667. *The Structure and Properties of Certain Polycyclic Indolo- and Quinolino-derivatives. Part VIII.* Derivatives of* 1 : 2 : 3 : 4-*Tetrahydro*-4-*oxoarsinoline and of* 1 : 6-*Dioxoarsulolidine.*

By Frederick G. Mann and A. J. Wilkinson.

1 : 2 : 3 : 4-Tetrahydro-7-methoxy-1-methyl-4-oxoarsinoline has been (*a*) converted *via* its phenylhydrazone into the indolo(3′ : 2′-3 : 4)arsinoline, and (*b*) converted by the Friedlander and the Pfitzinger reaction into the quinolino(3′ : 2′-3 : 4)arsinoline and its 4′-carboxylic acid respectively. 7-Methoxy-1 : 6-dioxoarsulolidine has been similarly converted into the indolo(2′ : 3′-1 : 2)arsuloline and the quinolino(2′ : 3′-1 : 2)arsuloline derivatives.

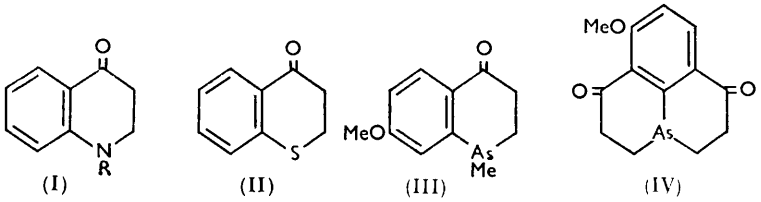
The properties of these compounds, particularly in comparison with those of their nitrogen analogues, are discussed.

Earlier Parts of this series contain a discussion of the structure of the indolo- and quinolino-derivatives of, in particular, various substituted 1 : 2 : 3 : 4-tetrahydro-4-oxoquinolines (I), where the substituent R has been a single group, or a portion of another ring. The main points arising in the structures of these derivatives may be briefly summarised: Indolisation of the phenylhydrazone of the oxo-amine (I) [1,2,3] gives a coloured ψ-indole, which readily adds acids to give colourless salts, in which the proton and the positive charge have been accepted by the indolo- and the quinolino-nitrogen atom respectively.

* Part VII, *J.*, 1955, 393.

[1] Mann, *J.*, 1949, 2816.
[2] Mann and Smith, *J.*, 1951, 1898.
[3] Braunholtz and Mann, *J.*, 1955, 381.

The application of the Pfitzinger reaction to the oxo-amine (I) has given a deep red 4′-carboxyquinolino-derivative, the colour of which is due to the formation of a zwitterion which has a number of canonical forms, one having the positive charge on the original quinolino-nitrogen atom. This zwitterion, on being heated, undergoes decarboxylation to a cream-yellow amine, which in hot acids undergoes the " allylic " transformation to to give an isomer: both isomers are oxidised readily in solution to give the cyclic acid amide in which the 2-methylene group in the quinoline (I) has become a $>CO$ group.



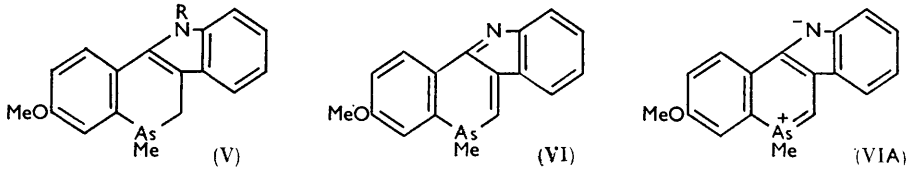
To determine whether the above properties, and particularly the high degree of resonance shown by the zwitterion, were determined specifically by the nitrogen group in (I), Kiang and Mann [4] repeated these reactions with 4-oxothiochroman (II), in which the sulphur atom in the corresponding derivatives could theoretically accept the positive charge previously carried by the nitrogen atom in (I). It was found that the compound (II) gave a normal indolo-derivative, and in the Pfitzinger reaction gave a 4′-carboxy-quinolino-derivative which again formed a zwitterion but on decarboxylation gave an amine which did not undergo atmospheric oxidation at the 2-methylene group.

The synthesis of 1 : 2 : 3 : 4-tetrahydro-7-methoxy-1-methyl-4-oxoarsinoline [5] (III) has now, however, provided a compound much more strictly analogous to the corresponding oxo-quinoline (I; R = Me) [3] than was the 4-oxothiochroman (II), and we have applied the above reactions both to this oxo-arsine (III) and to 7-methoxy-1 : 6-dioxoarsulolidine [5] (IV), which is the arsenic analogue of 1 : 6-dioxojulolidine [6] previously investigated.

Indolisation of the phenylhydrazone of the oxo-arsine (III) to give cream-coloured 1 : 2-dihydro-7-methoxy-1-methylindolo(3′ : 2′-3 : 4)arsinoline (V; R = H) required heating with zinc chloride and acetic acid, conditions much more vigorous than those necessary [3] with the phenylhydrazone of the quinoline (I; R = Me). On the other hand, indolisation of the methylphenylhydrazone and the diphenylhydrazone of the arsine (III) to give the colourless 1 : 1′-dimethyl and 1-methyl-1′-phenyl derivatives (V; R = Me and Ph respectively) proceeded very readily in hot ethanol–acetic acid.

The fact that the product from the phenylhydrazone is the true indole (V; R = H) and not the ψ-indole (VI) is clearly shown by its lack of colour, its non-basic character, and by its infrared spectrum, which shows a marked band at 2·96 μ due to the $>NH$ group.

It is, therefore, noteworthy that, although all the phenylhydrazones of the 4-oxo-quinolines of type (I) have, with one exception,[6] given ψ-indoloquinolines, this process does not occur in the corresponding indoloarsinolines (V). One potent factor in this

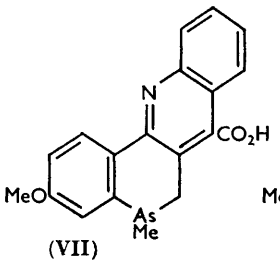


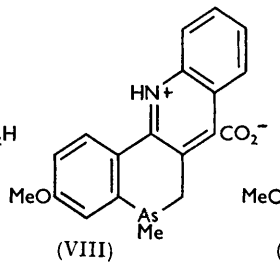
difference is that the yellow colour, and the avidity for union with acids and alkyl halides, shown by the ψ-indoloquinolines indicate a considerable degree of charge separation between the two nitrogen atoms, of which the counterpart in the ψ-indoloarsindole (VI)

[4] Kiang and Mann, *J.*, 1951, 1909.
[5] Mann and Wilkinson, preceding paper.
[6] Braunholtz and Mann, *J.*, 1955, 393.

would be (VIA) : salt formation with acids and alkyl halides then involves solely the addition of a proton or an alkyl group to the negative nitrogen in (VIA). But the disposition of the arsenic valencies in the ring system in (VIA)—and all the properties such a disposition would imply—are very rarely found (see preceding paper [5]) and presumably either are normally physically impossible or entail great instability, and hence the stable indoloarsinoline (V; R = H) is formed.

In the application of the Pfitzinger reaction, the oxo-arsine (III) and isatin in aqueous-ethanolic potassium hydroxide were boiled for 48 hours. Addition of acetic acid deposited


(VII)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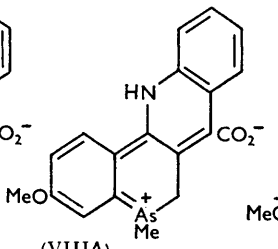
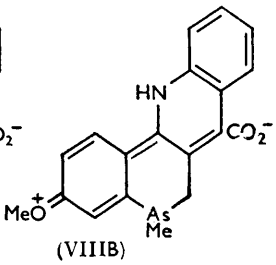
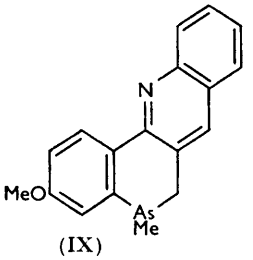

(VIIIA)


(VIIIB)

the yellow 1 : 2-dihydro-7-methoxyquinolino(3′ : 2′-3 : 4)arsinoline-4′-carboxylic acid (VII), which was insoluble in the usual solvents and could not be satisfactorily purified by recrystallisation or reprecipitation. In an attempted decarboxylation, the acid was heated in a high vacuum, a process, however, which yielded the pure unchanged crystalline acid. This distilled acid proved surprisingly to be the zwitterion (VIII), for its infrared spectrum showed no band in the 3 μ region, where a free $>$NH group would have become apparent, but showed a broad ill-defined band at 4·9 μ, attributed to the $:NH^+$ group, and two bands at 6·15 and 6·24 μ characteristic of the CO_2^- ion in amino-acids having the zwitterion structure.[3, 6] Such volatilisation without decomposition of amino-acids having this structure is rare : it is possible that the zwitterion (VIII) reverts to the covalent state (VII) in the vapour phase, and returns to the polar state (VIII) on solidification.

The fine structure of this acid (VIII) is of considerable interest. Apart from the methoxyl group, it is strictly analogous to the deep red zwitterion formed by 1 : 2-dihydro-1-methylquinolino(3′ : 2′-3 : 4)quinoline-4′-carboxylic acid,[3] the intense colour of which is undoubtedly partly caused by a marked contribution by the canonical form having a positive charge on the methylated amine group, but in the quinolinoarsinoline (VIII) the corresponding form (VIIIA) almost certainly does not exist. On the other hand, the canonical form (VIIIB) has necessarily no counterpart in our nitrogen analogues which do not contain a methoxyl group.

The acid (VIII) dissolves in aqueous sodium and potassium hydroxide to give colourless solutions, the resonance shown by the zwitterion being now absent. It also gives an unstable yellow hydrochloride.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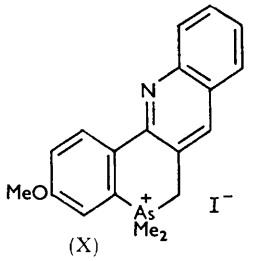
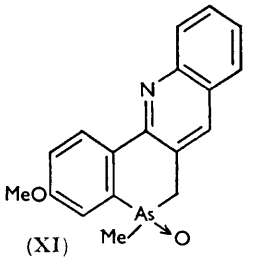
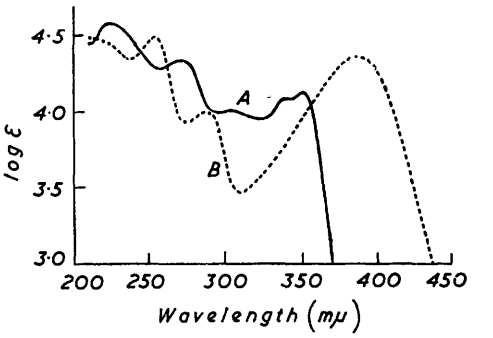

(X)


(XI)

Since the acid (VIII), unlike its nitrogen analogue, does not undergo decarboxylation when heated in a vacuum, the corresponding base, 1 : 2-dihydro-7-methoxy-1-methylquinolino(3′ : 2′-3 : 4)arsinoline (IX), was prepared by direct condensation of the oxo-arsine (III) and *o*-aminobenzaldehyde in an alkaline medium at room temperature. This

colourless base readily forms, at room temperature, an almost colourless methiodide, which must have the structure (X), for the nitrogen atom in these fused-ring systems usually requires vigorous conditions for quaternisation. The base (IX) formed a yellow hydrochloride, and the methiodide (X) formed a yellow methiodide hydriodide. These facts indicate strongly that, in the acid (VIII) and in derivatives of the base (IX), the yellow colour is directly associated with protonation of the nitrogen atom and, although the evidence is inconclusive, the colour may be due to resonance contributed by canonical forms of type (VIII) and (VIIIB). The Figure shows the ultraviolet absorption curves of the base (IX) in (*A*) ethanol, and (*B*) ethanol–hydrochloric acid. The curve (*B*) is similar in type to (*A*) with the main features now more prominent, and in particular with a general shift to longer wavelengths, the broad band at 385 mμ being responsible for the yellow colour. For comparable curves for the nitrogen analogue, 1 : 2-dihydro-1-methylquinoline(3′ : 2′-3 : 4)quinoline, see Braunholtz and Mann.[3]

The base (IX), unlike its nitrogen analogue, gave no indication of allylic isomerism when treated with hot acids. This is in accordance with the mechanism of this process



1 : 2-*Dihydro*-7-*methoxy*-1-*methylquinolino*(3′ : 2′-3 : 4)*arsinoline* (IX) *in* (*A*) *ethanol*, (*B*) *in ethanol diluted with an equal volume of* N/10-*hydrochloric acid.*

suggested by Braunholtz and Mann,[3] the first stage of which is the migration of a proton from the 1′-nitrogen atom to a basic hetero-atom in position 1 : in view of the neutral character of tertiary arsines,[7] this stage is clearly not possible in salts of the base (IX). Further, the base did not undergo atmospheric oxidation in organic solvents, although when treated with potassium permanganate it gave the expected arsine oxide (XI).

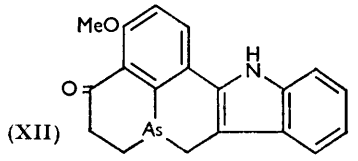
The bisphenylhydrazone of 7-methoxy-1 : 6-dioxoarsulolidine (IV), when heated in acetic acid containing zinc chloride, gave 7-methoxy-6-oxoindolo(2′ : 3′-1 : 2)arsuloline (XII), one of the hydrazone groups having undergone indolisation, and the other hydrolysis with regeneration of the oxo-grouping. This result is not unexpected, for Ittyerah and Mann [8] have shown that a 7-methyl group in 1 : 6-dioxojulolidine exerts a powerful steric influence on the neighbouring 6-oxo-group, an influence which, whilst allowing phenylhydrazone formation, suppresses several other reactions such as condensation with malononitrile. Further, the bisphenylhydrazone of *cyclo*hexane-1 : 2-dione under various conditions also undergoes indolisation of one hydrazone residue and hydrolysis of the other residue, with the formation of 1 : 2 : 3 : 4-tetrahydro-1-oxocarbazole.[9]

The structure of the compound (XII) is confirmed by its infrared spectrum which shows a band at 3·03 μ, attributed to the >NH group, and one at 6·02 μ, attributed to the >CO group. In this compound, therefore, no question of ψ-indole formation arises, undoubtedly for the same reasons as those previously discussed regarding the compound (V; R = H).

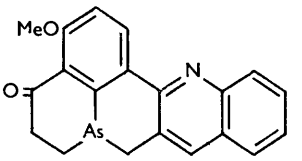
Application of the Pfitzinger reaction to the dioxoarsine (IV) gave only tarry products. The milder conditions of the Friedlander reaction, using *o*-aminobenzaldehyde, gave

[7] Davies and Addis, *J.*, 1937, 1622.
[8] Ittyerah and Mann, *J.*, 1956, 3179.
[9] Plancher, Cecchetti, and Ghigi, *Gazzetta*, 1929, **59**, 346; Bloink and Pausacker, *J.*, 1950, 1328.

7-methoxy-6-oxoquinolino(2′ : 3′-1 : 2)arsuloline (XIII), which after distillation formed a glass which could not be crystallised but gave a crystalline picrate. It is noteworthy that, in this reaction also, in spite of the use of an excess of the aldehyde, only one of the



(XII)



(XIII)

oxomethylene groups has undergone condensation, the other being again obstructed by the methoxyl group. Lack of material precluded further investigation of the properties of the compound (XIII).

Experimental

o-Aminobenzaldehyde.—The reported instability of this compound has been exaggerated. The following method, which is essentially a simplification of the recorded preparation,[10] gave a product which could be stored unchanged in a refrigerator for several weeks. A 3-necked flask of 1 l. capacity, fitted for stirring and rapid distillation of its contents, was placed in a water-bath at 90°, and water (175 c.c.), powdered ferrous sulphate heptahydrate (105 g.), concentrated hydrochloric acid (0·5 c.c.) and *o*-nitrobenzaldehyde (6 g.) were added in that order. Concentrated aqueous ammonia (25 c.c.) was added in one portion to the vigorously stirred mixture, and then three further portions, each of 10 c.c., at 2 min. intervals. After 8 min. in all, the mixture was steam-distilled as rapidly as possible, the receiver being cooled in ice-water. The distillate (500 c.c.), collected in *ca.* 20 min., was treated with powdered sodium chloride (140 g.) and stirred for 1 hr. at 5°, and the almost colourless *o*-aminobenzaldehyde (2·65 g., 55%) which had separated was collected, washed with ice-cold water, and dried at room temperature and atmospheric pressure.

1 : 2-*Dihydro*-7-*methoxy*-1-*methylindolo*(3′ : 2′-3 : 4)*arsinoline* (V; R = H).—A solution of the phenylhydrazone (0·5 g.) of the oxo-arsine (III) in glacial acetic acid (5 c.c.) containing pulverised zinc chloride (0·5 g.) was boiled under reflux in nitrogen for 15 min., and water was then added dropwise to the hot solution until a permanent turbidity was produced. The solution, when allowed to cool spontaneously, gave a deposit, partly tar and partly crystalline, which when recrystallised from aqueous ethanol gave the very pale cream-coloured *indoloarsinoline* (V; R = H), m. p. 137—139° (Found : C, 62·4; H, 5·3; N, 4·6. $C_{17}H_{16}ONAs$ requires C, 62·8; H, 5·0; N, 4·3%).

Only tarry products were isolated by boiling solutions of the phenylhydrazone in ethanolic hydrogen chloride, pure acetic acid, or acetic acid either saturated with hydrogen chloride or containing 10% of concentrated hydrochloric acid. The hydrazone was recovered unchanged after being heated with dilute sulphuric acid at 100° for 30 min.

1 : 2-*Dihydro*-7-*methoxy*-1 : 1′-*dimethylindolo*(3′ : 2′-3 : 4)*arsinoline* (V; R = Me).—A solution of the oxo-arsine (0·5 g.) and methylphenylhydrazine (0·26 g., 1·1 mol.) in ethanol (5 c.c.) containing acetic acid (0·5 c.c.) was boiled under nitrogen for 8 hr. The pale yellow precipitate (0·32 g., 48%) which separated on cooling, when recrystallised from ethanol, afforded the colourless *indoloarsinoline*, m. p. 115° (Found : C, 63·7; H, 5·05; N, 4·35. $C_{18}H_{18}ONAs$ requires C, 63·7; H, 5·3; N, 4·1%).

The 1-*methyl*-1′-*phenylindoloarsinoline* (V; R = Ph) was similarly prepared in 30% yield by using *as.*-diphenylhydrazine, and formed colourless plates, m. p. 157°, from ethanol (Found : C, 69·0; H, 5·2; N, 3·6. $C_{23}H_{20}ONAs$ requires C, 68·8; H, 5·0; N, 3·5%).

1 : 2-*Dihydro*-7-*methoxy*-1-*methylquinolino*(3′ : 2′-3 : 4)*arsinoline*-4′-*carboxylic Acid* (VII).—A solution of the oxo-arsine (III) (0·50 g.), isatin (0·30 g., 1·05 mol.) and potassium hydroxide (0·40 g.) in ethanol (4 c.c.) and water (1 c.c.) was boiled under reflux in nitrogen for 48 hr. The cold solution was poured into an excess of 10% aqueous acetic acid, giving a yellow precipitate (0·40 g., 53%) which was collected, washed with water, and dried. When it was heated in a glass tube at 250°/0·0005 mm., a yellow glass condensed on the cold portion of the tube. This glass crystallised when subsequently rubbed with boiling ethanol, in which it was insoluble, and

[10] Smith and Opie, *Org. Synth.*, 1948, **28**, 11.

afforded the pure yellow *acid* (VII), m. p. 220—250° (decomp.) after drying at 60°/0·1 mm. for 6 hr. (Found: C, 59·7; H, 4·5; N, 3·6. $C_{19}H_{16}O_3NAs$ requires C, 59·9; H, 4·2; N, 3·7%).

When the period of boiling was reduced to 24 hr., the yield was substantially reduced.

The acid appeared to be completely stable in air. When added to warm concentrated hydrochloric acid, it dissolved to give a yellow solution, from which the yellow hydrochloride rapidly separated. This salt was too unstable to be purified, and showed a m. p. identical with that of the acid, undoubtedly because of complete dissociation during heating.

When a mixture of equal weights of the acid and freshly powdered barium hydroxide (or soda-lime) was heated at 250°/0·001 mm., only a trace of a yellow glass condensed in the tube, and no evidence of decarboxylation could be obtained.

1 : 2-*Dihydro*-7-*methoxy*-1-*methylquinolino*(3′ : 2′-3 : 4)*arsinoline* (IX).—A solution of the oxo-arsine (III) (0·25 g.) and *o*-aminobenzaldehyde (0·13 g., 1·1 mols.) in ethanol (10 c.c.) was treated with 10% aqueous sodium hydroxide (0·5 c.c.) and set aside at room temperature for 3 days. It was then saturated with hydrogen chloride and taken to dryness on a steam-bath. The residue was dissolved in hot water (10 c.c.) and an excess of concentrated aqueous ammonia added, giving a gummy precipitate. In initial experiments, this precipitate, when collected, washed with water and dried, was heated at 180°/0·002 mm., giving a yellow distillate which on cooling formed a glass. Recrystallisation from warm ethanol (2—3 c.c.) yielded the colourless *arsinoline* (IX) (0·13 g., 39%), m. p. 136° (Found: C, 64·0; H, 4·8; N, 4·2. $C_{18}H_{16}ONAs$ requires C, 64·1; H, 4·8; N, 4·2%). In later preparations, when the crystalline product was available, the precipitate was recrystallised directly from ethanol, the solution on cooling being seeded and scratched to initiate the crystallisation.

A solution of the arsinoline (IX) (50 mg.) in ethanol (2 c.c.), when saturated with hydrogen chloride and then diluted with ether, deposited the yellow *hydrochloride*, which was purified by reprecipitation from ethanolic solution with ether, giving fine yellow crystals, m. p. 206° (decomp.), of the hydrated salt (Found: C, 54·4; H, 5·0; N, 3·45. $C_{18}H_{16}ONAs,HCl,1{\cdot}25H_2O$ requires C, 54·6; H, 5·0; N, 3·5%).

The yellow very insoluble *picrate*, m. p. 192°, was prepared in ethanol, and washed with hot ethanol (Found: C, 50·3; H, 3·1; N, 10·7. $C_{18}H_{16}ONAs,C_6H_3O_7N_3$ requires C, 50·9; H, 3·4; N, 9·9%).

A solution of the arsinoline (IX) in cold methyl iodide, when set aside overnight, deposited the almost colourless *methiodide* (X), m. p. 225° (decomp.) after washing with methyl iodide and ether (Found: C, 47·95; H, 3·9; N, 3·1. $C_{19}H_{19}ONIAs$ requires C, 47·6; H, 4·0; N, 2·9%): it could not be satisfactorily recrystallised.

Pure hydriodic acid (of constant b. p.) was added dropwise in slight excess to a cold methanolic solution of the methiodide (X), which immediately developed a deep yellow colour. The solution, when filtered into much ether, deposited the yellow microcrystalline *methiodide hydriodide hydrate*, which was collected, washed with ether, and dried in a vacuum: it had an indefinite m. p., becoming completely molten by 225° (Found: C, 34·5; H, 3·8; N, 2·1. $C_{19}H_{19}ONIAs,HI,3H_2O$ requires C, 34·5; H, 4·0; N, 2·1%). Dehydration of this salt was not attempted, in case dissociation of the hydriodide also occurred.

A solution of the arsinoline (IX) (50 mg.) in benzene (2 c.c.) was exposed to the air for 3 days, evaporation losses being made good from time to time. The solution was then evaporated to dryness, but the brown semicrystalline residue on recrystallisation from ethanol afforded only the unchanged arsinoline (27 mg.). This stability to oxidation is in marked contrast to the ready oxidation in these conditions which quinolino(2′ : 3′-1 : 2)juloline and its isomer,[2] and also 1 : 2-dihydro-1-methylquinolino(3′ : 2′-3 : 4)quinoline (I; R = Me) and its isomer,[3] undergo.

A saturated solution of potassium permanganate in acetone was added dropwise to a solution of the arsinoline (IX) (0·15 g.) in acetone (15 c.c.) until the latter retained a faint purple colour. The solution was filtered from manganese dioxide, which was extracted with boiling acetone (20 c.c.). The combined acetone extracts when evaporated gave a pale brown residue, a solution of which in hot ethanol was filtered and again evaporated. The colourless needles of the *arsinoline oxide* (XI) thus obtained had m. p. 232° (decomp.) after recrystallisation from ethanol and drying in a vacuum (Found: C, 57·9; H, 5·3; N, 4·1. $C_{18}H_{16}O_2NAs,H_2O$ requires C, 58·2; H, 4·9; N, 3·8%). The infrared absorption showed (*a*) no carbonyl absorption in the 6 μ region, hence the oxidation has not produced the ·AsMe·CO· derivative, comparable to the nitrogen analogue, (*b*) broad absorption in the 2·88—2·96 μ region, indicating the presence of

water, and the compound is, therefore, not the $\vdots As(OH)_2$ derivative isomeric with the hydrated oxide, for, in addition, the As(OH) group gives broad absorption above 3·3 μ.

The oxide in ethanol gave a *picrate*, yellow crystals, m. p. 192° (decomp.) after crystallisation from much ethanol (Found: C, 49·1; H, 3·3; N, 9·4. $C_{18}H_{16}O_2NAs,C_6H_3O_7N_3$ requires C, 49·5; H, 3·3; N, 9·6%). It is uncertain whether this picrate formation has occurred at the arsine oxide group or the nitrogen atom, but the former is the more likely.

7-Methoxy-6-oxoindolo(2′ : 3′-1 : 2)arsuloline (XII).—A solution of the bisphenylhydrazone (0·25 g.) of 7-methoxy-1 : 6-dioxoarsulolidine (IV) in glacial acetic acid (2·5 c.c.) containing zinc chloride (0·25 g.) was boiled under reflux in nitrogen for 3 hr., and water then added to the hot stirred solution until a permanent turbidity was obtained. The solution on cooling gave a gummy deposit, which on recrystallisation from aqueous ethanol afforded the almost colourless *indoloarsuloline* (XII), m. p. 232° (Found: C, 62·5; H, 4·9; N, 4·0. $C_{19}H_{16}O_2NAs$ requires C, 62·9; H, 4·4; N, 3·8%).

7-Methoxy-6-oxoquinolino(2′ : 3′-1 : 2)arsuloline (XIII).—A solution of the dioxo-arsine (IV) (0·20 g.) and *o*-aminobenzaldehyde (0·18 g., 2·2 mols.) in ethanol (20 c.c.) and 10% aqueous sodium hydroxide (0·7 c.c.) was set aside for 5 days, and then saturated with hydrogen chloride and evaporated to dryness. The residue, when stirred with hot dilute aqueous ammonia, gave an insoluble gum, which was collected, and dried. When heated at 200°/0·003 mm., it gave an orange distillate of the arsuloline (XIII), which on cooling formed a glass. This glass could not be induced to crystallise, and it was therefore treated with picric acid, both in ethanolic solution. The precipitated crystalline *picrate* of the arsuloline (XIII), when recrystallised from ethanol, formed the monoethanolate, yellow plates, m. p. 164—166° (Found: C, 51·35; H, 3·75; N, 8·7. $C_{20}H_{16}O_2NAs\ C_6H_3O_7N_3,C_2H_6O$ requires C, 51·55; H, 3·9; N, 8·6%).

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