

404. The Alkaloids of *Arundo Donax* L.

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From the leaves of *Arundo donax* L. a new alkaloid, $C_{12}H_{13}O_2N \cdot NMc$, has been isolated besides gramine (3-dimethylaminomethylindole). There are indications of the presence of a third alkaloid with phenolic properties.

Gramine reacting with methyl iodide in an alkaline medium undergoes a peculiar degradation, a quantitative yield of tetramethylammonium iodide and a substance $C_9H_8N \cdot OMe$ being obtained. The formation of a normal ethiodide takes place in the reaction of gramine with ethyl iodide in neutral solution, whereas tetramethylammonium iodide and trimethylamine are produced when methyl iodide is used.

FROM the leaves of the reed *Arundo donax* L., collected in Turkistan, Orékhov and Norkina (*Ber.*, 1935, **68**, 436) isolated an alkaloid $C_{11}H_{14}N_2$, for which they suggested the name donaxine. Von Euler, Erdtman, and Hellström (*Ber.*, 1936, **69**, 743) found donaxine to be identical with gramine, an alkaloid isolated by v. Euler *et al.* (*Z. physiol. Chem.*, 1935, **234**, 151; **235**, 37) from certain strains of barley. Gramine is 3-dimethylaminomethylindole and has been synthesised by Wieland and Chi Yi Hsing (*Annalen*, 1936, **526**, 188) and by Kühn and Stein (*Ber.*, 1937, **70**, 567). In addition to gramine, there has now been isolated from the leaves of *Arundo donax* L., collected in Catalonia, a small amount of another alkaloid, $C_{13}H_{16}O_2N_2$, for which the name *donaxarine* is suggested. Donaxarine shows a marked difference from gramine in its colour reactions. It gives no coloration when heated in acid solution with *p*-dimethylaminobenzaldehyde (Ehrlich's reagent) and the Hopkins-Cole test (glyoxylic reagent) is likewise negative; both reactions are positive in the case of gramine. The vapour of donaxarine gives the pine wood reaction, which is, however, not quite specific for indole derivatives. Donaxarine contains one *N*-methyl group and one active hydrogen atom, but no *O*-methyl and apparently no *C*-methyl group. It is optically inactive. By the Kuhn-Roth method no acetic acid was formed, whereas in a special experiment 0.5 equivalent of acetic acid was formed from physostigmine.

The presence of a third alkaloid with phenolic properties was indicated in the leaves of *Arundo donax* L., but it could not be obtained in a crystalline form. Analyses of the purest specimens showed large proportions of active hydrogen.

Before the synthesis of gramine by Wieland and Chi Yi Hsing (*loc. cit.*) had established its constitution, several attempts to degrade the alkaloid were made. Methyl iodide in an alkaline medium caused a peculiar degradation, resulting in a quantitative yield of tetramethylammonium iodide and a neutral substance $C_{10}H_{11}ON$ (Madinaveitia, *Nature*, 1937, **27**, 139). The latter is most likely 3-methoxymethylindole, formed by hydrolytic removal of the methylated dimethylamino-group and methylation of the hydroxyl

compound thus remaining. The dimethylamino-group of gramine is rather labile; alkali is not required for its hydrolysis. When gramine was allowed to react with methyl iodide in methyl-alcoholic solution, instead of the formation of the methiodide, m. p. 176°, described by Orčkhov and Norkina (*loc. cit.*), evolution of trimethylamine, followed by precipitation of tetramethylammonium iodide, was observed. Besides these two substances a water-insoluble compound that could not be crystallised was obtained: presumably it is 3-hydroxymethylindole, which was prepared by catalytic reduction of indolealdehyde, showed very similar properties, but crystallised readily. The formation of tetramethylammonium iodide, which does not melt at 300°, in the reaction of gramine with methyl iodide may perhaps account for the unusually high melting point of the quaternary iodide prepared by Wieland and Chi Yi Hsing (*loc. cit.*) and Kühn and Stein (*loc. cit.*) in order to characterise their synthetic gramine and considered by them to be its methiodide.

Although no methiodide could be obtained from gramine, an *ethiodide* was readily formed by interaction of the alkaloid and ethyl iodide in acetone solution. When this reaction was carried out in alkaline medium, a neutral compound, $C_{11}H_{13}ON$, probably 3-ethoxymethylindole, was formed, as well as dimethylethylamine (identified by its picrate).

EXPERIMENTAL.

Isolation of the Alkaloids.—An alcoholic extract of *Arundo donax* leaves (50 kg.) was evaporated to 5 l. and the non-basic constituents were removed with ether (3 l.). The acid solution was made slightly alkaline with ammonia, and the alkaloids extracted with ether. The ethereal solution of the bases was thoroughly extracted with dilute hydrochloric acid, and the acid solution strongly basified with sodium hydroxide. Extraction of the alkaline solution removed the non-phenolic bases, the phenolic bases remaining in solution (solution A).

Gramine. The ethereal solution containing the non-phenolic bases was dried with sodium sulphate, and the ether removed on the water-bath; the oily residue partly crystallised on standing. The crystalline constituent, after successive recrystallisations from acetone, methyl ethyl ketone (two), benzene, light petroleum (b. p. 80—100°), and alcohol, had all the properties of gramine: m. p. 133°; perchlorate, m. p. 146°; picrate, m. p. 140°. Yield, 13.8 g. (0.028%).

Donaxarine and phenolic bases. Carbon dioxide was passed through solution A, a voluminous precipitate being formed. When all the sodium hydroxide had been converted into carbonate, the alkaloids were extracted with ether. The ethereal solution was extracted with 2*N*-sodium hydroxide to remove the phenolic constituents, dried with sodium sulphate, and evaporated on the water-bath; the oily residue partly crystallised on standing. After being recrystallised once from acetone and twice from methyl alcohol, it gave 60 mg. of donaxarine, m. p. 217° [Found: C, 67.6, 67.7; H, 7.1, 7.2; N, 12.5; *N*-Me, 7.85; *M* (Rast), 204. $C_{13}H_{16}O_2N_2$ requires C, 67.2; H, 6.9; N, 12.1; 1 *N*-Me, 6.5%; *M*, 232]. The substance contains 1.35 equivs. of active hydrogen.

The alkaline solution containing the phenolic bases was saturated with carbon dioxide and extracted with ether, and the phenolic constituents removed with sodium hydroxide: this procedure was repeated three times. The oil finally obtained separated from hot carbon tetrachloride in white amorphous flocks, m. p. 127—128°, which resinified on standing.

Reaction of Gramine with Methyl Iodide in an Alkaline Medium.—A solution of gramine (1 g.) in methyl alcohol (5 c.c.), made alkaline with 25% methyl-alcoholic potassium hydroxide (2.5 c.c.) and treated with methyl iodide (1 c.c.) in methyl alcohol (4 c.c.), soon became hot, a basic odour was noticed, and a crystalline precipitate began to form. After standing at 20° for 12 hours, this was collected, washed with methyl alcohol, and recrystallised from methyl alcohol, tetramethylammonium iodide (1.2 g.) being obtained, m. p. above 360° (Found: C, 24.1, 24.2; H, 6.1, 6.1; N, 5.9, 5.8; I, 62.7, 62.5. Calc. for $C_4H_{12}NI$: C, 23.9; H, 5.9; N, 6.9; I, 63.2%). The picrate had m. p. 310° (Found: C, 40.1; H, 4.9; N, 17.9. Calc.: C, 39.6; H, 4.9; N, 18.5%).

The alcoholic solution from which the tetramethylammonium iodide had crystallised was poured into water (*ca.* 100 c.c.). 3-Methoxymethylindole separated in platelets (0.8 g.). Recrystallised from light petroleum (b. p. 60—80°), it formed long white needles, m. p. 99—100° (Found: C, 74.9, 74.4; H, 6.9, 6.9; N, 9.1; *O*-Me, 18.0. $C_{10}H_{11}ON$ requires C, 74.5; H, 6.9; N, 8.7; 1 *O*-Me, 19.2%). It contained 1.13 active hydrogen atoms. No *N*-Me could

be detected. In another experiment the substance responsible for the basic odour in the early stages of the reaction was isolated as the picrate and proved to be trimethylamine.

Reaction of Gramine with Methyl Iodide in Methyl-alcoholic Solution.—To a solution of gramine (0.2 g.) in methyl alcohol (0.7 c.c.), methyl iodide (0.1 c.c.) was added. After 1 hour's standing at 20° a strong basic smell was noticed and a crystalline precipitate formed. Air was bubbled through the mixture and then through alcoholic picric acid; the crystalline picrate formed had m. p. 215—216° (trimethylaminic picrate has m. p. 216°). When most of the trimethylamine had been eliminated, the precipitate was collected and recrystallised from methyl alcohol; it had m. p. above 300° and was converted into a picrate, m. p. 312° (tetramethylammonium picrate has m. p. 312—313°). The alcohol from which the tetramethylammonium iodide had separated was poured into water; the neutral amorphous precipitate became red on standing and was extremely sensitive to the action of acids.

Reduction of Indole-3-aldehyde.—The aldehyde (0.5 g.), dissolved in alcohol (70 c.c.), was shaken with Adams's catalyst (PtO₂) (0.1 g.) in an atmosphere of hydrogen. Absorption of 182 c.c. (calc., 164 c.c.) took place in 8 hours. The alcoholic solution was filtered, poured into water (ca. 100 c.c.), and extracted with ether. The ethereal solution was dried, and the greater part of the ether removed on the water-bath. On slow evaporation of the remainder 3-hydroxymethylindole crystallised in platelets, m. p. 90°, unchanged by recrystallisation from benzene [Found: N, 9.4, 9.5; *M* (Rast), 157. C₉H₉ON requires N, 9.5%; *M*, 147].

Reaction of Gramine with Ethyl Iodide in an Alkaline Medium.—A solution of gramine (0.2 g.) in alcohol (1 c.c.), made alkaline with 25% alcoholic potassium hydroxide (0.5 c.c.) and treated with ethyl iodide (0.2 c.c.), developed a basic odour after 1 hour. Air was bubbled through the solution and then into alcoholic picric acid; the reaction was complete in 12 hours and the crystalline picrate obtained had m. p. 204° (dimethylethylamine picrate has m. p. 194°). Addition of water to the residual solution precipitated 3-ethoxymethylindole, m. p. 93—94° after recrystallisation from light petroleum (b. p. 60—80°) (Found: C, 75.3, 75.1; H, 8.0, 8.0; N, 8.4. C₁₁H₁₃ON requires C, 75.4; H, 7.4; N, 8.0%).

Gramine Ethiodide.—Gramine (0.2 g.), dissolved in acetone (5 c.c.), was mixed with ethyl iodide (0.3 c.c.) and after 36 hours the crystals obtained were recrystallised from alcohol, giving white prisms, m. p. 176° (Found: C, 47.2; H, 5.2; N, 8.7. C₁₃H₁₉N₂I requires C, 47.3; H, 5.6; N, 8.5%).

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