The Structure and Synthesis of Barakol: a Novel Dioxaphenalene Derivative from *Cassia siamea*

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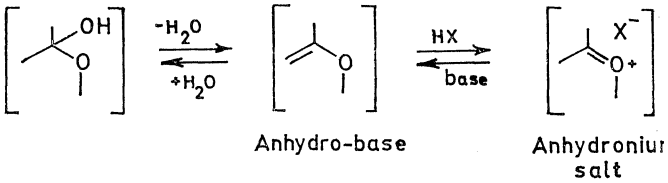
Barakol, from the leaves of *Cassia siamea*, is shown to be a novel dioxaphenalene derivative. A synthesis from 3,5-dihydroxyphenylacetic acid is described.

CHEMICAL investigations on extracts of the root and trunk bark of *Cassia siamea* have revealed the presence of a number of bianthraquinones,[1] but no work has been reported on the leaves of this plant. As part of a systematic investigation by one of us (A. H. W.) of Tanzanian *Cassia* species, the leaves of *Cassia siamea* plants found growing close to the campus of the University College of Dar-es-Salaam were collected for investigation. Extraction of the shredded leaves with dilute methanolic hydrochloric acid followed by careful neutralisation with sodium hydrogen carbonate afforded, in 0·05% yield, pale lemon yellow crystals of a substance which has been termed barakol.[2]

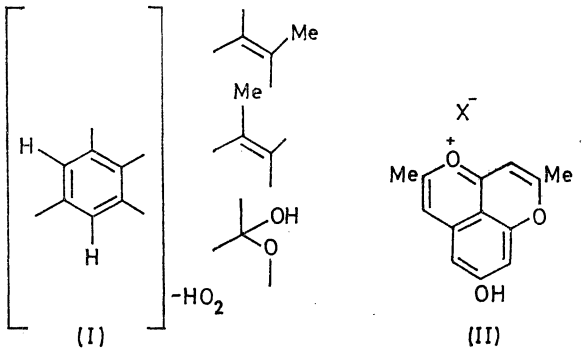
High resolution mass spectrometry and elemental analysis of barakol and its derivatives established the molecular formula as $C_{13}H_{12}O_4$. The mass spectrum exhibited a weak parent ion at *m/e* 232, with the base peak at *m/e* 214 corresponding to a loss of water from the molecular ion. Chemical dehydration of barakol was readily achieved over phosphorus pentoxide or *in vacuo*. The resulting dark green amorphous compound, anhydrobarakol, $C_{13}H_{10}O_3$, was extremely unstable; a solution in chloroform when briefly warmed turned brown and precipitated dark polymeric material, but anhydrobarakol could be reconverted into barakol by dissolution in aqueous methanol. The strong basic character of barakol was demonstrated by the fact that crystalline hydrobromide and hydrochloride derivatives, $C_{13}H_{10}O_3$,HX, salts of the anhydro-base, could be prepared by addition of concentrated hydrochloric or hydrobromic acid to a methanolic solution of barakol. The ready reversible dehydration and salt formation of barakol was reminiscent of anthocyanin chemistry and suggested the presence of the structural units outlined in the Scheme.

The i.r. spectra (Nujol) of barakol, anhydrobarakol, and the chloride exhibit strong bands at 1670, 1670, and 1660 cm.$^{-1}$, respectively, which are assignable either to a hydrogen-bonded carbonyl group or an enol ether. The u.v. spectrum of barakol shows maxima at 241 and 384 nm. (ε 34,700 and 13,000, respectively). The relatively simple 100 MHz ^{1}H n.m.r. spectrum ($CDCl_3$) of anhydrobarakol shows two methyl signals at τ 7·84 and 7·95, both exhibiting allylic fine coupling. Double-irradiation studies demonstrated that the high-field methyl protons were coupled to a vinyl proton (τ 3·97) and the low-field methyl protons were coupled to another vinyl proton (τ 4·23). The signals at τ 3·83 (1H, *J* 1·7 Hz) and 3·93 (1H, *J* 1·7 Hz) were assignable to an AB system due to two *meta*-coupled protons. The ^{1}H n.m.r. spectra of anhydrobarakol salts were essentially the same except that the low-field signals were all moved downfield by *ca.* 1 p.p.m.

On the basis of the spectral and chemical evidence we tentatively assigned the partial structure (I) to barakol. Since the oxidation levels of all the carbon atoms in the molecule had been accounted for it appeared likely that the remaining hydrogen and two oxygen atoms were present as a hydroxy-function and an ether linkage.



SCHEME



Attempts to verify the presence of a further hydroxy-group in barakol by methylation or acetylation led to no identifiable products. Attempts to hydrogenate barakol were equally unsuccessful. Oxidation experiments were also unrewarding in terms of degradative results, but attempted oxidation with chromic acid at room temperature afforded a dark purple crystalline product. The chemical and spectral properties of this compound were consistent with it being the chromate salt of the anhydro-base. This was confirmed by treating the salt with sodium carbonate; barakol was recovered. This observation illustrates the considerable stability of the protonated anhydro-base.

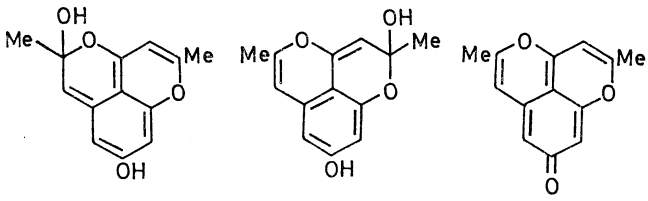
In view of the difficulties encountered in degradative experiments, and the relative scarcity of barakol, to-

[1] A. Chatterjee and S. R. Bhatterjee, *J. Indian Chem. Soc.*, 1964, **41**, 415; N. L. Dutta, A. C. Gosh, P. M. Nair, and K. Venkatara, *Tetrahedron Letters*, 1964, 3023.

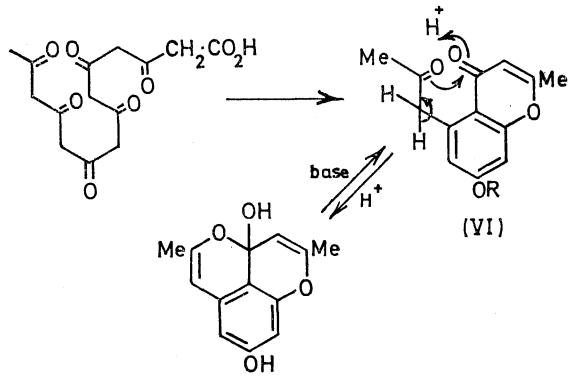
[2] A. Hassanali, T. J. King, and S. C. Wallwork, *Chem. Comm.*, 1969, 678.

gether with the fact that the spectral and chemical data did not allow an assignment of a unique structure, we undertook an *X*-ray crystallographic examination of anhydrobarakol hydrobromide. A preliminary account of this work has already been reported [2] and has allowed an assignment of structure, one canonical form of which is represented by (II; X = Br).

Barakol itself must therefore be one of the three possible carbinol bases (III), (IV), and (VII). The structures (III) and (IV) can be eliminated because the ^{1}H n.m.r. spectrum of barakol shows clearly the presence of two vinylic methyl groups, both exhibiting allylic coupling. The structure (VII) is also favoured on the basis of chemical evidence to be outlined later. It follows that anhydrobarakol is the methylene quinone derivative (V).



(III) (IV) (V)



(VI)

(VII)

Thus barakol is the first reported example of a naturally occurring compound containing both a chromone hemiacetal and a dioxaphenalene system, although an oxaphenalene quinone has recently been isolated [3] from *Capraria biflora* and it has also been suggested that the complex dimeric fungal metabolites of the duclauxin series are derived by oxidative coupling of an oxaphenalene intermediate.[4]

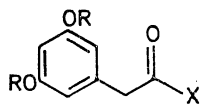
A possible biogenesis of barakol from a polyketide derived from seven acetate units and involving the intermediacy of the compound (VI), is illustrated. Cyclisation of (VI) to barakol can be regarded as either the interaction of an enolate anion with the chromone carbonyl or the nucleophilic attack of the chromone carbonyl on the side-chain ketone; only the former is represented.

[3] J. Comin, O. Gonclaves de Lima, H. N. Grant, L. M. Jackman, W. Keller-Schierlein, and V. Prelog, *Helv. Chim. Acta*, 1963, **46**, 409.

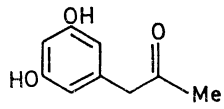
[4] S. Shinata, *Chem. in Britain*, 1967, **3**, 120.

It seemed reasonable that the reverse reaction [barakol (VII) ⟶ (VI; R = H)] might also occur. We had observed earlier that mild basic treatment of barakol afforded an unstable compound, which on methylation gave a crystalline *O*-methyl derivative. The spectral properties of this compound were in accord with the structure (VI; R = Me). On repeating this work the parent hydrolysis product (VI; R = H) was isolated, characterised, and found to be readily converted back into barakol in almost quantitative yield on treatment with concentrated sulphuric acid.

This observation not only provided a model for the proposed biosynthetic pathway but raised the question as to whether barakol was indeed a true natural product, since acid conditions had been used in the isolation procedure. The subsequent isolation of barakol from the neutral alcoholic and chloroform extracts of the leaves, established conclusively that barakol was not an artefact.



(VIII) R=H, X=OH
(IX) R=Ac, X=OH
(X) R=Ac, X=Cl
(XI) R=Ac, X=CH(CO$_2$Et)$_2$



(XII)

The ready conversion of (VI; R = H) into barakol also provided the basis of the subsequent synthesis, as the chromone (VI; R = H) represented a relatively simple synthetic goal. It has been shown [5] that 3,5-dihydroxyphenylacetic acid (VIII) is a valuable starting material for the synthesis of acetate-derived polycyclic aromatic compounds and it was envisaged that conversion of (VIII) into the ketone (XII) followed by a Simonis chromone synthesis [6] would yield the desired chromone (VI; R = H). To this end the diacetate (IX), prepared in good yield by acetylation of (VIII), was converted into the chloride (X).

This compound was not isolated but treated immediately with diethyl sodiomalonate, and the resulting acylmalonate (XI) was hydrolysed to give the ketone (XII). Reaction of (XII) with ethyl acetoacetate in the presence of phosphorus pentoxide afforded a complex mixture of products which on immediate treatment with concentrated sulphuric acid gave, in poor yield, the compound (VII), isolated as its anhydronium hydrochloride (II; X = Cl). This proved to be identical with anhydrobarakol hydrochloride.

The dioxaphenalenium system represents a stable form of a potential polyketide. Recently Money and Scott have described [7] elegant biogenetic-type syntheses involving polypyrone intermediates as sources of polyketides. It is envisaged that the dioxaphenalenium ion

[5] P. M. Baker and B. W. Bycroft, *Chem. Comm.*, 1968, 71.

[6] E. Petschek and H. Simonis, *Ber.*, 1913, **46**, 2014; H. Frei and H. Schmid, *Annalen*, 1957, **603**, 169.

[7] F. W. Comer, T. Money, and A. I. Scott, *Chem. Comm.*, 1967, **231**, and references cited therein.

may prove to be a valuable system in the synthesis of acetate-derived aromatics and investigations concerning this possibility are in hand.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. Mass spectra were determined with an A.E.I. MS9 spectrometer. U.v. spectra were recorded, for solutions in ethanol or chloroform, with a Unicam SP 700 spectrometer. I.r. spectra were recorded with a Unicam SP 200 spectrometer. ^{1}H N.m.r. spectra were determined with a Perkin-Elmer R10 spectrometer at 60 MHz (except where otherwise specified), with tetramethylsilane as internal standard.

Isolation of Barakol.—The shredded leaves of *Cassia siamea* (3·7 kg.) were soaked in methanolic hydrochloric acid (1%; 10 l.) at room temperature, for 48 hr. The extracts were filtered, concentrated under reduced pressure to 1·5 l., diluted with water (1·5 l.), and washed with trichloroethylene (200 ml. × 5). The aqueous layer was basified with a saturated solution of sodium carbonate and extracted with chloroform. The dried (Na_2SO_4) organic layer was evaporated to dryness under reduced pressure to yield a bluish-green solid (16·5 g.).

The product was divided into five portions and each was shaken vigorously with ethyl acetate (100 ml.). When the filtrates were shaken with a small amount of water, a crystalline precipitate (890 mg.) of barakol was deposited. A further crop of the product (243 mg.) was obtained by repeating the extraction with ethyl acetate on each of the five portions. Recrystallisation from aqueous methanol gave barakol as lemon-yellow needles (1·1 g.), m.p. 165° (decomp). T.l.c. [SiO_2; $CHCl_3$–MeOH (20 : 1)] examination of ethanol and chloroform extracts of the leaves showed the presence of barakol.

Barakol is soluble in methanol, ethanol, and acetone, moderately soluble in chloroform and dichloromethane, and readily soluble in benzene, carbon tetrachloride, ether, and water. The mass spectrum shows major ions at *m/e*, 232 (M^+, 232·0724. $C_{13}H_{12}O_4$ requires 232·0735) (1·5%), 214 (100%) 186 (59), 158 (23), 143 (6), 128 (6), 110 (17), 105 (15), 93 (10), 89 (8), and 51 (13); $\nu_{max.}$ (Nujol) 3450s, 1670s, and 1630s cm.$^{-1}$; $\lambda_{max.}$ (EtOH) 241 (ε 34,700), 246sh (30,600), and 384 (13,100) nm.

Anhydrobarakol.—Storing barakol in a vacuum dessicator over phosphorus pentoxide gave anhydrobarakol as a dark green amorphous product, m.p. 165° (decomp.), [*M*(mass spectrum), 214·0629. $C_{13}H_{10}O_3$ requires *M*, 214·0631], $\nu_{max.}$ (Nujol) 1670, 1628, and 1612 cm.$^{-1}$, $\lambda_{max.}$ ($CHCl_3$) 282 (ε 7780), 315 (3830), 392 (10,310), and 408 (9800) nm.

Anhydrobarakol Hydrochloride.—Barakol (75 mg.) was dissolved in the minimum amount of methanol and concentrated hydrochloric acid (0·5 ml.) was added. Anhydrobarakol hydrochloride slowly crystallised as yellow needles (60 mg.) and was recrystallised from aqueous 1,2-dimethoxyethane containing a small amount of hydrochloric acid; m.p. 205—207° (decomp.) (Found: C, 58·65; H, 4·9. $C_{13}H_{13}ClO_3,H_2O$ requires C, 58·1; H, 4·85%), $\nu_{max.}$ (Nujol) 3500, 3440, 1660, and 1620 cm.$^{-1}$, $\lambda_{max.}$ (H_2O) 242 (ε 34,800), 241 (36,700), and 372 (14,000) nm., τ (D_2O) 3·1 (4H, m), 7·30 (3H, s), and 7·52 (3H, s).

Anhydrobarakol Hydrobromide.—Barakol (110 mg.) was dissolved in a small amount of methanol and concentrated hydrobromic acid (1 ml.) was added. A crystalline precipitate was deposited almost immediately. Recrystallisation from ethanol containing a small amount of hydrobromic acid gave anhydrobarakol bromide (79 mg.) as tiny yellow needles, m.p. 246—249° (decomp). (Found: C, 52·95; H, 3·95. $C_{13}H_{13}BrO_3$ requires C, 52·9; H, 3·75).

Products from Mild Basic Treatment of Barakol.—*5-Acetonyl-7-methoxy-2-methylchromone* (VI; R = Me).—Barakol (543 mg.) was dissolved in methanol (10 ml.) and treated with 2N-sodium carbonate solution (10 ml.); the mixture was warmed on a water-bath at 50—60° for *ca.* 60 min., cooled, acidified, and extracted with dichloromethane (30 ml. × 5). The dried (Na_2SO_4) extract was filtered and evaporated to dryness to give a dark green product (377 mg.). The material gave a positive ferric chloride test (dark green) and t.l.c. (SiO_2) indicated the presence of two main products and several minor ones.

The crude mixture was methylated by refluxing with methyl iodide (2 ml.) in acetone (50 ml.) over anhydrous potassium carbonate for 24 hr. Preparative t.l.c. [silica gel G; chloroform–methanol (20 : 1)] gave 5-acetonyl-7-methoxy-3-methylchromone as colourless plates (55·1 mg.). The sample for microanalysis was purified by vacuum sublimination (104°/0·05 mm.) and had m.p. 136—146° (decomp.) (Found: C, 68·3; H, 5·5. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7%), $\nu_{max.}$ (KBr) 1710, 1650, 1620sh, and 1605 cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 213 (ε 19,900), 216 (20,000), 242 (17,100), 249 (16,200), 289 (11,700), and 297sh (10,600) nm., τ ($CDCl_3$) 7·78 (3H, s), 7·74 (3H, s), 6·23 (3H, s), 5·97 (2H, s), 4·14 (1H, s), 3·46 (1H, d, *J* 1·8 Hz), and 3·23 (1H, d, *J* 1·8 Hz).

5-Acetonyl-7-hydroxy-3-methylchromone (VI; R = H).—Barakol (250 mg.) suspended in 2N-sodium carbonate (5 ml.) was warmed to 50°. The reaction was monitored by following the disappearance of the u.v. absorption of barakol at 384 nm. At the end of 20 min., the brown solution was neutralised with hydrochloric acid and extracted with ethyl acetate (50 ml. × 4), and the combined extracts were filtered rapidly through a short column of silica. Removal of the solvent left a dark brown solid (210 mg.), which was dissolved in a small amount of hot chloroform and left at −5° overnight. The brownish precipitate deposited was collected and repeatedly crystallised from chloroform–methanol. The light tan crystalline product (101 mg.) thus obtained was sublimed at 140°/0·05—0·1 mm. to give colourless crystals, m.p. 218—220° (decomp.) (Found: C, 67·05; H, 5·2. $C_{13}H_{12}O_4$ requires C, 67·25; H, 5·2%), $\nu_{max.}$ 2600—3100 (hydrogen-bonded OH), 1708, 1645, 1625, and 1575 cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 213 (ε 20,400), 243 (16,700), 257 (17,400), 292 (12,100), and 299sh (11,200) nm., τ [$(CO_3)_2$-SO] 3·30 (1H, d, *J* 1·8 Hz), 3·38 (1H, d, *J* 1·8 Hz), 4·04 (1H, s), 5·88 (2H, s), 7·72 (3H, s), and 7·82 (3H, s).

Cyclisation of 5-Acetonyl-7-hydroxy-3-methylchromone to Anhydrobarakol Hydrochloride.—The chromone (20 mg.) was dissolved in a small amount of concentrated sulphuric acid (0·5 ml.) and the resulting yellow, fluorescent solution was left at room temperature for 20 min. The solution was diluted with ice-cold water (10 ml.) neutralised with 2N-sodium hydrogen carbonate, and extracted with chloroform (20 ml. × 4). Evaporation of the chloroform at 35° *in vacuo* left a yellowish-green material identical with barakol on t.l.c. [silica; chloroform–methanol (10 : 1)]. On dissolving in a minimum amount of methanol and adding a few drops of concentrated hydrochloric acid, yellow needles of anhydrobarakol hydrochloride precipitated, m.p. 205—207° (decomp.), identical (i.r. and u.v. spectra) with an authentic sample.

3,5-*Diacetoxyphenylacetic Acid* (IX).—A solution of 3,5-dihydroxyphenylacetic acid [8] (10 g.) in freshly distilled acetic anhydride (50 ml.) and pyridine (1 ml.) was kept at room temperature for 18 hr. The mixture was diluted with water (200 ml.) and extracted with ether (100 ml. × 6). The combined extracts were washed with water, dried (Na_2SO_4), and evaporated. Residual acetic acid was removed *in vacuo* over potassium hydroxide (several days) to give a pale yellow oil (11·8 g., 78%), characterised as the methyl ester, b.p. 158—160°/14 mm. (Found: C, 58·3; H, 5·1. $C_{13}H_{14}O_6$ requires C, 58·65; H, 5·3%), $\nu_{max.}$ ($CHCl_3$) 1760s (OAc) and 1704s (CO_2Me) cm.$^{-1}$, τ ($CDCl_3$) 3·08 (3H, s), 6·20 (3H, s), and 7·8 (6H, s).

3,5-*Dihydroxyphenylacetone* (XII).—The diacetoxy-compound (3·5 g.) was dissolved in ether (30 ml.), oxalyl chloride (3·5 g.) was added, and the mixture was heated under reflux for 3 hr. The acid chloride thus obtained after evaporation of the solvents was not purified further but dissolved in 1,2-dimethoxyethane (25 ml.), and the resulting solution was added dropwise to a solution of diethyl sodiomalonate (8·9 g.) in 1,2-dimethoxyethane. The mixture was heated under reflux in an atmosphere of nitrogen for 16 hr., cooled, and diluted with water (75 ml.). Extraction with ether (100 ml. × 5) followed by ethyl acetate (100 ml. × 2) and evaporation of the combined extracts afforded a colourless oil, which was dissolved in 2N-hydrochloric acid (175 ml.) and heated under reflux for 4 hr. The ethyl acetate extracts (100 ml. × 5) of the cooled acid hydrolysate were washed with 2N-sodium hydrogen carbonate (100 ml. × 2) and water (50 ml.), dried (Na_2SO_4), and evaporated to give a brown oil (1·4 g.). Chromatography on silica, with chloroform–methanol (50 : 1) as eluant afforded 3,5-dihydroxyphenylacetone as a colourless viscous oil (1·39 g., 49% overall), characterised as the dibenzoate, m.p. 84—85° (Found: C, 74·1; H, 4·0. $C_{23}H_{18}O_5$ requires C, 73·8; H, 4·8%), $\nu_{max.}$ ($CHCl_3$) 3340s (OH), 1705s (Ac), and 1605s (aromatic) cm.$^{-1}$, τ ($CF_3{\cdot}CO_2H$) 3·43 (3H, m), 6·13 (2H, s), and 7·7 (3H, s).

8-*Hydroxy*-2,5-*dimethyl*-1,4-*dioxaphenalenium Chloride* (*Anhydrobarakol Hydrochloride*).—The ketone (XII) (430 mg.) was added to a solution of phosphorus pentoxide (300 mg.) in ethyl acetoacetate (1 ml.) and heated at 80° for 4 hr. To the cooled solution was added concentrated sulphuric acid (1 ml.) and the mixture was left at room temperature for 0·5 hr. The product was isolated as previously described and converted into the hydrochloride (3·9 mg.), m.p. 205—207° (decomp.), with i.r. and u.v. spectra identical with those of anhydrobarakol hydrochloride.

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[8] W. Theilacker and W. Schmid, *Annalen*, 1950, **570**, 15.

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