74. *Pyrazine Derivatives. Part I.* 2-*Hydroxy*-3 : 6-*dimethylpyrazine.*

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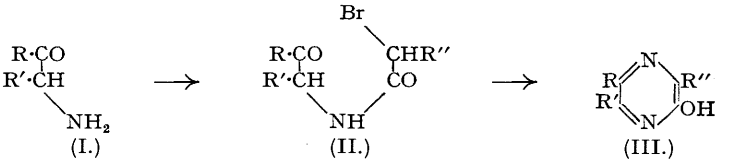
A synthesis of 2-hydroxy-3 : 6-dimethylpyrazine (VII) is described in which 2-*aminopropaldehyde diethylmercaptal* (V) is condensed with 2-bromopropionyl bromide to give 2-(2-*bromopropionamido*)*propaldehyde diethylmercaptal* (VI) which, when treated with mercuric chloride in the presence of cadmium carbonate and then with ammonia, gave the required hydroxypyrazine.

Treatment of aminopyrazine and of 2-amino-3 : 6-dimethylpyrazine with nitrous acid gave hydroxypyrazine and 2-hydroxy-3 : 6-dimethylpyrazine respectively.

An examination of methods for the synthesis of 2-hydroxypyrazines was undertaken with the object of synthesising deoxyaspergillic acid (see Part II, following paper). When this study commenced, two methods for the synthesis of hydroxyalkylpyrazines had been reported. The first, due to Gastaldi (*Gazzetta*, **1921**, **51**, I, 233), consisted in the treatment of *iso*nitrosoacetone with sodium bisulphite followed by reaction of the product with potassium cyanide to yield 2 : 5-dicyano-3 : 6-dimethylpyrazine which was converted into 2-hydroxy-3 : 6-dimethylpyrazine-5-carboxylic acid and thence into 2-hydroxy-3 : 6-dimethylpyrazine; this method will be discussed more fully in a later paper.

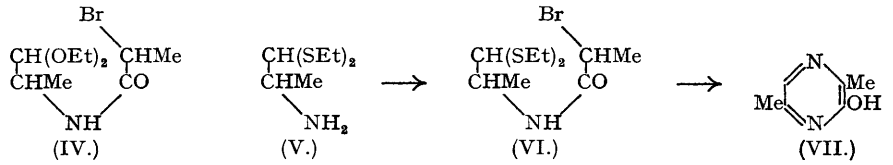
The second route is one described by Tota and Elderfield (*J. Org. Chem.*, 1942, **7**, 317) who developed a method for the condensation of the hydrochloride of an α-amino-ketone (I) with a 2-bromo-substituted acid halide to give, in poor yield, the corresponding 2-bromoacylamido-ketone (II) which on treatment with ammonia gave the hydroxyprazine (III), the last stage

involving the oxidation common to most pyrazine syntheses. Modification of the method to lead to the formation of a 2-hydroxy-3 : 6-dialkylpyrazine would involve the use of the



(I.) (II.) (III.)

hydrochloride of a 2-amino-aldehyde instead of an α-amino-ketone hydrochloride. The hydrochloride of 2-aminopropaldehyde was prepared by Fischer and Kametaka (*Annalen*, 1909, **365**, 7; Neuberg, *Ber.*, 1908, **41**, 956) who described it as a nearly colourless gum which could not be crystallised. We also were unable to crystallise this resin-like salt. Unsuccessful attempts were made to condense the resinous hydrochloride with 2-bromopropionyl bromide. In consequence of this unpromising result, the method was modified, the aldehyde group being protected during the condensation. This modification proved successful, condensation of 2-aminopropaldehyde diethylacetal (Burtles, Pyman, and Roylance, *J.*, 1925, **127**, 585) with 2-bromopropionyl bromide giving 2-(*2-bromopropionamido*)*propaldehyde diethylacetal* (IV) in



(IV.) (V.) (VI.) (VII.)

good yield. We were unable, in spite of many variations in reaction conditions, successfully to hydrolyse the acetal to the required bromo-aldehyde. Likewise, attempts to convert the acetal (IV) directly into 2-hydroxy-3 : 6-dimethylpyrazine failed. This failure we attribute to the difficulty of hydrolysis of the acetal group; when conditions were sufficiently drastic to accomplish this hydrolysis, cleavage of the amide linkage apparently occurred.

An alternative method for the protection of the aldehyde group was next examined in which use was made of an observation that mercaptals can be hydrolysed to the corresponding aldehyde by treatment with mercuric chloride in the presence of an insoluble carbonate (Levene and Meyer, *J. Biol. Chem.*, 1926, **69**, 175; 1927, **74**, 695; Wolfrom, *J. Amer. Chem. Soc.*, 1929, **51**, 2188; cf. Fischer, *Ber.*, 1894, **27**, 673). Treatment of 2-aminopropaldehyde diethylacetal with hydrochloric acid and ethylthiol gave 2-*aminopropaldehyde diethylmercaptal* (V), which reacted smoothly with 2-bromopropionyl bromide to give 2-(*2-bromopropionamido*)*propaldehyde diethylmercaptal* (VI). Treatment of the latter with mercuric chloride in the presence of cadmium carbonate, followed by treatment of the product with ammonia, gave the required 2-hydroxy-3 : 6-dimethylpyrazine (VII), characterised by the preparation of its *picrate*.

Another possible route to hydroxypyrazines was examined simultaneously. It consists in the preparation of an aminopyrazine and treatment of this with nitrous acid. By using this method, aminopyrazine was converted into hydroxypyrazine in 30% yield, and 2-amino-3 : 6-dimethylpyrazine into 2-hydroxy-3 : 6-dimethylpyrazine in 60% yield. Since this work was completed, Weijlard, Tishler, and Erickson (*J. Amer. Chem. Soc.*, 1945, **67**, 802) have prepared hydroxypyrazine by decarboxylation of 2-hydroxypyrazine-3-carboxylic acid, and more recently Erickson and Spoerri (*ibid.*, 1946, **68**, 400) obtained the same compound by treatment of aminopyrazine with nitrosylsulphuric acid.

Experimental.

(M. p.'s are uncorrected.)

2-(*2-Bromopropionamido*)*propaldehyde Diethylacetal.*—2-Bromopropaldehyde diethylacetal was prepared from propaldehyde by using an adaptation of Kuhn and Grundmann's method (*Ber.*, 1937, **70**, 1894) for the preparation of 2-bromo-*n*-valeraldehyde diethylacetal. This method is superior to that employed by Stoermer (*Annalen*, 1900, **312**, 271) and by Burtles, Pyman, and Roylance (*J.*, 1927, 581) and represents a marked improvement over that used by Dworzak and Pfifferling (*Monatsh.*, 1927, **48**, 251) starting from propaldehyde trimer but excluding irradiation with ultra-violet light. 2-Bromopropaldehyde diethylacetal was obtained as a slightly pink liquid, b. p. 63—64°/14 mm. (yield 63—64%); Stoermer gives b. p. 74—75°/15—16 mm. The bromo-acetal (70 g.) was heated to 125—130° with a solution of ammonia (134 g.) in absolute alcohol (500 g.) in an autoclave with stirring for 7½ hours. 2-Aminopropaldehyde diethylacetal was obtained as a colourless oil, b. p. 64—67° (mainly at 66°)/21 mm. (yield 39%); Burtles, Pyman, and Roylance (*loc. cit.*) give b. p. 79—80°/40 mm. A solution of 2-aminopropaldehyde diethylacetal (7·35 g.) and *N*-methylmorpholine (5·1 g.) in dry chloroform (50 c.c.)

was treated at 0° with one of 2-bromopropionyl bromide (10·8 g.) in dry chloroform (50 c.c.) added dropwise with stirring over 30 minutes. Stirring was continued for one hour during which the mixture was allowed to attain room temperature. The mixture was washed with water, dried, and the solvent removed under reduced pressure. After stripping at 100°/20 mm., the residual yellow oil (11·0 g.) crystallised on standing. Recrystallisation from light petroleum (b. p. 40—60°) at 0° gave 2-(2-*bromopropionamido*)*propaldehyde diethylacetal* as needles, m. p. 56·5—57° (Found: C, 43·0; H, 7·3; N, 4·6. $C_{10}H_{20}O_3NBr$ requires C, 42·6; H, 7·1; N, 4·9%).

2-*Aminopropaldehyde Diethylmercaptal*.—A solution of 2-aminopropaldehyde diethylacetal (18 g.) in water (10 c.c.) was treated successively with concentrated hydrochloric acid (80 c.c.) and ethylthiol (30 c.c.) at 0° and with stirring. The mixture was kept at room temperature for 24 hours with occasional shaking and was then homogeneous. The solution was poured on a mixture of sodium hydroxide solution (40%; 200 c.c.) and cracked ice (500 g.), and the oil which separated was extracted with chloroform (2 × 100 c.c.). The solvent was removed from the dried (sodium sulphate) extract and the residue distilled under reduced pressure to give 2-*aminopropaldehyde diethylmercaptal* as a colourless oil, b. p. 105°/3 mm. (yield, 73%) (Found: C, 46·3; H, 9·3. $C_7H_{17}NS_2$ requires C, 46·9; H, 9·5%). The mercaptal was characterised by the preparation of its *picrate*, which separated from benzene as plates, m. p. 153—154° (Found: C, 38·4; H, 5·2; N, 13·4. $C_{13}H_{20}O_7N_4S_2$ requires C, 38·2; H, 4·9; N, 13·7%).

2-(2-*Bromopropionamido*)*propaldehyde Diethylmercaptal*.—A mixture of 2-aminopropaldehyde diethylmercaptal (19·5 g.), *n*-butylpiperidine (15 g.), and dry chloroform (50 c.c.) was treated with a solution of 2-bromopropionyl bromide (25 g.) in chloroform (50 c.c.) added slowly with stirring at 0°. Stirring was continued for 1 hour at room temperature, and the solution washed successively with water, dilute hydrochloric acid, sodium carbonate solution, and water. After drying, the solvent was removed at 40° under reduced pressure. The residue (31 g.) solidified on standing; it was pressed on a porous tile and crystallised from light petroleum (b. p. 40—60°) to give 2-(2-*bromopropionamido*)*propaldehyde diethylmercaptal* as needles, m. p. 47—48°, which slowly decomposed on standing in air at room temperature (Found: C, 38·2; H, 6·4; N, 4·4. $C_{10}H_{20}ONBrS_2$ requires C, 38·2; H, 6·4; N, 4·5%).

2-*Hydroxy*-3 : 6-*dimethylpyrazine*.—(*a*) Cadmium carbonate (10 g.) was suspended in a solution of 2-(2-bromopropionamido)propaldehyde diethylmercaptal (3·14 g.) in ethanol (50 c.c.) and water (10 c.c.), and the mixture treated with a solution of mercuric chloride (5·6 g.) in ethanol (50 c.c.). The mixture was vigorously stirred for 24 hours, filtered, and the filtrate saturated with ammonia at 0°. After standing at room temperature for 48 hours, the mixture was again filtered, the filtrate evaporated to dryness under reduced pressure, and the residue extracted with warm benzene (100 c.c.). Evaporation of the extract gave a white crystalline solid contaminated with a yellow gum from which it was freed with difficulty and with considerable loss by crystallisation from benzene–light petroleum (b. p. 40—60°). 2-Hydroxy-3 : 6-dimethylpyrazine (250 mg.) was obtained as needles, m. p. 210—211° either alone or when mixed with a specimen prepared by the method described below. For analysis it was sublimed at 120°/10^{-3} mm. without altering the m. p. (Found: C, 58·1; H, 6·8; N, 22·5. Calc. for $C_6H_8ON_2$: C, 58·1; H, 6·45; N, 22·6%). 2-*Hydroxy*-3 : 6-*dimethylpyrazine picrate* separated from methanol as blades, m. p. 181—185° (Found: N, 19·6. $C_{12}H_{11}O_8N_5$ requires N, 19·8%).

(*b*) 2-Amino-3 : 6-dimethylpyrazine, m. p. 110—112°, was obtained in 20% yield from 2 : 5-dimethylpyrazine (Gabriel and Pinkus, *Ber.*, 1893, **26**, 2197) by the method described by Joiner and Spoerri (*J. Amer. Chem. Soc.*, 1941, **63**, 1929). A solution of this aminopyrazine (0·5 g.) in N-hydrochloric acid (15 c.c.) was treated with sodium nitrite (0·6 g.) added in small portions over 5 minutes at 0° with constant shaking. The solution was kept at room temperature for 2 hours, heated at 60° for 5 minutes, cooled, and neutralised by addition of sodium bicarbonate. The solution was evaporated to dryness under reduced pressure, and the dried residue extracted with boiling benzene (3 × 40 c.c.). Evaporation of the benzene extract gave 2-hydroxy-3 : 6-dimethylpyrazine, which separated from benzene as small felted needles, m. p. 210—211° (yield, 61%). It is very soluble in water and alcohols and sparingly soluble in boiling light petroleum (b. p. 40—60°) (Found: C, 57·9; H, 6·5; N, 22·3. Calc. for $C_6H_8ON_2$: C, 58·1; H, 6·45; N, 22·6%). The picrate separated from methanol as plates, m. p. 181—185°, either alone or when mixed with a specimen prepared by method (*a*).

2-*Hydroxypyrazine*.—The following modification of Gabriel and Sonn's method (*Ber.*, 1907, **40**, 4851) was employed for the preparation of aminopyrazine. Oxidation of quinoxaline gave an 80% yield of pyrazine-2 : 3-dicarboxylic acid which was converted into its dimethyl ester (73% yield) and thence into the diamide (93% yield), which separated as blades from methanol, m. p. 230° (decomp.). Treatment of the diamide with potassium hypobromite solution gave 2-aminopyrazine-3-carboxylic acid (light yellow needles from water, m. p. 210°, decomp.) in 56% yield, and decarboxylation of the amino-acid was effected by refluxing for 10 minutes in nitrobenzene solution to give aminopyrazine as colourless blades, m. p. 117—118° after sublimation at 100°/0·5 mm. (yield 86%). Gabriel and Sonn (*loc. cit.*) give m. p. 110—117°, Hall and Spoerri (*J. Amer. Chem. Soc.*, 1940, **62**, 664), m. p. 117—118°, and Weijlard, Tishler, and Erickson (*ibid.*, 1945, **67**, 804), m. p. 118—120° for aminopyrazine. The last authors obtained 2-aminopyrazine-3-carboxylic acid by hydrolysis of lumazine and effected decarboxylation by boiling the amino-acid with carbityl acetate. Treatment of aminopyrazine with nitrous acid as described in the preparation of 2-hydroxy-3 : 6-dimethylpyrazine (method *b*) gave hydroxypyrazine (yield 30%) as colourless needles from benzene–light petroleum (b. p. 40—60°), m. p. 187—189°. It is soluble in water and ethanol and sparingly soluble in light petroleum and chloroform; it sublimed at 170°/10^{-3} mm. to yield a colourless sublimate, m. p. 187—189° (Found: C, 50·5; H, 4·2. Calc. for $C_4H_4ON_2$: C, 50·0; H, 4·2%). Weijlard, Tishler, and Erickson (*loc. cit.*) describe hydroxypyrazine as forming brilliant yellow needles, m. p. 187—188°. The colour of their product is almost certainly due to impurity; we find that a specimen of the compound prepared as described by them is yellow and that the colour is extremely difficult to remove.

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