solvent was crystallised from light petroleum. Unnecessary heating of this ketone and its derivatives described below must be avoided.

β-Phenylaminopropiophenone, obtained when the chloro-ketone (1·1 g.) and aniline (1·4 g.) were heated with water (2 g.) for $\frac{1}{2}$ hour at 100°, crystallised from alcohol in white shining plates, m. p. 111—112° (Collet, *Bull. Soc. chim.*, 1897, **17**, 80, gives m. p. 111—112°).

It was, however, unnecessary to isolate this in the preparation of 4-phenylquinoline. The pure chloro-ketone (16·8 g.) was heated for 1 hour at 100° with aniline (18·6 g.), aniline hydrochloride (12·95 g.), and ethyl alcohol (13 g.), the mixture made alkaline with potassium hydroxide, and the base extracted with ether and dried over potassium carbonate. The fraction (11 g.), b. p. 100—290°/20 mm., was heated for 1 hour at 100° with acetic anhydride (12 g.). The unacetylated base (4 g.), extracted from the mass, was treated with alcoholic picric acid solution. The picrate separated from alcohol in yellow needles, m. p. 225° (Found : C, 58·0; H, 3·6; N, 13·0. Calc. for $C_{21}H_{14}O_7N_4$: C, 58·1; H, 3·2; N, 12·9%). Koenigs and Meimberg record 224° as the m. p. of 4-phenylquinoline picrate (*Ber.*, 1895, **28**, 1039).

A similar procedure was applied to various derivatives of benzene, and the relevant details of m. p., analyses, and yields are tabulated below. The last two instances given are those which respectively furnish the methyl and the ethyl ether of apocinchene. The validity of the melting points of the picrates and their mixtures as tests of identity was specially tested. In all cases sensible depression of melting point was observed when different picrates were mixed.

Substituents.	Chloro-ketone. M. p. and analysis (theo. figures below).	M. p. of anilide.	B. p. of basic portion used for acetylation.	M. p. and analysis of picrate isolated (theo. figures below).	Yield, %.
4-Methoxy	63—64° C, 60·1; H, 5·8; Cl, 18·0 (C, 60·4; H, 5·5; Cl, 17·9%)	130°	100—300°/ 20 mm.	232—234° (decomp.), shrinks and darkens at 223° C, 56·7; H, 3·7; N, 12·0 (C, 56·9; H, 3·4; N, 12·1%)	6
4-Methyl	80—81° C, 65·5; H, 6·3; Cl, 19·3 (C, 65·7; H, 6·0; Cl, 19·4%)	120	100—300/ 20 mm.	206° (decomp.), shrinks at 197° C, 58·6; H, 4·0; N, 12·8 (C, 58·9; H, 3·6; N, 12·5%)	7
2-Methoxy-5-methyl	60° C, 62·3; H, 6·3; Cl, 16·4 (C, 62·1; H, 6·1; Cl, 16·7%)		100—300/ 20 mm.	213° (decomp.) C, 57·4; H, 4·1; N, 11·4 (C, 57·7; H, 3·8; N, 11·7%)	5
4 : 5-Dimethyl	71—72° C, 67·0; H, 6·9; Cl, 18·1 (C, 67·2; H, 6·6; Cl, 18·1%)	93—94	100—290/ 20 mm.	250—253° (decomp.), darkens at 241° C, 60·0; H, 4·2; N, 12·3 (C, 59·7; H, 3·9; N, 12·1%)	9
2-Methoxy-4 : 5-dimethyl	76—77° C, 64·3; H, 6·7; Cl, 15·7 (C, 64·0; H, 6·7; Cl, 15·8%)		110—280/ 30 mm.	215° (decomp.) C, 58·3; H, 4·3; N, 11·6 (C, 58·5; H, 4·1; N, 11·4%)	3
2-Methoxy-4 : 5-diethyl	41° C, 65·7; H, 7·8; Cl, 14·1 (C, 66·0; H, 7·5; Cl, 14·0%)		100—280/ 20 mm.	200° decomp.), darkens at 197° C, 60·2; H, 4·8; N, 11·0 (C, 60·0; H, 4·6; N, 10·8%)	3
2-Ethoxy-4 : 5-diethyl	81—82° C, 66·9; H, 8·1; Cl, 12·9 (C, 67·0; H, 7·8; Cl, 13·2%)		from 100/ 20 mm. to 250/ 0·5 mm.	180—181° (decomp.) N, 10·5 (N, 10·5%)	1

m-*Ethylphenol.**—Comparative experiments on the nitration of acetophenone (Rupe, Braun, and Zembruski, *Ber.*, 1901, **34**, 3623; Mayer and English, *Annalen*, 1918, **417**, 82) showed it to be essential to use the pure crystalline ketone, and the best results followed when a mixture of the ketone (240 g.) with sulphuric acid (*d* 1·98; 660 c.c.) at − 10° was treated as quickly as possible with a mixture of nitric acid (*d* 1·42; 140 c.c.) and sulphuric acid (*d* 1·98; 300 c.c.), consistent with maintenance of the temperature below 0°; after being stirred for 1 hour, the whole was poured on ice (3 kg.). By crystallising the yellowish-white solid from alcohol (500 c.c.), *m*-nitroacetophenone (240 g.), m. p. 80—81°, was obtained. Its reduction was carried out satisfactorily by West's process (*J.*, 1925, **127**, 494), but rather better results were obtained when a solution of the nitro-ketone (30 g.) and aqueous ammonia (*d* 0·880; 16 c.c.) in alcohol (120 c.c.) was saturated with hydrogen sulphide, and the whole boiled for 2 hours. Yield, 24 g. *m*-Hydroxyacetophenone (Rupe and Majewski, *Ber.*, 1900, **33**, 3407) was converted into its *semicarbazone*, m. p. 194—196° (Found : N, 21·8. $C_9H_{11}O_2N_3$ requires N, 21·8%), and when an intimate mixture of this (10 g.) with potassium hydroxide (9 g.) was heated at 190° (compare Rabe and Jantzen, *Ber.*, 1921, **54**, 925), *m*-ethylphenol was obtained in quantitative yield; it was identified by conversion into its benzoate, m. p. 50° (Béhal and Choay, *Bull. Soc. chim.*, 1894, **11**, 212), and its p-*nitrobenzoate*, m. p. 68° (Found : N, 5·4. $C_{15}H_{13}O_4N$ requires N, 5·2%). The phenol was obtained more directly, but in much less satisfactory yield (34%), when a boiling mixture of amalgamated zinc (200 g.), water (150 c.c.), and the ketone (5 g.) was treated with hydrochloric acid (*d* 1·13; 100 c.c.) in the course of 20 minutes, and nine further portions of the ketone (5 g.) and acid (100 c.c.) were successively added in the same manner. Finally more acid (250 c.c.) was added and the whole boiled for 3 hours. We are indebted to Dr. G. Baddeley for carrying out this experiment.

4-*Hydroxy-2-ethylacetophenone.**—Freshly prepared aluminium chloride (60 g.) was added gradually to a solution of *m*-ethylphenyl acetate (50 g.), b. p. 222—223° (Béhal and Choay, *loc. cit.*), in dry nitrobenzene (125 g.) maintained at 0°. After 5 days, the mixture was decomposed by ice-water and treated with steam. The 2-hydroxy-4-ethylacetophenone thus removed awaits further examination. The material not volatile in steam consisted essentially of 4-*hydroxy-2-ethylacetophenone*,* b. p. 150—152°/0·45 mm., m. p. 102° (Found : C, 73·0; H, 7·6. $C_{10}H_{12}O_2$ requires C, 73·2; H, 7·3%). The yield varied inexplicably, and only exceptionally amounted to 50% of the theoretical. The *semicarbazone* was formed only after several weeks, and obtained in clusters of long needles, m. p. 172° (Found : N, 19·2. $C_{11}H_{15}O_2N_3$ requires N, 19·0%). The ketone was therefore more readily characterised by its p-*nitrobenzoate*,* m. p. 80° (Found : N, 4·6. $C_{17}H_{15}O_5N$ requires N, 4·5%). A solution of the ketone (0·8 g.) in 2N-potassium hydroxide (5 c.c.) was treated with 3% hydrogen peroxide solution (8·5 c.c.) in an atmosphere of coal gas. After ½ hour crystals of unchanged hydroxyethylacetophenone (0·3 g.), m. p. 102°, had separated; these were filtered off, and acidification of the dark-coloured mother-liquor gave a little impure material (0·1 g.), m. p. *ca.* 85°. Ether extraction of the liquors yielded ethylquinol, which was crystallised from benzene; m. p. 113—115° (Found : C, 69·3; H, 7·2. Calc. : C, 69·6; H, 7·2%). Bayric (*Bull. Soc. chim.*, 1894, **11**, 1130) gives m. p. 112—113°, Johnson and Hodge (*J. Amer. Chem. Soc.*, 1913, **35**, 1019) m. p. 113—114°, and Clemmensen (*Ber.*, 1914, **47**, 55) m. p. 112°. The product did not depress the m. p. of an authentic specimen prepared from quinol (Nencki and Schmid, *J. pr. Chem.*, 1881, **23**, 546; Johnson and Hodge, *loc. cit.*; Clemmensen, *loc. cit.*).

3 : 4-*Diethylphenol.*—The ketone (20 g.) was reduced by boiling it with amalgamated zinc (100 g.), hydrochloric acid (60 c.c., *d* 1·17), and water (60 c.c.), hydrochloric acid (625 c.c.) being gradually added in the course of 6 hours to the boiling solution; the whole was boiled for a further 1½ hours. By separating the oily layer from the cold mixture and extracting the aqueous layer with ether, 3 : 4-*diethylphenol* (15 g.), b. p. 106°/0·5 mm., was isolated (Found : C, 80·0; H, 9·4. $C_{10}H_{14}O$ requires C, 80·0; H, 9·3%); it was characterised by the p-*nitrobenzoate*, m. p. 81—82° (Found : N, 4·8. $C_{17}H_{17}O_4N$ requires N, 4·7%). A mixture of its *acetate* (17·7 g.), b. p. 113—115°/0·35 mm. (Found : C, 74·9; H, 8·1. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·3%), with aluminium chloride (26·5 g.) was heated at 140° for 2 hours. The resulting 2-*hydroxy-4* : 5-*diethylacetophenone* * (15·9 g.), b. p. 134—137°/0·75 mm. (Found : C, 74·6; H, 8·5. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·3%) (compare Auwers, Bundesmann, and Wieners, *Annalen*, 1926, **447**, 163), was characterised by its *semicarbazone*,* m. p. 240° (Found : N, 16·9. $C_{13}H_{19}O_2N_3$ requires N, 16·9%). Its *methyl* ether was prepared by the gradual addition of methyl sulphate (5 g.) to a solution of the phenol (4 g.) and potassium hydroxide (1·5 g.) in

* Compounds marked with an asterisk were first prepared by Mr. E. C. S. Jones in collaboration with one of us.

aqueous potassium hydroxide solution (2N; 12 c.c.). The operation was completed with the aid of further quantities of methyl sulphate (7·5 g.), potassium hydroxide (2 g.), and of the 2N-solution (10 c.c.). From an ethereal extract of the resulting mixture, aqueous sodium hydroxide solution (40%) caused precipitation of the sodium salt of the unchanged phenol, and this was removed on a fritted glass filter. The required methyl ether (2·7 g.), m. p. 35—39°, was isolated from the ethereal solution, and characterised by its *semicarbazone*, m. p. 128° (Found : N, 16·1. $C_{14}H_{21}O_2N_3$ requires N, 16·0%).

The Methyl Ether of Apocinchene.—(a) Apocinchene hydrobromide (Koenigs, *J. pr. Chem.*, *loc. cit.*), was treated in the usual manner with aqueous potassium hydroxide solution (2N) and methyl sulphate. The oily product (Koenigs, *Ber.*, 1885, **18**, 2380) was characterised by its *picrate*, m. p. 200° (decomp.) after darkening at 197° (Found : C, 60·3; H, 4·8; N, 11·0. $C_{26}H_{24}O_8N_4$ requires C, 60·0; H, 4·6; N, 10·8%).

(b) 3 : 4-*Diethylanisole*, from the corresponding phenol, is an oil, b. p. 124—125°/23 mm. (Found : C, 80·8; H, 10·0. $C_{11}H_{16}O$ requires C, 80·5; H, 9·8%). A cooled mixture of this ether (6·6 g.), aluminium chloride (5·2 g.), and carbon disulphide (12 c.c.) was treated gradually with a solution of β-chloropropionyl chloride (from the acid, 4·3 g., and phosphorus trichloride, 3·6 g.) in carbon disulphide (12 c.c.), and the mixture at once decomposed by ice-water. Spontaneous evaporation of the carbon disulphide layer furnished 2-*methoxy*-4 : 5-*diethyl-β-chloropropiophenone* (4 g.). It separated from light petroleum in colourless crystals, m. p. 41° (Found : C, 65·7; H, 7·8; Cl, 14·1. $C_{14}H_{19}O_2Cl$ requires C, 66·0; H, 7·5; Cl, 14·0%). If the reaction mixture were left for $\frac{1}{2}$ hour before being worked up, an oily product was produced. The details of its conversion into apocinchene methyl ether are included in the table above. The picrate of the synthetic material softened at 197° and melted at 200°, and did not depress the melting point of material derived from apocinchene itself.

The Ethyl Ether of Apocinchene (Koenigs, *Ber.*, 1885, **18**, 2381).—(a) An authentic specimen was prepared from apocinchene by use of ethyl sulphate, and converted into its *picrate*, m. p. 179—180° (Found : C, 60·4; H, 5·2; N, 10·7. $C_{27}H_{26}O_8N_4$ requires C, 60·7; H, 4·9; N, 10·5%).

(b) 3 : 4-*Diethylphenetole*, from the phenol by treatment with diazoethane, boiled at 120—125°/20 mm. (Found : C, 80·6; H, 10·4. $C_{12}H_{18}O$ requires C, 80·9; H, 10·1%), and was converted into the chloroethyl ketone and thence into apocinchene ethyl ether in the manner described for the corresponding methyl ether above. The picrate of the synthetic material melted at 179—180°, and did not depress the melting point of the authentic ethyl ether. Further, it was converted into the free base, m. p. 70—71° after crystallisation from dilute ethyl alcohol (Found : N, 4·8. $C_{21}H_{23}ON$ requires N, 4·6%). It did not depress the melting point of the authentic ether.