435. *The Synthesis of Tetracyclines. Part I. Some Model Diene Reactions.*

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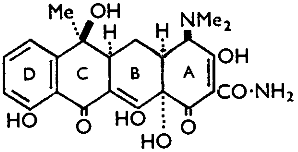
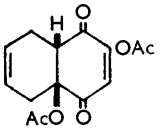
Several naphthalene and anthracene derivatives containing angular acetoxy-groups have been prepared by reaction of butadiene and *cyclo*pentadiene with 2-acetoxy-1 : 4-quinones, and their structures have been determined by chemical degradation and comparison of their spectra with those of known compounds.

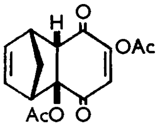
The tetracyclines are a group of powerful broad-spectrum antibiotics active [1] against both Gram-positive and Gram-negative bacteria and based [2] on the common structure (I). Our general synthetical study of this group began with an investigation of the stereochemically attractive [3] possibility of generating the *cis*-fused, angularly hydroxylated rings A and B by Diels–Alder reaction of a substituted diene with a 2-hydroxy-1 : 4-quinone. As only isolated examples of such reactions have been reported [4] we investigated first the reactions of simple dienes with 2 : 5-dihydroxybenzoquinone and 2-hydroxy-1 : 4-naphthaquinone and their derivatives.



(I)



(II)



(III)

2 : 5-Dihydroxybenzoquinone, prepared by oxidising resorcinol with peracetic acid, decomposed on attempted reaction with butadiene, but its diacetate reacted smoothly in benzene at 120° to give *cis*-2 : 10-diacetoxy-1 : 4 : 5 : 8 : 9 : 10-hexahydro-1 : 4-dioxonaphthalene (II) in 69% yield. The structure of this compound was indicated by the resemblance of its ultraviolet absorption spectrum to that of the well-known [5] adduct of butadiene and 1 : 4-benzoquinone, and by its infrared spectrum, which showed the presence of ester carbonyl groups and a conjugated ketonic carbonyl group. This structure (II) was confirmed by conversion of the adduct into 2-hydroxy-1 : 4-naphthaquinone by aerial oxidation in hot alkaline solution. A similar 1 : 1 adduct (III) was formed by the reaction of 2 : 5-diacetoxybenzoquinone with *cyclo*pentadiene.

Prolonged reaction of butadiene with 2 : 5-diacetoxybenzoquinone or the adduct (II) gave almost quantitative yields of the *cis-cis*-11 : 13-diacetoxy-1 : 4 : 5 : 8 : 11 : 12 : 13 : 14-octahydroanthraquinone (IVa or b). The insolubility of this compound in ethanol prevented complete mapping of its ultraviolet absorption spectrum, but the absence of any definite maximum at wavelengths greater than 2200 Å supports the structure proposed (cf. the similar ultraviolet spectrum of 1 : 4 : 5 : 8 : 11 : 12 : 13 : 14-octahydroanthraquinone). Further, the infrared absorption spectrum showed the presence of a ketonic group in a saturated environment. Aerial oxidation of the adduct in alkaline solution gave anthraquinone. It is of interest that when this diene reaction was carried out under forcing conditions in an attempt to accelerate it the only crystalline product, obtained in only 14% yield, was an unstable yellow compound $C_{14}H_{12}O_2$. The resemblance of the physical properties of this compound to those of the unstable 5 : 8-dihydro-1 : 4-naphtha-

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[1] Broschard, *Science*, 1949, **109**, 199; Finlay, *ibid.*, 1950, **111**, 85.

[2] Woodward, *et. al.*, *J. Amer. Chem. Soc.*, 1953, **75**, 5455; Booth, " Antibiotics Annual," Proc. Symposium on Antibiotics, 1953, p. 46; Woodward, *et. al.*, *J. Amer. Chem. Soc.*, 1954, **76**, 3567.

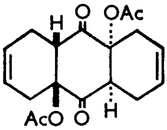
[3] Alder and Stein, *Angew. Chem.*, 1937, **50**, 510.

[4] Butz and Butz, *J. Org. Chem.*, 1942, **7**, 198; 1943, **8**, 497; Fieser and Seligman, *Ber.*, 1935, **68**, 1748.

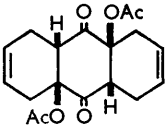
[5] Diels and Alder, *Ber.*, 1929, **62**, 2337.

quinones[6] suggested that it is 1 : 4 : 5 : 8-tetrahydroanthraquinone (V); this view was confirmed by the presence in its infrared spectrum of a strong maximum at 6·10 μ (cf. 2 : 3 : 5 : 6-tetramethylbenzoquinone which absorbs[7] at 6·10 μ in Nujol) and by its oxidation to anthraquinone in alkaline solution.

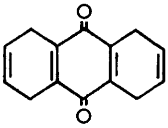
2-Hydroxy-1 : 4-naphthaquinone reacted sluggishly with butadiene in ethanol; the adduct (VI; R = H) could not be isolated but its formation was demonstrated by the isolation, in 35% yield, of anthraquinone on aerial oxidation of the reaction mixture in alkaline solution. 2-Methoxy-1 : 4-naphthaquinone similarly added butadiene with some difficulty. 2-Acetoxy-1 : 4-naphthaquinone, however, reacted smoothly with both butadiene and *cyclo*pentadiene to give the expected *cis*-fused acetates. The structure of the product (VI; R = Ac), formed in benzene at 100°, was shown by the resemblance of the ultraviolet absorption spectrum to that of 1 : 4 : 11 : 12-tetrahydroanthraquinone, by infrared bands showing the presence of ester and conjugated ketonic carbonyl groups, and by aerial oxidation in alkaline solution to anthraquinone. However, in a reaction at 130° addition was accompanied by elimination, only 1 : 4-dihydroanthraquinone being isolated. A similar adduct (VII) was obtained by the reaction of 2-acetoxy-1 : 4-naphthaquinone with *cyclo*pentadiene. Both the adducts (VI; R = Ac) and (VII) were comparatively stable to heat and sublimed *in vacuo* without change.



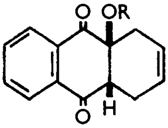
(IVa)



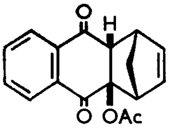
(IVb)



(V)



(VI)



(VII)

The stereochemistry of the adducts described in this paper has been assigned on the known stereochemical selectivity of the Diels–Alder reaction as codified in the Alder–Stein rules.[3] The thermal stability of the adducts, which are derivatives of β-hydroxy-ketones, supports the postulated *cis*-ring-fusion since *trans*-dehydration at the ring junction is impossible. The instability of the adducts to alkali is explained on the assumption that the reagent, by catalysing a reversible enolisation, converts the adducts into *trans*-fused systems which can readily undergo an E_2 elimination.

EXPERIMENTAL

M. p.s are corrected. Ultraviolet absorption spectra were obtained with ethanol solutions. Infrared absorption spectra were determined for paraffin pastes.

2 : 5-*Dihydroxybenzoquinone* (with B. N. CHUKWUDEBE).—Resorcinol (10 g.) in acetic acid (30 c.c.) was added slowly, with shaking and cooling, to 11% peracetic acid (200 c.c.). The dark red solution was kept overnight. The red-brown precipitate was collected, dried, and recrystallised from acetic acid, giving orange needles of 2 : 5-dihydroxybenzoquinone (8·7 g., 69%), m. p. 210—215° (decomp.) (Found: C, 51·7; H, 3·1. Calc. for $C_6H_4O_4$: C, 51·4; H, 2·9%). The diacetate was prepared by treating the quinone (5 g.) in acetic anhydride (15 c.c.) with 10% perchloric acid (0·5 c.c.). The mixture became yellow and heat was evolved. On cooling, lemon-yellow needles of 2 : 5-diacetoxybenzoquinone (5·2 g., 65%), m. p. 151—152°, separated (Found: C, 53·5; H, 3·6. Calc. for $C_{10}H_8O_6$: C, 53·6; H, 3·5%), $\lambda_{max.}$ 2600 Å (log ε 3·9), ν 5·65 (ester) and 6·0 μ (quinone).

cis-2 : 10-*Diacetoxy*-1 : 4 : 5 : 8 : 9 : 10-*hexahydro*-1 : 4-*dioxonaphthalene* (II).—2 : 5-Diacetoxybenzoquinone (25 g.), butadiene (10 c.c.), and benzene (50 c.c.) were heated in a sealed tube at 110° for 72 hr. The pale yellow solution obtained was evaporated to dryness, the residual gum was triturated with a little ether, and the buff solid formed was recrystallised from ether, yielding almost colourless rhombs of the *adduct* (II) (2·15 g., 69%), m. p. 120—121° (Found: C, 60·1; H, 5·2. $C_{14}H_{14}O_6$ requires C, 60·4; H, 5·0%), $\lambda_{max.}$ 240, 295 mμ (log ε 3·9, 3·05 respectively), ν 5·65, 5·75 (ester) and 5·9 μ (unsaturated ketone).

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[6] Fieser, *J. Amer. Chem. Soc.*, 1948, **70**, 3165.

[7] Yates, Ardao, and Fieser, *J. Amer. Chem. Soc.*, 1956, **78**, 650.

For comparison, *cis*-1 : 4 : 5 : 8 : 9 : 10-hexahydro-1 : 4-dioxonaphthalene was prepared by the method of Diels and Alder;[5] it had $\lambda_{\text{max.}}$ 220, 270 mμ (log ε 4·1, 2·7 respectively), ν 5·95 μ.

Oxidation of the Adduct (II) *to 2-Hydroxy-*1 : *4-naphthaquinone.*—The adduct (II) (1·5 g.), sodium ethoxide (1·8 g.) and methanol (10 c.c.) were heated under reflux for 4 hr., then cooled to 0°. The scarlet precipitate formed was collected, washed with a little cold methanol, dried, and dissolved in boiling water (15 c.c.). The filtered solution was acidified: the yellow precipitate was collected, dried, and sublimed *in vacuo*, yielding yellow needles of 2-hydroxy-1 : 4-naphthaquinone (0·39 g., 41%), m. p. 190—191° (decomp.) (Found: C, 68·6; H, 3·4. Calc. for $C_{10}H_6O_3$: C, 69·0; H, 3·5%). The infrared spectrum of the product was identical with that of authentic 2-hydroxy-1 : 4-naphthaquinone.

cis-2 : *10-Diacetoxy*-1 : 4 : 5 : 8 : 9 : *10-hexahydro*-5 : 8-endo*methylene*-1 : *4-dioxonaphthalene* (III).—2 : 5-Diacetoxybenzoquinone (1·0 g.), freshly prepared *cyclo*pentadiene (2 c.c.), and benzene (30 c.c.) were heated in a sealed tube at 130° for 7 hr. The pale yellow solution was evaporated to dryness and the residue was triturated with ether until a solid formed. The latter, recrystallised from tetrahydrofuran, yielded the *adduct* (III) (0·89 g., 68%) as rhombs, m. p. 112—113° (Found: C, 62·0; H, 4·9. $C_{15}H_{14}O_6$ requires C, 62·1; H, 4·8%), ν 5·70, 5·80, and 5·95 μ.

cis : cis-11 : 13-*Diacetoxy*-1 : 4 : 5 : 8 : 11 : 12 : 13 : *14-octahydroanthraquinone.*—The adduct (II) (0·5 g.), butadiene (5 c.c.), and benzene (25 c.c.) were heated in a sealed tube at 120° for 275 hr. The colourless solution obtained was evaporated to dryness and the residue was triturated with ether: a solid formed was recrystallised from ethyl acetate, yielding cis-cis-11 : *13-diacetoxy*-1 : 4 : 5 : 8 : 11 : 12 : 13 : *14-octahydroanthraquinone* (IV) (0·6 g., 100%) as rhombs, m. p. 211° (decomp.) (Found: C, 65·3; H, 6·1. $C_{18}H_{20}O_6$ requires C, 65·1; H, 6·0%), ν 5·75 and 5·8 μ. The ultraviolet spectrum showed no maximum beyond 2200 Å. The same product was formed by the reaction of 2 : 5-diacetoxybenzoquinone with butadiene under the same conditions.

cis : *cis*-1 : 4 : 5 : 8 : 11 : 12 : 13 : 14-Octahydroanthraquinone was prepared by the method of Diels and Alder.[5] Its ultraviolet spectrum showed no maximum beyond 2200 Å. Its infrared spectrum showed a maximum at 5·8 μ.

Oxidation of the Adduct (IV) *to Anthraquinone.*—The adduct (0·1 g.), potassium hydroxide (1·0 g.), and methanol (5 c.c.) were heated under reflux for 16 hr., then diluted with water (10 c.c.), and the pale yellow precipitate was collected, dried, and sublimed *in vacuo*, yielding anthraquinone (0·02 g., 32%), m. p. 285° (Found: C, 81·1; H, 4·1. Calc. for $C_{14}H_8O_2$: C, 80·7; H, 3·8%).

1 : 4 : 5 : *8-Tetrahydroanthraquinone.*—The adduct (II) (0·5 g.), butadiene (3 c.c.), and benzene (10 c.c.) were heated at 170° for 40 hr. Cooling the almost colourless solution precipitated a yellow solid which recrystallised from ethanol, yielding 1 : 4 : 5 : *8-tetrahydroanthraquinone* (V) (0·068 g., 14%) as yellow needles, m. p. 210—211° (decomp.), darkening rapidly in light (Found: C, 78·8; H, 5·6. $C_{14}H_{12}O_2$ requires C, 79·2; H, 5·7%), ν 6·10 μ. The mother-liquors, on treatment with hot alkali as in the previous experiment, gave anthraquinone (0·15 g., 33%), identified by means of its infrared spectrum.

The anthraquinone (V) (0·058 g.), potassium hydroxide (0·5 g.), and methanol (5 g.) were heated under reflux for 2 hr., then cooled. The precipitate was collected and worked up as before, yielding anthraquinone (0·058 g., 100%), m. p. 277—278° (Found: C, 80·6; H, 3·9%).

*Reactions of 2-Hydroxy- and 2-Methoxy-*1 : *4-naphthaquinones with Butadiene.*—2-Hydroxy-1 : 4-naphthaquinone (0·5 g.), butadiene (2 c.c.), and ethanol (30 c.c.) were heated at 135—140° for 65 hr. The deep orange solution, when evaporated, gave an intractable gum which was heated under reflux with potassium hydroxide (3 g.) and ethanol for 4 hr. The dark solution was then acidified, and the precipitate was collected, dried and sublimed *in vacuo*, giving pale yellow needles of anthraquinone (0·21 g., 35%), m. p. 278—280° (Found: C, 80·3; H, 3·9%). The infrared spectrum of the product was identical with that of authentic anthraquinone.

The reaction of 2-methoxy-1 : 4-naphthaquinone (0·5 g.), butadiene (2 c.c.), and benzene (20 c.c.) under the same conditions also gave anthraquinone (0·22 g., 33%).

*11-Acetoxy-*1 : 4 : 11 : *12-tetrahydroanthraquinone.*—2-Acetoxy-1 : 4-naphthaquinone (0·5 g.), butadiene (5 c.c.), and benzene (15 c.c.) were heated at 100° for 150 hr., then evaporated to dryness. The residual gum was triturated with ethanol (5 c.c.). After several hours, rosettes of buff needles were collected, dried, and sublimed *in vacuo*, yielding *11-acetoxy-*1 : 4 : 11 : *12-tetrahydroanthraquinone* (VI; R = Ac) (0·52 g., 83%), needles, m. p. 146—147° (Found: C, 71·0; H, 5·3. $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·2%), ν 5·75 and 5·9 μ, $\lambda_{max.}$ 2245, 3060 Å (log ε 4·5, 3·3 respectively).

The adduct (0·25 g.), sodium methoxide (1·0 g.), and methanol (10 c.c.) were heated under reflux for 12 hr. A buff solid separated later at 0°; this was collected and worked up as in previous experiments, giving anthraquinone (0·06 g., 33%), m. p. 275—277° (Found: C, 80·4; H, 4·0%).

1 : 4-*Dihydroanthraquinone*.—2-Acetoxy-1 : 4-naphthaquinone (0·5 g.), butadiene (5 c.c.), and benzene (20 c.c.) were heated at 130° for 150 hr., then evaporated to dryness. The semicrystalline residue, recrystallised from light petroleum–benzene, yielded 1 : 4-dihydroanthraquinone (10·24 g., 32%), yellow needles darkening in air, m. p. 215—217° (decomp.) (Diels and Alder [5] give m. p. 209—210°) (Found: C, 80·0; H, 4·8. Calc. for $C_{14}H_{10}O_2$: C, 80·1; H, 4·9%). Treatment with alkali as in previous experiments gave anthraquinone.

1 : 4 : 11 : 12-Tetrahydroanthraquinone, prepared by the method of Diels and Alder,[5] had ν 5·9, $\lambda_{max.}$ 2250, 3000 Å (log ε 4·4, 3·2 respectively).

11-*Acetoxy*-1 : 4 : 11 : 12-*tetrahydro*-1 : 4-endo*methyleneanthraquinone*.—2-Acetoxy-1 : 4-naphthaquinone (0·5 g.), freshly prepared *cyclo*pentadiene (2 c.c.), and benzene (5 c.c.) were heated at 130° for 74 hr. The colourless solution, when cooled, deposited a solid which was collected and recrystallised from benzene, yielding 11-*acetoxy*-1 : 4 : 11 : 12-*tetrahydro*-1 : 4-endo*methyleneanthraquinone* (VII) (0·33 g.) as rhombs, m. p. 197—199° (Found: C, 72·7; H, 5·1. $C_{17}H_{14}O_4$ requires C, 72·4; H, 5·0%), ν 5·8, 5·95 μ, $\lambda_{max.}$ 2300, 3000 Å (log ε 4·2, 3·15 respectively). Evaporation of the mother-liquor to dryness and treatment of the residual gum with benzene gave another 0·08 g. of the adduct (total yield 63%). The adduct distilled unchanged at atmospheric pressure.

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