# Steric Effects of Methoxy-groups in 2,2′-Bridged Biphenyls. Part I

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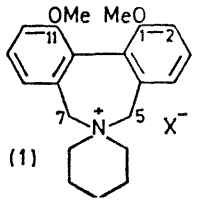
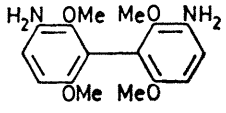
The preparation of (−)-6,7-dihydro-1,11-dimethoxy-5*H*-dibenz[*c,e*]azepine-6-spiro-1′-piperidinium iodide starting from (+)-6,6′-dimethoxydiphenic acid is described. Its optical stability has been determined approximately. Methyl 6-methoxydiphenate has been prepared and used for the synthesis of monomethoxydibenzazepinium salts.

THE effect of additional 6,6′-substituents on the optical stability of 2,2′-bridged biphenyls has been studied [1] for several types of bridging ring and for a range of substituents. Beaven *et al.*[2] resolved the dimethoxydibenzazepinium iodide (1; X = I) and found it to be highly optically stable, racemisation being incomplete after 8 h in boiling (160 °C) cyclohexanol solution. The methoxy-group is known to have a small steric effect as measured by the optical stability of unbridged biphenyls; [3] thus the diamine (2) forms a dicamphorsulphonate which mutarotates [4] at −17 °C and the diacid (3) does not show any evidence of optical activity; [4] indeed only fluoro- and hydroxy-groups are less effective in hindering rotation about the 1,1′-bond. Beaven *et al.* therefore attributed the optical stability of (1; X = I) to conformational stability of the seven-membered bridging ring but the subsequent discovery that the dinitro-compound (4) is racemised more readily [5] (half-life 156 min at 145 °C) than the dimethoxy-compound, in spite of the (normally) larger size of nitro-groups, together with evidence that bridged biphenyls without additional *ortho*-substituents are highly optically labile,[6] led to recognition of the fact that the methoxy-groups in (1) are having an anomalously large steric effect.



(1)



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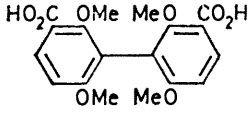

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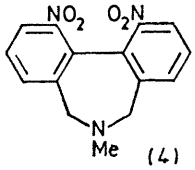


(4)

In order to determine whether the anomaly in the free energy of activation arises mainly in the energy term or in the entropy term, a more detailed study of the racemisation process was undertaken.

The original resolution of (1; X = I) through its camphorsulphonate had required an extensive and tedious series of fractional crystallisations; the active iodides thus obtained had very small rotations ($[\alpha]_{546}^{22}$ +4·0° and −3·8° in acetonitrile); unusually large amounts of active material would therefore be required for quantitative racemisation studies. An alternative approach of synthesis of the enantiomers of (1) from resolved [7,8] 6,6′-dimethoxydiphenic acids was therefore considered. Since the acid,[9] its sodium salt,[10] and its methyl ester [9,11] racemise at conveniently measurable rates at 80—100 °C it would be necessary to carry out the subsequent steps at temperatures below *ca.* 50 °C to avoid loss of optical activity *en route*.

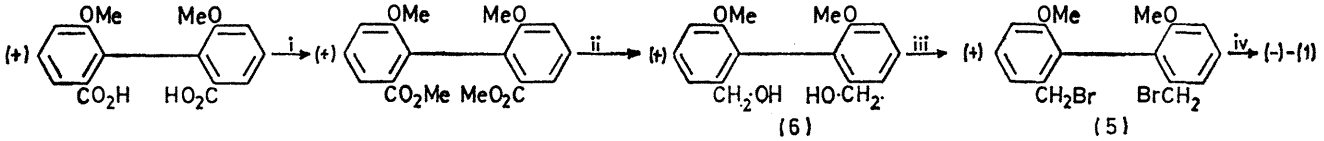
The steps used are shown for one of the enantiomers in Scheme 1. Reduction of the sparingly soluble ester was improved by using a very large volume of ether; direct reduction of the acid was unsatisfactory, some acid being recovered. Preparation of the active dibromide (5) by the method originally used [12] for the racemic compound gave an impure product which was nevertheless used in the first preparations of the active quaternary bromide. Subsequently benzene was introduced as a solvent for the reaction between the diol (6) and phosphorus tribromide and this gave crystalline dibromides (5), both with the racemic and the active compounds; this was much more satisfactory, especially for small-scale preparations. The racemic dibromide could also be prepared by the action of hot hydrobromic acid on the diol, a method originally avoided [12] in case it should cause demethylation.

Cyclisation of crude dibromide (5) with piperidine gave a quaternary salt (1; X = Br) of opposite sign of rotation in the visible region. It proved extremely difficult to obtain the quaternary bromide or iodide chemically pure, although there had been no similar

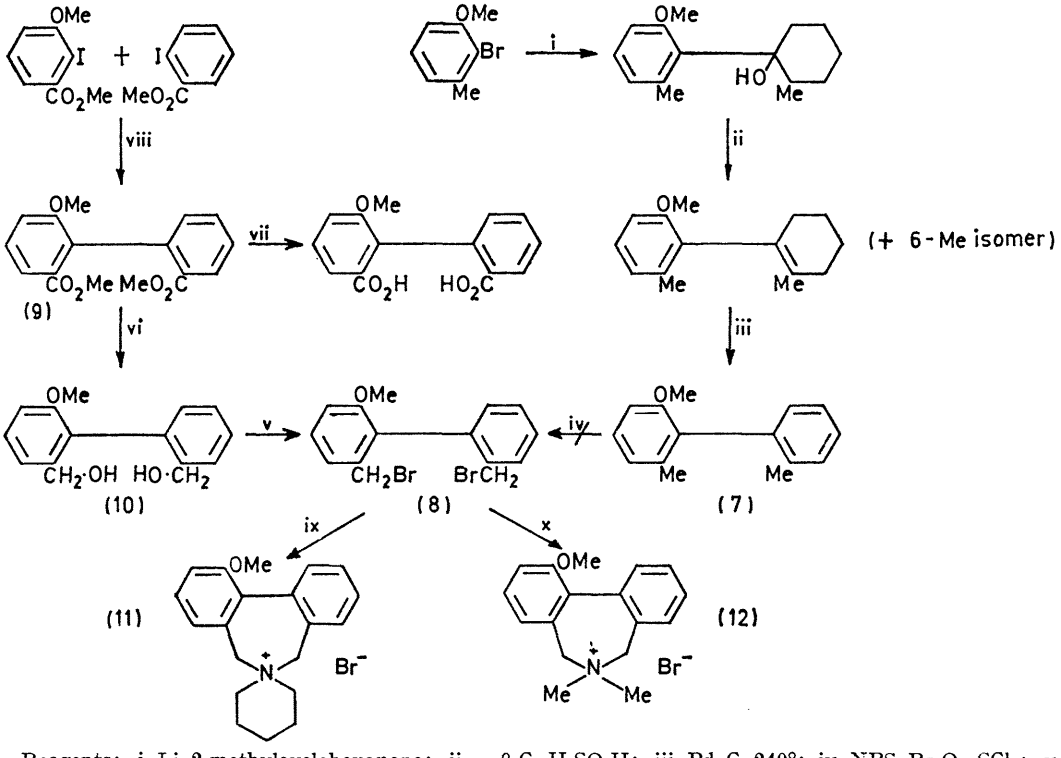
[1] D. M. Hall, in 'Progress in Stereochemistry 4,' eds. B. J. Aylett and M. M. Harris, Butterworths, London, 1969, p. 1, and references therein.
[2] G. H. Beaven, D. M. Hall, M. S. Lesslie, and E. E. Turner, *J. Chem. Soc.*, 1952, 854.
[3] R. Adams and H. C. Yuan, *Chem. Rev.*, 1933, **12**, 261.
[4] A. M. VanArendonk, M. E. Cupery, and R. Adams, *J. Amer. Chem. Soc.*, 1933, **55**, 4225.
[5] S. R. Ahmed and D. M. Hall, *J. Chem. Soc.*, 1958, 3043.
[6] D. C. Iffland and H. Siegel, *J. Org. Chem.*, 1956, **21**, 1056; *J. Amer. Chem. Soc.*, 1958, **80**, 1947; L. V. Dvorken, R. B. Smyth, and K. Mislow, *J. Amer. Chem. Soc.*, 1958, **80**, 486; S. R. Ahmed and D. M. Hall, *Chem. and Ind.*, 1958, 1329; *J. Chem. Soc.*, 1959, 3383.
[7] J. Kenner and H. A. Turner, *J. Chem. Soc.*, 1928, 2340.
[8] W. M. Stanley, E. McMahon, and R. Adams, *J. Amer. Chem. Soc.*, 1933, **55**, 706.
[9] B. M. Graybill and J. E. Leffler, *J. Phys. Chem.*, 1959, **63**, 1461.
[10] J. E. Leffler and B. M. Graybill, *J. Phys. Chem.*, 1959, **63**, 1457.
[11] G. Wittig and H. Petri, *Annalen*, 1933, **505**, 17.
[12] D. M. Hall and E. E. Turner, *J. Chem. Soc.*, 1951, 3072.

difficulty with the racemic compounds, and purification could only be achieved by extremely wasteful crystallisation. In particular the presence of impurity was shown by anomalous rotatory dispersion in the visible region ($\alpha_{578} > \alpha_{546}$); this was absent from the pure material. It can most readily be explained by the presence of non-cyclised material of opposite sign and different dispersion. It was at first thought that the camphorsulphonates is too small to make complete resolution possible unless several hundred grams of material are available.

A racemisation rate in dimethylformamide solution was determined on the pure iodide at 158 °C. Rates were also determined on the chemically impure iodide over the temperature range 140—172 °C; they showed no evidence of a second component racemising at a




SCHEME 1 Reagents: i, $CH_2N_2$, 0°; ii, $LiAlH_4$–$Et_2O$; iii, $PBr_3$–$C_6H_6$, ≯40°; iv, $C_5H_{11}N$–$C_6H_6$




SCHEME 2 Reagents: i, Li–2-methylcyclohexanone; ii, β-$C_{10}H_7SO_3H$; iii, Pd–C, 240°; iv, NBS–$Bz_2O_2$–$CCl_4$; v, HBr; vi, $LiAlH_4$–$Et_2O$; vii, hydrolysis; viii, Cu, 245—255°; ix, $C_5H_{11}N$–$C_6H_6$; x, $HNMe_2$–$C_6H_6$

failure to purify the dibromide was responsible for the difficulty in purifying the quaternary salts, but a later preparation of quaternary bromide by use of recrystallised dibromide (5) also gave impure product. A similar effect was observed with the morpholinium analogue but not with the compound made from dimethylamine (see Part II). In later preparations a less soluble crystalline form containing both the quaternary bromide (1; X = Br) and the non-cyclised impurity was obtained and separation could no longer be achieved.

The chemically pure (—)-azepinium bromide (1; X = Br) had $[\alpha]_{546}^{21}$ −46·9°, $[\alpha]_{578}^{21}$ −43·2° in acetonitrile, showing that the iodides previously obtained [2] had been very incompletely resolved. Clearly the difference in solubilities between the diastereoisomeric different rate and were consistent with the result obtained for the pure compound and also with the approximate experiment of Beaven *et al.*[2] From these data a value of 34 kcal $mol^{-1}$ was obtained for the energy of activation for racemisation and a value of $10^{13}$ $s^{-1}$ for *A*. Results obtained for closely related dimethoxy-compounds are given in Part II and support the view that the racemisation parameters for (1; X = I) given here are substantially correct. They are discussed more fully in Part II.

It was also our intention to study the steric effect of a single methoxy-group in suitable bridged biphenyls and in 6-methoxydiphenic acid and its derivatives. We have been unable to obtain any evidence of optical activity in methoxydiphenic acid. Crystalline brucine,

strychnine, and quinine salts were obtained but showed no mutarotation between 0 and 60 °C and on decomposition gave inactive acid. Attempted optical activation with nor-(+)-ψ-ephedrine or cinchonidine in solution [13] at temperatures down to −30 °C failed. Syntheses used for the monomethoxy-compounds are shown in Scheme 2.

6-Methoxy-2,2′-dimethylbiphenyl (7) was prepared in good yield but attempted bromination with *N*-bromosuccinimide in the presence of benzoyl peroxide gave only intractable gums, although this method has been used satisfactorily for a number of bitolyls.[14,5] The required dibromide (8) was therefore prepared from the monomethoxy-ester (9) *via* the diol (10). The ester (9) was obtained in 22% yield by a ' mixed ' Ullmann reaction. The dibromide (8) condensed readily with piperidine and with dimethylamine to give (11) and (12) respectively. Attempts at optical resolution are in progress. Demethylation of (7) proved unexpectedly difficult and 6-hydroxy-2,2′-dimethylbiphenyl could only be obtained in poor yield.

## EXPERIMENTAL

($l$ = 2 dm unless otherwise stated.)

(+)- *and* (−)-6,6′-*Dimethoxydiphenic Acids*.—(±)-6,6′-Dimethoxydiphenic acid, prepared as previously described,[12] was resolved through its diquinine salt.[7,8] The acids had m.p. 291—292 °C, $[\alpha]_D^{20.5}$ −117·8° (*c* 0·8830 in $Me_2CO$) (lit.,[7,8,11] $[\alpha]_D$ −115 to −116°), and m.p. 290—292 °C, $[\alpha]_D^{23}$ +116·8° (*c* 0·9630 in $Me_2CO$) (lit.,[8,10] $[\alpha]_D$ +104 to +108°).

(−)-*Dimethyl* 6,6′-*Dimethoxydiphenate*.[8,11]—This was made from the (−)-acid by reaction with diazomethane in ether–ethanol solution at 0 °C and had m.p. 104—106 °C, $[\alpha]_D^{21}$ −158·6° (*c* 0·9835 in $Me_2CO$).

(+)-*Dimethyl* 6,6′-*Dimethoxydiphenate*.[8,10]—This was prepared similarly and had m.p. 105—106 °C, $[\alpha]_D^{20}$ +154·3° (*c* 0·9460 in $Me_2CO$).

(−)-2,2′-*Bishydroxymethyl*-6,6′-*dimethoxybiphenyl* (6).—The (−)-ester was added as a finely ground solid (3·0 g) to a well stirred suspension of lithium aluminium hydride (1·1 g) in ether (120 ml) during ½ h, each lot being washed into the flask with ether (250 ml; 370 ml in all; with less ether reduction was incomplete). The mixture was heated under reflux for 1 h, and the product was isolated in the usual way. The (−)-*diol* (2·3 g, 92%) crystallised from benzene as clusters of rods, m.p. 134—136 °C, $[\alpha]_D^{19.5}$ −98·7° (*c* 1·0185 in $Me_2CO$) (Found: C, 70·1; H, 6·6. $C_{16}H_{18}O_4$ requires C, 70·1; H, 6·6%).

(+)-2,2′-*Bishydroxymethyl*-6,6′-*dimethoxybiphenyl* (6), made in the same way, had m.p. 135—137 °C, $[\alpha]_D^{18}$ +98·0° (*c* 0·9545 in $Me_2CO$) (Found: C, 69·9; H, 6·5; O, 23·5%).

(±)-2,2′-*Bisbromomethyl*-6,6′-*dimethoxybiphenyl* (5).—(*a*) A solution of phosphorus tribromide (2·5 ml) in benzene (3 ml) was added dropwise to a well-stirred, ice-cooled suspension of the (±)-diol (1·0 g) in benzene (10 ml). The mixture was stirred at room temperature for 1 h, at 35—40 °C for ¾ h, and was then poured on ice. The benzene solution was very thoroughly washed with ice-cold water and was dried ($MgSO_4$). Benzene was distilled off under reduced pressure and the residue was recrystallised from ethanol. The dibromide (0·96 g, 66%) had m.p. 114—115 °C, not depressed by authentic sample.[12]

(*b*) The diol (2·0 g) was added to hot (90 °C) hydrobromic acid (50 ml, 48%). The mixture was heated under reflux for 30 min and was then cooled in ice. The solution was decanted and the residual gum scratched under a little light petroleum (b.p. 60—80 °C), whereupon it crystallised. The product was left overnight in an evacuated desiccator (KOH) and was recrystallised from ethanol (75% yield, m.p. 114—116 °C).

(−)-2,2′-*Bisbromomethyl*-6,6′-*dimethoxybiphenyl* (5) was obtained from the (−)-diol (2·0 g) by method (*a*) above. It crystallised from ethanol as rods, m.p. 116—117 °C (2·1 g, 72%), and had $[\alpha]_D^{22}$ −80·7° ($l$ = 1, *c* 1·023 in $Me_2CO$) (Found: C, 48·1; H, 4·0; Br, 39·95. $C_{16}H_{16}Br_2O_2$ requires C, 48·0; H, 4·0; Br, 39·9%).

(+)-2,2′-*Bisbromomethyl*-6,6′-*dimethoxybiphenyl* (5) was similarly obtained from the (+)-diol and had m.p. 117—118·5 °C, $[\alpha]_D^{20}$ +80·6° ($l$ = 1, *c* 1·055 in $Me_2CO$) (Found: C, 47·8; H, 4·1; Br, 40·2%).

(−)-6,7-*Dihydro*-1,11-*dimethoxy*-5H-*dibenz*[c,e]*azepine*-6-*spiro*-1′-*piperidinium iodide* (1; X = I).—(+)-Dibromide, obtained as a sticky solid from 2·1 g of (+)-diol by the method originally used [12] for the racemic compound, was dissolved in benzene and the solution dried ($CaCl_2$). Piperidine (1·6 g, 2·2 mol, based on diol) was added to the solution and a gum was gradually deposited. After a time the solution was decanted and the gum washed with benzene and triturated with water. It was crystallised from acetone–light petroleum (b.p. 60—80 °C), giving 0·6 g (18% based on the diol), $[\alpha]_{546}^{25}$ −16·5°, $[\alpha]_{578}^{25}$ −17·7° (*c* 2·629 in MeCN). As it appeared to be partially hydrated, it was dissolved in water and the solution evaporated to convert it completely into the hydrate. Two crystallisations from ethanol–ethyl acetate gave the quaternary bromide (0·15 g) as needles, m.p. 230—232 °C (decomp.), with some shrinking at *ca.* 180 °C, $[\alpha]_{546}^{21}$ −46·9°, $[\alpha]_{578}^{21}$ −43·2° (*c* 0·6715 in MeCN). It was converted into the (−)-*dibenzazepinespiropiperidinium iodide* (0·1 g), m.p. 246—248 °C, $[\alpha]_{546}^{21}$ −46·0° (*c* 0·87 in $HCO{\cdot}NMe_2$) (Found: C, 55·7; H, 6·1; I, 27·8; N, 2·9; O, 6·9. $C_{21}H_{26}INO_2$ requires C, 55·9; H, 5·8; I, 28·1; N, 3·1; O, 7·1%).

*Racemisation Rates*.—These were determined by making up a solution of the iodide in dimethylformamide (16 ml) and sealing 2 ml samples under vacuum in small Pyrex tubes. The tubes were heated together in a boiling liquid of suitable b.p. and withdrawn at intervals, being chilled rapidly before the rotation was read in a 1 dm microtube at room temperature. After a tube had been kept at 162·5 °C for 30 h the rotation of the contents was zero.

The rate determined on the pure (−)-iodide was $k$ 4·61 × $10^{-5}$ $s^{-1}$ at 158·0 °C ($t_{\frac{1}{2}}$ 250 min). All other rates were determined on impure (+)- or (−)-iodides with $[\alpha]_{546}^{22}$ −22·9° or −7·9° or +11·0° in MeCN: $k_{140\cdot3}$ 7·4 × $10^{-6}$ $s^{-1}$; $k_{156\cdot2}$ 3·78 × $10^{-5}$ $s^{-1}$; $k_{160\cdot0}$ 4·72 × $10^{-5}$ $s^{-1}$; $k_{162\cdot5}$ 5·75 × $10^{-5}$ $s^{-1}$; $k_{172\cdot2}$ 1·54 × $10^{-4}$ $s^{-1}$ (all temps ±0·5 °C during a run). Whence $E$ = *ca.* 34 kcal $mol^{-1}$ (*ca.* 142 kJ $mol^{-1}$), $A$ = *ca.* $10^{13}$ $s^{-1}$, and $\Delta S^{\ddagger}$ *ca.* −2·4 cal $mol^{-1}$ $K^{-1}$.

*Attempted Preparation of* (+)-6,7-*Dihydro*-1,11-*dimethoxy*-5H-*dibenz*[c,e]*azepine*-6-*spiro*-1′-*piperidinium bromide* (1; X = Br).—At a later date, fresh attempts were made to prepare pure (+)-azepinium bromide, from both crude and purified (−)-dibromide, by the method described above for its enantiomer. In a typical experiment, the product of the

[13] M. M. Jamison and E. E. Turner, *J. Chem. Soc.*, 1938, 1646.
[14] W. Wenner, *J. Org. Chem.*, 1952, **17**, 523.

reaction of (−)-dibromide with piperidine in benzene was precipitated, in hydrated form, from aqueous solution by potassium hydroxide. It was recrystallised from acetone–light petroleum (b.p. 60—80 °C), acetone, acetonitrile–ethyl acetate, and ethanol–ethyl acetate. None of these recrystallisations produced any significant change in its physical properties: needles, m.p. 255—256 °C (with softening at *ca.* 120 °C); $[\alpha]_{589}^{30}$ *ca.* −0·5°, $[\alpha]_{578}^{30}$ −1·7°, $[\alpha]_{546}^{30}$ −6·0°, $[\alpha]_{436}^{30}$ −60·6° (*l* = 1, *c* 2·20 in MeCN); $[\alpha]_{589}^{25}$ +6·8°, $[\alpha]_{578}^{25}$ +5·9°, $[\alpha]_{546}^{25}$ +2·7°, $[\alpha]_{436}^{25}$ −45·0° (*l* = 1, *c* 2·00 in MeOH).

Subsequent attempts to repeat the preparation of (−)-azepinium bromide from (+)-dibromide gave similar results.

*2-Bromo-3-methoxytoluene.*— 3-Methoxy-2-nitrotoluene was reduced [15] and the amine converted into 2-bromo-3-methoxytoluene by the Sandmeyer reaction,[16] steam being used to complete the decomposition: m.p. 41—42 °C (lit.,[16] 35·5—36·5 °C).

*2-Lithio-3-methoxytoluene.*—(*a*) From the 2-bromo-3-methoxytoluene (5·0 g), lithium, and ether under nitrogen, the yield was 50%, determined by treatment with solid carbon dioxide and isolation of 2-methoxy-6-methylbenzoic acid (3·0 g). (*b*) From 2-bromo-3-methoxytoluene (5·0 g) and an ethereal solution of phenyl-lithium (from 4 g of bromobenzene and 0·4 g of lithium) the yield was 31% (2 g of acid obtained).

*1-(2-Methoxy-6-methylphenyl)-2-(and -6-)methylcyclohexene.*—An ethereal solution of 2-lithio-3-methoxytoluene was prepared by method (*a*) from 2-bromo-3-methoxytoluene (50 g). 2-Methylcyclohexanone (21 g) was added gradually to the cooled solution which was then heated (1 h). The solution was poured on crushed ice and acidified with dilute sulphuric acid; the product was worked up in the usual way. After removal of the ether, the residual oil was heated with naphthalene-2-sulphonic acid (1·5 g) for 1 h at 100—105 °C. Water was removed and the oil was again heated with a similar quantity of acid for 1 h at 120—125 °C. The product was isolated and distilled giving some 2-methylcyclohexanone (at 60—70 °C/12 mmHg) followed by *1-(2-methoxy-6-methylphenyl)-2-(and -6-)methylcyclohexene* at 130—135 °C/5 mmHg (61%, based on 2-methylcyclohexanone) (Found: C, 83·2; H, 9·2. $C_{15}H_{20}O$ requires C, 83·3; H, 9·3%).

*6-Methoxy-2,2′-dimethylbiphenyl* (7).—The above phenylcyclohexene (25 g) was heated with palladium–charcoal (5%, 4 g). The temperature was raised from 140 °C to 240 °C during 3 h, and was then kept at 240—250 °C for a further 3½ h. On cooling, the mixture was extracted with hot benzene. The solution was filtered and benzene removed by distillation. Distillation of the residue under reduced pressure gave *6-methoxy-2,2′-dimethylbiphenyl* (21 g, 86%), b.p. 131—136 °C/4 mmHg (Found: C, 84·8; H, 7·5. $C_{15}H_{16}O$ requires C, 84·9; H, 7·6%).

*Dimethyl 6-Methoxydiphenate* (9).—Copper bronze (30 g) was added, with stirring, during 25 min to methyl 2-iodo-3-methoxybenzoate [8] (18·0 g, 1 mol) and methyl 2-iodobenzoate (32·4 g, 2 mol) which were being heated at 230 °C, at such a rate that the temperature of the mixture did not rise above 255 °C. After being heated for a further 10 min at 245—255 °C, the mixture was cooled to 160 °C and was extracted with boiling chlorobenzene. The solution was filtered and most of the chlorobenzene was distilled off. A few ml of methanol were added to the residue, and this solution was kept in the refrigerator for two days to allow crystallisation of dimethyl 6,6′-dimethoxydiphenate, 1·8 g of which were obtained on recrystallisation from methanol, with m.p. 134—136 °C. The first methanolic filtrate was evaporated to dryness and the residue distilled under reduced pressure. Two fractions, boiling at 154—180 °C/2—3 mmHg, and at 180—195 °C/2—3 mmHg were obtained. The first fraction (10·9 g) was mixed with a few ml of methanol, and after 2 days in the refrigerator, dimethyl diphenate (6·1 g) crystallised, m.p. 69—71 °C after recrystallisation (MeOH). The second distillation fraction (9·9 g) was stirred with small volumes of light petroleum (b.p. 40—60 °C) until it went solid; more dimethyl diphenate could be recovered from these washings. The solid residue was dissolved in boiling light petroleum (b.p. 60—80 °C) (*ca.* 250 ml), the cooling of which solution gave an oil which slowly crystallised. Two types of crystal could be distinguished and be partially separated, transparent clumps of the monomethoxy-diester and opaque needles of the dimethoxy-diester. By allowing the mother-liquor to evaporate slowly, two or three more crops with the same mixed composition were obtained. The final residue gave more dimethyl diphenate. The monomethoxy-diester, still contaminated with a little dimethoxy-diester, was dissolved in boiling cyclohexane (*ca.* 130 ml). The first crop on cooling consisted entirely of the dimethoxydiphenate and this was followed by clumps of monomethoxy-diester (5·9 g), which was given one final recrystallisation from methanol. *Dimethyl 6-methoxydiphenate* (4·2 g, 22%), needles from methanol, had m.p. 66—68 °C (Found: C, 68·15; H, 5·7. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·4%).

*6-Methoxydiphenic acid*, m.p. 219—221 °C, was obtained in 80% yield by hydrolysis of dimethyl 6-methoxydiphenate (5·0 g) in boiling ethanolic KOH (Found: C, 66·2; H, 4·6. $C_{15}H_{12}O_5$ requires C, 66·2; H, 4·4%).

*2,2′-Bishydroxymethyl-6-methoxybiphenyl* (10).—A solution of dimethyl 6-methoxydiphenate (2·0 g) in dry ether (175 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0·8 g) in ether (60 ml), and the mixture was heated under reflux for 1 h. After water and dilute sulphuric acid had been added, the product was isolated as usual. Recrystallisation from carbon tetrachloride–light petroleum (b.p. 60—80 °C) gave the *diol* (1·53 g, 94%), m.p. 79—81 °C (Found: C, 73·6; H, 6·55. $C_{15}H_{16}O_3$ requires C, 73·75; H, 6·6%).

*2,2′-Bisbromomethyl-6-methoxybiphenyl* (8).—The diol (2·0 g) was added to hot (90 °C) hydrobromic acid (48%, 100 ml) and the mixture was heated under reflux for 20 min. It was then cooled and the aqueous solution decanted. The residual gum crystallised on scratching with light petroleum (b.p. 60—80 °C), and was kept in an evacuated desiccator (KOH) for two days. Recrystallisation from ethanol gave rods (2·29 g, 76%) of the *dibromide*, m.p. 92—94 °C (Found: C, 49·0; H, 3·9. $C_{15}H_{14}Br_2O$ requires C, 48·7; H, 3·8%).

*6,7-Dihydro-1-methoxy-5H-dibenz*[c,e]*azepine-6-spiro-1′-piperidinium Bromide* (11).—Piperidine (0·9 g) was added to a warm solution of 2,2′-bisbromomethyl-6-methoxybiphenyl (2·0 g) in benzene (30 ml). Reaction occurred almost immediately and the solution became cloudy, but it was left overnight before being decanted from the residual gum. This was washed three times with fresh benzene, dissolved in water, and treated with concentrated KOH solution.

[15] G. P. Gibson, *J. Chem. Soc.*, 1923, **123**, 1269.
[16] H. H. Hodgson and H. G. Beard, *J. Chem. Soc.*, 1925, **127**, 498.

The precipitated oil took several days to crystallise, whereupon it was filtered off, washed with a little cold water, dried, and recrystallised from acetonitrile–ethyl acetate. The quaternary *bromide* was obtained as a monohydrate in 88% yield. Melting sometimes occurred at 126—128 °C, but sometimes only shrinking was observed at this point and final clearance took place at 153 °C (Found: C, 61·1; H, 6·8; Br, 20·5; N, 3·8. $C_{20}H_{24}BrNO,H_2O$ requires C, 61·2; H, 6·7; Br, 20·4; N, 3·6%).

6,7-*Dihydro*-6,6-*dimethyl*-1-*methoxy*-5H-*dibenz*[c,e]*azepinium Bromide* (12).—Dimethylamine (*ca.* 2 ml) was added in two lots to an ice-cold solution of the dibromide (2·0 g) in benzene (15 ml). Several hours later the solution was decanted and the residual gum was washed three times with fresh benzene. It precipitated as a crystalline solid from saturated aqueous solution on the addition of a concentrated KOH solution, and recrystallised as a monohydrate from acetonitrile–ethyl acetate (1·7 g, 89%). The quaternary *bromide* had m.p. either 170—172 °C or 253—255 °C, with softening at 170 °C, depending on the rate of heating (Found: C, 57·8; H, 6·4; Br, 23·1; N, 4·2. $C_{17}H_{20}BrNO,H_2O$ requires C, 58·0; H, 6·3; Br, 22·7; N, 4·0%).

*Demethylation of* 2,2′-*Dimethyl*-6-*methoxybiphenyl*.—(*a*) Demethylation occurred when the bitolyl (4·0 g) was heated under reflux with hydrobromic acid (48%, 10 ml) and glacial acetic acid (40 ml) for 9½ h or when it was heated with pyridine (1·0 g) at 200—210 °C for 5 h in the presence of hydrogen chloride. In each case, the yield of 6-hydroxy-2,2′-dimethylbiphenyl, m.p. 41—43 °C (low-temperature recrystallisation from methanol) (Found: C, 84·5; H, 7·1. Calc. for $C_{14}H_{14}O$: C, 84·8; H, 7·1%), was small (<0·5 g), most of the starting material being recovered. Extended heating did not improve the yield (lit.,[17] m.p. 48·5—49 °C).

(*b*) The bitolyl (2·9 g, recovered from an unsuccessful demethylation attempt with hydriodic acid and acetic acid) was heated under reflux for 1 h with iodine-free hydriodic acid (6 ml) and acetic anhydride (30 ml); the solution was then poured into cold water and the precipitated oil was extracted with ether. The ether solution was washed twice with aqueous acidic sodium metabisulphite, many times with water, and was dried ($CaCl_2$). The residue, an oil, crystallised after four days and was recrystallised from ethanol. The product proved to be 6-*acetoxy*-2,2′-*dimethylbiphenyl* (1·0 g, m.p. 70—72 °C) (Found: C, 79·8; H, 6·6. $C_{16}H_{16}O_2$ requires C, 80·0; H, 6·7%), giving the phenol on hydrolysis. This preparation could not be repeated from freshly prepared bitolyl.

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