115. *Hydroacridones. Synthesis and Dehydrogenation.*

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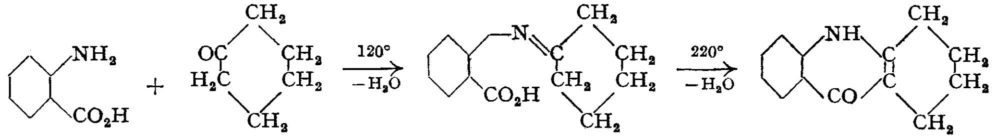
The five methylanthranilic acids have been condensed with *cyclo*hexanone at 220°. Anthranilic acid has been condensed similarly with 2-methyl*cyclo*hexanone. The condensation product obtained by Perkin and Sedgwick (J., 1924, **125**, 2441) from anthranilic acid and 3-methyl*cyclo*hexanone is shown to be 2-methyl-1 : 2 : 3 : 4-tetrahydroacridone by its dehydrogenation to 2-methylacridone. All these methyltetrahydroacridones have been dehydrogenated to the corresponding methylacridone by heating with copper in air at 360°.

The hydroacridones, hitherto but little studied, provide a good method for the preparation and proof of configuration of the substituted acridones and acridines. Tiedkte (*Ber.*, 1909, **42**, 621) heated *cyclo*hexanone with anthranilic acid at 120°, obtaining an anil, easily soluble in both acids and alkalis, and further heating at 220° afforded 1 : 2 : 3 : 4-tetrahydroacridone in 40% yield.



That anil formation is not essential for the subsequent formation of the tetrahydroacridone is shown by the fact that *N*-methylanthranilic acid condenses readily with *cyclo*hexanone to form *N*-methyl-1 : 2 : 3 : 4-tetrahydroacridone. In any case no anil was isolated by condensation at 120° of the four *C*-methylanthranilic acids, the only solid product being unchanged acid. Condensation at 220°, however, readily afforded methyl-1 : 2 : 3 : 4-tetrahydroacridones.

Hughes and Lions (*Proc. Roy. Soc. N.S.W.*, 1937, **71**, 458) prepared tetrahydroacridones by condensing primary aromatic amines with ethyl *cyclo*hexanone-2-carboxylate at room temperature with hydrogen chloride as catalyst, obtaining anils which were subsequently cyclised by being heated to 100° and added to liquid paraffin at 280°. In this way they prepared 7- and 9-methyl-1 : 2 : 3 : 4-tetrahydroacridones, both melting above 300°.

The hydroacridones now reported are high-melting solids, best recrystallised from pyridine. They show no fluorescence in alcoholic solution in daylight but are, with one exception, fluorescent under ultra-violet light, giving different colours or intensities of light under acid and alkaline conditions. Their solutions in cold concentrated sulphuric acid are yellow, without daylight fluorescence. These liquids when poured into 10 volumes of water produce clear, colourless solutions, evidence of the basic nature of these compounds.

The compounds are soluble in alcoholic alkali (the *N*-methyl member by virtue of its solubility in alcohol alone) but not in aqueous alkali. They also readily dissolve in 5N-hydrochloric acid, some yielding crystalline hydrochlorides on cooling. These hydrochlorides are hydrolysed by water but are stable in very dilute hydrochloric acid. All the hydrochloride solutions yield a precipitate of the corresponding dichromate on addition of *excess* of potassium chromate solution.

The hydroacridones, like the hydrocarbazoles, yield picrates from acetic acid which possess sharp melting points.

On heating with copper powder in air at 360° the tetrahydroacridones lose hydrogen, passing into the corresponding acridone. This method is the cleanest and best yet tried, being preferable to heating with lead oxide (von Braun and Wolff, *Ber.*, 1922, **55**, 3676), heating alone in air at 280° (Tiedkte, *loc. cit.*), or heating with sulphur in quinoline solution (Perkin and Plant, J., 1923, **123**, 694), the last method producing from tetrahydroacridone itself a substance containing sulphur which is not thioacridone.

EXPERIMENTAL.

All the corrected m. p.'s given were obtained in a liquid-paraffin bath. For m. p.'s well above 300°, the bath was heated at such a rate that a temperature of 300° was reached in 5 minutes. Heating was then continued at the normal rate.

1 : 2 : 3 : 4-*Tetrahydroacridone.*—A mixture of 2 g. of *cyclo*hexanone (94%, 1·3 mols.) and 2 g. of anthranilic acid was heated with occasional stirring to 220° during 1 hour and kept at 220—240° for 30 mins. To the warm residue were added 15 ml. of benzene, the mixture refluxed for 30 mins., and allowed to cool. After being filtered off, the solid was washed with benzene until the filtrate was colourless, and finally with ether, and dried in air. The cream-coloured solid was recrystallised from pyridine, giving colourless needles, m. p. 370° (Tiedkte, *loc. cit.*, gives 358°). The yield of crude product was 1·8 g. (60%). Titration of the picrate (m. p. 198°) to *m*-cresol-purple with 0·1N-sodium hydroxide gave for the base *M*, 202·5 (Calc. for $C_{13}H_{13}ON$: *M*, 199).

9-*Methyl*-1 : 2 : 3 : 4-*tetrahydroacridone.*—Prepared as above from 2 g. of 3-methylanthranilic acid (made as in D.R.-P. 375,616; see also *Org. Synth.*, 1925, **5**, 71; *Arch. Pharm.*, 1929, **267**, 578) and 2 g. of *cyclo*hexanone (94%, 1·5 mols.), this *compound* was obtained in a yield of 1·8 g. (64%); recrystallisation from pyridine gave colourless needles, m. p. 346° (Found : N, 6·3. $C_{14}H_{15}ON$ requires N, 6·6%). The picrate separates from acetic acid as yellow needles, m. p. 215—216°.

8-*Methyl*-1 : 2 : 3 : 4-*tetrahydroacridone.*—This compound was prepared from 2·2 g. of *cyclo*hexanone (94%) and 2 g. of 4-methylanthranilic acid (made essentially according to Niementowski, *J. pr. Chem.*, 1889, **40**, 1), the yield of solid, washed with alcohol in place of benzene, being 1·2 g. (42%); recrystallisation from pyridine gave cream-coloured plates, m. p. 378°. The *picrate* had m. p. 208—209° (Found, by titration : *M*, 441. $C_{14}H_{15}ON,C_6H_3O_7N_3$ requires *M*, 442).

7-*Methyl*-1 : 2 : 3 : 4-*tetrahydroacridone.*—2 G. of *cyclo*hexanone (94%) and 2 g. of 5-methylanthranilic acid (made as in D.R.-P. 375,616; see also *Org. Synth.* and *Arch. Pharm.*, *locc. cit.*), heated as above, gave 1·95 g. (69%) of the *acridone*; recrystallised from pyridine, this formed cream plates, m. p. 374° (Found : N, 6·4%). The picrate separates from acetic acid as yellow prisms, m. p. 194—196°.

6-*Methyl*-1 : 2 : 3 : 4-*tetrahydroacridone.*—7·8 G. of 6-methylanthranilic acid (m. p. 128—129°, decomp.; prepared as by Gabriel and Thieme, *Ber.*, 1919, **52**, 1079) and 10 ml. of *cyclo*hexanone (94%) were heated at 220° for 1½ hours, and the solid residue washed with alcohol; this afforded 3·9 g. (35%) of colourless prisms, m. p. 355°, purification being unnecessary. This compound, unlike the other methyltetrahydroacridones, shows no u.v. fluorescence in alcoholic solution under acid or alkaline conditions. The *picrate* had m. p. 165—185° (Found : *M*, 438·5).

2-*Methyl*-1 : 2 : 3 : 4-*tetrahydroacridone.*—One hour's heating of a mixture of 2 g. of anthranilic acid and 2·5 ml. of 3-methyl*cyclo*hexanone (98%) at 220° gave 2·4 g. (77%) of benzene-washed product; recrystallisation from pyridine yielded white to faintly pink leaflets, m. p. 362°. Titration of the *picrate* [m. p. 212° (decomp.) not raised by recrystallisation; 0·35 g. from 0·2 g. of each component] showed that the base had *M*, 210. The high yield of pure picrate indicates that only one of the two possible methyltetrahydroacridones was formed. Its configuration was proved by dehydrogenation to 2-methylacridone (see below).

1-*Methyl*-1 : 2 : 3 : 4-*tetrahydroacridone.*—A mixture of 20 g. of anthranilic acid and 25 g. of 2-methyl*cyclo*hexanone (93%), heated to 220° during 1½ hours and kept at 220° for a further 1½ hours, gave 15 g. (48%) of alcohol-washed product. Recrystallisation from pyridine yielded cream-coloured needles, m. p. 305°. Titration of the *picrate* (m. p. 183—184°) showed for the base *M*, 215.

10-*Methyl*-1 : 2 : 3 : 4-*tetrahydroacridone.*—A mixture of 10 g. of *N*-methylanthranilic acid (Houben and Brassert, *Ber.*, 1906, **39**, 3235; yield of pure acid 50%) and 12 ml. of *cyclo*hexanone (97·5%) after 3 hrs. at 220° gave a residue, solid when cold, which was recrystallised from benzene, giving 8·5 g. (60%) of pale yellow needles, melting over a wide range beginning at 86°; recrystallisation from pyridine yielded cream-coloured prisms, m. p. 170—172°. This compound, unlike the *C*-methyltetrahydroacridones, is easily soluble in alcohol. Titration of the *picrate* (m. p. 209—210°) showed that the base had *M*, 220.

Dehydrogenations.—Dehydrogenation was best achieved by heating at 360° with 2 parts by weight of copper powder, the mixture being intimately ground. The apparatus consisted simply of a Hirsch tube, as used for small-scale suction filtration, fitted with an inner boiling tube through which cold water was passed, to act as condenser. The mixtures were heated in a metal-bath at 360° for 30 minutes, the yellow sublimate removed by a long spatula, the residue reground and reheated at 360° for another ½ hour, and the procedure repeated once more. No more sublimate was obtained by a fourth period of heating. The combined sublimate was dissolved in a mixture of alcohol and 5N-sodium hydroxide and filtered hot. The acridone derivative separated on acidifying the filtrate with dilute hydrochloric acid, any unchanged tetrahydroacridone remaining in solution as the hydrochloride. After being cooled and filtered off, the yellow solid was recrystallised from a suitable solvent.

1 : 2 : 3 : 4-Tetrahydroacridone (2 g.) yielded 0·5 g. of pure acridone, m. p. 358° after recrystallisation from benzyl alcohol. A mixed m. p. with authentic acridone [prepared by cyclisation of *N*-phenylanthranilic acid (see *Org. Synth.*, 1939, **19**, 6) and purified as above] showed no depression.

2-Methyl-1 : 2 : 3 : 4-tetrahydroacridone (2 g.) gave 0·2 g. of 2-methylacridone; recrystallised from pyridine, the yellow needles had m. p. 337°. A mixed m. p. with 3-methylacridone, m. p. 338°, prepared from *p*-tolylanthranilic acid by cyclisation with concentrated sulphuric acid (Graebe and Kahn, *Annalen*, 1894, **279**, 272) gave a depression of 12°. The 8-methyl isomer (0·5 g.) gave 0·1 g. of 2-methylacridone, m. p. 342° (Bamberger, *Ber.*, 1909, **42**, 1719, gives m. p. 344°) after recrystallisation from alcohol; mixed m. p. with above 2-methylacridone, 339°, confirming the orientation of 2-methyl-1 : 2 : 3 : 4-tetrahydroacridone.

6-Methyl-1 : 2 : 3 : 4-tetrahydroacridone (1 g.) yielded 0·3 g. of 4-methylacridone, m. p. 318° (Gleu and Nitzsche, *J. pr. Chem.*, 1939, **153**, 219, give m. p. 315°) after crystallisation from aqueous alcohol. This methylacridone is much more soluble in hot alcohol than its three *C*-methyl isomers. A mixed m. p. determination with the product from 2-methyl-1 : 2 : 3 : 4-tetrahydroacridone gave a depression of 7°. It seems probable that 4-methylacridone was the isomer, m. p. 312°, obtained by Senier and Shepheard (J., 1909, **95**, 444) by dry distillation of salicyl-*m*-toluidide.

9-Methyl-1 : 2 : 3 : 4-tetrahydroacridone (0·5 g.) gave 0·15 g. of 1-methylacridone after recrystallisation from acetic acid. The yellow needles, m. p. 342°, gave no depression on mixing with a sample of authentic 1-methylacridone, m. p. 345°, prepared by cyclisation of *o*-tolylanthranilic acid (Graebe and Locher, *Annalen*, 1894, **279**, 279), but gave a depression of 11° with 2-methylacridone.

1-Methyl-1 : 2 : 3 : 4-tetrahydroacridone (0·5 g.) yielded 0·1 g. of yellow needles, m. p. 342°, after recrystallisation from acetic acid, undepressed when mixed with authentic 1-methylacridone; and the 7-methyl compound (0·5 g.) yielded 0·2 g. of 3-methylacridone after crystallisation from acetic acid, m. p. and mixed m. p. 339°. The 10-methyl compound (0·5 g.) yielded 0·1 g. of *N*-methylacridone, m. p. 201°, after three crystallisations from alcohol (Graebe and Lagodzinski, *Annalen*, 1893, **276**, 47, give m. p. 203°); this compound is insoluble in cold alcoholic alkali.

Dimethyltetrahydroacridones and dihydrobenzacridones have also been prepared and dehydrogenated and this investigation will be reported in a later publication.

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