145. *The Synthetic Application of* o-β-*Bromoethylbenzyl Bromide. Part II. The Preparation and Properties of* 2-*Substituted* 1 : 2 : 3 : 4-*Tetrahydro*iso*arsinolines.*

By Frederick G. Holliman and Frederick G. Mann.

By the Michaelis condensation of *o*-β-bromoethylbenzyl bromide with phenyl- and methyl-dichloroarsine in the presence of metallic sodium and ethyl acetate, 2-*phenyl*- and 2-*methyl*-1 : 2 : 3 : 4-*tetrahydro*iso*arsinoline* have been prepared. This novel heterocyclic system proved to have considerable stability, and the spontaneous fission of the heterocyclic ring shown by the quaternary methiodide of 1-methyl-1 : 2 : 3 : 4-tetrahydroarsinoline in solution does not occur with the *iso*arsinoline analogues. A number of derivatives of the *iso*arsinolines have been prepared, but none of the compounds tested possessed trypanocidal or antimalarial activity.

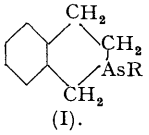
o-β-Bromoethylbenzyl bromide is now readily available (Holliman and Mann, J., 1942, 737) and we are investigating its use in the synthesis of various heterocyclic systems. It is known to condense with primary amines to give 2-substituted 1 : 2 : 3 : 4-tetrahydro*iso*quinolines, and consequently we have investigated first its utilisation for the preparation of derivatives of the unknown 1 : 2 : 3 : 4-tetrahydro*iso*arsinoline.

In preliminary experiments, we attempted to prepare a " double Grignard " reagent by the interaction of the dibromo-compound with 2 equivs. of magnesium, with the intention of subsequently treating this reagent with, *e.g.*, phenyldichloroarsine. Since, however, all attempts to prepare this Grignard reagent proved unsatisfactory, we had recourse to the Michaelis reaction, and treated an ethereal solution of the bromide and the dichloroarsine directly with metallic sodium. Very little reaction occurred even in the boiling solution until a small quantity of ethyl acetate was added; this caused a brisk reaction to ensue, and, provided oxygen was carefully excluded throughout the preparation, distillation of the final solution gave 2-*phenyl*-1 : 2 : 3 : 4-*tetrahydro*iso*arsinoline* (I; R = Ph) as a colourless liquid, b. p. 128—130°/0·05 mm.

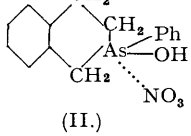
This arsine showed many of the normal properties of a tertiary arsine : *e.g.*, with methyl iodide it gave a quaternary *methiodide*, and with nitric acid it gave the characteristic and highly crystalline *hydroxy-nitrate* (II). This can clearly be regarded as a salt of the *iso*arsinoline oxide or the corresponding dihydroxide, but neither of these oxy-compounds could be isolated in the pure crystalline state. The *iso*arsinoline in chloroform solution readily absorbed one mol. of bromine to give the arsine dibromide, which, however, when treated with aqueous ammonia furnished ultimately only a colourless glassy product; this was obviously the oxide or dihydroxide, since with nitric acid it gave the hydroxy-nitrate, and with alcoholic hydrogen chloride the *arsine dichloride*.

It has been shown by Mann (J., 1932, 958) and Mann and Chaplin (J., 1936, 527) that tertiary arsines react with chloramine-T to give either an arsinimine, $R_3As{\rightarrow}N{\cdot}SO_2{\cdot}C_6H_4Me$, or the corresponding hydroxysulphonamide, $R_3As(OH){\cdot}NH{\cdot}SO_2{\cdot}C_6H_4Me$, the direction of the reaction being determined by the nature of the groups R. The phenyl*iso*arsinoline (I; R = Ph) reacted readily with anhydrous chloramine-T in absolute alcohol, but only an amorphous glass was isolated; this, when treated with water, gave toluene-*p*-sulphonamide, and the aqueous extract must therefore have contained the arsine oxide or dihydroxide : again, however, all attempts to isolate these compounds failed, but their presence in the solution was clearly shown by the fact that addition of nitric acid gave the hydroxy-nitrate, and picric acid precipitated the crystalline *hydroxy-picrate*. In contrast to this failure to isolate the oxide, the corresponding iso*arsinoline sulphide* was readily obtained as a highly crystalline solid by the interaction of the *iso*arsinoline dibromide and hydrogen sulphide.

A Michaelis condensation between *o*-β-bromoethylbenzyl bromide, sodium, and methyldichloroarsine, when also stimulated by ethyl acetate, similarly gave 2-*methyl*-1 : 2 : 3 : 4-*tetrahydro*iso*arsinoline* (I; R = Me), a liquid of b. p. 131°/18 mm., which was more susceptible to atmospheric oxidation than the phenyl analogue.



(I).



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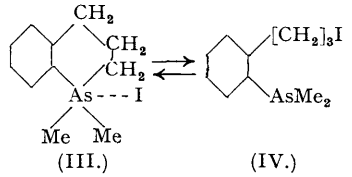


(III.) (IV.)

It formed a crystalline *methiodide*; oxidation with nitric acid did not, however, give a crystalline oxide or hydroxy-nitrate, but the aqueous solution of the product readily furnished a crystalline *hydroxy-picrate*.

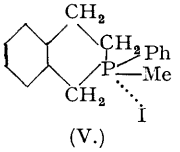
Chloramine-T reacted with the methyl*iso*arsinoline, giving only a viscous syrup, which on treatment with water gave toluene-*p*-sulphonamide, the aqueous extract again furnishing with picric acid the *iso*arsinoline hydroxy-picrate. The methyl*iso*arsinoline, unlike its phenyl analogue, failed to form a crystalline sulphide.

The methyl*iso*arsinoline is of particular interest because it is isomeric with the 1-methyl-1 : 2 : 3 : 4-tetrahydroarsinoline first prepared by Burrows and Turner (J., 1921, **119**, 430) and further investigated by Roberts, Turner, and Bury (J., 1926, 1443). They adduced evidence that the methiodide (III) of their compound underwent partial ring fission in alcoholic solution, and thus existed in equilibrium with *o*-(γ-iodo-*n*-propyl)phenyldimethylarsine (IV). The establishment of this equilibrium was indicated by the fact that the cold colourless solution of (III) on warming became yellow, but on cooling again became colourless: strong evidence of the equilibrium, however, was obtained from the fact that a rapid estimation of ionic iodine in the cold alcoholic solution always gave low values.

We at first suspected that a similar equilibrium occurred in alcoholic solutions of the quaternary iodides of our tetrahydro*iso*arsinolines. It was noteworthy that the methiodide of (I; R = Ph) was markedly more soluble in cold alcohol than that of (I, R = Me); moreover, the former gave a faintly yellow solution even in cold alcohol. Further evidence showed, however, that the tetrahydro*iso*arsinoline ring system must have great stability and it is unlikely that any such ring fission in solution occurs. Estimation of ionic iodine in our two methiodides, even when carried out as rapidly as possible in cold solution, always showed complete ionisation of iodine present; moreover, the isolation of optically stable quaternary salts of (I; R = Ph) (see following paper) would have been impossible had any such equilibrium arising from ring fission occurred. It is concluded that the pale yellow colour of alcoholic solutions of the methiodide of (I; R = Ph) probably arose from slight photochemical decomposition.

The methyl*iso*arsinoline readily united with chlorine in carbon tetrachloride solution to give the *arsine dichloride*, which on heating lost methyl chloride and generated 2-*chloro*-1 : 2 : 3 : 4-*tetrahydro*iso*arsinoline* (I; R = Cl). By boiling this compound with pyridine, we attempted to remove hydrogen chloride and thus prepare 3 : 4-dihydro*iso*arsinoline, but there was no appreciable change. Roberts, Turner, and Bury (*loc. cit.*) record a similar failure to remove hydrogen chloride from 1-chloro-1 : 2 : 3 : 4-tetrahydroarsinoline by the action of diethylaniline. These failures are not unexpected for theoretical reasons. The tetrahydro-arsinolines and -*iso*arsinolines are presumably stabilised by "buckling" of the reduced arsine ring; the completely unreduced compounds—if they could be isolated—would undoubtedly be stabilised by resonance: the intermediate dihydro-compounds possess neither of these stabilising factors in full measure and hence are apparently highly unstable.

Many attempts were made to prepare 2-*phenyl*-1 : 2 : 3 : 4-*tetrahydro*iso*phosphinoline* by a Michaelis reaction between *o*-β-bromoethylbenzyl bromide, sodium, and phenyldichlorophosphine. The reaction in ether or in benzene, with or without ethyl acetate, failed to give any satisfactory distillate; the addition of antimony chloride as a catalyst (see Worrall, *J. Amer. Chem. Soc.*, 1930, **52**, 2933) was without apparent effect in our experiments. The reaction in ether using ethyl acetate did give a very small distillate, which evidently contained the required phosphinoline in an impure condition, since treatment with methyl iodide ultimately gave the pure crystalline *methiodide* (V).



(V.)

Similar attempts to prepare the corresponding *iso*stibinoline also failed, no definite product being obtained when phenyldi-iodostibine was used in the Michaelis condensation, in spite of wide variation in the conditions employed.

In view of the novel character of the tetrahydro*iso*arsinoline derivatives, they have been examined for possible therapeutic activity of various types. Dr. G. Brownlee, of the Wellcome Physiological Research Laboratories, has compared the compounds (I; R = Ph), (II), and (I; R = Me) and its methiodide with neoarsphenamine for their ability to protect from death mice infected with lethal inocula of *Trypanosoma equiperdum*: for this purpose, the substances were administered (*a*) suspended in gum acacia and given by mouth, (*b*) suspended in olive oil and injected intraperitoneally, (*c*) mixed in propylene glycol and similarly injected, (*d*) emulsified in Lanette wax and similarly injected. He has also compared (II) and the above methiodide in 0·2% aqueous solutions with neoarsphenamine for their ability to protect mice similarly infected, the compounds being administered by the tail-vein in doses of 0·16 mg./20 g. mouse, each test being carried out with a group of 10 mice. All tests gave negative results, and the compounds are apparently devoid of trypanocidal activity.

Dr. Ann Bishop, of the Molteno Institute of Parasitology, has also tested (II) and both methiodides [from (I; R = Ph or Me)] against infections of *Plasmodium relictum* induced in canaries by inoculation with infected blood: none of the compounds showed any significant antimalarial action.

Dr. E. Baldwin and Dr. E. Friedmann, of the Cambridge University Biochemical Laboratory, have also tested (II) in 0·05% aqueous solution on isolated pieces of pig *Ascaris*, but these were unaffected.

General considerations, based on active drugs which also contain heterocyclic systems, would indicate that the marked therapeutic inactivity of these *iso*arsinoline compounds is probably closely associated with the unsubstituted benzene ring, and that the introduction of amino-, chloro-, or ethoxy-groups into this ring might render the compounds physiologically active. The introduction of such groups into the original *o*-β-bromoethylbenzyl bromide is exceedingly difficult, in view of the various stages in its synthesis. Consequently, such groups would have to be inserted in the final tetrahydro*iso*arsinoline molecule, *e.g.*, by direct

nitration followed by replacement of the nitro-group by the desired substituent; but sufficient quantities of the *iso*arsinolines are not yet available for experiments on these lines.

Experimental.

2-*Phenyl*-1 : 2 : 3 : 4-*tetrahydro*iso*arsinoline* (I; R = Ph).—A solution of *o*-β-bromoethylbenzyl bromide (50 g.) in dry ether (750 c.c.) was prepared in a 1500-c.c. round-bottomed flask fitted with a 3-neck adaptor which carried a reflux water-condenser, a dropping funnel, and an inlet tube by which a current of nitrogen could be passed through the apparatus. Phenyldichloroarsine (40 g., 1 mol.) and fine sodium wire (35 g., 8·3 atoms) were added, the air displaced by dry nitrogen, and ethyl acetate (5 c.c.) finally added. The mixture was refluxed for 6 hours, ethyl acetate (5 c.c.) again added, and the refluxing continued for a further 3 hours, by which time the sodium wire had completely disintegrated and a heavy brown precipitate had formed in the brown solution. A slow current of nitrogen was passed into the flask throughout these operations. The reflux condenser was now replaced by a glass ∩-tube, one limb of which reached to the extreme bottom of the reaction flask, and the other led through a cork which securely closed the top of a sintered-glass filter-funnel, the stem of which was fitted in turn into the main neck of a 50-c.c. Claisen distilling flask. The latter carried a condenser fitted with a rotating series of receivers. It was thus possible by means of the compressed nitrogen (or carbon dioxide) to force the ethereal solution of the arsine slowly over into the sintered filter, and allow the filtrate to enter the distilling flask without exposure to oxidation; the ether was meanwhile gently distilled off, so that ultimately the distilling flask contained the whole of the crude arsine. The latter was now distilled under reduced pressure, and a main fraction, b. p. 156—162°/0·4 mm., collected: this on refractionation gave the pure iso*arsinoline* (I; R = Ph), b. p. 110—112°/0·01 mm., 128—130°/0·05 mm.; yield 12·8 g. (31·5%) (Found: C, 66·1; H, 5·6. $C_{15}H_{15}As$ requires C, 66·7; H, 5·6%).

Methiodide. A mixture of the *iso*arsinoline and excess of methyl iodide was refluxed for 30 mins., the unchanged iodide then allowed to evaporate spontaneously, and the dark oily residue dissolved in a small quantity of ethyl alcohol and set aside. Crystallisation started after several days and was increased by cautious addition of ether. The crystals were collected, and redissolved in alcohol, from which the pure colourless *methiodide* slowly separated, m. p. 136—137° [Found: C, 46·9; H, 4·6; ionic I, 30·2; I (Carius), 31·5. $C_{16}H_{18}IAs$ requires C, 46·6; H, 4·4; I, 30·8%]. The ionic iodine was estimated by dissolving the iodide (*ca.* 0·4 g.) in cold 95% alcohol (200 c.c.), adding 40% aqueous silver nitrate solution (1 c.c.) containing 2 or 3 drops of concentrated nitric acid, shaking the mixture for 2—3 mins., and then without delay collecting the silver iodide in a Gooch crucible in the usual manner.

Oxidation of (I; R = Ph).—(a) *With nitric acid.* The *iso*arsinoline (1 g.) was just covered with water, and concentrated nitric acid (2—3 c.c.) added; oxidation and heat evolution occurred, and the oily product rapidly solidified on cooling and stirring. Two recrystallisations from dilute aqueous nitric acid gave the colourless crystalline *hydroxy-nitrate* (II), m. p. 149—150° (Found: C, 51·7; H, 4·4; N, 4·1. $C_{15}H_{16}O_4NAs$ requires C, 51·6; H, 4·6; N, 4·0%).

(b) *With bromine.* A cooled solution of the *iso*arsinoline (1·32 g.) in chloroform (30 c.c.) was treated with a solution (7·5 c.c.) of bromine in chloroform (10·63 g./100 c.c.), *i.e.*, with 1 mol. of bromine. The bromine was at once absorbed, and the colourless solution was then shaken with excess of dilute aqueous ammonia. The aqueous layer was separated and evaporated to dryness, the residue extracted with chloroform, and the united chloroform extracts evaporated. The hygroscopic glassy residue could not be crystallised, but its identity as the arsine oxide or dihydroxide was shown by two experiments. (i) A solution of a portion of the residue in hot water was treated with nitric acid, and the above hydroxy-nitrate crystallised on cooling; after recrystallisation from dilute nitric acid, it had m. p. and mixed m. p. 149—150°. (ii) A solution of another portion in hot alcohol was saturated with hydrogen chloride; on cooling, colourless crystals of the iso*arsinoline dichloride* separated, which, after recrystallisation from alcoholic hydrochloric acid, had m. p. 147—149° (Found: Cl, 19·9. $C_{15}H_{15}Cl_2As$ requires Cl, 20·8%). This dichloride, when treated with water and nitric acid, again furnished the hydroxy-nitrate.

(c) *With chloramine-T.* Anhydrous chloramine-T (1·5 g.) was added to a solution of the *iso*arsinoline (1·7 g., 1 mol.) in absolute alcohol (30 c.c.), heat being immediately evolved and sodium chloride precipitated. The mixture was refluxed for 5 mins., filtered, and the cold filtrate evaporated in a desiccator at room temperature. The residual glass could not be recrystallised from any anhydrous solvent. On trituration with water, toluene-*p*-sulphonamide separated (m. p. after recrystallisation from benzene, 136—137°, mixed and unmixed): the presence of the arsine oxide or dihydroxide in the aqueous extract was shown by two experiments. (i) A portion of the extract, treated with nitric acid, gave the hydroxy-nitrate, m. p. 149—150° (Found: N, 4·0%). (ii) Another portion, when treated with saturated aqueous picric acid solution, gave an emulsion: addition of alcohol to the heated mixture then gave a clear solution, which on cooling deposited the *hydroxy-picrate*, m. p. 116—118° after recrystallisation from alcohol (Found: C, 48·7; H, 3·8; N, 8·4. $C_{21}H_{18}O_8N_3As$ requires C, 48·9; H, 3·5; N, 8·15%).

2-*Phenyl*-1 : 2 : 3 : 4-*tetrahydro*iso*arsinoline Sulphide.*—Hydrogen sulphide was passed for 30 mins. into a chilled solution of the arsine dibromide in chloroform prepared as above. The solution was filtered from traces of sulphur and evaporated on the water-bath; the oily residue, diluted with alcohol, readily gave the solid *sulphide*, which crystallised from alcohol in colourless needles, m. p. 124° (Found: C, 60·1; H, 5·3; S, 10·7; *M*, ebullioscopic in 1·23% alcoholic solution, 310. $C_{15}H_{15}SAs$ requires C, 59·6; H, 5·0; S, 10·6%; *M*, 304).

Methyldichloroarsine.—We are indebted to Dr. A. F. Crowther for the following modification of Uhlinger and Cook's preparation (*J. Ind. Eng. Chem.*, 1919, **11**, 105). Sodium hydroxide (128 g., 7·6 mols.) and arsenious oxide (84 g., 1 mol.) were dissolved in turn in water (375 c.c.), and the solution stirred mechanically and cooled externally in ice-water whilst methyl sulphate (128 g., 97 c.c., 2·4 mols.) was slowly added. When addition was complete, the solution was heated at 85° for 2·5 hours with continuous stirring. It was then cooled (ice-water), saturated with sulphur dioxide, and dilute sulphuric acid (200 c.c., 1 vol. acid : 9 vols. water) added to decompose the sodium sulphite. The mixture was heated on a boiling water-bath under reflux whilst being saturated with hydrogen chloride; an oil and some solid matter separated. The total product was "steam distilled" in the vapour of constant-boiling hydrochloric acid. The heavy layer of methyldichloroarsine which separated in the distillate was collected, dried (sodium sulphate), and distilled; yield 51 g. (38% of the theoretical), b. p. 133—135°.

2-*Methyl*-1 : 2 : 3 : 4-*tetrahydro*iso*arsinoline* (I; R = Me).—This was prepared as for the phenyl analogue, but by using methyldichloroarsine (29 g., 1 mol.) in place of the phenyl compound. The lower b. p. of the final product allowed distillation at water-pump pressure. The *methyl*iso*arsinoline* was obtained as a liquid, b. p. 130°/16 mm. (6 g., 16% of theoretical), which on refractionation had b. p. 131°/18 mm. (Found: C, 57·4; H, 6·4. $C_{10}H_{13}As$ requires C, 57·7; H, 6·3%). This *iso*arsinoline, when dissolved in excess of cold methyl iodide, readily deposited white crystals. The excess of iodide was allowed to evaporate, and the solid residue recrystallised from alcohol; the *methiodide* was obtained in colourless crystals, m. p. 179—181° [Found: C, 37·9; H, 4·7; ionic I 36·3; I (Carius), 36·5. $C_{11}H_{16}IAs$ requires C, 37·7; H, 4·6; I, 36·3%. The ionic iodine was estimated precisely as above]. This methiodide in alcoholic solution, treated with picric acid, readily gave the *methopicrate*, m. p. 163—164° after crystallisation from alcohol (Found: C, 45·5; H, 4·35; N, 9·7. $C_{17}H_{18}O_7N_3As$ requires C, 45·2; H, 4·0; N, 9·3%).

Oxidation of (I; R = Me).—(a) *With nitric acid.* Conditions precisely similar to those used for (I; R = Ph) afforded a clear aqueous solution and no crystalline oxide or nitrate could be isolated. The solution was neutralised with sodium hydroxide and on treatment with picric acid solution deposited the *hydroxy-picrate*, which after crystallisation from alcohol had m. p. 164—165·5°, with softening at 160° (Found: C, 42·6; H, 3·7; N, 9·3. $C_{16}H_{16}O_8N_3As$ requires C, 42·4; H, 3·6; N, 9·3%).

(b) *With chloramine-T.* Anhydrous chloramine-T (0·45 g.) was added to a solution of the *iso*arsinoline (0·41 g., 1 mol.) in absolute alcohol (20 c.c.), and the mixture refluxed for 5 mins. The solution, filtered from sodium chloride, was evaporated in a vacuum at room temperature, but the semi-solid, sticky residue could not be crystallised. When treated with cold water, it immediately deposited toluene-*p*-sulphonamide, m. p. and mixed m. p. 136—137°; a portion of the filtrate, treated with picric acid, gave the above hydroxy-picrate; the remainder was concentrated in a vacuum and after removal of a further crop of sulphonamide gave ultimately an oil, which, although presumably the arsine oxide or dihydroxide, could not be obtained crystalline.

A chloroform solution of the *iso*arsinoline (I; R = Me), treated with bromine (1 mol.), rapidly became again colourless. Saturation with hydrogen sulphide, followed by filtration and evaporation of the solvent, gave a viscous oil which slowly solidified to a glass; this was presumably the arsine sulphide, but it could not be crystallised.

2-*Methyl*-1 : 2 : 3 : 4-*tetrahydro*iso*arsinoline Dichloride.*—A standard solution of chlorine (1 mol.) in carbon tetrachloride was slowly added to the *iso*arsinoline (I; R = Me) in the same solvent at 0°; a white precipitate of the *dichloride* rapidly separated, and, after removal of the solvent in a vacuum, was collected, washed with petrol, and dried (Found: Cl, 23·65. $C_{10}H_{13}Cl_2As$ requires Cl, 25·45%). A portion of this dichloride, dissolved in water and treated with picric acid, gave the above hydroxy-picrate, m. p. and mixed m. p. 165—166°. The remainder was gently heated at 15 mm. pressure; fusion occurred at *ca.* 120°, followed by vigorous effervescence, the pressure rising to 35 mm. The temperature was maintained at 130—140° until decomposition was complete and the pressure again 15 mm.; fractional distillation of the liquid residue then gave 2-*chloro*-1 : 2 : 3 : 4-*tetrahydro*iso*arsinoline* (I; R = Cl) as a colourless liquid, b. p. 157°/14 mm. (Found: C, 47·6; H, 4·6; Cl, 15·2. $C_9H_{10}ClAs$ requires C, 47·3; H, 4·4; Cl, 15·5%). When a solution of this compound in excess of dry pyridine was boiled for several hours and then fractionally distilled, much of it was recovered unchanged. When the pyridine solution after prolonged boiling was poured into water, a small quantity of solid was obtained; this appeared to be the arsonic acid, formed by hydrolysis and oxidation after the boiling with pyridine. These results, and scarcity of material, caused abandonment of further attempts to prepare 3 : 4-dihydro*iso*arsinoline.

2-*Phenyl*-1 : 2 : 3 : 4-*tetrahydro*iso*phosphinoline Methiodide* (V).—Of the many attempts to prepare the parent *iso*phosphinoline, only the following gave any positive result. A mixture of *o*-β-bromoethylbenzyl bromide (50 g.), phenyldichlorophosphine (32 g., 1 mol.), ether (750 c.c.), sodium wire (40 g., 9·7 atoms), and ethyl acetate (5 c.c.) was refluxed in a nitrogen atmosphere for 12 hours, a further quantity of ethyl acetate (5 c.c.) being added after the first 6 hours. The product was then worked up precisely as described for (I; R = Ph). Final distillation of the residue after removal of the solvent first gave two very small fractions, b. p. 52°/14 mm. and 102°/14 mm.; further distillation of the residue at lower pressure gave a small indefinite fraction, b. p. 130—160°/0·2 mm. This on further refractionation gave a minute fraction which was apparently the crude 2-*phenyl*-1 : 2 : 3 : 4-*tetrahydro*iso*phosphinoline* (Found: C, 83·8; H, 8·0. $C_{15}H_{15}P$ requires C, 79·7; H, 6·6%). The fraction of b. p. 130—160°/0·2 mm. did, however, react vigorously with methyl iodide, and the oily product was ultimately crystallised from alcohol–ether; the pure *methiodide* (V) was thus obtained in colourless crystals, m. p. 116—118° (Found: C, 51·9; H, 4·8. $C_{16}H_{18}IP$ requires C, 52·2; H, 4·9%).

We are greatly indebted to Drs. Brownlee, Bishop, Baldwin, and Friedmann for the therapeutic tests which they have kindly conducted.

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