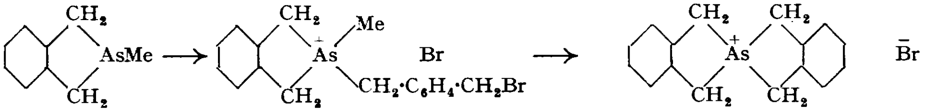
14. *The Synthetic Application of* o-β-*Bromoethylbenzyl Bromide. Part VI. The Preparation and Optical Resolution of a Spirocyclic Arsonium Salt possessing Molecular Dissymmetry.*

By FREDERICK G. HOLLIMAN and FREDERICK G. MANN.

2-Methyl-1 : 2 : 3 : 4-tetrahydro*iso*arsinoline unites with *o*-*β*-bromoethylbenzyl bromide to give a quaternary salt which on heating loses methyl bromide, forming the highly crystalline As-spiro-*bis*-1 : 2 : 3 : 4-*tetrahydro*-iso*arsinolinium bromide* (VI). The arsenic atom in this compound is symmetric, but the disposition of the ring systems around this tetrahedral atom causes the compound to possess molecular dissymmetry. It has therefore been resolved *via* the bromocamphorsulphonates, and the d- and l-*iodides* isolated having $[M]_D + 342°$ and $- 344°$ in chloroform solution. The stability of the heterocyclic rings gives the compound high optical stability, and the rotation of the iodide remains unchanged in chloroform at 18° for four weeks.

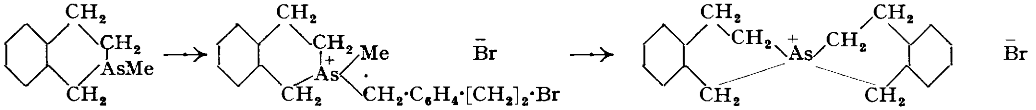
The only other known optically stable arsonium salt is 2-phenyl-2-*p*-chlorophenacyl-1 : 2 : 3 : 4-tetrahydro*iso*arsinolinium iodide, which contains an asymmetric arsenic atom (Holliman and Mann, J., 1943, 550).

IT has recently been shown by Lyon and Mann (this vol., p. 30) that 2-methyl*iso*arsindoline (I) readily combines with one equivalent of *o*-xylylene dibromide to form 2-*o*-(bromomethyl)benzyl-2-methyl*iso*arsindolinium bromide (II), which on heating loses methyl bromide with the formation of the highly crystalline *As-spiro*-bis*iso*arsindolinium bromide (III). It appeared probable that this novel method for the synthesis of spirocyclic arsonium salts could be applied to other heterocyclic arsines, provided the ring system in the latter possessed sufficient stability to remain unchanged throughout the necessary reactions; moreover, our earlier work on the tetrahydro*iso*arsinolines (Holliman and Mann, J., 1943, 547) offered a promising means whereby dissymmetric arsonium salts might be obtained by the above series of reactions.



(I.) (II.) (III.)

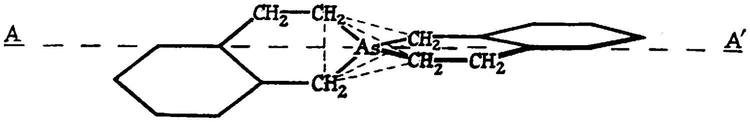
Accordingly, we have treated 2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*arsinoline (IV) with one molecular equivalent of *o*-β-bromoethylbenzyl bromide; union occurred readily, but the arsonium bromide formed a viscous glass and purification was not attempted. Its constitution is uncertain, but since the bromomethyl group in *o*-β-bromoethylbenzyl bromide is undoubtedly more reactive than the β-bromoethyl group, this intermediate arsonium salt has probably the structure (V). When this glassy product was heated at 14 mm. pressure, it formed a mobile liquid which underwent marked effervescence as the temperature rose above 100°, and ultimately, after one hour's heating at 200°, it crystallised even at this elevated temperature. The cold product, after recrystallisation from water or alcohol (each containing a small quantity of hydrobromic acid), furnished the crystalline As-spiro-*bis*-1 : 2 : 3 : 4-*tetrahydro*iso*arsinolinium bromide* (VI), m. p. 288—290°, in 38% yield. There were indications that other reactions also occurred during the thermal decomposition, but the by-products were not investigated.



(IV.) (V.) (VI.)

The arsonium bromide (VI) has very considerable stereochemical interest. Physical evidence shows that the 4-covalent arsenic atom has the tetrahedral configuration (Mann, Purdie, and Wells, J., 1936, 1503; 1937, 1828; Mann and Wells, J., 1938, 702), although there is no decisive chemical evidence on this point. If this configuration applies also to the arsonium bromide (VI), it follows that, although the arsenic atom in this compound is not asymmetric, the salt itself, by virtue of the disposition of the ring systems, should possess molecular dissymmetry and therefore be susceptible to optical resolution. The configuration of the arsonium ion is shown in (VIA), where an axis *A* --- *A′* of the tetrahedral arsenic atom has been inserted to emphasise the dissymmetry of the arsonium ion.

The arsonium bromide (VI) was therefore converted into the d-*bromocamphorsulphonate*; this was initially obtained as a viscous syrup which could not be recrystallised from organic solvents, but readily separated from a warm aqueous solution as colourless crystals, having m. p. 70—74°, and $[M]_D + 202°$ in alcoholic solution. Fractional recrystallisation from water now caused the m. p. to rise and the rotation to fall; after



(VIA.)

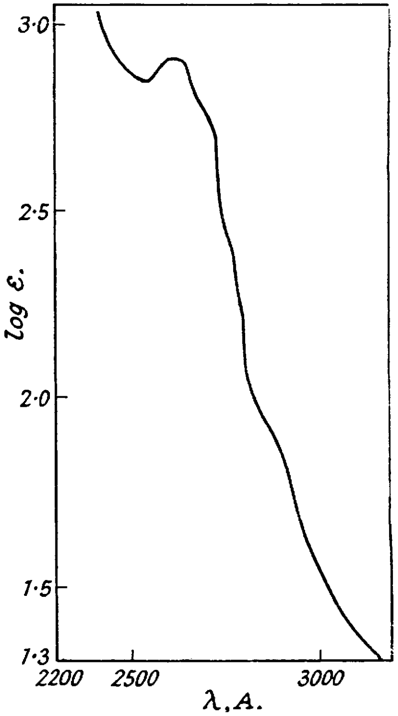
five recrystallisations these values became constant, and the optically pure *l*-arsonium *d*-bromocamphorsulphonate was thus obtained, m. p. 186—187°, $[M]_D + 119°$ in alcoholic solution.

Treatment of the above *d*-bromocamphorsulphonate with sodium iodide in alcoholic solution furnished long, colourless needles of the optically pure l-As-spiro-*bis*-1 : 2 : 3 : 4-*tetrahydro*iso*arsinolinium iodide* (as VI), having m. p. 226—228° and $[M]_D - 344°$ in chloroform solution. The rotation of this compound was unaffected by recrystallisation from hot alcohol, and that of a solution in chloroform remained unchanged during four weeks at 18° when protected from light: the iodide has therefore very considerable optical activity.

The following values for the rotatory dispersion in the visible spectrum have been obtained for a 0·385% solution of the *l*-iodide in chloroform. The calculated rotations are based on the equation $\alpha = k/(\lambda^2 - \lambda_0^2)$, where the rotation constant $k = 0{\cdot}3547$ and $\lambda_0^2 = 0{\cdot}0536$. The close agreement between the observed and the calculated rotations shows that the iodide possesses simple rotatory dispersion. From this equation, the dispersion constant $\lambda_0 = 2316$ A.

Source of light.	Li.	Li.	Na.	Hg.	Hg.	Cu.*	Cu.*	Zn.*	Hg.
λ, A.	6708	6104	5893	5780	5461	5219	5105	4811	4358
α, obs.	−0·90°	−1·09°	−1·21°	−1·27°	−1·45°	−1·60°	−1·71°	−2·02°	−2·60°
[*M*]	−256	−310	−344	−363	−413	−455	−487	−575	−740
α, calc.	−0·89	−1·11	−1·21	−1·26	−1·45	−1·62	−1·71	−2·00	−2·60
α, obs.—α, calc.	+0·01	−0·02	0·00	+0·01	0·00	−0·02	0·00	+0·02	0·00

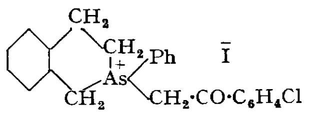
* Obtained from brass arc.



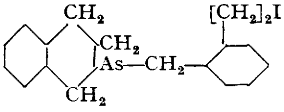
To obtain the dextrorotatory arsonium iodide, the mother-liquors from the first three recrystallisations of the above *d*-bromocamphorsulphonate were treated with potassium iodide, and a sample of the arsonium iodide rich in the dextro-form was thus precipitated. This was then converted into the arsonium *l*-bromo camphorsulphonate, which after four recrystallisations from water furnished the optically pure *d*-arsonium *l*-sulphonate, having m. p. 186—187° and $[M]_D - 123°$ in alcoholic solution. This in turn gave the pure d-As-spiro-*bis*-1 : 2 : 3 : 4-*tetrahydro*iso*arsinolinium iodide*, m. p. 225—228°, $[M]_D + 342°$ in chloroform solution.

The noteworthy feature of our new spirocyclic arsonium salts is their high optical stability, which is vividly shown by the fact that the activity of the bromocamphorsulphonates can withstand boiling water, whilst that of the iodides remains unchanged in chloroform, a solvent noted for its ready racemisation of optically active quaternary ammonium iodides (Pope and Harvey, J., 1901, **79**, 831; Jones *et al.*, J., 1904, **85**, 228; 1906, **89**, 285; 1908, **93**, 300). This optical stability must be in turn dependent on high chemical stability. When discussing the resolution of the only other arsonium salt hitherto obtained in an optically stable form, *viz.*, 2-phenyl-2-*p*-chlorophenacyl-1 : 2 : 3 : 4-tetrahydro*iso*arsinolinium iodide (VII) (J., 1943, 550), we pointed out that the only probable mechanism whereby an optically active arsonium salt could racemise was by the formation in solution of a " dissociation-equilibrium " of the type $[\text{abcdAs}]\text{X} \rightleftarrows \text{abcAs} + \text{dX}$, originally suggested by Burrows and Turner (J., 1921, **119**, 426). Arsonium salts whose resolution had been attempted by earlier workers had possessed at least one alkyl group joined to the arsenic atom, and consequently the above " dissociation-equilibrium " was readily attained; hence the optical activity, if detected at all, was small and fleeting. In our salt (VII), we had evidence that the heterocyclic ring possessed great stability and that, in addition, the presence of the *p*-chlorine atom in the phenacyl radical appeared to strengthen the linkage of this radical to the arsenic atom; consequently very little (if any) dissociation to a tertiary arsine occurred, and the salt was in consequence optically stable in solution. It is evident that the heterocyclic ring in the phenylarsonium salt (VII) must retain its high chemical stability also in our spirocyclic arsonium salt (VI) and that, as we confidently predicted, the spirocyclic system has not imposed any appreciable strain on the two heterocyclic rings. Had one ring of our spirocyclic iodide undergone fission in solution to give even a small proportion of the tertiary arsine (VIII), racemisation would undoubtedly have been rapid.

(VII.)

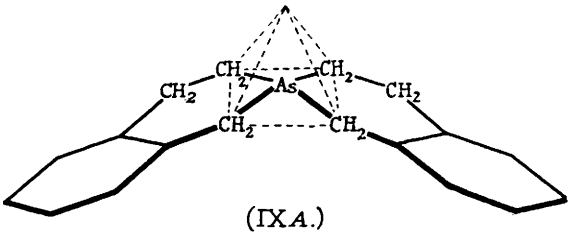


(VIII.)

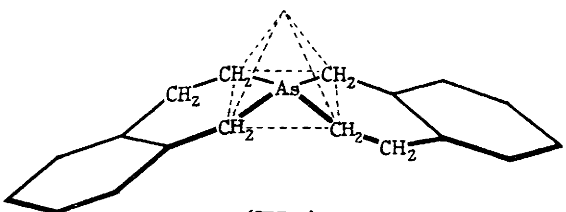


Dr. C. B. Allsopp has kindly measured the absorption spectrum of a 0·694% ethyl-alcoholic solution of the racemic spirocyclic arsonium bromide (VI), using a Hilger " Spekker " photometer and intermediate quartz spectrograph (see Figure). It shows a marked absorption band at *ca.* 2635 A., which is undoubtedly due to the two phenylene groups, but is otherwise without notable features over the range of wave-lengths used. The absorption spectrum of the *p*-chlorophenacyl arsonium iodide (VII) also showed this band, but showed in addition a more intense band at 3115 A., due apparently to the *p*-chlorophenacyl radical. The two arsonium salts have similar dispersion constants [λ_0 = 2316 A. for (VI) and 2443 A. for (VII)], suggesting that in both compounds the optical activity originates mainly in electronic transitions which are centred at the arsenic atom and correspond to absorption in this region; this cannot be determined decisively, however, without extending the rotatory dispersion to much shorter wave-lengths. It is noteworthy that the two salts have also closely similar rotations; *e.g.*, the *l*-arsonium iodide (VII) in 0·508% chloroform solution had $[M]_D$ − 352°, and this close proximity of the two rotatory powers is maintained throughout the visible spectrum (cf. Holliman and Mann, *loc. cit.*, p. 554).

Although the spirocyclic arsonium salt (VI) has some structural resemblance to the 4-phenyl-4′-carbethoxy-bispiperidinium-1 : 1′-spiran bromide resolved by Mills and Warren (J., 1925, **127**, 2507), it should be emphasised that the resolution of our arsonium salt confirms, but does not prove, the tetrahedral configuration of the 4-covalent arsenic atom. Mills and Warren's spirocyclic ammonium salt could have shown optical activity only if the 4-covalent nitrogen atom possessed a tetrahedral configuration: had this atom possessed the Bischoff pyramidal configuration, the salt could have existed in *cis*- and *trans*-isomerides, neither of which could have shown optical activity. If the 4-covalent arsenic atom possessed this pyramidal configuration, our spirocyclic salt (VI) could also exist in geometric isomers, but of these only the *cis*-form (IXA) has a plane of symmetry, and the *trans*-form (IXB), having no element of symmetry, could show optical activity. None of the salts containing our spirocyclic arsonium ion showed, however, any evidence of existing in two geometric isomers.



(IXA.)



(IXB.)

EXPERIMENTAL.

All rotations were measured in a 4-dm. tube at 18°, the source of light (unless otherwise stated) being the sodium-D line, λ 5893.

dl-As-spiro-*Bis*-1 : 2 : 3 : 4-*tetrahydro*iso*arsinolinium Bromide* (VI).—A mixture of 2-methyl-1 : 2 : 3 : 4-tetrahydro-*iso*arsinoline (6·9 g.) and *o*-β-bromoethylbenzyl bromide (9·2 g., 1 mol.) when stirred readily formed a clear solution which within a few minutes became warm and then set to a viscous glass. The latter was then heated under reflux at 14 mm. pressure, the temperature being slowly increased to 200° and maintained there for 1 hour. The mixture effervesced just above 100° and began to darken, and a colourless liquid refluxed in the condenser. After 1 hour at 200°, crystallisation occurred, and heating for a further 1·5 hours at 200° made no perceptible change, although rapid refluxing of the volatile liquid continued. The latter was therefore distilled off (b. p. *ca.* 68°/17 mm.), and the residue extracted with boiling alcohol (25 c.c.) to which a few drops of aqueous hydrobromic acid had been added to give complete solution. The latter on cooling deposited the colourless crystalline *bromide* (VI), which was collected, washed with alcohol and ether, and dried (5 g., 38%); it was recrystallised from very dilute hydrobromic acid, or from alcohol, or from alcoholic ether; m. p. 288—290° (Found: C, 55·6; H, 5·3. $C_{18}H_{20}BrAs$ requires C, 55·25; H, 5·1%).

The above appear to be the optimum conditions for the preparation of the bromide: other experiments, in which the manner, time, and degree of heating were varied over wide limits, gave lower yields.

When a hot saturated alcoholic solution of the bromide was treated with a cold saturated alcoholic solution of sodium iodide, the dl-*arsinolinium iodide* separated on cooling as colourless crystals, which when recrystallised from alcohol had m. p. 231—233° with darkening from 225° (Found: C, 49·5; H, 4·8. $C_{18}H_{20}IAs$ requires C, 49·3; H, 4·6%).

Resolution of the Arsonium Ion.—Solutions of the bromide (VI) and of silver *d*-bromocamphorsulphonate (1 mol.), each in boiling 96% alcohol, were mixed, shaken to coagulate the silver bromide, filtered, and the solvent then removed under reduced pressure. The oily residue could not be obtained crystalline from any organic solvent; a solution in hot water (charcoal) on slow cooling, however, deposited the crystalline *d*-bromocamphorsulphonate, m. p. 70—74°; a 0·678% alcoholic solution had α + 0·88°, [*M*] + 202°. Successive recrystallisations from water gave the sulphonate at first as hydrated crystals which in a vacuum over sulphuric acid readily effloresced, affording the hygroscopic anhydrous salt, but after four recrystallisations as hydrated crystals which underwent similar dehydration but without apparent loss of their crystal form: the powdered anhydrous salt had necessarily to be weighed in a dry atmosphere. The data for the crops from the final crystallisations, after dehydration, were:

Total number of crystallisations.	M. p.	Concn. of alcoholic solution (g. solute/100 c.c. solution).	α.	[*M*].
4	185 —187°	0·824	+0·66°	+124°
5	184·5—186·5	1·005	+0·75	+116
6	186 —187	0·900	+0·69	+119

The optically pure l-*arsonium* d-*bromocamphorsulphonate* had therefore been isolated after 5 recrystallisations: the powdered dehydrated salt from the final recrystallisation on exposure to air formed a *monohydrate* (Found, for the anhydrous salt: C, 53·8; H, 5·5; Br, 13·2; increase in weight on exposure to air, 2·9. $C_{28}H_{34}O_4BrSAs$ requires C, 54·1; H, 5·5; Br, 12·9; increase in weight on monohydrate formation, 2·9%. Found, for the salt after exposure: C, 52·7; H, 6·1; Br, 13·5, 13·7. $C_{28}H_{34}O_4BrSAs,H_2O$ requires C, 52·6; H, 5·6; Br, 12·5%). A 0·928% alcoholic solution of the monohydrate had α + 0·69°, [*M*] + 119°.

l-As-spiro-*Bis*-1 : 2 : 3 : 4-*tetrahydro*iso*arsinolinium Iodide* (as VI).—When an ice-cold solution of the above sulphonate (0·7 g.) in alcohol (40 c.c.) was treated with an excess of a solution of sodium iodide in 95% alcohol, colourless needles of the l-*iodide* separated; these were collected, and washed with alcohol and ether; 0·42 g. A portion of this iodide, when dried in a vacuum, had m. p. 225—228°, and in 0·389% chloroform solution had α − 1·22°, [*M*] − 343°. The remainder, recrystallised from alcohol, separated as magnificent long needles, of unchanged m. p. (Found : C, 48·6; H, 4·4; I, 29·1. $C_{18}H_{20}IAs$ requires C, 49·3; H, 4·6; I, 29·0%); a 0·385% chloroform solution had α − 1·21°, [*M*] − 344°, these values remaining unchanged during one month at 18°. The full rotatory dispersion values are given on p. 46. It is clear from these results that the arsonium ion has a much greater rotation in chloroform than in alcoholic solution.

The d-*arsonium* l-*bromocamphorsulphonate*. The aqueous filtrates from the first three recrystallisations of the above *d*-bromocamphorsulphonate, when treated with aqueous potassium iodide, deposited the optically impure *d*-iodide. This was collected, dried, and, by treatment with silver *l*-bromocamphorsulphonate, converted into the arsonium *l*-bromocamphorsulphonate. Four recrystallisations from water afforded the optically pure d-*arsonium* l-*sulphonate*, m. p. 185—187° (Found for the dehydrated salt : C, 53·6; H, 6·11%); a 0·931% alcoholic solution had α − 0·73°, [*M*] − 123°. Further recrystallisation did not affect the rotation of this salt, which however always separated as a *hydrate* (Found : C, 52·05; H, 6·0; Br, 12·8%), which readily lost its water and crystalline form in a vacuum.

d-As-spiro-*Bis*-1 : 2 : 3 : 4-*tetrahydro*iso*arsinolinium Iodide* (as VI).—This *salt* was prepared from the *l*-sulphonate as previously described, and after recrystallisation from alcohol was obtained as long colourless needles, m. p. 226—228° (Found : C, 49·3; H, 4·4; I, 29·3. $C_{18}H_{20}IAs$ requires C, 49·3; H, 4·6; I, 29·0%); a 0·384% chloroform solution had α + 1·20°, [*M*] + 342°.

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