26. *The Application of Pfitzinger Reactions to the Synthesis of Quinoline Derivatives: A Novel Route to 4-Hydroxyquinolines.*

By Ng. Ph. Buu-Hoï and René Royer.

In continuation of earlier work (Buu-Hoï, *J.*, 1946, 795) upon the effect of steric hindrance on the course of Pfitzinger reactions, the condensations of isatins and methyl ketones are shown to involve mostly the methyl group, except in the case of methyl ethyl ketone; pinacoline gave only traces of condensation products. Symmetrical dialkyl ketones react normally, except in the case of highly branched ketones such as di*iso*butyl ketone.

In many instances, the pyrolysis of 2-alkylcinchoninic acids is shown to afford not only the expected 2-alkylquinolines through decarboxylation, but also the corresponding 4-hydroxy-2-alkylquinolines, through decarbonylation.

In recent papers (Buu-Hoï, *loc. cit.*; Buu-Hoï and Cagniant, *Bull. Soc. chim.*, 1946, **13**, 123), Pfitzinger reactions between isatins and alicyclic or arylaliphatic ketones $Ar{\cdot}CO{\cdot}CH_2R$ have been shown to be highly sensitive towards steric hindrance. These studies have now been extended to methyl alkyl ketones and to symmetrical dialkyl ketones.

Pfitzinger (*J. pr. Chem.*, 1897, **56**, 283) found that methyl ethyl ketone reacts with isatin to give 2 : 3-dimethylcinchoninic acid; we have confirmed this work, and this proves that the methylene belonging to an ethyl group is far more reactive than the methyl group, this observation being consistent with previous experiments bearing upon the halogenation of ethylenic hydrocarbons (Ziegler, *et al.*, *Annalen*, 1942, **551**, 80) and alkylnaphthalenes (Buu-Hoï and Lecocq, *J.*, 1946, 830) by means of *N*-bromoamides. These observations may readily be accounted for on the basis of the theory of hyperconjugation (cf. Buu-Hoï and Daudel, *Rec. Trav. chim.*, 1946, **65**, 731).

Surprisingly, this effect is completely reversed in the case of higher homologues of the ethyl radical, the methylene group becoming less active than the methyl. Thus, isatin reacts with methyl *n*-propyl ketone to give, as the chief product, 2-*n*-propylcinchoninic acid, which has previously been synthesised in a different way (Tonella, *Rec. Trav. chim.*, 1897, **16**, 361), although there was some evidence of the presence of a higher-melting isomeric acid. Similarly, methyl *iso*butyl ketone and isatin give the already known 2-*iso*butylcinchoninic acid (Doebner, *Annalen*, 1887, **242**, 282). The homogeneous reaction products from isatin with methyl *n*-hexyl ketone and with methyl *n*-nonyl ketone must then be considered as 2-*n*-hexyl- and 2-*n*-nonylcinchoninic acid. This assumption was proved by chromic acid oxidation of the corresponding alkylquinolines, *n*-valeric acid being obtained in the former case, and *n*-octoic acid in the latter.

From the results of those experiments, it may be inferred that Pfitzinger reactions performed with homologues or halogen derivatives of isatin must take the same course. In this respect, a series of cinchoninic acids bearing substituents on both benzenoid and pyridinic nuclei have been obtained by combining 5-methylisatin, 5-bromoisatin, and 5 : 7-dichloroisatin with the above-mentioned methyl alkyl ketones : details are given later. Owing to steric hindrance, only traces of reaction products could be obtained from condensation of pinacolin with isatin and 5-bromoisatin.

The Pfitzinger reaction between isatins and symmetrical dialkyl ketones occurs normally, except when a strong steric hindrance is present in the ketonic molecule. Thus, isatin and di-*n*-propyl ketone gave high yields of 3-ethyl-2-*n*-propylcinchoninic acid, whereas di*iso*butyl ketone did not give appreciable amounts of the normal condensation products either with isatin or with 5-bromoisatin. Even high-molecular ketones such as palmitone $(n\text{-}C_{15}H_{31})_2CO$ react (palmitone and isatin give the low-melting 3-n-*tetradecyl*-2-n-*pentadecylcinchoninic acid*).

Since the earlier work (*e.g.*, Koenigs, *Ber.*, 1879, **12**, 98; Doebner, *loc. cit.*), decarboxylation of cinchoninic acids by heating them either alone or in the presence of lime or soda-lime has frequently been used for the synthesis of substituted quinolines. We have now found that the simple dry distillation of substituted cinchoninic acids without any alkaline catalyst affords not only a very convenient method of preparation for homologues and halogen derivatives of quinoline, but this technique also leads in many instances to the corresponding 4-hydroxyquinolines, the pyrolysis resulting sometimes in a loss of carbon monoxide. In those cases, the presence of carbon monoxide among the gaseous pyrolysis products was detected by means of iodic anhydride.

For example, distillation of 2-methylcinchoninic acid gave a mixture of quinaldine and 4-hydroxy-2-methylquinoline; in the same manner, 6-bromo-4-hydroxyquinaldine was obtained along with 6-bromoquinaldine from 6-bromo-2-methylcinchoninic acid prepared from acetone and 5-bromoisatin.

Similarly, small quantities of 4-hydroxy-2 : 3-dimethylquinoline could be detected in the distillation products from 2 : 3-dimethylcinchoninic acid. 2-*n*-Propylcinchoninic acid yielded 2-*n*-propylquinoline, whereas its 6-bromo-derivative gave rise almost entirely to 6-bromo-4-hydroxy-2-*n*-propylquinoline; 2-*iso*butylcinchoninic acid afforded a mixture of 2-*iso*butyl- and 4-*hydroxy*-2-iso*butyl*-quinoline. In some cases, pyrolysis proceeded as expected, as, for instance, 6-*bromo*-2-iso*butylcinchoninic acid* afforded a mixture of 6-*bromo*-2-iso*butylquinoline* with its 4-*hydroxy*-derivative, but 6 : 8-*dichloro*-2-iso*butylcinchoninic acid* yielded only 6 : 8-*dichloro*-4-*hydroxy*-2-iso*butylquinoline*. On the other hand, from the distillation products of 6-*methyl*-2-iso*butylcinchoninic acid*, only 6-*methyl*-2-iso*butylquinoline* could be isolated. Nevertheless, the promoting effect of the presence of substituents in the molecules of the related cinchoninic acids upon the formation of 4-hydroxyquinolines is shown by the following examples. Whereas 2-n-*hexyl*- and 6-*methyl*-2-n-*hexyl-cinchoninic acid* gave rise to 2-n-*hexyl*- and 6-*methyl*-2-n-*hexyl-quinoline* respectively, the distillation of 6 : 8-*dichloro*-2-n-*hexylcinchoninic acid* afforded a mixture of 6 : 8-*dichloro*-4-*hydroxy*-2-n-*hexylquinoline* and a small quantity of the non-hydroxylic compound, isolated as its *picrate*. 2-n-*Nonylcinchoninic acid* was readily decarboxylated to 2-n-*nonylquinoline*, whereas 6-*methyl*-2-n-*nonylcinchoninic acid* gave rise only to 4-*hydroxy*-6-*methyl*-2-n-*nonylquinoline*; 6-*bromo*-2-n-*nonylcinchoninic acid* afforded 6-*bromo*-4-*hydroxy*-2-n-*nonylquinoline*, along with traces of 6-bromo-2-*n*-nonylquinoline (*picrate*). An apparent exception to this rule is afforded by 6-*bromo*-2-n-*hexylcinchoninic acid*, which gave the corresponding 6-*bromo*-2-n-*hexylquinoline* as the sole isolable pyrolysis product.

This new route to 4-hydroxyquinolines may be useful for the preparation of compounds of this class not accessible through the Conrad–Limpach synthesis. Investigations along these lines are being continued.

EXPERIMENTAL.

Pyrolysis of 2 : 3-*Dimethylcinchoninic Acid*.—This acid was prepared (yield 10 g.) from isatin (10 g.), methyl ethyl ketone (15 g.), and potassium hydroxide (14 g.) dissolved in water (70 c.c.); m. p. > 310°. It was thoroughly dried at 100°, and heated in a vacuum; the distillate, which partly solidified on cooling, was treated with cold alcohol, and the insoluble portion recrystallised from toluene, thus giving 4-hydroxy-2 : 3-dimethylquinoline (0·2 g.) as colourless needles, m. p. 310° (Conrad and Limpach, *Ber.*, 1891, **24**, 2991, gave m. p. 305°). On treatment with picric acid, the alcoholic filtrate (above) gave

2 : 3-dimethylquinoline picrate (6 g.) in silky yellow needles, m. p. 227° (from alcohol) (Pfitzinger, *loc. cit.*, gave m. p. 229°).

6-*Bromo*-2 : 3-*dimethylcinchoninic Acid.*—A mixture of 5-bromoisatin (5 g.), methyl ethyl ketone (5·5 g.), and potassium hydroxide (6·5 g.), dissolved in water (50 c.c.), was treated as above. The cinchoninic *acid* thus obtained (6 g.) crystallised from alcohol in prismatic colourless needles, m. p. 290—291° (Found : N, 5·2. $C_{12}H_{10}O_2NBr$ requires N, 5·0%). Dry distillation of this acid (4 g.) in a vacuum (10 mm.) gave a thick yellowish jelly, which was dissolved in hot benzene and converted into a *picrate* (3 g.); this was almost insoluble in alcohol, and crystallised from toluene in fine bright yellow needles, m. p. 225° (decomp. above 200—205°) (Found : N, 11·9. $C_{11}H_{10}NBr,C_6H_3O_7N_3$ requires N, 12·0%). This picrate yielded on treatment with aqueous ammonia 6-*bromo*-2 : 3-*dimethylquinoline*, which crystallised from light petroleum in colourless silky needles, m. p. 82° (Found : N, 6·0. $C_{11}H_{10}NBr$ requires N, 6·3%).

6 : 8-*Dichloro*-2 : 3-*dimethylcinchoninic Acid.*—5 : 7-Dichloroisatin (2·5 g.), methyl ethyl ketone (3 g.), and potassium hydroxide (3·5 g.) dissolved in water (30 c.c.) gave a moderate yield of this *acid* (1 g.), which crystallised from aqueous alcohol in almost colourless prismatic needles which decomposed progressively on heating, without melting below 305° (Found : N, 5·4. $C_{12}H_9O_2NCl_2$ requires N, 5·1%).

Pyrolysis Experiments with 2-*Methylcinchoninic Acid.*—On dry distillation under atmospheric pressure this acid (14 g.) gave a mixture of quinaldine (5 g.), b. p. 245—246°, characterised by its picrate, m. p. 194° (Ciamician and Silber, *Ber.*, 1905, **38**, 3816), and of a solid product (5 g.) which crystallised from alcohol in colourless, readily sublimable leaflets, m. p. 242° (Found : N, 8·8. Calc. for $C_{10}H_9ON$: N, 8·7%), not depressed by admixture with a sample of 4-hydroxyquinaldine prepared by means of the Conrad–Limpach reaction (*Ber.*, 1887, **20**, 947). The gaseous products of the pyrolysis contained both carbon monoxide and dioxide.

6-*Bromo*-2-*methylcinchoninic Acid.*—A mixture of 5-bromoisatin (5 g.), acetone (5 g.), and potassium hydroxide (6·5 g.) dissolved in water (40 c.c.) was refluxed during 16 hours, and the dark brown solution twice extracted with ether, evaporated to half bulk, filtered from the deposited tarry material, and acidified with acetic acid. After cooling, the thick magma of needles thus obtained was filtered off and crystallised from 50% aqueous alcohol. 6-*Bromo*-2-*methylcinchoninic acid* (3 g.) formed glistening, slightly yellowish prisms, m. p. 269° (decomp. above 255°) (Found : N, 5·1. $C_{11}H_8O_2NBr$ requires N, 5·3%). The solid mass obtained on vacuum pyrolysis was triturated with a small quantity of cold ethanol, and the insoluble product (0·1 g. from 2 g. of the cinchoninic acid) crystallised from boiling alcohol; 6-*bromo*-4-*hydroxyquinaldine* formed slightly yellowish needles which readily sublimed above 230° and melted at 269° (Found : N, 5·9. $C_{10}H_8ONBr$ requires N, 5·8%). The alcoholic filtrates gave on treatment with an excess of picric acid a *picrate* (1 g.), which crystallised from toluene in glistening yellow needles, m. p. 205° (sintering above 190°) (Found : N, 12·2. $C_{10}H_8NBr,C_6H_3O_7N_3$ requires N, 12·4%). Decomposition of this picrate by means of aqueous ammonia gave 6-bromoquinaldine, which formed colourless needles, m. p. 100° from light petroleum (Bartow and MacCollum, *J. Amer. Chem. Soc.*, 1904, **26**, 704, gave m. p. 96—97°).

2-n-*Propylcinchoninic Acid.*—A mixture of isatin (15 g.), methyl *n*-propyl ketone (10 g.), and potassium hydroxide (19 g.) dissolved in 10% aqueous alcohol was refluxed during 18 hours. After standard treatment (including concentration to small bulk on a water-bath), the apparently heterogeneous solid obtained (13 g.) was twice recrystallised from water, yielding 2-*n*-propylcinchoninic acid (8 g.) in glistening, silky, colourless leaflets, m. p. 156° (Tonella, *loc. cit.*, gave m. p. 152·8°). A higher-melting isomeric acid was detected in the mother-liquors, but could not be obtained pure. The yellowish oil obtained in the pyrolysis of 2-*n*-propylcinchoninic acid afforded, on redistillation, pure 2-*n*-propylquinoline, b. p. 205°/70 mm., $n^{17\cdot1^\circ}$ 1·5900; the corresponding picrate had m. p. 159—160° (Delaby and Hiron, *Bull. Soc. chim.*, 1930, **47**, 1398, gave b. p. 142—145°/13 mm. and m. p. 159°, respectively). No hydroxyquinoline could be detected.

6-*Bromo*-2-n-*propylcinchoninic Acid.*—5-Bromoisatin (2 g.), methyl *n*-propyl ketone (2 g.), and potassium hydroxide (3 g.) dissolved in 30% aqueous alcohol (20 c.c.) gave a cinchoninic *acid* (1·5 g.), which formed fine, glistening, yellowish needles, m. p. 212° from methanol (Found : N, 4·8. $C_{13}H_{12}O_2NBr$ requires N, 4·7%). Pyrolysis of this acid under 1 mm. yielded a solid brown product, which, after two recrystallisations from methanol, gave 6-*bromo*-4-*hydroxy*-2-n-*propylquinoline* (0·5 g.) as glistening, yellowish needles, m. p. 214° (Found : N, 5·4. $C_{12}H_{12}ONBr$ requires N, 5·2%). No picrate could be obtained in pure condition from the mother-liquors.

2-iso*Butylcinchoninic Acid.*—Methyl *iso*butyl ketone (9 g.), isatin (10 g.), and potassium hydroxide (13 g.) in 20% aqueous alcohol (40 c.c.) gave after 24 hours' heating 2-*iso*butylcinchoninic acid (8·3 g.), which crystallised from very dilute aqueous alcohol in glistening, colourless needles, m. p. 192° (Doebner, *loc. cit.*, gave m. p. 186°). Pyrolysis of this acid (7 g.) afforded a yellow oil which partly solidified, and was therefore triturated with small quantities of cold ethanol. The remaining 4-*hydroxy*-2-iso*butylquinoline* (0·8 g.) was filtered off, and recrystallised from dilute alcohol; silky, colourless needles, m. p. 189°, very soluble in alcohol, were thus obtained (Found : N, 7·1. $C_{13}H_{15}ON$ requires N, 6·9%). The alcoholic filtrate was evaporated, and the residue redistilled in a vacuum, giving 2-*iso*butylquinoline (3 g.), b. p. 268—270°, which yielded a picrate crystallising from alcoholic benzene in long, silky, golden-yellow needles, m. p. 164° (Doebner, *loc. cit.*, gave m. p. 161°).

6-*Methyl*-2-iso*butylcinchoninic Acid.*—5-Methylisatin (4·3 g.), methyl *iso*butyl ketone (5·2 g.), and potassium hydroxide (5·5 g.) dissolved in 30% aqueous alcohol (30 c.c.) gave 6-*methyl*-2-iso*butylcinchoninic acid* (3 g.), which crystallised from methanol in silky, colourless needles, m. p. 192° (Found : N, 5·6. $C_{15}H_{17}O_2N$ requires N, 5·7%). Pyrolysis of this product (2 g.) yielded a viscous oil, which was redistilled in a vacuum. 6-*Methyl*-2-iso*butylquinoline* thus obtained (1 g.) was a yellowish liquid with a pleasant aromatic smell, b. p. 180°/20 mm., n^{16° 1·5766 (Found : N, 7·0. $C_{14}H_{17}N$ requires N, 7·1%), and gave a *picrate* crystallising from alcohol–benzene in glistening yellow needles, m. p. 156° (Found : N, 13·2. $C_{14}H_{17}N,C_6H_3O_7N_3$ requires N, 13·0%). No traces of hydroxyquinoline could be obtained.

6-*Bromo*-2-iso*butylcinchoninic Acid.*—Methyl *iso*butyl ketone (7 g.), 5-bromoisatin (16 g.), and potassium hydroxide (20 g.) in 20% aqueous alcohol (50 c.c.) gave a cinchoninic *acid* (10 g.), which formed glistening, silky, yellowish needles, m. p. 189°, from dilute ethanol (Found: N, 4·4. $C_{14}H_{14}O_2NBr$ requires N, 4·5%). Standard treatment of the pyrolysis products obtained from this acid (8·5 g.) gave 6-*bromo*-4-*hydroxy*-2-iso*butylquinoline* (2 g.) which crystallised from alcohol–benzene in colourless, alkali-soluble prisms, m. p. 191—192° (Found: N, 5·1. $C_{13}H_{14}ONBr$ requires N, 5·0%), and 6-*bromo*-2-*isobutylquinoline* (3 g.) as a pleasant smelling, viscous, yellowish oil, b. p. 215°/14 mm., which slowly solidified; after recrystallisation from light petroleum, colourless prisms, m. p. 46°, were obtained (Found: N, 5·3. $C_{13}H_{14}NBr$ requires N, 5·3%). The corresponding *picrate* formed a microcrystalline, yellow powder, m. p. 192°, from benzene (Found: N, 11·2. $C_{13}H_{14}NBr,C_6H_3O_7N_3$ requires N, 11·5%).

6 : 8-*Dichloro*-2-iso*butylcinchoninic Acid.*—5 : 7-Dichloroisatin (3·4 g.), methyl *iso*butyl ketone (3 g.), and potassium hydroxide (5 g.) dissolved in 40% aqueous alcohol (25 c.c.) gave the *acid* (3 g.), which crystallised from alcohol in fine, glistening, yellowish needles, m. p. 186° (Found: N, 4·6. $C_{14}H_{13}O_2NCl_2$ requires N, 4·7%). Pyrolysis of this acid (2 g.) in a high vacuum (1 mm.) yielded 6 : 8-*dichloro*-4-*hydroxy*-2-iso*butylquinoline* (1 g.), which formed colourless, glistening prisms, m. p. 186°, from methanol (Found: N, 5·0. $C_{13}H_{13}ONCl_2$ requires N, 5·2%).

2-n-*Hexylcinchoninic Acid.*—Octan-2-one (10 g.), isatin (10 g.), and potassium hydroxide (12 g., dissolved in 10 c.c. of water and 15 c.c. of alcohol) gave a homogeneous *acid* (15 g.), which formed tiny, colourless prisms, m. p. 139—140°, from methanol (Found: N, 5·2. $C_{16}H_{19}O_2N$ requires N, 5·4%). The alkaline solutions of this acid gave a persistent foam when shaken. Pyrolysis of the acid (10 g.) yielded 2-n-*hexylquinoline* (5 g.) as a yellow, mobile oil with a pleasant smell; b. p. 298—300°, n^{18° 1·5620 (Found: N, 6·4. $C_{15}H_{19}N$ requires N, 6·5%), which gave a *picrate*, crystallising from ethanol in long, yellow needles, m. p. 112° (Found: N, 12·4. $C_{15}H_{19}N,C_6H_3O_7N_3$ requires N, 12·6%). A mixture of the foregoing quinoline (4 g.) with chromic acid (4 g.) dissolved in dilute sulphuric acid (40 c.c. of water; 5 g. of acid) was boiled during one hour, and the reaction product steam-distilled. *n*-Valeric acid was thus obtained and characterised by the m. p. of its diamide with 1 : 5-diaminonaphthalene (cf. Buu-Hoï, *Bull. Soc. chim.*, 1945, **12**, 590).

6-*Bromo*-2-n-*hexylcinchoninic Acid.*—5-Bromoisatin (3 g.), octan-2-one (1·7 g.), and potassium hydroxide (3·3 g.) dissolved in 50% aqueous alcohol (30 c.c.) yielded, after 18 hours' heating, the expected cinchoninic *acid* (3·5 g.). This crystallised from ethanol in slightly yellowish, silky needles, m. p. 152—153° (Found: N, 4·2. $C_{16}H_{18}O_2NBr$ requires N, 4·1%). Vacuum pyrolysis of this acid (2·8 g.) afforded, after redistillation, 6-*bromo*-2-n-*hexylquinoline* (2 g.) as a viscous, yellow oil, b. p. 238—240°/25 mm., $n^{18\cdot1^\circ}$ 1·5910 (Found: N, 4·8. $C_{15}H_{18}NBr$ requires N, 4·7%). The corresponding *picrate* formed fine, yellow, glistening prisms, m. p. 154°, from alcohol–benzene (Found: N, 11·0. $C_{15}H_{18}NBr,C_6H_3O_7N_3$ requires N, 10·8%).

6 : 8-*Dichloro*-2-n-*hexylcinchoninic Acid.*—5 : 7-Dichloroisatin (2 g.), octan-2-one (1·2 g.), and potassium hydroxide (2·3 g.) dissolved in 50% aqueous alcohol (20 c.c.) gave the corresponding cinchoninic *acid* (2·3 g.) as almost colourless, silky needles, m. p. 145° (from alcohol) (Found: N, 4·2. $C_{16}H_{17}O_2NCl_2$ requires N, 4·3%). Vacuum pyrolysis of this acid (2·5 g.) yielded after standard treatment 6 : 8-*dichloro*-4-*hydroxy*-2-n-*hexylquinoline* (1 g.), which crystallised from aqueous methanol in tiny, glistening, colourless prisms, m. p. 128°, extremely soluble in hot ethanol (Found: N, 4·6. $C_{15}H_{17}NCl_2$ requires N, 4·7%). The alcoholic mother-liquors afforded on treatment with picric acid a small quantity of the *picrate* of 6 : 8-dichloro-2-*n*-hexylquinoline, which formed yellow prisms, m. p. 141°, from ethanol (Found: N, 11·1. $C_{15}H_{17}NCl_2,C_6H_3O_7N_3$ requires N, 10·8%).

6-*Methyl*-2-n-*hexylcinchoninic Acid.*—This *acid* (2 g.) was obtained from 5-methylisatin (2 g.) and octan-2-one (1·6 g.), and formed slightly yellowish, silky needles, m. p. 159°, from ethanol (Found: N, 5·2. $C_{17}H_{21}O_2N$ requires N, 5·1%). Its pyrolysis afforded as the sole isolable product 6-*methyl*-2-n-*hexylquinoline* as a yellowish oil, b. p. 218—220°/60 mm. (Found: N, 6·3. $C_{16}H_{21}N$ requires N, 6·1%), which gave a *picrate* crystallising from ethanol in glistening, yellow prisms, m. p. 114° (Found: N, 12·5. $C_{16}H_{21}N,C_6H_3O_7N_3$ requires N, 12·3%).

2-n-*Nonylcinchoninic Acid.*—Isatin (7 g.), undecan-2-one (15 g.), and potassium hydroxide (9 g.) gave excellent yields of 2-n-*nonylcinchoninic acid* (15 g.), which formed silky, soft, colourless needles, m. p. 145°, from ethanol (Found: N, 4·8. $C_{19}H_{25}O_2N$ requires N, 4·7%). The alkaline solutions of this acid gave a strong persistent foam when shaken in a test-tube. On pyrolysis, 2-n-*nonylquinoline* (12 g.) was obtained in the form of a yellowish oil, b. p. 230—232°/25 mm.; $n^{16\cdot5^\circ}$ 1·5470 (Found: N, 5·4. $C_{18}H_{25}N$ requires N, 5·5%), which gave *n*-octoic acid by treatment with chromic acid, following the same procedure as for the hexyl derivative. The correspodning *picrate* crystallised from ethanol in bright yellow, glinting prisms, m. p. 96° (Found: N, 11·8. $C_{18}H_{25}N,C_6H_3O_7N_3$ requires N, 11·5%).

6-*Methyl*-2-n-*nonylcinchoninic Acid.*—Condensation of 5-methylisatin (0·5 g.) with undecan-2-one (0·8 g.) in the presence of potassium hydroxide (0·7 g.) dissolved in 50% aqueous alcohol (15 c.c.) resulted in the formation of a cinchoninic acid (1·1 g.), which crystallised from hot alcohol in almost colourless, silky needles, m. p. 152—153° (Found: N, 4·6. $C_{20}H_{27}O_2N$ requires N, 4·4%). Vacuum pyrolysis of this acid gave 4-*hydroxy*-6-*methyl*-2-n-*nonylquinoline* (0·5 g.) as a microcrystalline, yellowish powder, m. p. 154° (Found: N, 5·0. $C_{19}H_{27}ON$ requires N, 4·9%). No traces of picrate of a non-hydroxylated quinoline could be isolated.

6-*Bromo*-2-n-*nonylcinchoninic Acid.*—This *acid* (2·7 g.) was obtained from 5-bromoisatin (2 g.) and undecan-2-one (1·5 g.), and formed silky, cream-coloured needles, m. p. 150°, from ethanol (Found: N, 3·8. $C_{19}H_{24}O_2NBr$ requires N, 3·7%). Pyrolysis of this product (2 g.) yielded after standard treatment, 6-*bromo*-4-*hydroxy*-2-n-*nonylquinoline* (0·4 g.), which crystallised from ethanol in cream-coloured prisms, m. p. 146°, the alkaline solutions of which gave a persistent foam on agitation (Found: N, 4·1. $C_{18}H_{24}ONBr$ requires N, 4·0%). As a by-product, 6-*bromo*-2-n-*nonylquinoline picrate* (0·2 g.) was obtained; it crystallised from hot ethanol in bright yellow prisms, m. p. 137° (Found: N, 9·8. $C_{18}H_{24}NBr,C_6H_3O_7N_3$ requires N, 10·0%).

3-*Ethyl*-2-n-*propylcinchoninic Acid.*—Di-*n*-propyl ketone (5·5 g.), treated with isatin (7·2 g.) and potassium hydroxide (8·5 g.) dissolved in 50% aqueous alcohol (30 c.c.), gave the corresponding cinchoninic *acid* in excellent yield (11 g.). After crystallisation from 50% aqueous ethanol, almost colourless prisms, m. p. 214°, were obtained (Found : N, 5·6. $C_{15}H_{17}O_2N$ requires N, 5·7%).

No cinchoninic acid could be obtained from isatin and di*iso*butyl ketone, even after 6 days' heating

3-n-*Tetradecyl*-2-n-*pentadecylcinchoninic Acid*.—A mixture of palmitone (6 g.) (obtained by pyrolysis of calcium palmitate), isatin (1 g.), and potassium hydroxide (2 g.) dissolved in alcohol (30 c.c.) was refluxed during 3 days on a water-bath. Most of the solvent was removed by evaporation, and the residue twice extracted with hot water, after removal of palmitone by means of benzene, the aqueous solution was acidified with acetic acid. The yellowish precipitate of the *acid* was collected, and recrystallised several times from alcohol, soft, colourless needles (0·5 g.), m. p. 101°, extremely soluble in benzene, being thus obtained (Found : N, 2·3. $C_{39}H_{65}O_2N$ requires N, 2·4%).

The authors gratefully acknowledge their indebtedness to Dr. Ch. Mentzer for the gift of samples of some ketones mentioned in this work.

LABORATORY OF ORGANIC CHEMISTRY,
RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS.

[*Received, March* 10*th*, 1947.]