CCCLVII.—*The Amino-1-methylbenzoxazoles and their Conversion into the Arsinic Acids of* o-*Aminophenol.*

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5-AMINO-1-METHYLBENZOXAZOLE has been described by Newbery and Phillips (J., 1928, 122). The three other possible amino-1-methylbenzoxazoles have now been prepared and their conversion into the corresponding *o*-aminophenylarsinic acids has been investigated.

The benzoxazoles in general are very unstable to hydrolytic agents and the methods employed for the formation of the benz-*iso*oxazine system (Newbery, Phillips, and Stickings, J., 1928, 3051) or for the benziminazole system (Phillips, J., 1928, 172, 2393, 3134; 1929, 2820) were generally inapplicable. *o*-Acetamidophenol gave a small quantity of 1-methylbenzoxazole on treatment with hot dilute alkali or mineral acid but was mainly converted into *o*-aminophenol, and under similar conditions acyl and diacyl nitro-*o*-aminophenols were completely hydrolysed.

Good yields of the *nitro-1-methylbenzoxazoles* were, however, obtained by distillation under reduced pressure of the nitroacetamido- or, better, of the nitrodiacetamido-phenols (compare F.P. 575663). In the same way, small yields of 4-acetamido-1-methylbenzoxazole were obtained from 4-amino-2-acetamido- and 2 : 4-diacetamido-phenol. The amino-derivatives are, however, best prepared by reduction of the nitro-compounds.

The nitro-1-methylbenzoxazoles are very unstable to cold mineral acids or cold caustic alkalis; the 5- and the 7-nitro-derivative are hydrolysed even by hot water. The 4- and the 6-nitro-compound, however, can be crystallised from hot water containing a little acetic acid. The amino-compounds are more stable to hot water, only the 4-amino-derivative being appreciably decomposed. They

are all unstable to warm acids and alkalis. The *acetamido*-derivatives are more stable to hydrolytic action than are the amino-compounds, but are decomposed readily by warm mineral acids. In all cases the products of hydrolysis are derivatives of *o*-aminophenol:

$$R{\cdot}C_6H_3\!<\!\overset{N}{O}\!>\!CMe \longrightarrow R{\cdot}C_6H_3(NH_2){\cdot}OH.$$

The diazo-compounds of the amino-1-methylbenzoxazoles couple readily with alkaline resorcinol, giving deep red dyes; only from 3-*amino*-1-*methylbenzoxazole* is a similar product obtained by means of alkaline β-naphthol.

The instability of the benzoxazole system is well instanced by the fact that application of the Bart reaction (even in neutral solution) to the amino-compounds gave in every case the corresponding acetamidohydroxyphenylarsinic acid, no trace of the cyclic arsinic acid being found:

$$NH_2{\cdot}C_6H_3\!<\!\overset{N}{O}\!>\!CMe \longrightarrow AsO_3H_2{\cdot}C_6H_3(OH){\cdot}NHAc.$$

The analogous 5(or 6)-amino-2-methylbenziminazole gave, on similar treatment, 2-methylbenziminazole-5(or 6)-arsinic acid (Phillips, J., 1928, 3136).

The nitration of 1-methylbenzoxazole is known to give a difficultly separable mixture of the 4- and the 5-nitro-derivative in the proportion of 1 : 4 (Hewitt and King, J., 1926, 822; Newbery and Phillips, *loc. cit.*). The solubilities of the corresponding amino-compounds have now been examined and it has been shown that in the reduction of the crude nitration product as described by Newbery and the author (*loc. cit.*) only the 5-isomeride separates and that the product of the Bart reaction on this compound was a single substance, 4-acetamido-3-hydroxyphenylarsinic acid.

4-Acetamido-3-hydroxyphenylarsinic acid has also been obtained by application of the Bart reaction to 5-amino-2-acetamidophenol; the *urethane* of 4-amino-3-hydroxyphenylarsinic acid was obtained similarly from 5-*amino*-2-*carbethoxyaminophenol* (compare Carpmael, B.P. 278,789 of 1927, which anticipated this work).

Although nitrohydroxyphenylarsinic acids are in general best obtained from nitroaminophenols by application of the Bart reaction, the method fails with 6-nitro-3-aminophenol. The best method for preparing 4-nitro (and 4-amino)-3-hydroxyphenylarsinic acid would seem to be that of Balaban (J., 1928, 809).

EXPERIMENTAL.

1-Methylbenzoxazole was obtained in 15% yield by treatment of *o*-acetamidophenol (5 g.) with 5*N*-hydrochloric acid (25 c.c.) for

40 minutes at 90°. Addition of sodium acetate and ether-extraction of the filtrate from the precipitated *o*-aminophenol gave the cyclic compound. It was similarly obtained by the action of 2*N*-sodium hydroxide on the acetamidophenol for 1 hour at 90°.

1-*Methylbenzoxazole hydrochloride* was obtained in quantitative yield by dissolving the base in 1 part of acetic anhydride and adding ethereal hydrogen chloride in excess. It formed white prisms, readily hydrolysed by cold water (Found : N, 8·0; Cl, 20·4. C_8H_7ON,HCl requires N, 8·3; Cl, 20·7%).

The nitro-1-methylbenzoxazoles were obtained (yields, 60—80% of the theoretical) by distillation at 10—20 mm. of the corresponding nitro-acetyl- or -diacetyl-aminophenols.

3-*Nitro*-1-*methylbenzoxazole* crystallised from acetic anhydride in white or pale yellow prisms, m. p. 125° (Found : N, 15·5. $C_8H_6O_3N_2$ requires N, 15·7%).

4-*Nitro*-1-*methylbenzoxazole* formed colourless rhombs, m. p. 154°, from the same solvent (Found : N, 15·9%). With alcohol and ethereal hydrogen chloride it formed a *hydrochloride*, readily dissociated by water (Found : N, 13·0; Cl, 16·8. $C_8H_6O_3N_2,HCl$ requires N, 13·1; Cl, 16·5%).

5-Nitro-1-methylbenzoxazole (Found : N, 15·7%) melts at 151° and forms plates from acetic acid or anhydride. The melting points of mixtures with the 4-nitro-derivative in the proportions of 20, 60, and 80% of the latter are 147°, 138°, and 148°, respectively (compare Newbery and Phillips, *loc. cit.*). Its hydrochloride (Found : N, 13·2; Cl, 16·4%) is hydrolysed readily by water.

6-*Nitro*-1-*methylbenzoxazole* is much more soluble in acetic anhydride or acetic acid than its isomerides. It was, therefore, purified by redistillation under reduced pressure (colourless needles, b. p. 240—250°/18 mm., m. p. 112°. Found : N, 15·8%). It is not decomposed by 30% acetic acid and can be crystallised from this solvent.

By treatment of the nitro-compounds with dilute mineral acids or caustic alkalis for a short time the corresponding nitroaminophenols were obtained in good yield; cold sodium carbonate solution gave the *N*-acetyl derivatives.

The amino-compounds were generally obtained by reduction of the nitro-compounds (10 g.) with iron powder (5 g.) in boiling 10% acetic acid (50 c.c.) and separated after neutralisation with ammonium hydroxide solution, filtration, and concentration. The crude mixture of 4- and 5-nitro-1-methylbenzoxazoles obtained by nitration of 1-methylbenzoxazole (Newbery and Phillips, *loc. cit.*) thus gave, on filtration and cooling, a 64% yield of pure 5-amino-1-

methylbenzoxazole, m. p. 147°. This on treatment with boiling dilute hydrochloric acid gave a 90% yield of 2 : 5-diaminophenol (isolated as the diacetyl derivative, m. p. 250°. Found : N, 13·3; calc., 13·4%). The mother-liquor on concentration gave a mixture which on hydrolysis yielded about 15% of 2 : 4-diaminophenol (acetyl derivative, m. p. 220°. Found : N, 13·6%); alternatively, addition of acetic anhydride to the mother-liquor from the reduction gave a similar yield of 4-acetamido-1-methylbenzoxazole, m. p. 205° (see later).

After the reduction of 4-nitro-1-methylbenzoxazole it was necessary to extract the filtered solution with ether in order to obtain the very soluble base; alternatively, it could be isolated as the dihydrochloride by addition of ethereal hydrogen chloride to the dried concentrated ethereal solution. In addition, 4-amino-1-methylbenzoxazole was obtained in poor yield by distillation at 10—20 mm. of 4-amino-2-acetamidophenol.

3-*Amino*-1-*methylbenzoxazole* separated in colourless prisms, m. p. 67°, from water, in which it is sparingly soluble. It is very soluble in ether (Found : N, 18·6. $C_8H_8ON_2$ requires N, 18·9%).

3-*Acetamido*-1-*methylbenzoxazole* (white needles, m. p. 218°, from water) can be obtained by addition of acetic anhydride to the base or to the filtered solution after reduction of the nitro-compound (Found : N, 14·7. $C_{10}H_{10}O_2N_2$ requires N, 14·7%).

4-*Amino*-1-*methylbenzoxazole* differs from its isomerides in its greater solubility in water and its consequent rapid hydrolysis by this solvent. Purified by distillation, it boils at 160—170°/20 mm. and forms colourless plates, m. p. 77—78°, very soluble in chloroform, benzene, ether, the alcohols, and ethyl acetate, and insoluble in boiling light petroleum (Found : N, 18·8%). The *dihydrochloride* (Found : N, 12·8; Cl, 32·2. $C_8H_8ON_2,2HCl$ requires N, 12·7; Cl, 32·1%) is readily soluble in water.

4-*Acetamido*-1-*methylbenzoxazole* formed stout colourless prisms, m. p. 205°, from boiling water (solubility, 1 part in 90) (Found : N, 14·6%).

5-*Acetamido*-1-*methylbenzoxazole*, obtained by acetylation of the amino-derivative (Newbery and Phillips, *loc. cit.*), formed a *dihydrate*, m. p. 83° (Found : H_2O, 16·4. $C_{10}H_{10}O_2N_2,2H_2O$ requires H_2O, 15·9%). The anhydrous compound crystallised from benzene and melted at 120° (Found : N, 14·4%).

6-*Amino*-1-*methylbenzoxazole* crystallised from boiling water (solubility, 1 in 100) in long needles, m. p. 106° (Found : N, 18·8%), and its *acetyl* derivative, m. p. 145—146°, from water or alcohol in long colourless needles (Found : N, 14·65%).

4-Amino-2-acetamidophenol (white plates, m. p. 164°) was

obtained by a modification of Balaban's method (this vol., p. 1686) which involved acidification of the filtered reduction mixture with sulphur dioxide. No unchanged material was observed and the yield was 75% (Found : N, 16·7; calc., 16·9%). On treatment of the filtered reduction mixture with acetic anhydride, 2 : 4-diacetamidophenol, m. p. 220°, was obtained (yield, 82%) (Found: N, 13·4%).

5-Amino-2-acetamidophenol was obtained by reduction of 5-nitro-2-acetamidophenol (10 g.) by means of boiling water (50 c.c.), acetic acid (2 c.c.), and iron powder (10 g.). On neutralisation with ammonia, filtration, concentration, and addition of excess of concentrated hydrochloric acid the *hydrochloride* separated (Found : N, 13·7; Cl, 17·7. $C_8H_{10}O_2N_2$,HCl requires N, 13·8; Cl, 17·5%). Acetylation of this compound with acetic anhydride gave an excellent yield of 2 : 5-diacetamidophenol, m. p. 260° (from water).

5-*Nitro*-2-*carbethoxyaminophenol* (yellow plates, m. p. 170°, from alcohol or benzene) was obtained in 80% yield from 5-nitro-2-aminophenol, ethyl chlorocarbonate, and sodium hydroxide (Found : N, 12·5. $C_9H_{10}O_5N_2$ requires N, 12·4%).

5-*Amino*-2-*carbethoxyaminophenol* was prepared by adding sodium hyposulphite (18 g.) to a solution of the nitro-compound (5 g.) in 2*N*-sodium hydroxide at 30°, more of the alkali being added as required to dissolve the precipitate formed; the amino-compound separated on acidification of the filtered solution with acetic acid, and crystallised from benzene in colourless rhombs, m. p. 129° (yield, 60%) (Found : N, 14·2. $C_9H_{12}O_3N_2$ requires N, 14·3%).

5-*Acetamido*-2-*carbethoxyaminophenol*, obtained by addition of acetic anhydride to the alkaline solution obtained in the reduction, as described above, of 5-nitro-2-carbethoxyaminophenol, formed colourless prisms, m. p. 233°, from water (Found : N, 11·6. $C_{11}H_{14}O_4N_2$ requires N, 11·8%).

The reduction of 2-nitro-4-acetamidophenol by iron and dilute acetic acid, sodium hyposulphite, and other reducing agents failed to yield 2-amino-4-acetamidophenol, but 3-nitro-4-acetamidophenol on reduction with activated aluminium and 90% alcohol gave a 30% yield of 3-amino-4-acetamidophenol, isolated as the *hydrochloride* (Found : N, 14·0; Cl, 17·7%).

Application of the Bart Reaction to the Four Amino-1-*methylbenzoxazoles.*—The base (7 g.) in water (100 c.c.) containing concentrated hydrochloric acid (10 c.c.) was diazotised at 0° with 3·3 g. of sodium nitrite in water (10 c.c.). The diazo-solution was added to the copper arsenite from arsenious oxide (6 g.), sodium hydroxide (9 g.), water (8 c.c.), and 2*N*-copper sulphate solution (2·5 c.c.); the mixture was kept neutral to litmus by addition of 4*N*-sodium

hydroxide as required. After remaining for 1 hour at 40°, the solution was rendered faintly acid to Congo-red with hydrochloric acid, treated with charcoal (1 g.), and filtered. On concentration to half volume and cooling, the corresponding acetamidohydroxyphenylarsinic acid separated: it was purified by solution in sodium bicarbonate and reprecipitation with dilute mineral acid.

3-Acetamido-4-hydroxyphenylarsinic acid (yield, 30%) (Found: As, 27·4; calc., 27·3%) forms colourless prisms, m. p. 240° (decomp.). The barium salt is microcrystalline and the magnesium salt amorphous.

4-Acetamido-3-hydroxyphenylarsinic acid (yield, 30%) (Found: As, 27·5%), consisting of colourless diamond-shaped plates decomposing at 245° and giving an amorphous magnesium salt, was also obtained from 5-amino-2-acetamidophenol by the Bart reaction. On hydrolysis, 4-amino-3-hydroxyphenylarsinic acid was formed, but the green colour reaction with chromic acid observed by Newbery and the author (*loc. cit.*, p. 122) could not be reproduced. Since the production of this colour may depend upon slight changes of conditions, the distinction between this acid and its isomerides cannot be considered trustworthy.

3-Acetamido-2-hydroxyphenylarsinic acid (Found: As, 27·2%) and 2-acetamido-3-hydroxyphenylarsinic acid (Found: As, 27·45%) were also obtained similarly in yields of 20—25% from 6-amino-1-methyl- and 3-amino-1-methyl-benzoxazole respectively; these have been described by Newbery, Phillips, and Stickings (J., 1928, 3054, 3065).

4-*Carbethoxyamino*-3-*hydroxyphenylarsinic acid*, obtained in 20% yield from 5-amino-2-carbethoxyaminophenol by the Bart reaction, consisted of clusters of colourless hexagonal prisms insoluble in water or mineral acids (Found: As, 24·3. $C_9H_{12}O_6NAs$ requires As, 24·6%). On hydrolysis with mineral acid it gave 4-amino-3-hydroxyphenylarsinic acid in 80% yield (Found: As, 32·0; calc., 32·2%).

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