

1032. *The Stereochemistry of 2,6-Addition of Dienophiles to Bicyclo[2,2,1]heptadiene.*

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Addition of maleic anhydride and acrylic esters and nitriles to bicyclo[2,2,1]heptadiene produces nortricyclene derivatives, the *endo*-configuration of which is shown by cyclisation of the carboxylic acids to γ -lactones through attack on the cyclopropane ring. Tetracyanoethylene adds to the double bond of the benzo-diene (X) to form a cyclobutane derivative.

SOME years ago we observed the 2,6-addition of dienophiles¹ to bicyclo[2,2,1]heptadiene (I), but gave up our work when reports of the same reaction appeared soon afterwards from several other laboratories.²⁻⁵ More recently, we have taken up the reaction again,^{6,7} especially the examination of its stereochemistry, which is the main theme of this Paper.⁸

¹ Cookson, Crundwell, Hill, and Hudec, *J.*, 1964, 3062.

² Ullman, *Chem. and Ind.*, 1958, 1173.

³ Blomquist and Meinwald, *J. Amer. Chem. Soc.*, 1959, **81**, 667.

⁴ Hall, *J. Org. Chem.*, 1960, **25**, 42.

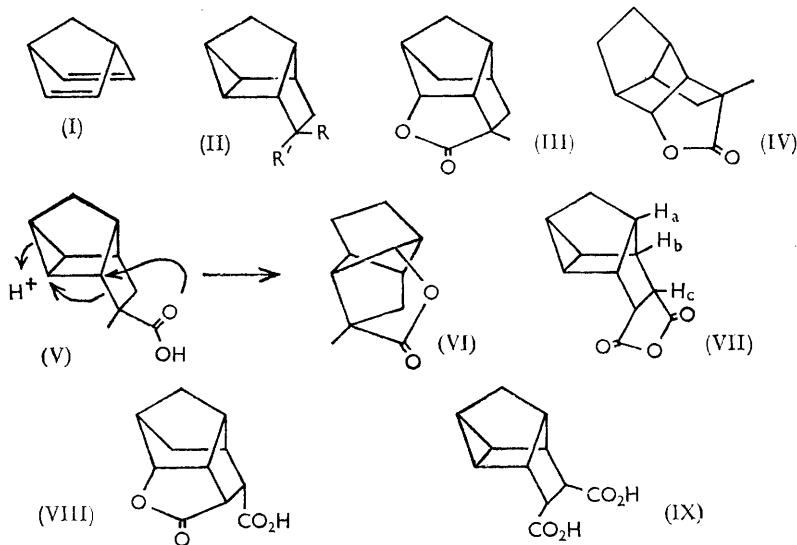
⁵ Cairns, Krespan, and McKusick, *J. Amer. Chem. Soc.*, 1961, **83**, 3428.

⁶ Cookson, Gilani, and Stevens, *Tetrahedron Letters*, 1962, 165.

⁷ Cookson and Dance, *Tetrahedron Letters*, 1962, 879.

⁸ For a full account, see Dance, Ph.D. Thesis, Southampton, 1962.

Acetylenes,^{5,7} azo-compounds,^{6,9} and tetracyanoethylene³ can form only a single 2,6-adduct with bicyclo[2,2,1]heptadiene, but any olefin lacking a plane of symmetry at right angles to the double bond and through its two carbon atoms can form two isomeric adducts (*endo* and *exo*). We set out to determine the proportions of epimeric adducts formed with various dienophiles, and to identify the *endo*-epimers by cyclisation of a suitable nucleophilic centre during opening of the cyclopropane ring with an electrophilic catalyst.



Since there was some risk of inversion of the cyano-group during hydrolysis to the carboxylic acid in the acrylonitrile adduct (II; R = H, R' = CN),⁴ the methyl derivative (II; R = Me, R' = CN) was made by addition of methacrylonitrile to the diene (I) at 150° (32% yield). As well as other expected infrared peaks, the two liquid adducts (II; R = H or Me, R' = CN) showed the peaks at 800 cm.⁻¹ diagnostic of nortricyclenes. The unmethylated compound (II; R = H, R' = CN), with alkaline hydrogen peroxide,¹⁰ readily gave the crystalline amide (II; R = H, R' = CONH₂), but conversion of the tertiary nitrile (II; R = Me, R' = CN) to the amide was more troublesome. Alkaline hydrolysis of the nitriles afforded the crystalline acids (II; R = H or Me, R' = CO₂H); epimerisation may have occurred in the acrylonitrile adduct to give (II; R = H, R' = CO₂H), but not, of course, for the methyl-acid (II; R = Me, R' = CO₂H).

At 200°, methyl methacrylate and the diene (I) gave only a low yield of the adduct, hydrolysis of which with lithium iodide in boiling collidine¹¹ led to the same acid (II; R = Me, R' = CO₂H) as was obtained from the nitrile (II; R = Me, R' = CN). Whereas gas chromatography revealed no hint of a second component in the nitrile (II; R = Me, R' = CN), the ester consisted of a mixture of two isomers in the ratio of about 11 : 1. These are assumed to be the two possible epimers; the minor component (II; R = CO₂H, R' = Me) must have been lost during purification of the acid (II; R = Me, R' = CO₂H) (which, like some other compounds in this series, was difficult to recrystallise).

Treatment of the methyl-acid (II; R = Me, R' = CO₂H) with boron trifluoride in benzene transformed it, in quantitative yield, into an oily lactone, which seemed to be homogeneous although not proved so. The significant features in its infrared spectrum were the complete disappearance of the band at 800 cm.⁻¹ and the presence of a sharp band at 1775 cm.⁻¹. Although formation of a γ -lactone under these conditions is not conclusive

⁹ Cristol, Allred, and Wetzel, *J. Org. Chem.*, 1962, **27**, 4058.

¹⁰ Radziszewski, *Ber.*, 1885, **18**, 355.

¹¹ Elsinger, Schreiber, and Eschenmoser, *Helv. Chim. Acta*, 1960, **43**, 113.

proof of the *endo*-configuration of the acid, it is most consistent with simple opening of the cyclopropane ring to give either (III) or (IV). [More strain is relieved on breaking the cyclopropane ring to give (III) than to give (IV).] Formation of a γ -lactone by rearrangement of the *exo*-acid (II; R = CO₂H, R' = Me) is still a possibility, however, *e.g.*, through the multi-stage process, summarised by the arrows in formula (V), leading to the strained structure (VI \equiv IV). This evidence for the *endo*-configuration of the acid, therefore, remains rather inconclusive.

Heating the diene (I) with maleic anhydride at 200°, using freshly distilled diene and quinol to reduce radical polymerisation, increased the yield of the adduct (VII) from "a small amount"² to 37%. Another preparation, in which the unpurified diene was used as supplied by the manufacturer, gave a yield of 78% and almost no polymer. Hydrolysis of the anhydride (VII) in very weak aqueous acid led directly to a γ -lactone-acid (VIII) rather than the *cis*-diacid. The *trans*-diacid (IX) was made by addition of methanol to the anhydride (VII), treatment of the half-ester with diazomethane, epimerisation with sodium methoxide, and hydrolysis. The equilibrated acid is assigned the *trans*-configuration (IX) rather than *cis-exo*, by analogy with bicyclo[2,2,1]heptane- and bicyclo[2,2,1]heptene-2,3-dicarboxylic acids and from failure to form an anhydride.¹² Under the conditions that gave a high yield of the crystalline lactone (VIII) from the anhydride (VII), as well as with boron trifluoride in benzene and with similar acid catalysts, the *trans*-diacid (IX) gave mixtures (with carbonyl absorption around 1766 cm.⁻¹) which could not be crystallised. It is tempting to suppose that the smooth conversion of (VII) to the lactone may be due to the ability of one protonated carboxyl group, $-\overset{+}{C}(OH)_2$ to deliver the proton to the cyclopropane ring internally, when the second carboxyl group immediately adds to the resulting carbonium ion. If the lactone is formed in this way, it must have the structure (VIII) and not the one corresponding to (III) which would result from breaking a bond out of reach of the protonated carboxyl group. In any event, the clean conversion of the anhydride into the lactone under such mild conditions is convincing evidence of its *endo*-configuration (VII).

The proton magnetic resonance spectra of the anhydride and the methyl half-ester from addition of methanol support the configuration (VII) arrived at on chemical grounds. In deuteriochloroform, the anhydride (corresponding peaks for the half-ester are given in parentheses) had a quartet (total width 5 c.p.s.) at 6.46* (6.74) due to the two protons H_c, a broad singlet (6 c.p.s. at half-height) at 7.43 (7.69) due to the two protons H_b, another singlet (6 c.p.s. at half-height) at 7.77 (8.14) due to the lone proton H_a, a singlet from the methylene bridge at 8.34 (8.48), and a multiplet with its most intense peak at 8.81 (8.69) due to the three protons on the cyclopropane ring. The signals from all the protons, except those on the cyclopropane ring, appeared at higher field in the half-ester than in the anhydride, as expected from the greater inductive pull of the anhydride group. The opposite shift in the resonance from the cyclopropane protons on opening the anhydride ring would be inexplicable if the anhydride had the *exo*-configuration, but can be ascribed in the *endo*-isomer (VII) to the magnetically induced currents in the plane of the anhydride group, which shield these three protons, for they are held directly above it. In the ester-acid the electron circulation may well be reduced, and in any case the planarity and favourable geometry of the carbonyl system is destroyed. (In nortricyclene itself¹³ the cyclopropane protons have τ 9.00.) The spectrum of the lactone (VIII) was also quite consistent with its structure, even if it could not be said to prove it.

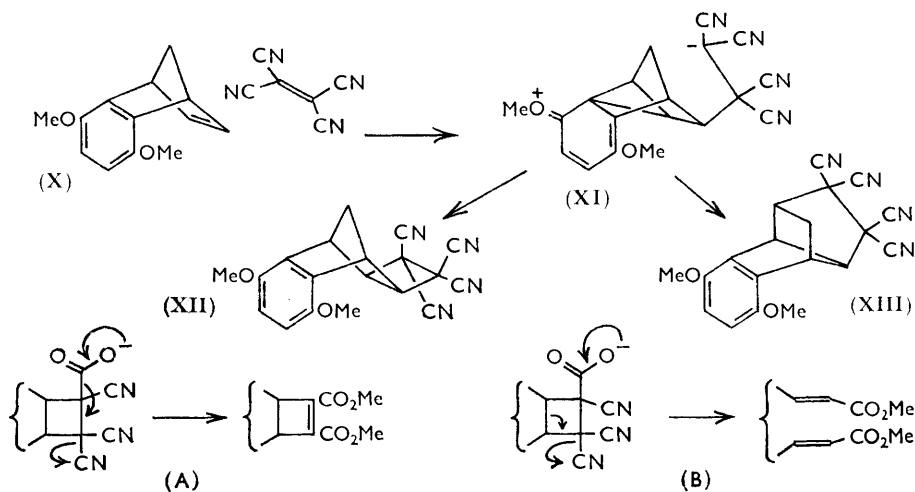
* Positions of peaks are given in p.p.m. to lower field than the peak from tetramethylsilane taken as 10.00, at 60 Mc./sec. For singlets or, for example, centres of symmetrical doublets, this, of course, gives the chemical shift units of τ . For unanalysed multiplets where chemical shifts have not been calculated, it is merely a convenient way of giving positions of lines (which may change position at a different oscillator frequency).

¹² Diels and Alder, *Annalen*, 1928, **460**, 98, 111; Alder and Stein, *ibid.*, 1933, **504**, 216.

¹³ Srinivasan, *J. Amer. Chem. Soc.*, 1961, **83**, 4923; Dauben and Cargill, *Tetrahedron*, 1961, **15**, 197

This stereochemistry is very reminiscent of that of the normal Diels–Alder reaction, where, for example, maleic anhydride adds to cyclopentadiene only from the *endo*-direction.¹² From the small amount of evidence available, bicycloheptadiene seems to have a greater preference for *endo*-addition, for much *exo*-ester results from addition of methyl methacrylate to cyclopentadiene¹⁴ whereas bicycloheptadiene gives very largely what seems to be *endo*-ester; * even more striking is the formation of only *exo*-nitrile from methacrylonitrile with the first diene¹⁵ and only *endo*-nitrile with the second.

If Diels–Alder addition to a sufficiently electron-deficient dienophile goes through a dipolar intermediate, it might be possible to fill the role of the second double bond with other mobile electrons and to incorporate a rearrangement into the addition. Our attempts to realise this in several systems have so far failed. For example, addition of tetracyanoethylene to the dimethoxybicycloheptadiene (X) might give an intermediate like (XI), having resonance forms with an electron-deficient cyclopropane ring (the precise distribution of the electrons in this kind of hypothetical structure is hardly



worth discussing, since there is no evidence for its existence), which could lead to the *exo*-cyclobutane adduct (XII), without rearrangement, or to the rearranged adduct (XIII).

In the event, no 1:1-adduct could be isolated from (X) with acrylonitrile, methacrylonitrile, diethyl azodicarboxylate, or maleic anhydride, but a crystalline adduct was formed with tetracyanoethylene in boiling benzene, or, better, at 100° in the absence of solvent. The ultraviolet spectrum showed only the *p*-dimethoxybenzene chromophore, and the adduct was saturated towards permanganate. Alkaline hydrolysis, followed by treatment with diazomethane, gave a crystalline diester that gave analyses fitting $C_{19}H_{20}O_8$ (*i.e.*, one mol. of H_2 less than that expected from hydrolysis and loss of two mol. of CO_2); it may have arisen from some such elimination of cyanide as those shown in A or B [assuming (XII) for the adduct]. In agreement with A, the diester absorbed one mol. of hydrogen over Adams catalyst. [So did the original adduct, however, perhaps with hydrogenolysis of the $(NC)_2C-C(CN)_2$ bond.]

In chloroform solution, the adduct had a peak at 4.70 due to the two aromatic protons, a singlet (3 c.p.s. at half-height) at 5.99 due to the bridge-head protons, a sharp singlet at

* Admittedly the total yield of ester was small.

¹⁴ Berson, Hamlet, and Mueller, *J. Amer. Chem. Soc.*, 1962, **84**, 297.

¹⁵ Schwarz and Maienthal, *J. Org. Chem.*, 1960, **25**, 499.

7.79 due to the methoxy-groups, a singlet at 7.94 (3 c.p.s. at half-height) due to the cyclobutane protons, and a quartet (τ 8.53 and 8.13, J 12 c.p.s.), each peak being further split into a triplet (J 1.4 c.p.s.), due to the methylene bridge. It is unlikely that the peaks from the four different tertiary protons in the rearranged structure (XIII) would happen to fall into two pairs, and the adduct must then be the cyclobutane (XII); the lack of coupling¹⁶ between the tertiary protons suggests that it has the *exo*-configuration (XII). Tetracyanoethylene is known to add to many other olefins to form tetracyanocyclobutanes.^{3,17}

EXPERIMENTAL

4-Cyano-4-methyltetracyclo[4,2,1,0^{2,9},0^{3,7}]nonane, (II; R = Me, R' = CN).—Methacrylonitrile (55 ml.), freshly distilled bicyclo[2,2,1]heptadiene (65 ml.), and quinol (100 mg.) were heated together at 150° for 24 hr. The mixture was poured into cyclohexane (450 ml.), filtered, and the solvent evaporated. The residue was taken up in acetone and a solution of potassium permanganate (12 g.) and magnesium sulphate (12 g.) in water (400 ml.) was added. The excess of permanganate was decolourised with sulphur dioxide and the mixture filtered. Both the solid and the filtrate were extracted with cyclohexane and the extracts dried (Na₂SO₄). The product was fractionally distilled under reduced pressure; it had b. p. 110–112°/14 mm. (32%) (Found: C, 82.6; H, 8.3; N, 8.95. C₁₁H₁₃N requires C, 83.0; H, 8.2; N, 8.8%).

Methyl 4-Methyltetracyclo[4,2,1,0^{2,9},0^{3,7}]nonane-4-carboxylate (II; R = Me, R' = CO₂Me).—Methyl methacrylate (41 ml.), freshly distilled bicyclo[2,2,1]heptadiene (44 ml.), and cupric acetate (300 mg.) were heated at 200° for 12 hr. The work-up procedure was as above. The product was fractionally distilled under reduced pressure; it had b. p. 112–114°/15 mm. (3%).

4-Methyltetracyclo[4,2,1,0^{2,9},0^{3,7}]nonane-4-carboxylic Acid (II; R = Me, R' = CO₂H).—(a) *From the nitrile*. A solution of the above nitrile (II; R = Me, R' = CN) (13.13 g.) and sodium hydroxide (12.5 g.) in ethyl alcohol (15 ml.) and water (35 ml.) was refluxed for 7 days. The ethyl alcohol was distilled off and the mixture extracted with ether (3 × 50 ml.). The aqueous layer was acidified and again extracted with ether (3 × 50 ml.). The combined extracts were dried (Na₂SO₄) and evaporated, leaving a viscous gum which solidified on standing for a week. The acid, recrystallised from n-hexane, had m. p. 92.5–94° (42%), ν_{\max} . 1695 cm.⁻¹ (Nujol and CHCl₃) (Found: C, 74.1; H, 8.0; O, 17.9. C₁₁H₁₄O₂ requires C, 74.1; H, 7.9; O, 18.0%). The unmethylated acid (II; R = H, R' = CO₂H)⁹ had ν_{\max} . 1695 and 1710 cm.⁻¹ (Nujol) or 1700br cm.⁻¹ (CHCl₃).

(b) *From the ester*. A solution of the ester (II; R = Me, R' = CO₂Me) (2.15 g.) and lithium iodide (10 g.; dried at 80°/1.5 mm. for 24 hr.) in collidine (225 ml.) was refluxed for 4 hr. under nitrogen. After cooling to room temperature, the solution was poured into a mixture of ether (200 ml.), methylene chloride (100 ml.), 4*N*-hydrochloric acid (200 ml.), and ice, shaken to dissolve the solid, and separated. The aqueous layer was further extracted with ether–methylene chloride (2 : 1), and the combined organic extracts were shaken with 4*N*-hydrochloric acid and then with saturated sodium chloride solution. After evaporation to small bulk, the organic layer was extracted with saturated sodium hydrogen carbonate solution, which, on acidification, gave a sticky, solid product, m. p. 92–94° (from n-hexane).

2-Hydroxy-4-methyltricyclo[4,2,1,0^{2,9}]nonane-4-carboxylic Acid Lactone (III or IV).—To a solution of the acid (II; R = Me, R' = CO₂H) in benzene, was added an excess of a solution of boron trifluoride in benzene. The mixture was set aside for 1 hr. and was then evaporated under reduced pressure. The residue was treated, in ether, with saturated sodium hydrogen carbonate solution. After drying (Na₂SO₄), the solvent was evaporated, but the resulting viscous oil could not be induced to crystallise; it had ν_{\max} . 1775 cm.⁻¹ (Nujol or CHCl₃) (Found: C, 74.9; H, 7.9; O, 17.5. C₁₁H₁₄O₂ requires C, 74.1; H, 7.9; O, 18.0%).

4-Methyltetracyclo[4,2,1,0^{2,9},0^{3,7}]nonane-4-carboxamide (II; R = Me, R' = CO·NH₂).—The nitrile (II; R = Me, R' = CN) (1.50 g.) and 10% hydrogen peroxide (10 ml.) were mixed with isopropyl alcohol until a homogeneous liquid was obtained (50 ml.). This solution was maintained at 40–50° for 15 min., and then allowed to cool to room temperature. Addition of 2% aqueous potassium hydroxide (5 ml.) caused a slow but prolonged evolution of oxygen.

¹⁶ Karplus, *J. Chem. Phys.*, 1959, **30** 11; *J. Amer. Chem. Soc.*, 1963, **85**, 2870.

¹⁷ Williams, Wiley, and McKusick, *J. Amer. Chem. Soc.*, 1962, **84**, 2210.

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On evaporation, a viscous liquid was obtained which showed only a slight tendency to crystallise. Chromatography on a silica column gave the following fractions.

Eluent	Wt. of solid (mg.)	M. p.	$\nu_{C=O}$ (cm. ⁻¹)
2% Ethyl acetate in benzene	233	60—95°	1610 and 1660
5% Ethyl acetate in benzene	440	120—126	1610 and 1658
10% Ethyl acetate in benzene	357	137—140	1616 and 1655

Tetracyclo[4,2,1,0^{2,9},0^{3,7}]nonane-4-carboxamide (II; R = H, R' = CO·NH₂).—The nitrile (II; R = H, R' = CN)³ (2.99 g.) was treated as above. During the evolution of oxygen, however, the product crystallised out. A second crop of crystals was obtained by diluting the solution with water. Both crops were free from unreacted nitrile. After three recrystallisations from isopropyl alcohol, the *amide* (86%) had m. p. 215.5—216° (Found: C, 73.6; H, 7.9; N, 8.5; O, 10.2. C₁₀H₁₃NO requires C, 73.6; H, 8.0; N, 8.6; O, 9.8%).

Tetracyclo[4,2,1,0^{2,9},0^{3,7}]nonane-4,5-dicarboxylic endo-Anhydride (VII).—Maleic anhydride (5.0 g.), freshly distilled bicyclo[2,2,1]heptadiene (10 ml.), and quinol (250 mg.) were heated together at 200° for 5 hr. The mixture was extracted with ethyl acetate and the resulting solution diluted with an equal volume of benzene. Polymer was filtered off and the filtrate evaporated. The residue, in benzene, was chromatographed on a silica column; the benzene fraction gave, after recrystallisation from chloroform–light petroleum, a white solid, m. p. 121.5—122° (lit.,¹ 120°) (37%). A later preparation, on the same scale, using a commercial sample of the diene (Shell Research Ltd.), gave a 78% yield.

5-endo-Carboxy-2-hydroxytricyclo[4,2,1,0^{3,7}]nonane-4-endo-carboxylic Acid Lactone (VIII).—The anhydride (VII) (3.6 g.) was refluxed overnight with water (150 ml.) containing 3 drops of concentrated hydrochloric acid. The solution was extracted with chloroform (3 × 100 ml.) and the combined extracts, after drying (Na₂SO₄), were evaporated. The *lactone-acid*, recrystallised from chloroform–light petroleum, had m. p. 215—216° (90%), ν_{max} . 1710 and 1780 cm.⁻¹ (Nujol) or 1720 and 1775 cm.⁻¹ (CHCl₃) (Found: C, 63.2; H, 5.7; O, 28.6. C₁₁H₁₂O₄ requires C, 63.45; H, 5.8; O, 30.7%).

Methyl 5-endo-Carboxyltricyclo[4,2,1,0^{2,9},0^{3,7}]nonane-4-endo-carboxylate.—The anhydride (VII) (5.25 g.) was refluxed in anhydrous methanol (150 ml.) for 16 hr. The solution was then evaporated and the resulting white solid recrystallised from chloroform–light petroleum; the *product* had m. p. 155—156° (82%) (Found: C, 64.9; H, 6.4; O, 28.5. C₁₂H₁₄O₄ requires C, 64.85; H, 6.35; O, 28.8%), ν_{max} . 1695 and 1735 cm.⁻¹ (Nujol) or 1715 and 1740 cm.⁻¹ (CHCl₃). There were no peaks corresponding to an anhydride or a γ -lactone.

Tetracyclo[4,2,1,0^{2,9},0^{3,7}]nonane-4-endo,5-exo-dicarboxylic Acid (IX).—An excess of a solution of diazomethane in benzene was added to a solution, in benzene (150 ml.), of the above mono-ester (4.90 g.). After 1 hr., the yellow colour was discharged by addition of acetic acid and the solution was evaporated. The product, which showed infrared carbonyl absorption at 1735 cm.⁻¹ only (Nujol), could not be induced to crystallise. Sodium methoxide in methanol (6 g. sodium in 100 ml. methanol) was then added and the mixture was refluxed for 5 hr. The methanol was evaporated and water added to dissolve the solid. Sodium hydroxide (40 g.) was then added and the mixture refluxed for a further 5 hr. After cooling, the solution was made just acid with sulphuric acid and the *product* was extracted with chloroform. On recrystallisation from chloroform–light petroleum it had m. p. 182—183° (83%) (Found: C, 63.7; H, 5.6; O, 30.6. C₁₁H₁₂O₄ requires C, 63.45; H, 5.8; O, 30.7%). This compound showed carbonyl peaks at 1695 and 1710 cm.⁻¹ only (Nujol), or a broad band at 1705 cm.⁻¹ (CHCl₃).

3,3,4-Tetracyano-3',6'-dimethoxy-7,8-benzotricyclo[4,2,1,0^{2,5}]nonane (XII).—The olefin (X) (4.01 g.) and tetracyanoethylene (1.86 g.) were heated in a sealed tube at 100° for 4 hr. The contents were then chromatographed on silica gel, the benzene fraction yielding a 60% recovery of (X). The fraction from 5% ethyl acetate in benzene gave a 22% yield of a crude brown product. Three recrystallisations from chloroform–light petroleum gave white leaflets of the *adduct*, m. p. 162° (decomp.) (Found: C, 68.85; H, 4.2; O, 9.8; N, 17.1. C₁₉H₁₄N₄O₂ requires C, 69.1; H, 4.3; O, 9.7; N, 17.0%). The adduct (58 mg.) in ethyl acetate over Adams catalyst absorbed hydrogen (3.86 ml.) equivalent to 0.96 mol.

Hydrolysis of the Above Adduct.—The crude adduct (1.24 g.) was refluxed for 24 hr. with sodium hydroxide (12 g.), ethanol (15 ml.), and water (30 ml.). The reaction mixture was added to excess of dilute hydrochloric acid and extracted with ether. The combined extracts

were dried (Na_2SO_4) and evaporated. The acidic product could not be crystallised and was treated, in ether solution, with excess of diazomethane. The resulting product was chromatographed on silica gel, the benzene fraction giving a 29% overall yield of a *solid* which, on recrystallisation from chloroform–light petroleum, had m. p. 225° (Found: C, 66.3; H, 5.8; O, 27.2; OMe, 31.4. $\text{C}_{19}\text{H}_{20}\text{O}_6$ requires C, 66.3; H, 5.85; O, 27.9; OMe, 35.5%).

The diester (65 mg.) in ethyl acetate over Adams catalyst absorbed hydrogen (3.93 ml.) equivalent to 0.93 mol.

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