638. *Peroxides of Tetrahydrocarbazole and Related Compounds.*
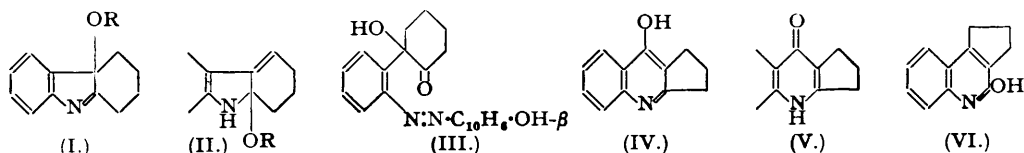*Part II.*

By R. J. S. Beer, L. McGrath, and Alexander Robertson.

Following the recognition of formula (I; R = H) for the reduction product, m. p. 153°, of tetrahydrocarbazolyl hydroperoxide (Part I, *J.*, 1950, 2118) the structure (I; R = OH) for the hydroperoxide is affirmed.   With the aid of its benzoyl and methyl derivatives the amphoteric compound, m. p. 330° (decomp.), obtained from (I; R = OH), has been shown to be 4-hydroxy-2 : 3-*cyclo*pentenoquinoline (IV or V) and not the isomeride (VI).   A comparison of the ultra-violet absorption spectra of (IV), (VI), 1 : 2 : 3 : 4-tetrahydroacridone, and carbostyril supports this conclusion.
    The decomposition of the hydroperoxide (X; R = OH) of *cyclo*pentane*spiro*-2-(4 : 5 : 6 : 7-tetrahydro-ψ-indoxyl) with alkaline agents has been examined.

FROM the available evidence it was concluded in Part I (*J.*, 1950, 2118) that tetrahydrocarbazolyl hydroperoxide had either formula (I; R = OH) or formula (II; R = OH), of which (I; R = OH) was considered the more probable.   On reduction with sodium hydrosulphite (dithionite) the peroxide gave a compound, m. p. 153° (Plant and Tomlinson, *J.*, 1933, 298) which behaved as a primary aromatic amine in acid solution; Plant *et al.* (*Nature*, 1950, **16**, 928) (cf. Patrick and Witkop, *J. Amer. Chem. Soc.*, 1950, **72**, 633) have now concluded that this is 1 : 2 : 3 : 4-tetrahydro-11-hydroxycarbazolenine (I; R = H) and not 1 : 2 : 3 : 10-tetrahydro-10-hydroxycarbazole (II; R = H); the empirical formula of the azo-dye (III) formed from its diazonium salt and β-naphthol has been shown to be $C_{22}H_{20}O_3N_2$ and not $C_{22}H_{18}O_2N_2$ originally proposed by Plant and Tomlinson (*loc. cit.*).   Our conclusions regarding the structure (I; R = H) for the compound, m. p. 153°, are in agreement with those of Plant *et al.* (*loc. cit.*) but we have invariably found that the azo-dye (III) has m. p. 165° and not m. p. 143°, and have confirmed

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its ketonic nature by preparing the oxime. Consequently it is now clear that tetrahydro-carbazolyl hydroperoxide has the formula (I ; R = OH) which we provisionally adopted (*Nature*, 1949, **164**, 362). The apparent behaviour of this hydroperoxide as a secondary amine has been re-examined. When a solution of the compound in mineral acid is treated with nitrous acid some yellow ether-soluble product is formed but the mixture behaves as if it contains a diazonium salt and gives a red colour with β-naphthol. Thus, as regards its basic properties, the hydro-peroxide resembles the alcohol (I ; R = H).

By the action of aqueous sodium hydroxide on (I ; R = OH) there is formed a weakly acidic (phenolic) base $C_{12}H_{11}ON$, m. p. *ca.* 330° (decomp.) (Part I, *loc. cit.*), which has a red ferric reaction in alcohol but does not react with nitrous acid. On benzoylation in alkaline solution this amphoteric compound yields a product which, since it has basic properties but is insoluble in aqueous alkali, is clearly an *O*-benzoate. By the methyl sulphate–alkali or methyl iodide–potassium carbonate method the amphoteric compound yields a basic methyl derivative which, although it gives a negative Zeisel and methylimide estimation may well be an *N*-methyl rather than a *C*-methyl derivative. From an examination of the literature it appeared that the amphoteric compound, m. p. *ca.* 330° (decomp.), was either 4-hydroxy-2 : 3-*cyclo*penteno- (IV) or (V), m. p. 327°, or, less probably, 2-hydroxy-3 : 4-*cyclo*penteno-quinoline (VI), m. p. 256°, which have been synthesised and formulated by Blount *et al.* (*J.*, 1929, 1975) who, however, did not record the acid–base properties of their products or prepare derivatives. A comparison of the amphoteric compound from the peroxide with (IV) obtained by direct synthesis and of their respective benzoyl and methyl derivatives showed conclusively that they are identical.

Although the compounds (IV) and (VI) clearly had the structures proposed by Blount *et al.* (*loc. cit.*) it seemed advisable, in view of the recent communication of Witkop (*J. Amer. Chem. Soc.*, 1950, **72**, 1428), to obtain further evidence. This author has assigned formula (VI) to a compound, m. p. 298° (with blackening), obtained by the action of alkali on a rearrangement product (VII) of tetrahydrocarbazolyl hydroperoxide. In agreement with its properties and


synthesis from authentic *cyclo*pentanone-2-carboxyanilide it has now been confirmed that Blount *et al.*'s compound, m. p. 256° (m. p. 262°, in present work), has formula (VI). Further, in its amphoteric properties and its ferric reaction the compound assigned structure (IV) resembles 4-hydroxy-2-methylquinoline (VIII) rather than 2-hydroxy-4-methylquinoline (IX). Moreover, a comparison of the ultra-violet absorption spectra of (IV) and of tetrahydroacridone (see figure), which is obtained unambiguously from anthranilic acid (Tiedtke, *Ber.*, 1909, **42**, 624), clearly shows that the two compounds have related structures. On the other hand, the spectrum of (VI) resembles that of carbostyril (Morton and Rogers, *J.*, 1925, **127**, 2698). It is possible that the compound, m. p. 298° (with blackening), obtained by Witkop is essentially the amphoteric 4-hydroxy-2 : 3-*cyclo*pentenoquinoline (IV) and consequently that the rearrangement of the peroxide (I ; R = OH) to (IV) in alkaline solution may take place by way of the intermediate (VII) isolated by Witkop (*loc. cit.*).

The ultra-violet absorption spectrum of the methyl derivative of 4-hydroxy-2 : 3-*cyclo*pentenoquinoline resembles that of the parent compound, a result which we believe supports the *N*-methyl structure for this compound since it has been shown (private communication from Professor R. A. Morton, F.R.S.) that the ultra-violet absorption spectra of 4-hydroxyquinolines and their *N*-alkyl derivatives resemble one another and are different from the spectra of the *O*-alkyl derivatives.

The formation of (IV) from tetrahydrocarbazole by peroxidation and subsequent rearrange-ment of the product is an example of the conversion of an indole into a quinoline system under comparatively mild conditions. Superficially, at least, the process resembles the well-known

conversion *in vivo* of tryptophan into kynurenic acid (see Neuberger, *Ann. Reports*, 1944, **41**, 237):
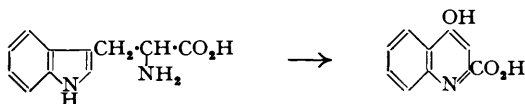
Changes of this type may well prove to have some bearing on the problem of the biological origin of the quinoline nucleus and in this connection it is of interest to note the suggestion of Gouteral *et al.* (*Helv. Chim. Acta*, 1950, **33**, 150) that cinchonine and the indole alkaloid cinchonamine may be related biogenetically.

Absorption Spectra.
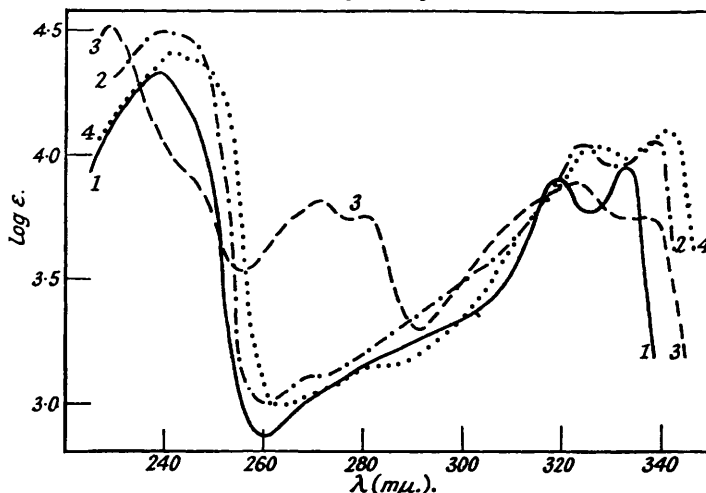
1. 4-*Hydroxy-*2 : 3-*cyclopentenoquinoline.*
2. 1 : 2 : 3 : 4-*Tetrahydroacridone.*
3. 2-*Hydroxy-*3 : 4-*cyclopentenoquinoline.*
4. *Methyl derivative of* 1.

(*All absorption measurements were made in alcohol solution.*)

The peroxide (X; R = OH) derived from *cyclo*pentane*spiro*-2-(4 : 5 : 6 : 7-tetrahydro-ψ-indoxyl) (Part I, *loc. cit.*) has been found to give the corresponding alcohol (X; R = H) on treatment with alkalis, alkaline sodium dithionite, or sodium sulphite. Unlike (I; R = OH) this peroxide (X; R = OH) does not undergo rearrangement with alkali and under the conditions required for the conversion of (I; R = H) into *cyclo*pentane*spiro*-2-ψ-indoxyl the alcohol (X; R = H) is recovered unchanged, whereas more drastic treatment gives intractable products.

EXPERIMENTAL.

1 : 2 : 3 : 4-*Tetrahydro-*11-*hydroxycarbazolenine* (I; R = H).—This compound was diazotised and coupled with β-naphthol (Plant and Tomlinson, *J.*, 1933, 298), and the resulting azo-compound crystallised from ethyl alcohol, forming red prisms, m. p. 165° (Found : C, 73·3; H, 5·3; N, 7·9. Calc. for $C_{22}H_{20}O_3N_2$: C, 73·3; H, 5·6; N, 7·8%) (Plant *et al.*, *loc. cit.*, gave m. p. 143°). On being heated with hydroxylamine hydrochloride (1 g.), sodium acetate (3 g.), alcohol (40 ml.), and water (10 ml.) on the steam-bath for ½ hour this azo-derivative (1·05 g.) gave the *oxime* (0·9 g.) which formed a mass of slender red needles, m. p. 240° (decomp.), from much alcohol (Found : C, 70·2; H, 5·5; N, 11·2. $C_{22}H_{21}O_3N_3$ requires C, 70·4; H, 5·6; N, 11·2%).

4-*Hydroxy-*2 : 3-*cyclopentenoquinoline* (IV).—(*a*) Prepared from tetrahydrocarbazolyl hydroperoxide, this compound, m. p. 330° (decomp.) (Part I, *loc. cit.*) (2·5 g.), was methylated with N-sodium hydroxide (40 ml.) and methyl sulphate (3 ml.; added during 30 minutes), and the mixture warmed on the steam-bath for 10 minutes. The *methyl* derivative (2·2 g.), m. p. 218°, which separated from the cooled reaction mixture, was recrystallised from water, forming hydrated colourless, slender, silky needles, m. p. 219—220°, soluble in dilute mineral acids, and insoluble in aqueous alkalis [Found, in specimen dried in a high vacuum at 80° : C, 78·2; H, 6·5; N, 7·6; *M* (Rast), 199·3. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·5; N, 7·0%; *M*, 199].

The interaction of 4-hydroxy-2 : 3-*cyclo*pentenoquinoline (0·5 g.) with benzoyl chloride (1 ml.) in N-sodium hydroxide (10 ml.) gave a sticky product which was dried and extracted with boiling light

petroleum (b. p. 60—80°). Concentration of the extract gave the *benzoyl* derivative (0·21 g.) which had m. p. 134° after recrystallisation from the same solvent (Found : C, 79·1; H, 5·3; N, 4·9. $C_{19}H_{15}O_2N$ requires C, 78·9; H, 5·2; N, 4·8%). This compound was readily soluble in dilute mineral acids and insoluble in aqueous alkalis.

(*b*) Synthesised by the method of Blount *et al.* (*loc. cit.*) who gave m. p. 327°, a specimen of 4-hydroxy-2 : 3-*cyclo*pentenoquinoline had m. p. 330°, after darkening at 290—300°, and on methylation gave the methyl derivative, m. p. 220°, identical with product prepared in (*a*). Similarly the benzoyl derivative had m. p. and mixed m. p. 134°.

2-*Hydroxy*-3 : 4-cyclo*pentenoquinoline* (VI).—In the preparation of this compound (Blount *et al.*, *loc. cit.*) the intermediate *cyclo*pentanone-2-carboxyanilide, m. p. 104°, was isolated (Found : C, 70·9; H, 6·4. Calc. for $C_{12}H_{13}O_2N$: C, 70·9; H, 6·4%) and cyclised. The resulting 2-hydroxy-3 : 4-*cyclo*-pentenoquinoline had m. p. 262° after purification (Blount *et al.* give m. p. 256°) (Found : C, 77·9; H, 6·0; N, 7·5. Calc. for $C_{12}H_{11}ON$: C, 77·8; H, 5·9; N, 7·6%). This compound, which is insoluble in dilute mineral acids or in aqueous alkalis, gave a pale orange ferric reaction in alcohol whereas the isomeride (V) gave a red colour.

*cyclo*Pentanone-2-carboxyanilide readily formed a 2 : 4-*dinitrophenylhydrazone*, separating from alcohol in glistening orange plates, m. p. 182° (Found : C, 56·6; H, 4·6; N, 18·5. $C_{18}H_{17}O_5N_5$ requires C, 56·4; H, 4·4; N, 18·3%).

cyclo*Pentane*spiro-2-(4 : 5 : 6 : 7-*tetrahydro-ψ-indoxyl*).—The hydroperoxide of *cyclo*pentane*spiro*-2-(4 : 5 : 6 : 7-tetrahydro-ψ-indoxyl) (Part I, *loc. cit.*) (0·74 g.) was agitated with a solution of sodium dithionite (1·5 g.) in N-sodium hydroxide (15 ml.) containing ether (40 ml.) for 1 hour. After the separation of the ethereal solution the aqueous phase was extracted thrice with ether and the combined dried ethereal solutions were evaporated, leaving a crystalline product (0·39 g.) which on purification from warm benzene gave 9-*hydroxy*cyclo*pentane*spiro-2-(4 : 5 : 6 : 7-*tetrahydro-ψ-indoxyl*) (X ; R = H) in small colourless prisms, m. p. 182° (Found : C, 69·6; H, 8·4; N, 6·8. $C_{12}H_{17}O_2N$ requires C, 69·6; H, 8·2; N, 6·8%). The same compound (0·32 g.) was formed when the hydroperoxide (0·41 g.) was agitated with 30% aqueous sodium sulphite (10 ml.) and ether (40 ml.) and also when a solution of the peroxide in N-sodium hydroxide was kept at room temperature for 12 hours.

Compared with 1 : 2 : 3 : 4-tetrahydro-11-hydroxycarbazolenine, the compound (X ; R = H) was relatively stable to the action of aqueous acids and alkalis.