652. *Olefinic Acids. Part VI. α-Bromo-γ-methoxycrotonic Acid.*

By L. N. Owen and M. U. S. Sultanbawa.

The cis- and trans-*forms* of *α-bromo-γ-methoxycrotonic acid* have been synthesised from *αβ-dibromo-γ-methoxybutyric acid*, the allocation of the stereochemical structures being based on relative melting points, methods of preparation, and absorption spectra. The bromo-acid shows high reactivity towards alkoxides; with methanolic sodium methoxide it undergoes addition (with elimination of hydrogen bromide) to give *βγ-dimethoxycrotonic acid*, and also a succession of prototropic and anionotropic changes which lead to the formation, after hydrolysis, of β-formylacrylic acid. Unlike α-bromocrotonic acid, it also undergoes addition reactions with toluene-ω-thiol, thiolacetic acid, and diazomethane. The theoretical aspects of the increased reactivity, caused by the presence of the methoxy-group in the γ-position, are briefly discussed.

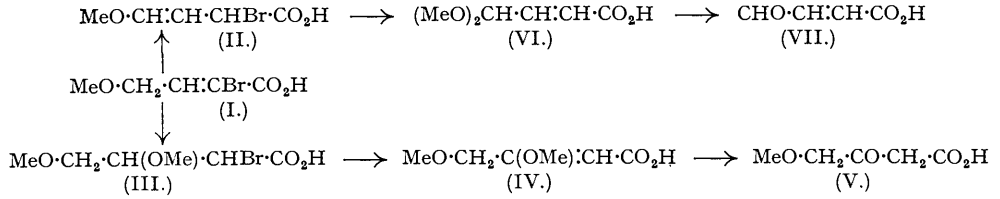
The formation of the lactone of α-bromo-γ-hydroxycrotonic acid, by the action of alkali on αβγ-tribromobutyric acid, necessitates a revision of the classical formulæ for the α- and β-halogeno-crotonolactones, and of some related compounds.

The preparation of γ-methoxycrotonic acid, and some of its properties, have been discussed in Part V (preceding paper). The α-bromo-derivative was required in order to compare its reactivity with that of other αβ-unsaturated α-bromo-acids (Parts I—IV; Owen *et al.*, *J.*, 1945, 385; 1947, 1030; this vol., pp. 236, 3089). The addition of bromine to γ-methoxycrotonic acid was very rapid in carbon disulphide, carbon tetrachloride, or chloroform, and in daylight there was considerable evolution of hydrogen bromide, suggesting the occurrence of simultaneous attack on the methoxy-group. When, however, the calculated amount of bromine was added to a cooled solution of the acid in carbon tetrachloride, light being excluded, a smoother reaction occurred, and *αβ-dibromo-γ-methoxybutyric acid* was formed. The yield of crystalline dibromide was *ca.* 70% on a small scale, but was much less when larger quantities were used; this dibromide was always accompanied by a liquid product, probably consisting largely of the stereoisomeric form. Even the pure solid dibromo-acid was rather unstable and evolved hydrogen bromide when kept for a few weeks.

Elimination of hydrogen bromide from an αβ-dibromo-acid can be effected by treatment either with alkali or with organic bases, and, when *cis-trans*-isomerism is possible in the product, the stereoisomer obtained may depend not only on the particular form of the dibromo-acid used, but also on the nature of the reagent. Thus the higher-melting stereoisomer of αβ-dibromobutyric acid gives mainly *cis*-α-bromocrotonic acid when aqueous alkali is used, whereas the lower-melting stereoisomer under these conditions gives a greater proportion of the *trans*-acid; with pyridine, on the other hand, the *trans*-acid is obtained irrespective of whether the higher- or lower-melting dibromide is used (James, *J.*, 1910, **97**, 1565; Pfeiffer, *Ber.*, 1910, **43**, 3042). The solid αβ-dibromo-γ-methoxybutyric acid reacted vigorously with dry pyridine to give trans-*α-bromo-γ-methoxycrotonic acid* (I), m. p. 83—84°; the cis-*isomer*, m. p. 55°, was obtained by the use of cold aqueous sodium hydroxide. The allocation of *trans*- and *cis*-structures, suggested by the methods of preparation and by the relative melting points of the isomers, is supported by the absorption spectra, since the higher-melting form shows maximum absorption at a lower wave-length than the acid of m. p. 55°, in conformity with the behaviour of the *cis*- and *trans*-forms of α-chloro- and α-bromo-crotonic acid (see Table); furthermore, the intensity of the absorption is greater for the *trans*- than for the *cis*-compounds (cf. Koch, *Chem. and Ind.*, 1942, 273; Bowden, Braude, and Jones, *J*, 1946, 946; see also Part VII, following paper).

The reactivity of α-bromo-acrylic, -crotonic, and -ββ-dimethylacrylic acid towards alkoxides has already been discussed in Part IV (*loc. cit.*). In comparison with α-bromocrotonic acid, α-bromo-γ-methoxycrotonic acid would be expected to show enhanced reactivity, since the presence of the methoxy-group ($-I$ property) should increase the mobility of the system and also, as with γ-methoxycrotonic acid itself, favour the prototropic change into the βγ-unsaturated form (II). Furthermore, the methoxy-acid should show a greater ability to add nucleophilic reagents. In α-bromocrotonic acid the hyperconjugation of the methyl group with the double bond results in deactivation of the β-carbon atom, so that addition is less easy than with α-bromo-

acrylic acid; but in α-bromo-γ-methoxycrotonic acid the $-I$ effect of the methoxy-group acts in opposition to the hyperconjugation of the remaining two hydrogen atoms, and the β-carbon atom is therefore deactivated to a smaller extent. Both the prototropic change and the addition reaction would result in the bromine atom ceasing to be attached to an ethylenic carbon atom; replacement or elimination could then be expected to occur. Comparative experiments showed that with aqueous alkali the halogen atom in (I) was completely liberated in 1½ hours, the corresponding times for α-bromocrotonic and α-bromo-ββ-dimethylacrylic acids being 2 and 7 hours respectively.

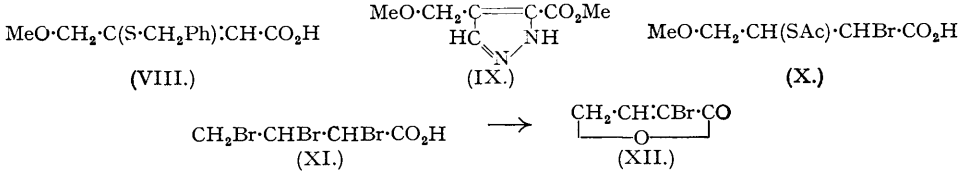


α-Bromo-γ-methoxycrotonic acid reacted readily with methanolic sodium methoxide to give, together with much polymeric material, a small yield of a crystalline product which was shown, on the following evidence, to be *βγ-dimethoxycrotonic acid* (IV). It showed a light-absorption maximum at 2320 A. and was therefore αβ-unsaturated, whilst on treatment with 2 : 4-dinitrophenylhydrazine sulphate in dilute sulphuric acid it gave the 2 : 4-*dinitrophenylhydrazone* of γ-methoxyacetoacetic acid (V); this derivative was decarboxylated by heating it in ethyl acetate solution and gave the 2 : 4-dinitrophenylhydrazone of methoxyacetone, the isolation of which definitely established the position of the β-methoxy-group. This indicates the occurrence of the addition reaction, to give (III), followed by elimination of hydrogen bromide.

The liquid portion from the sodium methoxide reaction was hydrolysed with sulphuric acid to convert enol ethers into keto-acids, and, preliminary tests having shown that the 2 : 4-dinitrophenylhydrazones of these acids could not be effectively purified by chromatography, the acids were esterified with diazomethane and then treated with methanolic 2 : 4-dinitrophenylhydrazine sulphate. Chromatography of the derivatives on alumina gave the 2 : 4-*dinitrophenylhydrazone* of methyl β-formylacrylate. The formation of β-formylacrylic acid (VII) indicates that in the reaction of (I) with sodium methoxide an initial prototropic change to (II) is followed by replacement of bromine with anionotropic change, to give γγ-dimethoxycrotonic acid (VI). In the reactions of α-bromocrotonic and α-bromo-ββ-dimethylacrylic acid with alkoxides only the "direct" substitution products were observed, although the postulated intermediates were anionotropic systems (Part IV, *loc. cit.*). In the present instance, although the conditions were the same, the occurrence of anionotropic rearrangement suggests that a S_N1 mechanism must play at least some part in the reaction (*cf.* the reaction of α-bromo-ββ-dimethylacrylic acid with aqueous alkali; Part IV, *loc. cit.*). This can be explained by the $+T$ effect of the methoxy-group, which, coming into play in the βγ-unsaturated structure (II), facilitates the ionisation of the bromine atom; the consequent formation of a free carbonium ion also accounts for the formation of the polymeric by-product.

Interaction of the bromo-acid (I) with sodium ethoxide similarly gave a considerable amount of polymer, together with a little *γ-methoxy-β-ethoxycrotonic acid*, the structure of which was proved in the same way as for the βγ-dimethoxy-compound.

The ease of addition to α-bromo-γ-methoxycrotonic acid, compared with α-bromocrotonic acid, was shown by its reactions with toluene-ω-thiol, diazomethane, and thiolacetic acid. Subsequent elimination of hydrogen bromide occurred in the first two cases, and the products



were respectively β-*benzylthio-γ-methoxycrotonic acid* (VIII), *methyl* 4-*methoxymethylpyrazole*-3-*carboxylate* (IX), and α-*bromo*-β-*acetylthio-γ-methoxybutyric acid* (X). Since in similar experiments with α-bromocrotonic acid no addition had been observed with any of these reagents (Part II, *loc. cit.*), the activating effect of the methoxy-group is very apparent.

Absorption spectra in alcohol were kindly determined by Dr. E. A. Braude and are recorded in the Table.

	$\lambda_{max.}$, A.	$\varepsilon_{max.}$		$\lambda_{max.}$, A.	$\varepsilon_{max.}$
cis-MeO·CH_2·CH:CBr·CO_2H ...	2370	5,500	MeO·CH_2·CH(SAc)·CHBr·CO_2H	2290	6,000
	2420 *	5,100	*cis*-Me·CH:CCl·CO_2H	2280	7,000
trans- ,, ,, ,,	2290	6,000	*trans-* ,, ,, ...	2220	10,500
MeO·CH_2·C(OMe):CH·CO_2H ...	2320	15,500	*cis*-Me·CH:CBr·CO_2H	2380	4,500
MeO·CH_2·C(OEt):CH·CO_2H	2320	17,000	*trans-* ,, ,, ...	2280	7,500
	2370 *	16,500			
MeO·CH_2·C(S·CH_2Ph):CH·CO_2H	2680	6,500			

* Inflexion.

In an alternative approach to the synthesis of α-bromo-γ-methoxycrotonic acid, an attempt was made to convert αβγ-tribromobutyric acid (XI) into αγ-dibromocrotonic acid by treatment with two equivalents of alkali (*i.e.*, one equivalent in excess of that required for neutralisation of the carboxyl group). Two bromine atoms, however, were removed by this treatment, and the product was a crystalline solid, $C_4H_3O_2Br$, m. p. 59—60°, which showed a light-absorption maximum at 2210 A. (ε 10,000). The remaining bromine atom must be the most stable of the three originally present in the tribromo-acid, and is clearly in the α-position; the compound, consequently, is the *lactone* (XII) of α-bromo-γ-hydroxycrotonic acid. A compound of this structure, but of m. p. 77°, is described in the early literature, whereas an isomer, m. p. 58°, is said to be the β-bromo-lactone (Beilstein, " Handbuch," 4th edn., **17**, 250). It is therefore necessary to consider the evidence on which the older structures for these lactones were based.

The so-called α-bromo-lactone was prepared by several methods, but with one exception they throw no light on the structure of the product. This exception, the addition of aqueous hydrobromic acid to γ-hydroxytetrolic acid (Lespieau and Vignier, *Compt. rend.*, 1909, **148**, 241), would be expected on modern views to yield not the α- but the β-bromo-lactone; tetrolic acid itself under these conditions gives β-bromocrotonic acid (Michael and Shadinger, *J. Org. Chem.*, 1939, **4**, 128), and the presence of the hydroxyl group in the γ-position would not be expected to reverse the direction of the addition.

The so-called β-bromo-lactone was obtained, apart from non-definitive methods, by the action of concentrated aqueous hydrobromic acid on " 3 : 5-dibromofuran-2-carboxylic acid " (Hill and Cornelison, *Amer. Chem. J.*, 1894, **16**, 188, 277). According to Gilman, Vanderwal, Franz, and Brown (*J. Amer. Chem. Soc.*, 1935, **57**, 1146) the latter acid is actually 3 : 4-dibromofuran-2-carboxylic acid, and similar revisions of structure apply also to certain other halogen derivatives of furan-2-carboxylic acid; it follows that the structures allocated to the bromolactones should be interchanged (cf. also Vanderwal, *Iowa State Coll. J. Sci.*, 1936, **11**, 128).

These revisions imply also that similar corrections should be applied to the lactones of the following substituted γ-hydroxycrotonic acids: α-chloro-, β-chloro-, α-anilino-, β-bromo-α-anilino-, β-chloro-α-iodo-, and β-bromo-α-iodo-. It follows also that " αββ-tribromobutyrolactone " is actually the ααβ-compound.

Experimental.

(Light petroleum, unless otherwise stated, was the fraction, b. p. 40—60°.)

αβ-Dibromo-γ-methoxybutyric Acid.—A solution of bromine (0·55 c.c.) in carbon tetrachloride (5 c.c.) was added to γ-methoxycrotonic acid (1·2 g.) in carbon tetrachloride (2·5 c.c.). After 8 days at 0°, colourless crystals (2 g.) of *αβ-dibromo-γ-methoxybutyric acid* had separated; these formed prisms (1·7 g.), m. p. 79—80° [from light petroleum (b. p. 60—80°)], which slowly evolved hydrogen bromide when kept at room temperature (Found: C, 22·3; H, 3·1; Br, 56·75. $C_5H_8O_3Br_2$ requires C, 21·75; H, 2·9; Br, 57·9%). On a larger scale the yield was lower (58 g. of crude dibromide from 70 g. of γ-methoxycrotonic acid), and recrystallisation of quantities more than 2—3 g. at a time resulted in considerable loss. Evaporation of the original carbon tetrachloride mother-liquors under reduced pressure gave a yellow oil probably containing the stereoisomer (see below).

trans-*α-Bromo-γ-methoxycrotonic Acid.*—The dibromo-acid (32 g.) was dissolved in dry pyridine (120 c.c.) and heated on the steam-bath for 1 hour. The cooled solution was then poured into an excess of 25% sulphuric acid and extracted with ether; removal of the solvent gave a solid residue (12·5 g.), a further small quantity being obtained by continuous ether-extraction of the solution. trans-*α-Bromo-γ-methoxycrotonic acid* crystallised from light petroleum (b. p. 60—80°) in long needles, m. p. 82·5—84° (Found: C, 30·9; H, 3·9; Br, 40·7. $C_5H_7O_3Br$ requires C, 30·8; H, 3·6; Br, 41·0%). Light absorption: see Table. The same product was obtained by treatment, with pyridine, of the liquid residues from the preparation of the dibromo-acid (see above).

cis-*α-Bromo-γ-methoxycrotonic Acid.*—The crude liquid dibromo-acid (4·5 g.) was dissolved, with cooling, in N-sodium hydroxide (35 c.c.), set aside for 24 hours, and then acidified with sulphuric acid. Ether extraction gave a pasty solid (1·7 g.), which on crystallisation from light petroleum gave cubes of cis-*α-bromo-γ-methoxycrotonic acid*, m. p. 55° (Found: C, 30·9; H, 3·7; Br, 40·9. $C_5H_7O_3Br$ requires C, 30·8; H, 3·6; Br, 41·0%). Light absorption: see Table.

Action of Sodium Methoxide on α-Bromo-γ-methoxycrotonic Acid.—The *trans*-acid (4·95 g.) in methanol (25 c.c.) was treated with 4·3N-methanolic sodium methoxide (17·8 c.c.) and heated under reflux for 1½ hours. Most of the methanol was then removed under reduced pressure, and the residue was dissolved in water, acidified with sulphuric acid, and immediately extracted with ether. The dried (Na_2SO_4) extracts gave an oil (2·7 g.), which on distillation gave 1·0 g., b. p. 110°/0·001 mm., the remainder being resinous. The distillate partly crystallised. The solid (0·3 g.) was collected, and on crystallisation from carbon tetrachloride gave needles, m. p. 111°, of *βγ-dimethoxycrotonic acid* (Found: C, 49·5; H, 7·15. $C_6H_{10}O_4$ requires C, 49·3; H, 6·9%). Light absorption: see Table. On treatment with 2 : 4-dinitrophenylhydrazine in dilute sulphuric acid it gave the 2 : 4-*dinitrophenylhydrazone* of γ-methoxyacetoacetic acid, which formed needles, m. p. 149—150°, from ethyl acetate–ether (Found: C, 43·2; H, 4·25; N, 18·7. $C_{11}H_{12}O_7N_4$ requires C, 42·3; H, 3·9; N, 17·9%). Difficulty was experienced in the purification of this derivative owing to its ready decarboxylation; when heated under reflux in ethyl acetate solution for several hours it gave the 2 : 4-dinitrophenylhydrazone of methoxyacetone, m. p. and mixed m. p. 160—162°.

In a subsequent experiment, carried out under essentially the same conditions, except for a shorter reaction time (1 hour), a different *solid* was obtained, which crystallised from acetone–light petroleum in prisms, m. p. 148—154° (Found: C, 50·45; H, 4·6. $C_9H_{10}O_6$ requires C, 50·5; H, 4·7%). Light absorption: Max., 2700 A.; ε = 13,000 in alcohol. On treatment with aqueous 2 : 4-dinitrophenylhydrazine sulphate this gave a 2 : 4-*dinitrophenylhydrazone*, red prisms, m. p. 171—174°, from methanol (Found: C, 45·4; H, 3·75; N, 13·95. $C_{15}H_{14}O_9N_4$ requires C, 45·7; H, 3·6; N, 14·2%). Light absorption: Max., 2640 and 3980 A.; ε = 18,500 and 31,000 respectively, in chloroform. The analyses and light absorptions agree with a structure such as 2-keto-5-methoxy*cyclo*hex-3-en-1 : 4-dicarboxylic acid, which might be formed by intermolecular elimination of hydrogen bromide from two molecules of bromo-acid, followed by rearrangement and ketonisation, but the amount of product was insufficient for further study.

The liquid portions from the main reaction products were combined and heated with 2N-sulphuric acid for ½ hour at 100°. The cooled solution on extraction with ether gave an acid oil, which was converted into the methyl ester by treatment with diazomethane, and thence into the 2 : 4-dinitrophenylhydrazone with methanolic 2 : 4-dinitrophenylhydrazine sulphate. The derivative was dissolved in ethyl acetate and then adsorbed on a column of alumina; on development with ethyl acetate, a main yellow band appeared. The material recovered by ethyl acetate extraction of this band was taken up in benzene and transferred to another column of alumina. Development with benzene gave a small yellow band, which gave an oily product, and a main orange band, which was subsequently divided into 4 parts. The first of the orange bands gave a trace of material which crystallised from ethyl acetate–light petroleum in orange prisms, m. p. 171—173°, insufficient for analysis. The second gave the 2 : 4-*dinitrophenylhydrazone* of methyl β-formylacrylate, which crystallised from ethyl acetate in stout orange needles, m. p. 199—200° (Found: C, 45·5; H, 3·65; N, 19·0. $C_{11}H_{10}O_8N_4$ requires C, 44·9; H, 3·4; N, 19·05%). Light absorption: Max., 3680 A.; ε = 34,000. Infl. 3750 A.; ε = 31,500. The remaining two bands gave only a small amount of impure material.

Action of Sodium Ethoxide on α-Bromo-γ-methoxycrotonic Acid.—On the addition of 2·7N-ethanolic sodium ethoxide (11·1 c.c.) to a solution of the bromo-acid (1·95 g.) in ethanol (4 c.c.), a precipitate of the sodium salt appeared, which persisted after 15 minutes' heating on the steam-bath but was brought into solution by the addition of more ethanol (5 c.c.). The solution was heated under reflux for a further 20 minutes and then evaporated under reduced pressure. The residue was dissolved in water, acidified, and extracted with ether. Evaporation of the dried (Na_2SO_4) extracts gave an oil (1·1 g.) which deposited some solid (0·075 g.) after a few days. Recrystallisation from light petroleum gave colourless plates of *γ-methoxy-β-ethoxycrotonic acid*, m. p. 93° (Found: C, 52·7; H, 7·5. $C_7H_{12}O_4$ requires C, 52·5; H, 7·55%). Light absorption: see Table. On treatment with aqueous 2 : 4-dinitrophenylhydrazine sulphate, as for the dimethoxy-analogue, the 2 : 4-dinitrophenylhydrazone of methoxy-acetone, m. p. and mixed m. p. 163—164°, was obtained.

Addition Reactions of α-Bromo-γ-methoxycrotonic Acid.—(a) *With toluene-ω-thiol.* The bromo-acid (1 g.) was heated with toluene-ω-thiol (1 g.) and pyridine (1 c.c.) for 1½ hours on the steam-bath. The product was dissolved in excess of sodium hydrogen carbonate solution and extracted with ether, these extracts being rejected. After acidification, the solution was again extracted with ether, to yield a yellow viscous oil (0·44 g.), which on distillation gave a lower-boiling fraction, containing some unchanged bromo-acid, and a main fraction, b. p. 210° (bath temp.)/0·0004 mm., which partly solidified. The crystals were drained on porous tile and recrystallised from light petroleum in leaflets of *β-benzylthio-γ-methoxycrotonic acid*, m. p. 67° (Found: C, 60·7; H, 6·1. $C_{12}H_{14}O_3S$ requires C, 60·5; H, 5·9%). Light absorption: see Table.

(b) *With thiolacetic acid.* The bromo-acid (0·4 g.) was dissolved in thiolacetic acid (1 c.c.) and set aside for 2 months. Excess of thiolacetic acid was then removed under reduced pressure, and the residual oil was distilled at 100° (bath temp.)/0·0001 mm., to give *α-bromo-β-acetylthio-γ-methoxybutyric acid* as a deep yellow viscous liquid, n_D^{18} 1·5248 (Found: C, 30·5; H, 4·6. $C_7H_{11}O_4SBr$ requires C, 31·0; H, 4·1%). Light absorption: see Table.

(c) *With diazomethane.* The bromo-acid (1 g.) in dry ether (10 c.c.) was treated with 2 equivalents of ethereal diazomethane and set aside in the dark for 5 days. Removal of solvent gave a deep yellow viscous oil (1·34 g.) which spontaneously lost hydrogen bromide on drying *in vacuo* at ordinary temperature, and left a semi-solid residue, crystallisation of which from alcohol, and then from water, gave needles of *methyl 4-methoxymethylpyrazole-3-carboxylate* (0·2 g.), m. p. 153° (Found: C, 49·7; H, 5·9; N, 16·5. $C_7H_{10}O_3N_2$ requires C, 49·4; H, 5·9; N, 16·5%).

Methyl αβγ-Tribromobutyrate.—A solution of methyl γ-bromocrotonate (33 g.) and bromine (11 c.c.) in carbon tetrachloride (50 c.c.) was set aside for 2 weeks and then exposed to ultra-violet light for 2 hours. Removal of the solvent, and fractionation, gave *methyl αβγ-tribromobutyrate* (42 g.), b. p. 110—111°/4 mm., n_D^{19} 1·5531 (Found: Br, 70·6. $C_5H_7O_2Br_3$ requires Br, 70·8%).

αβγ-Tribromobutyric Acid.—γ-Bromocrotonic acid (2·65 g.) was dissolved in carbon tetrachloride

(20 c.c.) in a silica tube; bromine (1 c.c.) was added, and the solution was exposed to ultra-violet light for 20 minutes. The tribromo-acid (3·6 g.), crystallising in plates from light petroleum (b. p. 100—120°), had m. p. 130—131° (Rambaud, *Bull. Soc. chim.*, 1934, [v], **1**, 1342, gives m. p. 132°).

Action of Alkali on the Tribromo-acid.—$\alpha\beta\gamma$-Tribromobutyric acid (1·1 g.) was dissolved in 50% aqueous methanol (10 c.c.), treated with 0·78N-aqueous potassium hydroxide (8·5 c.c., 2 equivs.) and set aside for 5 days. Methanol was then removed under reduced pressure, and the remaining aqueous solution was extracted with ether to yield an oil which partly crystallised. The *lactone* of *α-bromo-γ-hydroxycrotonic acid* was drained on porous tile and crystallised from light petroleum (b. p. 100—120°) in needles, m. p. 58·5—60° (Found: C, 30·1; H, 2·1; Br, 48·9. $C_4H_3O_2Br$ requires C, 29·55; H, 1·9; Br, 49·15%). Light absorption: Max., 2210 A.; $\varepsilon = 10{,}000$.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7.

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