947. *Quassin and* neo*Quassin. Part V.**

By R. J. S. Beer, B. G. Dutton, D. B. Jaquiss, Alexander Robertson, and W. E. Savige.

The conversion of a reduction product of *neo*quassin into 1 : 2 : 8-trimethylphenanthrene with selenium suggests that quassin and *neo*quassin are diterpenoid compounds.

Fusion of quassin with alkali gives creosol and an acidic lactone, $C_{13}H_{14}O_4$, the structure of which is discussed.

On being heated with selenium, *neo*quassin undergoes extensive decomposition and the only product identified was 3 : 4 : 5-trimethylguaiacol,[1] derived presumably from the α-diketone enol ether system (I) designated chromophore (A) in Part III.[2] Exploratory experiments with other dehydrogenating agents (*e.g.*, palladised charcoal) were not encouraging and it was concluded that a necessary preliminary to successful dehydrogenation in this series was the development of a method of reducing the high oxygen content of quassin or *neo*quassin. Accordingly, *neo*quassin was reduced by Clemmensen's method under a variety of conditions. By the Martin technique it was converted into a non-crystalline product which did not exhibit significant absorption in the ultraviolet region above 220 mμ. Other modifications of the Clemmensen reduction gave similar products from which only small amounts of two crystalline compounds were isolated. Of these, one is apparently a tetrahydronor*neo*quassin, $C_{20}H_{29}O_5 \cdot OMe$, the ultraviolet absorption spectrum of which indicated the absence of conjugated carbonyl groups whilst the infrared absorption spectrum had peaks at 3401 cm.$^{-1}$ and at 1721 cm.$^{-1}$, due to a hydroxyl group and (probably) to a *cyclo*hexanone residue, respectively. On the basis of the partial formula (II) for *neo*quassin this product is probably (III).

The second crystalline product, $C_{20}H_{29}O_3 \cdot OMe$, also had no significant absorption in the ultraviolet region (above 220 mμ) and its infrared absorption spectrum did not contain a peak due to a hydroxyl group. The presence of at least one unconjugated carbonyl group in this compound is indicated by the formation of a pale orange 2 : 4-dinitrophenylhydrazone ($\lambda_{max.}$ 370 mμ in alcohol). This reduction product, which is probably formed *via* compound (III), can be tentatively formulated as (IV).

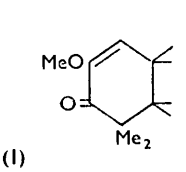
Since neither of the crystalline reduction products of *neo*quassin could be obtained in good yield, it was decided to attempt selenium dehydrogenation of the non-crystalline material from the Martin reduction. The resulting crude dehydrogenation product was separated by distillation into two fractions. On further purification the more volatile fraction gave a colourless oil which is probably an alkylated benzene but which has not been fully characterised. From the high-boiling fraction there was isolated a crystalline hydrocarbon, $C_{17}H_{16}$, which formed well-defined derivatives with picric acid and with

* Part IV, *J.*, 1956, 3280.

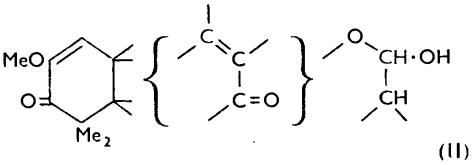
[1] Beer, Jaquiss, Robertson, and Savige, *J.*, 1954, 3672.

[2] Hanson, Jaquiss, Lamberton, Robertson, and Savige, *ibid.*, 4238.

trinitrobenzene, and which from its composition and ultraviolet absorption spectrum [3] appeared to be a trimethylphenanthrene. A survey of the literature suggested 1 : 2 : 8-trimethylphenanthrene [4] (V) and this conclusion was shown to be correct by direct comparison with an authentic sample, kindly supplied by Professor R. D. Haworth, F.R.S.



(I)



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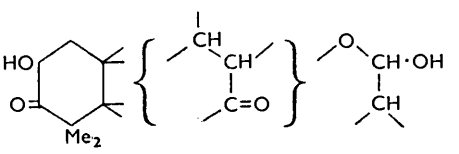

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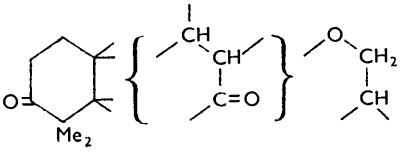
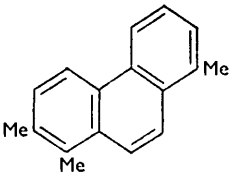


(IV)

In addition to 1 : 2 : 8-trimethylphenanthrene, the high-boiling fraction from the dehydrogenation gave an almost colourless oil, the ultraviolet absorption spectrum of which was similar in general outline to that of 1 : 2 : 3 : 4-tetrahydrophenanthrene. The orange-red trinitrobenzene derivative melted over a range (73—80°) even after repeated recrystallisation. Analysis of the oil indicated the formulæ $C_{17}H_{22}$ or $C_{17}H_{20}$, the latter corresponding to a tetrahydrotrimethylphenanthrene. In this connexion it is noteworthy that selenium dehydrogenation of dihydroxycassanic acid is reported to yield a mixture of 1 : 2 : 8-trimethylphenanthrene and its tetrahydro-derivative; [5] the latter is a liquid, forming an orange-red trinitrobenzene derivative, m. p. 85—87°.



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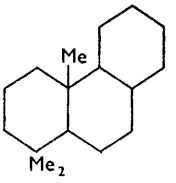

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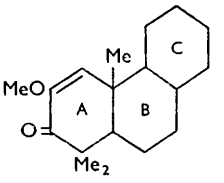

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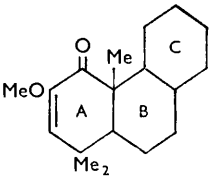


(VIII)

The formation of 1 : 2 : 8-trimethylphenanthrene (V) by dehydrogenation of a *neo*-quassin derivative provides the first definite evidence that quassin and *neo*quassin are diterpenoid compounds. The nature of the functional groups and the number of double bonds present being taken into account, it is reasonably certain that quassin contains the carbocyclic system (VI) which is elaborated in partial structures (VII) and (VIII) so as to accommodate the two possible arrangements of chromophore (A). The complete structure for quassin must include: (i) three extra carbon atoms, probably attached to ring C and associated with the lactone system; (ii) a second αβ-unsaturated ketonic system [chromophore B of Part III,[2] possibly sited in ring B]; (iii) a second methoxyl group.

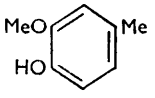
With hot 10% aqueous sodium hydroxide quassin gives a mixture of *allo*quassinolic acid and an isomer,[2] compounds which are evidently stable to the further action of aqueous alkali since they are also obtained when quassin is treated with boiling 50% aqueous sodium hydroxide. Fusion with alkali has now been found to effect extensive degradation

[3] von Heilbronner, Daniker, and Plattner, *Helv. Chim. Acta*, 1949, **32**, 1723; Askew, *J.*, 1935, 509; Barton, Fawcett, and Thomas, *J.*, 1951, 3147.
[4] Haworth and Mavin, *J.*, 1932, 2720.
[5] Ruzicka and Dalma, *Helv. Chim. Acta*, 1939, **22**, 1516.

of the quassin molecule and, when carried out in an open vessel, gives rise to small amounts of two well-defined products, one of which was easily recognised as creosol (IX). This guaiacol derivative could arise from ring A in formulæ (VII) and (VIII) or less probably from the ring carrying the second methoxyl group present in quassin. The second product was a monobasic acid, $C_{13}H_{14}O_4$, containing at least two *C*-methyl groups, giving a positive hydroxamic acid test for an ester or lactone group, and forming a monobromo-derivative in which the bromine atom is inert. On methylation with methyl sulphate and alkali, this acid (referred to in the sequel as the C_{13}-acid) was converted into a methoxy-dicarboxylic acid, $C_{13}H_{15}O_4{\cdot}OMe$, which with diazomethane yielded a dimethyl ester, $C_{11}H_{13}(OMe)(CO_2Me)_2$. These results, together with the fact that in alkaline solution the C_{13}-acid couples with phenyldiazonium chloride, support the view that this acid contains a masked phenolic group as part of a lactone system. Our failure to isolate the corresponding hydroxy-acid implies that the lactone system is very readily formed and suggests that the C_{13}-acid may be a derivative of α-coumaranone (X) containing a carboxyl group and four other carbon atoms which must be present as alkyl groups. Clearly the free carboxyl group of the C_{13}-acid is attached to the aromatic ring since the ultraviolet absorption spectrum of this acid ($\lambda_{max.}$ in alcohol 274, 283 mμ; log ε 2·91, 2·90) is very similar to that of benzoic acid [6] ($\lambda_{max.}$ 271, 279 mμ; log ε 2·88, 2·74).

It is not possible at present to assign a particular structure to the C_{13}-acid but certain restrictions can be placed on the arrangement of the substituents. Thus it is unlikely that the carboxyl group occupies the 4-position of (X) because the corresponding methoxy-dicarboxylic acid does not form an anhydride under conditions which bring about anhydride formation with homophthalic acid and similar compounds. The 5-position is probably blocked by an alkyl substituent since the C_{13}-acid gives a negative Gibbs test, in which case the 7-position must be unsubstituted in order to explain the positive coupling reaction. The free carboxyl group is therefore most probably in the 6-position. Bromination of the C_{13}-acid apparently occurs in the 4-position since the bromo-derivative is still capable of coupling with diazonium salts presumably at the 7-position. On the basis of these arguments, it would appear that the C_{13}-acid has a structure of type (XI; R + R′ + R″ = C_4H_{11}).

Attempts to clarify this structural problem by oxidative degradation of the methoxy-dicarboxylic acid have been unsuccessful. The fact that with diazomethane in ether and



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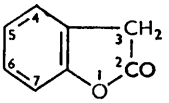
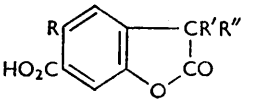


(X)



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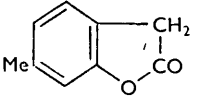

(XII)

methanol the C_{13}-acid gave a liquid product with a higher methoxyl content than would correspond to esterification of one carboxyl group was at first thought to indicate that the coumaranone carbonyl group had some enolic character, as suggested by Berner [7] for the lactone (XII). This would imply that at least one hydrogen atom is attached to the β-position of the coumaranone ring, but it was subsequently found that on prolonged treatment with diazomethane the C_{13}-acid was converted into the dimethyl ester of the methoxy-dicarboxylic acid. It is clear therefore that the lactone ring is slowly opened under the conditions employed.

The limited conclusions reached regarding the structure of the C_{13}-acid do not provide a firm basis for a discussion of its relation to quassin. It may well be that the acid is not simply related to the parent molecule. For this reason and because the preparation of the C_{13}-acid involves the destruction of relatively large amounts of quassin, the authors do not at present contemplate any extension of this part of the investigation.

[6] Moser and Kohlenburg, *J.*, 1951, 804.
[7] Berner, *Acta Chem. Scand.*, 1949, **3**, 1117.

Experimental

Unless otherwise stated, the light petroleum used had b. p. 60—80°. Ultraviolet absorption spectra were measured with a Unicam spectrophotometer and infrared absorption spectra with a Grubb–Parsons double-beam spectrometer, a paste of the material in " Nujol " being used.

Reduction of neo*Quassin.*—The amalgamated zinc used in these reductions was prepared by slowly adding a solution of mercuric chloride (0·65 g.) in concentrated hydrochloric acid (1·25 ml.) to an agitated slurry of zinc dust (5 g.) in water (6·5 ml.). After 15 min. the amalgamated zinc was collected, washed with several portions of water, and used immediately.

(*A*) A mixture of *neo*quassin (10 g.), toluene (600 ml.), amalgamated zinc (50 g.), concentrated hydrochloric acid (50 ml.), and water (25 ml.) was vigorously heated under reflux for 70 hr., with additions of more zinc (20 g.) at intervals of 8 hr. and concentrated hydrochloric acid (4 ml.) hourly. The toluene layer was separated, the aqueous liquor extracted several times with chloroform, and the extract combined with a solution obtained by grinding the residual zinc amalgam with chloroform. The concentrated chloroform (15 ml.) and the toluene solutions were combined, washed with successive portions of 2N-aqueous sodium hydroxide and finally with water, dried, and evaporated, giving a yellow gum (8·18 g.) which did not exhibit significant absorption in the ultraviolet region above 220 mμ.

(*B*) A solution of *neo*quassin (1 g.) in methanol (30 ml.) was added to amalgamated zinc (10 g.) and concentrated hydrochloric acid (5 ml.), and the mixture heated under reflux for 36 hr., with the addition of more zinc (4 g. at 7-hourly intervals) and concentrated hydrochloric acid (3 ml. at 2-hourly intervals). The residual amalgam was ground with several portions of chloroform and the solution combined with the chloroform extract of the reaction mixture. Evaporation of the washed (as in method *A*), dried extracts gave an almost colourless gum (0·79 g.), a solution of which in benzene–light petroleum (2 : 3) was passed through alumina. Triturated with light petroleum, the gum (0·56 g.) from the eluate solidified and was repeatedly crystallised from this solvent, giving a *product* in needles, m. p. 160—163°, after sintering at 158° (Found, in a sample dried at 60° for 4 hr. : C, 72·5; H, 9·4; OMe, 8·9. $C_{20}H_{29}O_3$·OMe requires C, 72·4; H, 9·25; OMe, 8·9%). The 2 : 4-dinitrophenylhydrazone separated from chloroform in orange feathery needles, m. p. 272—275°, $\lambda_{max.}$ 370 mμ.

(*C*) A mixture of concentrated hydrochloric acid (5 ml.), amalgamated zinc (20 g.), *neo*quassin (1 g.), and acetic acid (10 ml.) was kept at room temperature for 17 hr., the liquid was decanted, and the amalgam washed with dilute acetic acid. The combined acidic liquors were treated gradually with 5N-aqueous potassium hydroxide (67 ml.) followed by water (50 ml.), heated to 80° for 1 min., cooled, filtered (the pH was 9), and extracted with chloroform. Evaporation of this extract left a gum (0·29 g.) which was dissolved in the minimum amount of ethyl acetate; the gradual addition of light petroleum to this solution gave *tetrahydronor*neo*quassin* which was repeatedly recrystallised from ethyl acetate–light petroleum forming needles, m. p. 232—233°, after sintering at 227°, with a negative ferric or tetranitromethane reaction (Found, in a sample dried in a vacuum at 120° for 14 hr. : C, 66·85; H, 8·7; OMe, 8·4. $C_{20}H_{29}O_5$·OMe requires C, 66·3; H, 8·5; OMe, 8·2%). This compound was insoluble in 2N-aqueous sodium hydroxide and stable to neutral permanganate solution.

When the reaction mixture obtained at room temperature (Method *C*) was boiled for 16 hr. with the addition of more concentrated hydrochloric acid (5 ml. at 4-hourly intervals) the sole crystalline product isolated after chromatographic purification was identical with the product, m. p. and mixed m. p. 160—163°, obtained by Method (*B*) (Found, in a sample dried *in vacuo* at 80° for 10 hr. : C, 72·2; H, 9·5%).

1 : 2 : 8-*Trimethylphenanthrene.*—The gum (8·18 g.) from method (*A*) was warmed and intimately mixed with powdered selenium (16·3 g.), and the mixture kept at 320—340° for 36 hr. The sticky reaction mixture was triturated with hot light petroleum and then extracted with this solvent in a Soxhlet apparatus for 15 hr. After removal of a little brown, non-crystalline acidic material with 2N-aqueous sodium hydroxide, evaporation of the light petroleum extract left a viscous red oil (3·64 g.) which was distilled, giving three fractions: (i) b. p. 80—100°/0·05 mm. (2—3 drops), (ii) b. p. 160—230°/0·025 mm. (2·23 g.), and (iii) b. p. 230—300°/0·025 mm. (trace). Redistillation of fraction (ii) gave a mixture of oil and crystals, from which the oil was removed with a small pipette. After being washed with a little light petroleum, the residual crystals (110 mg.), m. p. 118—124°, were combined with similar material from another dehydrogenation experiment on 3·9 g. of gum and purified by chromatography on alumina. Elution with light petroleum gave a solid (100 mg.) which on repeated purification

from alcohol afforded 1 : 2 : 8-trimethylphenanthrene in plates, m. p. and mixed m. p. 144—145° (Haworth and Mavin record [4] m. p. 146°); light absorption in 95% ethanol; $\lambda_{max.}$ in mμ (log ε) values as follows: 214 (4·68), 254·5 (4·68), 262 (4·78), 284 (4·10), 295 (4·10), 308 (4·19), 324 (2·62), 340 (2·54), 356 (2·13); $\lambda_{min.}$ in mμ (log ε) as follows: 234 (4·09), 257 (4·67), 280 (4·02), 290 (3·92), 301 (3·83), 321·5 (2·61), 334 (2·39), 354 (2·05); points of inflection: 225 (4·40), 345 (2·32), 349 (2·24) (Found: C, 93·0; H, 7·5. Calc. for $C_{17}H_{16}$: C, 92·7; H, 7·3%). Prepared in alcohol, the picrate formed orange needles, m. p. 165—166° (Found: C, 61·4; H, 4·0; N, 9·3. Calc. for $C_{17}H_{16},C_6H_3O_7N_3$: C, 61·5; H, 4·3; N, 9·35%). Haworth and Mavin record [4] m. p. 163° for 1 : 2 : 8-trimethylphenanthrene picrate. The *trinitrobenzene derivative* separated from alcohol in long yellow needles, m. p. 190—191° (Found: C, 63·9; H, 4·1; N, 9·8. $C_{17}H_{16},C_6H_3O_6N_3$ requires C, 63·7; H, 4·4; N, 9·7%).

The oil accompanying the crystalline phenanthrene was purified by chromatography from light petroleum on alumina and eluted with the same solvent, leaving the more strongly absorbed 1 : 2 : 8-trimethylphenanthrene (90 mg.) on the column. Distillation then gave as the main fraction a pale yellow oil (0·16 g.), which on being twice distilled afforded an almost colourless oil, b. p. 160—170°/0·025 mm.; light absorption in 95% ethanol; $\lambda_{max.}$ values in mμ (log ε) 232 (4·67), 286 (3·51), 330 (2·78); $\lambda_{min.}$ in mμ (log ε), 251 (3·18), 324 (2·63); inflection, 314 (2·90) (Found: C, 90·3, 90·35; H, 9·4, 9·6. $C_{17}H_{20}$ requires C, 91·0; H, 9·0. $C_{17}H_{22}$ requires C, 90·2; H, 9·8%). Prepared in alcohol, the trinitrobenzene derivative formed orange-red warts which even after repeated purification had indefinite m. p. (73—80°).

Decomposition of Quassin with Alkali.—A mixture of quassin (20 g.), methanol (40 ml.), and a solution of potassium hydroxide (26 g.) and sodium hydroxide (38 g.) in water (60 ml.) was heated in a nickel crucible, at first on the steam-bath (until most of the methanol had evaporated) and subsequently in a metal bath, the temperature of which was raised to 240° during 1 hr. and then kept at 240—260° for 15 min. A solution of the reaction mixture in water (500 ml.) was saturated with carbon dioxide, and the phenolic product isolated by continuous extraction with ether. On distillation this gave an oil, b. p. *ca.* 130°/2 mm., with a strong guaiacol-like odour and a greenish-blue ferric reaction. With phenyl *iso*cyanate in light petroleum (b. p. 80—100°), this substance gave the *carbanilate* of creosol which crystallised from light petroleum, containing a little benzene, in needles, m. p. 139—140° (Found: C, 69·8; H, 5·9; N, 5·5; OMe, 12·0. $C_{14}H_{12}O_2N{\cdot}OMe$ requires C, 70·0; H, 5·8; N, 5·5; OMe, 12·1%). This compound was identified by comparison with a specimen, m. p. 139—140°, from authentic creosol (5-methylguaiacol) (Found: N, 5·5; OMe, 11·9%).

After removal of the phenolic fraction the aqueous liquors were acidified with hydrochloric acid and the continuous ether-extraction process repeated, giving a black tarry acidic fraction. Repeated extraction of this product with hot light petroleum, containing a little ethyl acetate, gave a pale yellow gum which on trituration with a little cold ethyl acetate furnished an *acid* (1·85 g.), m. p. 204—208°. Purified by recrystallisation and then by sublimation [160—180° (bath temp.)/0·002 mm.], this compound, the C_{13} "*acid*," had m. p. 212—214° [Found: C, 66·6, 66·8; H, 6·0, 5·9; *C*-Me, 10·5%; *M* (Rast), 212. $C_{13}H_{14}O_4$ requires C, 66·7; H, 6·0%; *M*, 234]. The acid gave a positive hydroxamic acid test for an ester or lactone and coupled in alkaline solution with diazotised aniline but did not give a coloration with 2 : 6-dichloroquinone chloroimide. Attempts to decarboxylate the acid, *e.g.* by the glycerol–copper bronze method, were unsuccessful.

Methylation of the C_{13} *Acid.*—Methyl sulphate (4 ml.) was added portionwise in 30 min. to an agitated solution of the C_{13}-acid (0·6 g.) in 2N-aqueous sodium hydroxide and, after the addition of more aqueous sodium hydroxide (10 ml.), the mixture was heated on the steam-bath for 2 hr. From the cooled, acidified solution the *methyl ether* (0·6 g.) was isolated by extraction with ether and with ethyl acetate and crystallised from ethyl acetate–light petroleum, forming irregular prisms, m. p. 212—214°; the analytical sample, prepared by sublimation, had the same m. p. (Found: C, 63·1; H, 6·9; OMe, 11·7; *C*-Me, 15·0. $C_{13}H_{15}O_4{\cdot}OMe$ requires C, 63·2; H, 6·8; OMe, 11·7%). This methyl ether reacted with sodium hydrogen carbonate, did not couple in alkaline solution with diazotised aniline, and was recovered in good yield from an attempted decarboxylation at 250° in glycerol containing copper bronze. With ethereal diazomethane containing a little methanol this compound was slowly converted into a *dimethyl ester*, which was purified by distillation (b. p. 192—202°/0·05 mm.), and then by crystallisation from ether–light petroleum (b. p. 40—60°), forming stout needles, m. p. 72° [Found: C, 65·2; H, 7·7; OMe, 31·7. $C_{13}H_{13}O_2(OMe)_3$ requires C, 65·3; H, 7·5; OMe, 31·6%]. The same ester, m. p. and mixed m. p. 72°, was obtained in low yield by prolonged treatment (*ca.* 20 days) of the C_{13}-acid with excess of ethereal methanolic diazomethane at 0° (Found: OMe, 31·6; *C*-Me, 10·5%).

Bromination of the C_{13} *Acid.*—A solution of the C_{13}-acid (0·2 g.) in acetic acid (2 ml.), containing bromine (0·6 g.) and a trace of iodine, was kept in the dark for 18 hr., and then diluted with water. The precipitated *bromo-derivative* (0·18 g.), m. p. *ca.* 195°, separated from aqueous alcohol and then from ethyl acetate–light petroleum, in rectangular plates, m. p. 201—202° (Found: C, 49·8; H, 4·3; *C*-Me, 11·5. $C_{13}H_{13}O_4Br$ requires C, 49·9; H, 4·2%). This product was recovered in good yield after being heated with 10% aqueous potassium hydroxide for 2 hr.

UNIVERSITY OF LIVERPOOL. [*Received, July 23rd,* 1956.]