Reactions with α-Diazo-ketones. Part II.[1] Intramolecular Cyclisation of Bisdiazo-ketones

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Catalytic decomposition of 1,5-bisdiazo-3,3-bis-(2-methylprop-2-enyl)pentane-2,4-dione (1b) and its 3-(but-3-enyl)-3-(prop-2-enyl) analogue (1c) yielded the spirobi{bicyclo[3.1.0]hexane}dione (4) and its analogue (12), respectively, both formed by intramolecular double addition of the intermediate bisketocarbene systems to the olefinic bonds. As by-products, isomeric spiro-lactones (7) and (8) were obtained. Assignment of stereochemistry to the products is based on n.m.r. spectral properties and/or chemical transformations.

ALTHOUGH a number of bisdiazo-ketones have been described, their reactions have received scant attention;

reports are mainly devoted to Wolff rearrangement and chloro-ketone formation.[2] We have recently begun a study of the intramolecular double addition of bisdiazo-ketones to olefinic bonds, and have reported the formation of the isomeric spiro-diketones (2) and (3). Since it

[1] Part I, S. Bien and D. Ovadia, *J. Org. Chem.*, 1970, **35**, 1028.

[2] W. C. J. Ross, *J. Chem. Soc.*, 1950, 752; M. Frankel and M. Harnik, *J. Amer. Chem. Soc.*, 1952, **74**, 2120; E. Fahr, *Annalen*, 1960, **638**, 27.

appears that this reaction represents a feasible route to a new class of bicyclo-spiro-compounds, and in view of recent interest[3] in the chiroptical properties of the spiro[4.4]nonane system, further examples of the reaction have now been investigated.

The new bisdiazo-ketones (1b and c) were prepared by addition of diazomethane to suitably alkylated malonyl chlorides obtained from the corresponding acids with oxalyl chloride. Since the diazo-ketone (1b) was an unstable oil, it was used directly without purification. Its catalytic decomposition in dry ether, effected by π-allylic palladium chloride complex[1,4,5] at low temperature, led to a complex mixture from which the spiro-diketone (4), representing one of the three theoretically possible stereoisomers (4)—(6), was isolated.

(1)

a, $R^1 = R^2 = CH_2=CH-CH_2$

b, $R^1 = R^2 = CH_2=CMe-CH_2$

c; $R^1 = CH_2=CH-CH_2$
$R^2 = CH_2=CH-CH_2-CH_2$
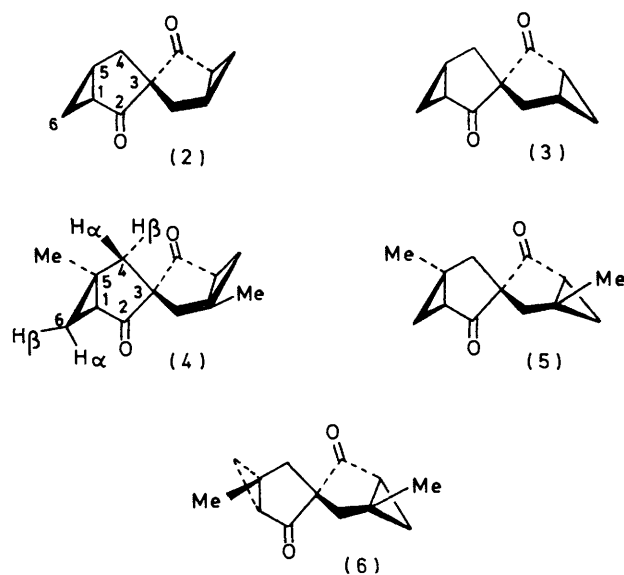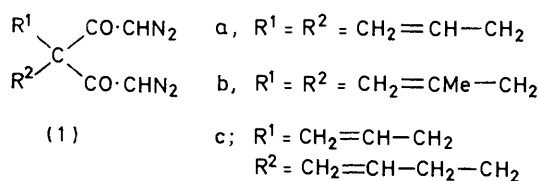
The structure was assigned on the basis of the n.m.r. spectrum. Integration showed an even-numbered proton distribution compatible only with structures (4) and (6), both having a two-fold axis of symmetry, but not

* The effects of both the carbonyl group and the cyclopropane ring are reflected in the corresponding signals measured for compound (3) (Table).

[3] H. Gerlach and W. Müller, Helv. Chim. Acta, 1968, 51, 1587; 1972, 55, 2277; W. Hug and G. Wagnière, Tetrahedron, 1972, 28, 1241; D. A. Lightner, G. D. Christiansen, and J. L. Melquist, Tetrahedron Letters, 1972, 2045; H. J. Wüthrich, A. Siewinski, H. Schaffner, and O. Jeger, Helv. Chim. Acta, 1973, 56, 239; J. H. Brewster and R. T. Prudence, J. Amer. Chem. Soc., 1973, 95, 1217; R. K. Hill and D. A. Cullison, ibid., p. 1229.

[4] W. T. Dent, R. Long, and A. J. Wilkinson, J. Chem. Soc., 1964, 1585.

with (5) which is asymmetric. A decision in favour of structure (4) was finally made by comparing the H-6β and H-4β resonances in the spectra of the product and of the previously prepared diketones (2) and (3).

As shown in the Table, the multiplets due to the geminal cyclopropyl protons and H-4β in (4) appear in a range similar to that of the corresponding signals for the diketone (2). In the alternative structure (6), however, the geminal cyclopropyl protons would experience the paramagnetic effect of the distant carbonyl group of the other ring. Similarly, H-4β in structure (6), affected only by the anisotropic effect of the distant carbonyl group, but not by the shielding volume above the plane of the cyclopropane ring,[6-9] would resonate at lower field.* This comparative method seems to be justified, since the detailed first-order analysis[1] made for compounds (2) and (3) enabled correct assignment of their structure to be made, as confirmed recently by X-ray analysis of compound (2).[10]

Chemical shift ^{a} data

Compound	H-6α	H-6β	H-4β
(2)	0·72	1·22	2·54
(4)	0·95	1·18	2·35
(7)	1·08	1·35	2·84
(3)	1·20	2·00	2·96
(8)	1·18	>1·70	2·80
(12)			3·08

^{a} Centres of multiplets reported as δ values.

In addition to diketone (4), two further crystalline products, (7) and (8), were isolated by preparative g.l.c. following preliminary column chromatography. Identification of these compounds is based both on spectral data and on chemical reactions. Reduction of the spiro-lactone (7) with sodium borohydride and with lithium aluminium hydride gave the alcohols (10) and (11), respectively. The n.m.r. spectra of both these alcohols show a low-field doublet (1H, J 5 Hz) at δ 4·93 and 4·33, respectively, attributed to the tertiary 2β-proton. The splitting of this absorption is explained as resulting from coupling with the cis-proton H-1β, and shows that H-2β is trans with respect to the cyclopropane ring in both products. This conclusion agrees with results of earlier experiments dealing with metal hydride reduction of conjugated cyclopropyl ketones.[11,12] The upfield shift of the H-2β signal after the reductive opening of the lactone ring [e.g. in (11)] indicates a cis-relationship between this proton and the lactonic carbonyl group in compound (10) and thus indirectly supports the relative configuration assigned to the cyclopropane ring in the spiro-lactones (7) and (8).

The presumed precursor of these spiro-lactones is (9),

[5] R. K. Armstrong, J. Org. Chem., 1966, 31, 618.

[6] D. J. Patel, M. E. H. Howdan and J. D. Roberts, J. Amer. Chem. Soc., 1963, 85, 3218.

[7] S. Forsen and T. Norin, Tetrahedron Letters, 1964, 2845.

[8] H. Prinzbach, H. Hagemann, J. H. Hartenstein, and R. Kitzing, Chem. Ber., 1965, 98, 2201.

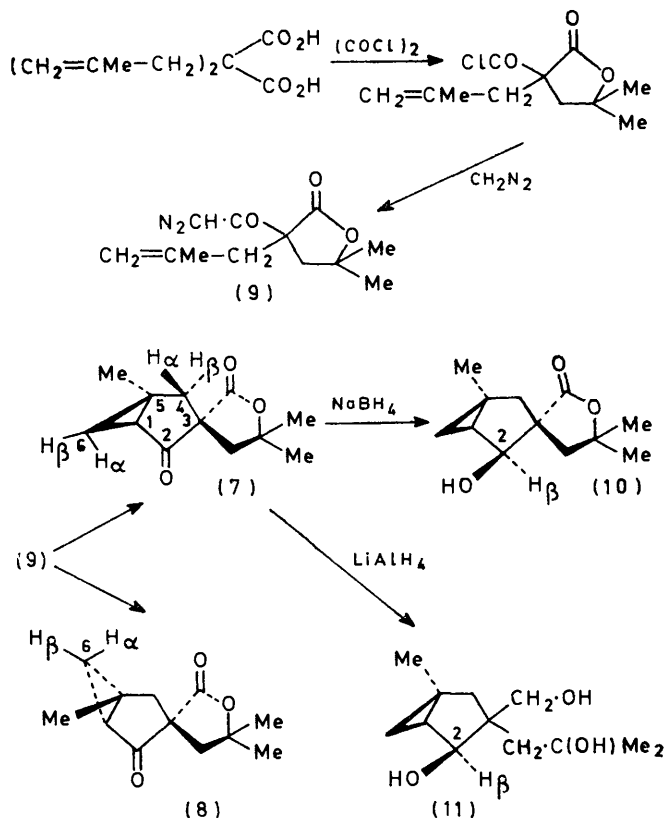[9] K. Tori and K. Kitahonoki, J. Amer. Chem. Soc., 1965, 87, 386.

[10] F. H. Herbstein and H. Regev, J. Chem. Soc. (B), 1971, 1696.

[11] J. R. Williams and H. Ziffer, Tetrahedron, 1968, 24, 6725.

[12] M. Hanack and H. Allmendiger, Chem. Ber., 1964, 97, 1669.

a reasonable by-product in the standard preparation of the corresponding bisdiazo-ketone (1b). Although acid-catalysed intramolecular lactonisation involving suitably located olefinic bonds is well known,[13] in the preparation of the bisdiazo-ketone (1a) no concomitant lactone formation has been observed. In the present case, however, under the standard conditions used, lactonisation involving the 2-methylprop-2-enyl group became a dominant side-reaction, suppressing acid chloride formation. This may explain the decreased yield of the desired spiro-diketone (4).*

A ring-size effect is demonstrated in the catalytic decomposition of the unsymmetrical bisdiazo-ketone (1c). From the complex reaction mixture only one of the four theoretically possible stereoisomeric spiro-diketones was isolated, in moderate yield. In view of
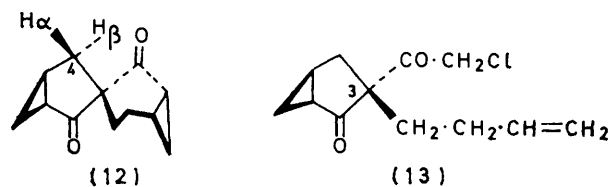

the close similarity of the n.m.r. data for this isomer with those for the spiro-diketone (3), structure (12) was assigned. As a by-product the chloro-ketone (13) was obtained in low yield. The low yield of (12), as compared with yields of the spiro-diketones (2) and (3), is in accord with earlier results[15] showing that ketocarbene

cyclisation to give the bicyclohexanone occurs in preference to formation of the bicycloheptanone system.

EXPERIMENTAL

I.r. spectra were determined on a Perkin-Elmer Infracord spectrophotometer. N.m.r. spectra were recorded on a Varian A-60 or T-60 spectrometer for solutions in $CDCl_3$ unless otherwise stated, with Me_4Si as internal standard.

Diethyl Bis-(2-methylprop-2-enyl)malonate.—Diethyl malonate (32 g) was added dropwise, with stirring, to a suspension of sodium hydride (4·8 g) in dry dimethylformamide (100 ml). Stirring was continued until all the hydride had reacted and to the mixture 3-chloro-2-methylpropene (18 g) was added dropwise. The reaction is exothermic. After addition was complete the solution was stirred for 0·5 h at room temperature, then sodium hydride (4·8 g) was added in portions, followed by 3-chloro-2-methyl-propene (20 g).† After being stirred at 80° for 2 h, the mixture was poured into cold water and extracted with ether. The extract was washed with water (3 × 100 ml), dried (Na_2SO_4), and evaporated. Distillation of the oily residue gave pure ester (45 g), b.p. 140° at 11 mmHg (lit.,[16] 115° at 5 mmHg); $\nu_{max.}$ (CHCl₃) 1730 (ester C=O) and 1640 cm⁻¹ (CH_2=C); δ 1·25 (6H, t, O·CH_2·CH_3), 1·70 (6H, s, =C·CH_3), 2·76 (4H, s, C·CH_2), 4·18 (4H, q, O·CH_2), and 4·83 (4H, d, with fine splitting, CH_2=C).

Bis-(2-methylprop-2-enyl)malonic Acid.—To a mixture of aqueous potassium hydroxide (36 g in 54 ml) and the foregoing ester (38 g), ethanol was added until a homogeneous solution was obtained. The mixture was heated under reflux for 4 h, ethanol was removed under reduced pressure, and the cooled solution was washed with ether. The alkaline layer was acidified with cold 10% hydrochloric acid, saturated with sodium chloride, and extracted several times with ether. The combined extracts were dried (Na_2SO_4) and evaporated. The residue solidified slowly and crystallisation from cyclohexane afforded the pure *acid* (12 g), m.p. 106° (this compound has been reported both as an oil [17] and as a solid,[16] m.p. 176°); δ 1·73 (6H, s, =C·CH_3), 2·80 (4H, s, C·CH_2), and 4·87 (4H, d, with fine splitting, CH_2=C) (Found: C, 62·3; H, 7·8. $C_{11}H_{16}O_4$ requires C, 62·25; H, 7·6%).

1,5-Bisdiazo-3,3-bis-(2-methylprop-2-enyl)pentane-2,4-dione (1b).—To a stirred, ice-cooled mixture of bis-(2-methyl-prop-2-enyl)malonic acid (21·2 g), dry benzene (200 ml), and anhydrous pyridine (1 ml) a solution of freshly distilled oxalyl chloride (60 ml) in dry benzene (60 ml) was added dropwise. The ice-bath was then removed and the mixture was slowly heated to 40° and kept at this temperature for 2 h, then at 60° for an additional 2 h. The excess of oxalyl

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* The observed lactonisation is in accord with the fact that lactone formation is easier at a tertiary rather than at a secondary or primary carbon atom.[14] In the present work no attempts have been made to avoid lactonisation by changing the reaction conditions.

† The sodium hydride was allowed to react completely before addition of the chloride.

[13] 'Methoden der Organischen Chemie (Houben-Weyl),' vol. VI/2, ed. E. Müller, Georg Thieme, Stuttgart, 1963, p. 602.

[14] G. S. Skinner and R. DeV. Huber, *J. Amer. Chem. Soc.*, 1951, **73**, 3321.

[15] M. M. Fawzi and C. D. Gutsche, *J. Org. Chem.*, 1966, **31**, 1390.

[16] R. Ya. Levina and N. N. Godovikov, *Zhur. obschchei Khim.*, 1954, **24**, 1572.

[17] E. Lobba, *Bol. Dept. Eng. Quim. E.P.U.S.P.*, 1964, **19**, 44.

chloride and benzene were removed and the residue was washed with dry ether (3 × 50 ml). For characterisation of the dichloride a sample was withdrawn from the combined extracts and evaporated; the residual oil [$\nu_{max.}$ (dry CCl$_4$) 1800 (COCl) and 1645 cm^{-1} (CH$_2$=C)] was converted into the *dianilide*, m.p. 175° (from cyclohexane) (Found: C, 76·0; H, 7·1; N, 7·9%; M^+, 362. C$_{23}$H$_{26}$N$_2$O$_2$ requires C, 76·2; H, 7·2; N, 7·7%; M, 362·45).

The combined extracts were added dropwise with swirling to ice-cold ethereal diazomethane [from nitrosomethylurea (60 g)]. After 1 h the solution was filtered and evaporated under reduced pressure giving the crude, oily, unstable bisdiazo-ketone (22 g).

Catalytic Decomposition of the Bisdiazo-ketone (1b).—A cold solution of crude, freshly prepared bisdiazo-ketone (1b) (3·5 g) in dry ether (250 ml) was added dropwise to a stirred, ice-cold suspension of π-allylic palladium chloride complex [1] (0·15 g) in dry ether (500 ml). Decomposition started immediately and the addition was regulated according to the rate of gas evolution. Stirring was then continued until the i.r. band at 2110 cm^{-1} disappeared. The solution was filtered and concentrated, and the residue was purified by column chromatography on Florisil (60—100 mesh; 120 g). Elution with light petroleum (b.p. 40—60°) yielded a small amount of an oily mixture which was not further investigated. Elution with benzene then gave a semi-solid mixture which was separated by preparative g.l.c. on a 1/4 in × 5 ft column packed with 3% XE-60 on 100—200 mesh GasChrom Q at a column temperature of 170°, yielding (i) (1RS,1′RS,-3SR,5RS,5′RS)-5,5′-*dimethyl*-3,3′-*spirobi{bicyclo*[3.1.0]*hexane}*-2,2′-*dione* (4) (0·3 g), m.p. 115° (from cyclohexane), $\nu_{max.}$ 1740 and 1706 cm^{-1} (Found: C, 76·8; H, 8·1%; M^+, 204. C$_{13}$H$_{16}$O$_2$ requires: C, 76·4; H, 7·9%; M, 204·3); (ii) (1RS,3SR,5RS)-5,5′,5′-*trimethylspiro{bicyclo*[3.1.0]*hex-ane*-3,3′-(*tetrahydrofuran*)}-2,2′-*dione* (7) (0·3 g), m.p. 102° (from cyclohexane); $\nu_{max.}$ 1720 (ketone C=O) and 1765 cm^{-1} (lactone C=O) (Found: C, 68·9; H, 7·8%; M^+, 208. C$_{12}$H$_{16}$O$_3$ requires C, 69·2; H, 7·7%; M, 208·25); and (iii) (1RS,3RS,5RS)-5,5′,5′-*trimethylspiro{bicyclo*[3.1.0]*hexane*-3,3′-(*tetrahydrofuran*)}-2,2′-*dione* (8) (0·12 g), m.p. 90° (from hexane); $\nu_{max.}$ 1720 (ketone C=O) and 1760 cm^{-1} (lactone C=O) (Found: C, 69·5; H, 7·5%; M^+, 208).

Reduction of the Spiro-lactone (7).—(a) *With sodium borohydride.* To a solution of the lactone (7) (0·15 g) in methanol (15 ml), sodium borohydride (0·15 g) was added. The mixture was left overnight at room temperature, the solvent was removed, and water was added. The solution was carefully neutralised (to pH 7) with dilute hydrochloric acid and extracted with ether. The crude crystalline (1RS,2RS,3SR,5RS)-2-*hydroxy*-5,5′,5′-*trimethylspiro{bicyclo*-[3.1.0]*hexane*-3,3′-(*tetrahydrofuran*)}-2′-*one* (10) (0·14 g), obtained after the usual work-up, had m.p. 88° (from cyclohexane); $\nu_{max.}$ 3590 and 1750 cm^{-1} (Found: C, 68·3; H, 8·45%; M^+, 210. C$_{12}$H$_{18}$O$_3$ requires C, 68·5; H, 8·6%; M, 210·3).

(b) *With lithium aluminium hydride.* To a dry ethereal solution (45 ml) of the lactone (7) (0·15 g), the hydride (0·15 g) was added, and the mixture was stirred for 0·5 h. The complex and the excess of reagent were then decomposed with 10% hydrochloric acid and, after the usual work-up, the solid (1RS,2RS,3RS,5RS)-3-*hydroxymethyl*-3-(2-*hydroxy*-2-*methylpropyl*)-5-*methylbicyclo*[3.1.0]*hexan*-2-*ol* (11)

was isolated (0·13 g), m.p. 101° (from cyclohexane); $\nu_{max.}$ 3400 and 3600 cm^{-1} (Found: C, 67·3; H, 10·05%; M^+, 214, C$_{12}$H$_{22}$O$_3$ requires C, 67·25; H, 10·35%; M, 214·3), m/e 196 (M^+ − H$_2$O; required, 196·3).

Diethyl But-3-enylmalonate.—The carbanion formed from diethyl malonate (32 g) and sodium hydride (4·8 g) in dry dimethylformamide (100 ml) was alkylated with 4-bromobutene (27·2 g). The reaction was complete after the mixture had been heated at 90° for 3 h (pH dropped to 7). The work-up was similar to that described for the preparation of diethyl bis-(2-methylprop-2-enyl)malonate. The pure ester (36 g) had b.p. 120° at 11 mmHg (lit.,[18] 116—121° at 12 mmHg).

Diethyl Allyl(but-3-enyl)malonate.—The carbanion formed from the foregoing but-3-enylmalonate (42·8 g) and sodium hydride (4·8 g) was alkylated in dry dimethylformamide (100 ml) with allyl bromide (25 g) by the standard procedure. The pure *ester* (40 g) had b.p. 140° at 11 mmHg; $\nu_{max.}$ 1730 cm^{-1} (CO$_2$Et); δ 1·97 (4H, d), 2·67 (2H, d), and 4·80—6·20 (6H, m) (Found: C, 66·0; H, 8·6. C$_{14}$H$_{22}$O$_4$ requires C, 66·1; H, 8·7%).

Allyl(but-3-enyl)malonic Acid.—The foregoing ester (40 g) was hydrolysed as for the preparation of bis(2-methylprop-2-enyl)malonic acid. The *product* (25·5 g) melted at 112° (from benzene); δ 2·05 (4H, d), 2·70 (2H, d), 4·80—6·20 (6H, m), and 11·03 (2H, s) (Found: C, 60·8; H, 7·0. C$_{10}$H$_{14}$O$_4$ requires C, 60·6; H, 7·1%).

3-(But-3-enyl)-1,5-bisdiazo-3-(prop-2-enyl)pentane-2,4-di-one (1c).—This was obtained from allyl(but-3-enyl)malonic acid as described for the bisdiazo-ketone (1b). The intermediate allyl (but-3-enyl)malonyl chloride [$\nu_{max.}$ (CCl$_4$) 1790 and 1645 cm^{-1}] was characterised as the *dianilide*, m.p. 173° (from benzene) (Found: C, 75·7; H, 6·8; N, 8·15%; M^+ 348. C$_{22}$H$_{24}$N$_2$O$_2$ requires C, 75·8; H, 6·9; N, 8·0%; M, 348·4).

The *bisdiazo-ketone* was obtained as a solid, m.p. 78° (from ether), $\nu_{max.}$ 2100 and 1630 cm^{-1}; δ 1·93 (4H, d), 2·63 (2H, d), 5·53 (2H, s), and 4·80—6·20 (6H, m) (Found: C, 58·7; H, 5·5. C$_{12}$H$_{14}$N$_4$O$_2$ requires C, 58·5; H, 5·7%).

Catalytic Decomposition of the Bisdiazo-ketone (1c).—The bisdiazo-ketone (3·5 g) was decomposed under the same conditions as (1b). The crude product was chromatographed on Florisil (60—100 mesh; 120 g). Elution with light petroleum (b.p. 40—60°) gave an oil which was purified by g.l.c. on a 1/4 in × 5 ft column of 3% XE-60 on 100—120 mesh Chromosorb W at a column temperature of 190° to give (1RS,3RS,5RS)-3-(*but-3-enyl*)-3-*chloroacetylbicyclo*[3.1.0]-*hexan-2-one* (13) in a low yield; $\nu_{max.}$ 1640, 1710, and 1725 cm^{-1}; δ 0·60—0·80 (1H, m, H-6α), 0·90—1·38 (1H, m, H-6β), 3·03 (1H, d, H-4β), 4·38 (2H, s, CO·CH$_2$Cl), and 4·80—6·10 (3H, m, vinylic H) (Found: C, 63·8; H, 6·8%; M^+, 226. C$_{12}$H$_{15}$ClO$_2$ requires C, 63·6; H, 6·7%; M, 226·7).

Elution with light petroleum–benzene (1 : 1) gave crystalline (1RS,1′SR,3RS,5′SR,6SR)-*spiro{bicyclo*[4.1.0]*heptane*-3,3′-*bicyclo*[3.1.0]*hexane}*-2,2′-*dione* (12) (0·46 g), m.p. 109° (from cyclohexane), $\nu_{max.}$ 1675 and 1720 cm^{-1}; δ 0·67—1·50 (4H, m, cyclopropyl protons) and 3·07 (1H, m, H-4β); $\lambda_{max.}$ (MeOH) 295 nm (ε 85) (Found: C, 75·6; H, 7·2%; M^+, 190. C$_{12}$H$_{14}$O$_2$ requires C, 75·7; H, 7·4%; M, 190·2).

[18] R. P. Linstead and H. N. Rydon, *J. Chem. Soc.*, 1934, 1955.