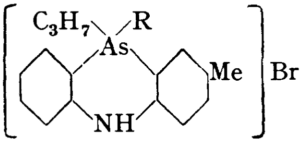
387. *The Asymmetric Arsenic Atom. Attempts to prepare Optically Active Arsenicals.*

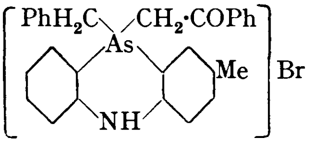
By John D. A. Johnson.

Attempts to obtain optically active arsenicals have rarely been successful. The experiments now recorded, which are based on fundamental ideas slightly different from those previously used, have likewise met with no success.

If the difficulty in resolving asymmetric organic arsenicals lies in the ease of racemisation, a factor which might assist in the resolution is restriction of the motion of the attached groups (a) by making the arsenic atom common to two or three rings or (b) by increasing the bulk of the groups. A combination of (a) and (b) might also be very effective, *e.g.*, a heterocyclic arsenic atom attached to two bulky groups. Attempts to prepare *spiro*-compounds conforming to (a) have not been successful, although evidence of their formation was obtained. Substances containing arsenic in a ring and also joined to two groups, being easily obtainable, were first studied.

(I.)



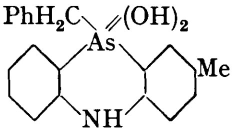


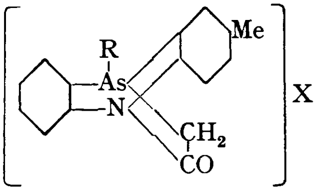
(II.)

2-Methyl-10-*n*-propyl-5 : 10-dihydrophenarsazine, obtained from the 10-chloro-compound (J., 1931, 2518), reacted readily at 100° with benzyl bromide to give 10-*benzyl*-2-*methyl*-10-n-*propyl*-5 : 10-*dihydrophenarsazonium bromide* (I; R = CH_2Ph). In a similar manner, by means of ω-bromoacetophenone, 10-*phenacyl*-2-*methyl*-10-n-*propyl*-5 : 10-*dihydrophenarsazonium bromide* (I; R = $CH_2{\cdot}COPh$) was prepared. The *d*-α-bromocamphor-π-sulphonate corresponding to the former bromide was a gum, but the d-*camphor*-β-*sulphonate* was readily obtained and fractionally crystallised from absolute alcohol, the only suitable solvent : only a small difference in rotatory power was exhibited by the first and the last fraction. The *d*-camphor-β-sulphonate corresponding to the second bromide was a gum.

10-*Benzyl*-2-*methyl*-5 : 10-*dihydrophenarsazine*, obtained by the Grignard reaction from benzyl bromide and 10-chloro-2-methyl-5 : 10-dihydrophenarsazine, reacted readily with ω-bromoacetophenone to give 10-*phenacyl*-10-*benzyl*-2-*methyl*-5 : 10-*dihydrophenarsazonium* *bromide* (II), a sparingly soluble salt which, however, reacted readily in alcohol with silver *d*-camphor-β-sulphonate to give the corresponding *d-camphor-β-sulphonate*. Fractional crystallisation of this from alcohol effected no separation into portions differing in rotatory power : the mother-liquors had the same rotation when examined as soon as obtained and also some time later, so the racemisation, if any, must have been extremely rapid.

(III.)





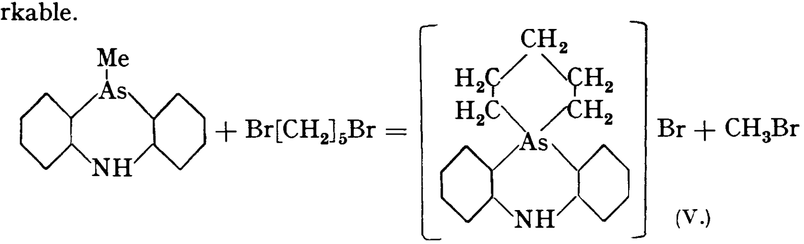
(IV.)

As the original ideas underlying these resolutions did not require that the anion should be large, and as the large anions present in the substances described above were probably, by increasing the molecular weight, decreasing the solubility, it was decided to form salts with small anions by treating the hydroxide corresponding to (II) with optically active acids of low molecular weights. The interaction of the *iodide* corresponding to (II) with moist silver oxide led, however, to what is presumed to be 10-*benzyl*-2-*methyl*-5 : 10-*dihydrophenarsazonium dihydroxide* (III), the phenacyl radical being eliminated.

The next line of attack was to attempt to prepare substances of the type (IV), which might be obtained by the action of (a) bromoacetic acid on 10-alkyl(aryl)-2-methyl-5 : 10-dihydrophenarsazine or (b) more directly by the action of bromoacetic anhydride on the same substance. 10-Methyl-5 : 10-dihydrophenarsazine could be acetylated only by means of boiling acetic anhydride (compare Aeschlimann, J., 1927, 413), but it reacted vigorously at 100° with bromoacetic anhydride; nothing, however, could be isolated from the product. When bromoacetic acid was heated with 10-benzyl-2-methyl-5 : 10-dihydrophenarsazine, benzyl bromide was evolved and a gum obtained.

Some evidence was obtained that the acetylation of 10-chloro-5 : 10-dihydrophenarsazine is a reversible reaction with the position of equilibrium not entirely in favour of the formation of the acetyl derivative.

Finally, attempts were made to prepare *spiro*-compounds of the type (V) by heating pentamethylene dibromide with 10-methyl-5 : 10-dihydrophenarsazine, but the product was unworkable.

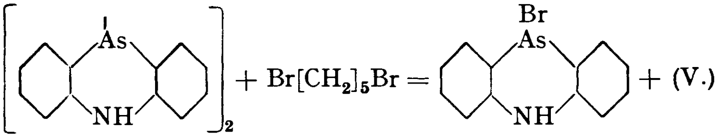


(V.)

It is known that when cacodyls are heated with alkyl halides the following reaction takes place :

$$R_2As{\cdot}AsR_2 + 2RX = R_2AsX + R_4AsX.$$

An attempt was consequently made to prepare the compound (V) by heating pentamethylene dibromide and 10 : 10′-bis-5 : 10-dihydrophenarsazinyl, the following reaction being anticipated :



The substance isolated was purified with difficulty and the analytical figures indicated that, though the reaction had proceeded in the manner anticipated, some pentamethylene dibromide had interacted with the :NH group also. Hence, to establish whether under the conditions of the experiment there was a tendency for the :NH group to react, a simpler reaction was studied.

Ethyl bromide reacted with 10 : 10′-bis-5 : 10-dihydrophenarsazinyl at 100° in sealed tubes, giving 10 : 10-*diethyl*-5 : 10-*dihydrophenarsazonium bromide* and 10-bromo-5 : 10-dihydrophenarsazine. The former was also synthesised from 10-ethyl-5 : 10-dihydrophenarsazine and ethyl bromide for comparison. There appeared to be no tendency for the :NH group to react with ethyl bromide, but the product held tenaciously some alcohol (from which it was crystallised) which lowered the melting point from 152° to 130°. Ethyl bromide would not react with 5-acetyl-10-methyl-5 : 10-dihydrophenarsazine or with 10 : 10′-bis-5-acetyl-5 : 10-dihydrophenarsazinyl.

EXPERIMENTAL.

10-*Benzyl*-2-*methyl*-10-n-*propyl*-5 : 10-*dihydrophenarsazonium Bromide*.—Benzyl bromide (4·3 g.) and 2-methyl-10-*n*-propyl-5 : 10-dihydrophenarsazine (7·1 g.) were heated in a sealed tube at 100° for 4 hours, the product dissolved in a small quantity of hot alcohol and cooled, and ether added. The solid precipitated was colourless and the solution green. The *bromide* crystallised from ethyl alcohol–acetone in minute colourless prisms, which became deep yellow at 190° and decomposed at the m. p., 206—207°. It is soluble in methyl and ethyl alcohols (Found : Br, 17·1. $C_{23}H_{25}NBrAs$ requires Br, 17·0%).

10-*Phenacyl*-2-*methyl*-10-n-*propyl*-5 : 10-*dihydrophenarsazonium bromide* was similarly prepared from the phenarsazine (6 g.) and ω-bromoacetophenone (4 g.). The solid obtained in quantitative yield was boiled with acetone and cooled, and the insoluble material crystallised from a little alcohol. It resembled the foregoing compound (Found : Br, 15·7. $C_{24}H_{25}ONBrAs$ requires Br, 16·0%).

10-*Benzyl*-2-*methyl*-10-n-*propyl*-5 : 10-*dihydrophenarsazonium* d-*camphor*-β-*sulphonate* was obtained by boiling a mixture of the corresponding bromide (4·7 g.) with silver *d*-camphor-β-sulphonate (3·39 g.) in alcohol (50 c.c.) for 2 hours, removing the silver bromide, and concentrating the filtrate. The colourless crystals had m. p. 262° (decomp.) after turning green at 250° (Found : As, 12·0. $C_{33}H_{40}O_4NSAs$ requires As, 12·1%). A large quantity of this substance was subjected to a searching and systematic crystallisation; the rotatory powers of the least and the most soluble fraction were $[\alpha]_{5461}^{20^\circ}$ + 21·0° and + 21·5° respectively, the m. p.'s were identical, and both fractions contained 12·0% of arsenic.

10-*Benzyl*-2-*methyl*-5 : 10-*dihydrophenarsazine*.—The Grignard reagent prepared from benzyl bromide (156 g.), magnesium (22 g.), and ether (440 c.c.) in a 3-litre flask was cooled and treated with 10-chloro-2-methyl-5 : 10-dihydrophenarsazine (128 g.), added in small portions through a long wide condenser. After ½ hour dilute sulphuric acid and ice were added, the ether evaporated, and the product crystallised from 95% alcohol; it formed pale yellow needles, m. p. 132·5° (Found : As, 22·1. $C_{20}H_{18}NAs$ requires As, 21·6%). Dibenzyl was isolated from the mother-liquor.

10-*Phenacyl*-10-*benzyl*-2-*methyl*-5 : 10-*dihydrophenarsazonium bromide* was obtained by heating the last-mentioned phenarsazine (3·47 g.) and ω-bromoacetophenone (1·99 g.) in a sealed tube for 6 hours at 100°. The product was boiled with alcohol; the insoluble material obtained after cooling crystallised from methyl alcohol in small prisms, which turned yellow at about 195° and orange at 200° and melted to an orange-red liquid at 203° (Found : Br, 14·6. $C_{28}H_{25}ONBrAs$ requires Br, 14·65%).

The corresponding d-*camphor*-β-*sulphonate* was prepared from the bromide (11·25 g.), silver *d*-camphor-β-sulphonate (7·0 g.), and alcohol (125 c.c.) (Found : As, 10·95. $C_{38}H_{40}O_5NSAs$ requires As, 10·75%); it crystallised from alcohol in small colourless needles, m. p. 187—188°. About 44 g. of the salt were fractionally crystallised from alcohol : the least and the most soluble fraction had $[\alpha]_{5461}^{20^\circ}$ + 17·25° (*c* 1·4857) and + 17·62° (*c* 1·5383) respectively in absolute alcohol.

10-*Phenacyl*-10-*benzyl*-2-*methyl*-5 : 10-*dihydrophenarsazonium iodide* was obtained by adding a warm solution of potassium iodide (16 g.) in water (300 c.c.) to a boiling solution of the *d*-camphor-β-sulphonate (50 g.) in alcohol (95%, 500 c.c.). Crystals began to separate immediately and, after cooling, were filtered off; as they were insoluble in the usual solvents, the material was boiled with alcohol; m. p. (after turning red) 179° (Found : I, 21·2. $C_{28}H_{25}ONIAs$ requires I, 21·4%).

Treatment of the iodide (5·93 g.) in suspension in hot water (50 c.c.) with silver oxide (from 3·40 g. of silver nitrate in water, 20 c.c.), followed by the addition of alcohol (30 c.c.) and heating to boiling, seemed to cause little reaction, and the mixture was heated on the water-bath for 2 hours with constant shaking. On filtration while hot, some oil separated and later crystals were deposited; the latter were recrystallised from a little alcohol (Found : As, 19·9. $C_{20}H_{20}O_2NAs$ requires As, 19·7%). The m. p. was indefinite and the substance is presumed to be (III).

Action of Ethyl Bromide on 10 : 10′-*Bis*-5 : 10-*dihydrophenarsazinyl*.—These substances (12·6 g. and 4·0 g. respectively) were heated in a sealed tube at 100° for 3 hours, left over-night, and then heated for a further 6 hours. Two liquid layers formed, and the lower one solidified on cooling. The whole was boiled with benzene and alcohol, and the solution evaporated to small bulk and boiled with a further quantity of benzene. The benzene solution was separated, and the residual oil boiled again with benzene. The final residual oil crystallised from a small quantity of alcohol in colourless needles, m. p. 125° (previous softening). After further crystallisation from the same solvent the air-dried material had m. p. 129—132° (frothing) (Found : As, 17·9. $C_{16}H_{19}NBrAs,EtOH$ requires As, 17·6%). After drying under reduced pressure over potassium hydroxide and then standing in the air for several days, it had m. p. 152—153° (decomp.) (Found : As, 19·5. $C_{16}H_{19}NBrAs$ requires As, 19·7%). The same behaviour was shown by a specimen of 10 : 10-*diethyl*-5 : 10-*dihydrophenarsazonium bromide* obtained by heating 10-ethyl-5 : 10-dihydrophenarsazine (4·8 g.) with ethyl bromide (6·0 c.c.) in a sealed tube at 100° for 75 minutes (Found : As, 19·2%). The corresponding *iodide*, obtained by adding concentrated potassium iodide solution to a solution of the bromide (4·6 g.) in hot water (35 c.c.), crystallised from hot water in colourless needles, m. p. 230° (decomp.) (Found : I, 29·0. $C_{16}H_{19}NIAs$ requires I, 29·7%).

10-Chloro-5-acetyl-5 : 10-dihydrophenarsazine (6·3 g.), dissolved in a boiling mixture of acetone (100 c.c.) and alcohol (450 c.c.), was treated with a mixture of hypophosphorous acid (*d* 1·136, 8 c.c.) and alcohol. After a few minutes' boiling, 10 : 10′-bis-5-acetyl-5 : 10-dihydrophenarsazinyl was deposited in colourless crystals (compare Burton and Gibson, J., 1926, 2247). This compound did not react with ethyl bromide during several hours' heating at 100°.

Action of Pentamethylene Dibromide on 10 : 10′-*Bis*-5 : 10-*dihydrophenarsazinyl*.—A mixture of 8·6 g. of the latter and 28·5 g. of the former was heated in a boiling water-bath for 8 hours with occasional shaking. The product was extracted with hot alcohol, the solution evaporated, and the residue extracted twice with hot benzene. The insoluble oil was dissolved in a little alcohol, and crystallisation induced by scratching. After extraction with acetone, the residue crystallised from alcohol in small yellow plates, m. p. 155° (decomp.) (Found : Br, 28·4; As, 15·6. $C_{22}H_{28}NBrAs$ requires Br, 29·5; As, 13·9%. $C_{17}H_{19}NBrAs$ requires Br, 20·4%). When the yellow crystals were boiled with ethyl alcohol–ethyl acetate, the colour was removed; the residue, when recrystallised from alcohol, was obtained in small colourless plates, m. p. 166° (decomp.) (Found : Br, 27·2; As, 15·55%).

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GUY'S HOSPITAL MEDICAL SCHOOL (UNIVERSITY OF LONDON),
LONDON, S.E. 1.

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