91. *Antiplasmodial Action and Chemical Constitution. Part VII. Derivatives of Quinine and* iso*Quinine.*

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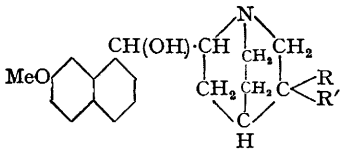
Quinine and *β-iso*quinine were ozonised, and the resultant quininal and 3-acetyl-6 -methoxyrubanol reduced catalytically to the corresponding carbinols. Although active, none of the compounds showed antiplasmodial action equal to that of quinine when tested on *Plasmodium relictum* in canaries.

As experiments are in progress in this laboratory designed to synthesise compounds related to quinine, the effect upon antiplasmodial action of minor alterations in the quinine molecule has been investigated.

Seekles (*Rec. Trav. chim.*, 1923, **42**, 69) prepared quininal (I; R = H, R′ = CHO) by ozonisation of quinine (I; R = H, R′ = CH:CH_2), followed by decomposition of the ozonide with water, but did not test the aldehyde for antiplasmodial properties. Quininal was prepared by Seekles' method and was reduced to quininol (I; R = H, R′ = CH_2·OH) by use of Adams's catalyst. Although quininal proved active in bird malaria, quininol was inactive.



Recently there has been disagreement between Rabe (*Ber.*, 1943, **76**, 320, and earlier papers) and Prelog (*Ber.*, 1941, **74**, 648) over the alleged antiplasmodial properties of synthetic 6′-methoxyrubanol (I, R = R′ = H). It was hoped that β-*iso*quinine, which differs from quinine by having the vinyl side chain in the form :CH·CH_3, on ozonisation might give a ketone which could be reduced to 6′-methoxyrubanol. Unfortunately *iso*quinine ozonide on decomposition with water gave, without loss of carbon atoms, 3-*acetyl*-6′-*methoxyrubanol* (I; R = H, R′ = CO·CH_3), which was reduced to 3-hydroxyethyl-6′-methoxyrubanol, characterised as its crystalline *dihydrobromide*. The alternative procedure of obtaining 6′-methoxyrubanol by decarboxylation of quitenine (I; R = H, R′ = CO_2H) has not so far proved feasible.

The results of tests on bird malaria due to *P. relictum* in canaries are shown in the table:

Substance.	Dose, mg. per 20 g. body weight.	Day of appearance of parasites in blood.	Remarks.
Quinine	6 × 2·5 *	12th—14th	—
Quininal	6 × 2·5	12th—14th	M.T.D.†
	6 × 0·625	8th	—
Quininol	6 × 5	6th	M.T.D.
Acetyl-6′-methoxyrubanol	6 × 10	10th—11th	M.T.D.
Hydroxyethyl-6′-methoxyrubanol	6 × 10	10th—12th	M.T.D.
Controls	—	5th	—

* A dose of 2·5 mg. daily on 6 consecutive days. † M.T.D. = maximum tolerated dose.

3-Hydroxyethyl-6′-methoxyrubanol (α-hydroxydihydroquinine) was previously prepared and fully characterised by Henry, Solomon, and Gibbs (J., 1937, 601), by methylation of α-hydroxydihydro*apo*quinine, and a sample prepared by this method was kindly supplied by Mr. Solomon. The base prepared by reduction of 3-acetyl-6′-methoxyrubanol could not be crystallised even on inoculation with the above α-base, but gave a crystalline *dihydrobromide*, which melted with decomposition at 192—195° and had a specific rotation of $[\alpha]_D^{20°}$ — 142° (*c* = M/80) in N/10-hydrobromic acid. The crystalline base supplied by Mr. Solomon gave a dihydrobromide with similar solubilities and crystalline form, but with a melting point between 198° and 210° and a specific rotation of $[\alpha]_D^{20°}$ — 120° (*c* = M/80). As two asymmetric centres are involved in the formation of these bases, the new base in the form of its dihydrobromide is one of the remaining diastereoisomerides.

The failure of Henry, Solomon, and Gibbs (*loc. cit.*) to obtain more than traces of acetaldehyde on ozonisation of β-*iso*quinine now receives a simple explanation. It is due to the formation of 3-acetyl-6′-methoxyrubanol and this observation does not vitiate, in any way, the structure assigned to β-*iso*quinine.

Experimental.

Quininal.—The method of Seekles (*loc. cit.*) was found to be satisfactory only when extreme precautions were taken to dry the ethyl acetate and petroleum used in the purification of the ozonide.

Quininol.—As there is considerable loss in the purification of quininal, it was found more satisfactory to reduce crude quininal obtained by treatment of the ozonide with water. Purified ozonide (6 g.), decomposed with water and reduced catalytically in ethanol with Adams's catalyst (500 c.c . of hydrogen), gave crystalline quininol dihydrobromide, $[\alpha]_D^{18°}$ — 146° (*c* = M/50, water). The free base could not be crystallised, and the dihydrobromide, although crystalline, gave unsatisfactory analytical results owing to decomposition on drying. However, *quininol monosulphate*, m. p. 149°, crystallised readily from water [Found for material dried at 90° in a vacuum: C, 60·3; H, 6·9; N, 7·2. $(C_{19}H_{24}O_3N_2)_2,H_2SO_4$ requires C, 60·5; H, 6·6; N, 7·4%].

3-*Acetyl*-6′-*methoxyrubanol.*—β-*iso*Quinine (5 g.) was dissolved in dry chloroform (50 c.c.), and dry ozone (3 l. of 13% ozone) bubbled slowly through the solution cooled in ice-salt. Chloroform was removed at reduced pressure without rise in temperature, and 3% acetic acid (50 c.c.) added. After keeping for 48 hours at room temperature, excess of aqueous ammonia was added, and the product extracted with chloroform. The residue after removal of chloroform was separated by fractional crystallisation from acetone into unchanged β-*iso*quinine (1·5 g.), readily soluble, and 3-*acetyl*-6′-*methoxyrubanol* (2·4 g.), needles, m. p. 198—200°, sparingly soluble in acetone (Found: C, 70·5; H, 7·1; N, 8·2. $C_{20}H_{24}O_3N_2$ requires C, 70·6; H, 7·1; N, 8·2%). Acetylmethoxyrubanol dihydrochloride crystallised from alcohol in prisms, but owing to decomposition on drying could not be analysed.

An ethylene oxide formulation of acetylmethoxyrubanol is not impossible, but is considered unlikely, since the compound is stable under conditions which normally rupture the ethylene oxide ring.

3-*Hydroxyethyl*-6′-*methoxyrubanol.*—Acetylmethoxyrubanol (0·5 g.), reduced catalytically in the same way as quininal, gave an oily base. The *dihydrobromide* obtained from the base melted at 192—194° (decomp.) and crystallised in clusters of needles from a mixture of equal parts of alcohol and acetone (Found for material dried at 90°: C, 47·3; H, 5·8; N, 5·3. $C_{20}H_{26}O_3N_2,2HBr$ requires C, 47·6; H, 5·6; N, 5·5%).

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