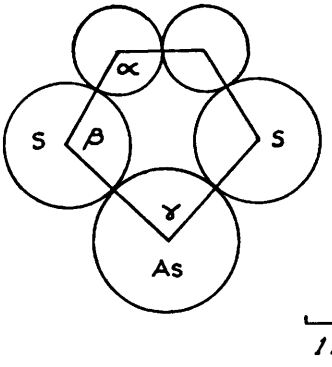
387. *Stereochemistry of Tervalent Arsenic Compounds. Part II.* Optical Resolution of* 2-p-*Carboxyphenyl-5-methyl-*1 : 3-*dithia-2-arsaindane.*

By I. G. M. Campbell.

The compound named in the title has been resolved into (+)- and (−)-forms, $[\alpha]_D^{20}$ ±8·7° ± 0·5°, which are optically stable in chloroform at room temperature and in ethanol at 110°, but are racemised in aqueous alkali. The existence of these enantiomers provides further evidence that arsenic is capable of retaining a stable pyramidal disposition of bonds when present as a tervalent atom in a heterocyclic ring.

The dissymmetry of the 9-arsafluorenes has been demonstrated by the optical resolution of two members of the series, 2-amino-9-phenyl- and 9-*p*-carboxyphenyl-2-methoxy-9-arsafluorene.[1] The reason for the existence of the enantiomers is, most probably, the stable pyramidal arrangement of the bonds from the arsenic atom, for the alternative explanation, the "skew" configuration of the diphenyl residue in the molecule, seems unlikely on several counts. Nevertheless it seemed of interest to examine other heterocyclic arsenic compounds in which no alternative to a pyramidal molecule was possible, and derivatives of 1 : 3-dithia-2-arsaindane were chosen for study because they were readily prepared and appeared to possess suitable physical properties.



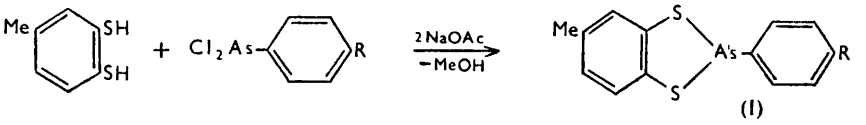
Models and scale drawings of 2-*p*-carboxyphenyl-5-methyl-1 : 3-dithia-2-arsaindane (I; R = CO_2H) indicate a planar configuration for the condensed ring system with the *p*-carboxyphenyl group lying above or below the plane at the pyramidal angle. The methyl group in the 5-position then renders the molecule dissymmetric. The bond angles in the five-membered ring, measured on a model or scale drawing (see Figure) are C–C–S (α) 120°, C–S–As (β) 104·5°, and S–As–S (γ) 89·5°. The arsenic angle, γ, is therefore very close to that found [2] in arsine, 91·5°, and the sulphur angle, β, lies between the value of 92·25° in hydrogen sulphide [2] and 113° ± 3° found in diphenyl sulphide [3] and close to 105°, the value generally accepted for dimethyl sulphide.[4] Consequently, any distortion of the bonds from the benzene ring is

* Part I is considered to be *J.*, 1956, 1195.

[1] Campbell and Poller, *J.*, 1956, 1195.
[2] Mulliken, *J. Amer. Chem. Soc.*, 1955, **77**, 887.
[3] Sutton and Hampson, *Trans. Faraday Soc.*, 1935, **31**, 945.
[4] Brockway and Jenkins, *J. Amer. Chem. Soc.*, 1936, **58**, 2036; Thompson, *Trans. Faraday Soc.*, 1941, **37**, 38.

highly improbable, and, if enantiomers occur, they must do so by virtue of the stable pyramidal disposition of the bonds from arsenic.

Heterocyclic arsenic compounds of this type have been prepared by the interaction of arylarsonous oxides or chlorides with aliphatic or aromatic dithiols,[5] and have been examined for chemotherapeutic action, but their stereochemistry has not been investigated. 5-Methyl-2-phenyl-1 : 3-dithia-2-arsaindane and the corresponding *p*-carboxyphenyl derivative were readily isolated in good yield from the reaction formulated :

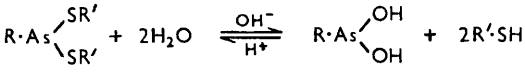


(I)

Both were bright yellow, highly crystalline compounds, soluble in a wide range of organic solvents, and the acid (I; R = CO_2H) dissolved in aqueous sodium hydrogen carbonate and was reprecipitated unchanged, so that the arsenic–sulphur bond appeared to be stable.

Resolution of (±)-2-*p*-carboxyphenyl-5-methyl-1 : 3-dithia-2-arsaindane (I; R = CO_2H) was carried out by crystallisation of the (+)-1-phenylethylamine and the quinine salt, the former yielding the (−)-acid, $[\alpha]_D^{20}$ −8·7°, and the latter the (+)-acid, $[\alpha]_D^{20}$ +8·9° (*c* ~0·5 in $CHCl_3$). The specific rotation of the active acids was unaffected by crystallisation from boiling ethanol or by heating in ethanol at 110° for 2 hr. The optical stability of this compound is therefore comparable with that of 2-amino-9-phenyl-9-arsafluorene under similar conditions.[1] In pyridine, however, the rotation of the (−)-acid, $[\alpha]_D$ −6·9°, fell slowly at room temperature and had reached half-value in about six weeks. Much more rapid racemisation occurred when the (−)-acid was dissolved in 0·1N-sodium hydroxide. The specific rotation of the solution was low, $[\alpha]_D$ −2·1°, and that of acid regained from it had dropped from −8·7° to −3·2°. Further, when the (+)-acid was dissolved in saturated sodium hydrogen carbonate solution, a crystalline sodium salt separated. This dissolved on dilution, but polarimetric examination was impossible because the initially clear solution became opalescent before readings could be taken. Acidification of the solution regenerated the cyclic acid but in optically inactive condition.

This rapid racemisation is undoubtedly caused by fission of the arsenic–sulphur bonds by aqueous alkali and subsequent reversal of the reaction by acid, a type of behaviour noted in triaryl thioarsenites,[6] and studied by Cohen, King, and Strangeways [5a] in compounds somewhat similar to the one under discussion. The latter authors have shown conclusively that, in solution in sodium hydroxide, alkyl thioarsenites exist in equilibrium with the constituent arsenoxide and thiol, and have formulated the reaction as :



In one of the compounds studied, cysteine was introduced as the alkyl group, R'S, and, judging from polarimetric observations, the authors concluded that in saturated sodium hydrogen carbonate solution the equilibrium did not shift markedly to the right. The results of racemisation experiments on the arsaindane, however, indicate that sodium hydrogen carbonate is equally effective, for, under comparable conditions of temperature and time, the (+)-acid was completely racemised in 0·3N-sodium hydrogen carbonate, whereas the (−)-acid, regained from solution in 0·1N-sodium hydroxide, still retained one-third of its original rotation.

Racemisation possibly occurs, also, on heating, for both the active and the inactive acid melt between 200° and 202°, and, although a mixture of (+)- with (±)-acid softened at 197°, no significant melting-point depression could be demonstrated. The compounds differ in solubility, however, for it was possible to obtain optically pure (−)-acid, $[\alpha]_D$ −8·7°, from

[5] (*a*) Cohen, King, and Strangeways, *J.*, 1931, 3043; (*b*) E. A. H. Friedheim. B.P. 655,435, 1951 (*Chem. Abs.*, 1953, **47**, 144).

[6] Klement and May, *Ber.*, 1938, **71**. 890.

a specimen, $[\alpha]_D$ −6·6°, regenerated from the more soluble quinine salt, by repeated recrystallisation from ethanol.

Experimental

Rotations were measured in 2 dm. tubes, unless otherwise stated.

Toluene-3 : 4-dithiol (0·5 g.) and sodium acetate (0·55 g.) were dissolved together in warm methanol (15 ml.), and phenylarsonous chloride (0·7 g.) was added to the cold solution. A yellow oil separated, along with sodium chloride, and the mixture was extracted with chloroform (20 ml.) and water (30 ml.). The chloroform extract was washed, dried, and evaporated, leaving a viscous oil which solidified after 48 hr. in a desiccator. Recrystallisation from ethanol containing a little light petroleum (b. p. 40—60°) gave *5-methyl-2-phenyl-1 : 3-dithia-2-arsaindane* as pale yellow prisms, m. p. 53—55° (0·6 g.) (Found : C, 50·05; H, 3·5; As, 24·6. $C_{13}H_{11}S_2As$ requires C, 51·0; H, 3·6; As, 24·5%). Similarly when *p*-carboxyphenylarsonous chloride (2·67 g.) in methanol (10 ml.) was added to toluene-3 : 4-dithiol (1·56 g.) and sodium acetate (1·6 g.) in methanol (30 ml.) a yellow precipitate separated. Extraction of this solid with boiling methanol gave 2-p-*carboxyphenyl-5-methyl-1 : 3-dithia-2-arsaindane* as yellow needles, m. p. 200—202° (3·4 g.) (Found : C, 48·5; H, 3·3; As, 21·1. $C_{14}H_{11}O_2S_2As$ requires C, 48·0; H, 3·2; As, 21·4%).

Optical Resolution.—The acid (5 g.) was dissolved in a hot solution of (+)-1-phenylethylamine (3·5 g., 2 equivs.) in ethanol (300 ml.). The first fraction of salt, F1 (4·2 g.), was filtered off after 2 hr., and two further fractions, F2 and F3 (1·05 g. and 0·75 g.), were obtained by successive evaporations. F1, $[\alpha]_D$ +5·3° (*c* 0·25 in EtOH), was recrystallised thrice from ethanol and gave pure (−)-*acid–(+)-base salt* (1·6 g.), m. p. 199—200°, $[\alpha]_D$ 0° (*c* 0·233 in EtOH) (Found : C, 56·3; H, 4·9. $C_{22}H_{22}O_2NS_2As$ requires C, 56·0; H, 4·7%). Recrystallisation of F2 and F3, combined, failed to yield the more soluble salt in optically pure condition. Repetition of the resolution gave almost identical results, and the most dextrorotatory salt isolated had $[\alpha]_D$ +11·3°, but decomposition showed it to be optically impure.

Acid (2·5 g.), $[\alpha]_D$ +1·5° (*c* 0·525 in pyridine), recovered from the more soluble fractions of (+)-1-phenylethylamine salts, was combined with quinine (2·3 g.) in ethanol–chloroform (3 : 1) (400 ml.). Two fractions of salt were separated; the first (3·9 g.) had m. p. 202—207°, $[\alpha]_D$ −99·2° (*c* 0·255 in " AnalaR " $CHCl_3$), and the second (0·75 g.), m. p. 204—206°, $[\alpha]_D$ −103·3° (*c* 0·237). Four recrystallisations of the first fraction from ethanol–chloroform (3 : 1) gave the (+)-*acid–quinine salt*, m. p. 206—207°, $[\alpha]_D$ −97·0° (*c* 0·263) (1·2 g.) (Found : C, 60·5; H, 5·2. $C_{34}H_{35}O_4N_2S_2As$ requires C, 60·5; H, 5·2%). Crystallisation of the second fraction of salt did not alter its specific rotation but acid regenerated from it had $[\alpha]_D$ −2·5° (in pyridine) and was later shown to be optically impure. This resolution was repeated with (±)-acid and similar results were obtained. Optically impure (−)-acid, $[\alpha]_D$ −6·6° (in $CHCl_3$), obtained from the more soluble fractions of salt was recrystallised four times from ethanol and then had $[\alpha]_D$ −8·7° ± 0·5° (*c* 0·516 in " AnalaR " $CHCl_3$).

Isolation of (+)- *and* (−)-*Acid.*—The required salt was dissolved in ethanol (100 ml. per g.) and decomposed by addition of 0·1N-sulphuric acid at <0°. Precipitation was completed by the addition of water. In this way the (+)-1-phenylethylamine salt (0·5 g.), $[\alpha]_D$ 0°, gave the (−)-*acid* (0·35 g.), $[\alpha]_D^{21}$ −6·8° ± 0·2° (*c* 1·058 in pyridine), $[\alpha]_D^{20}$ −8·7° ± 0·3° (*c* 0·490 in " AnalaR " $CHCl_3$; 4 dm. tube). Recrystallisation from boiling ethanol gave yellow needles, m. p. 201—202°, $[\alpha]_D^{20}$ −6·6° ± 0·3° (*c* 0·607 in pyridine) (Found : C, 47·8; H, 3·4. $C_{14}H_{11}O_2S_2As$ requires C, 48·0; H, 3·2%).

The quinine salt (0·5 g.), $[\alpha]_D$ −97·0°, gave (+)-*acid* (0·23 g.), m. p. 201—202°, $[\alpha]_D^{20}$ +6·8° ± 0·4° (*c* 0·548 in pyridine), $[\alpha]_D^{20}$ +8·9° ± 0·5° (*c* 0·528 in " AnalaR " $CHCl_3$) (Found : C, 48·3; H, 3·3%). A specimen obtained in the second resolution had $[\alpha]_D^{20}$ +8·6° ± 0·4° (*c* 0·320 in " AnalaR " $CHCl_3$; 4 dm. tube).

Racemisation Experiments.—A solution of (+)-acid (0·1008 g.), $[\alpha]_D^{20}$ +10·4°, in ethanol (20 ml.), in a sealed bulb, was heated in a thermostat at 110° ± 0·1° for 2 hr., cooled rapidly, and examined at 20°. The rotation was unaltered.

(−)-Acid (0·0975 g.), $[\alpha]_D^{20}$ −8·7° (in $CHCl_3$), was dissolved by warming to 40° in 0·1N-sodium hydroxide (20 ml.) and found to have $[\alpha]_D^{18}$ −2·1°. The solution was then cooled to 0° and acidified with 0·1N-sulphuric acid. The precipitated acid had $[\alpha]_D^{20}$ −3·2° (*c* 0·464 in $CHCl_3$). (+)-Acid (0·1002 g.) was dissolved in saturated aqueous sodium hydrogen carbonate (20 ml.) by warming to 35°. On cooling, the sodium salt separated and was redissolved by dilution to 50 ml. The clear solution was transferred to a 4 dm. polarimeter tube, but satisfactory readings could not be obtained because cloudiness developed rapidly. The solution was cooled to 0° and

acidified with 0·1N-sulphuric acid. The acid regained (0·0858 g.) was optically inactive, m. p. 199—201° (Found : C, 47·6; H, 3·4%).

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