370. *Pyrazine Derivatives. Part V. A General Method for the Synthesis of Aminopyrazine Derivatives.*

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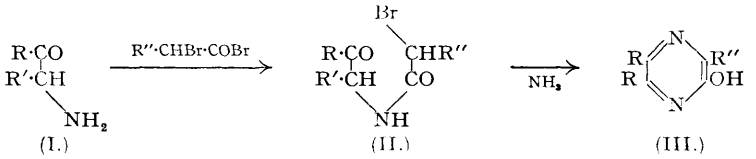
It is known that treatment of α-bromopropionyl derivatives of amino-ketones of the type $R{\cdot}CO{\cdot}CHR^1{\cdot}NH_2$ with ammonia gives rise to trisubstituted hydroxypyrazines (III). In contrast to this behaviour, it is now shown that α-bromopropionyl derivatives of amino-methyl ketones (*i.e.*, $R{\cdot}CO{\cdot}CH_2{\cdot}NH_2$) when treated with ammonia undergo a remarkable reaction to give 2-propionamidopyrazine derivatives [*e.g.*, (IV)] in high yield.

Tota and Elderfield (*J. Org. Chem.*, 1942, **7**, 317) have described a method for the synthesis of 5 : 6-disubstituted and 3 : 5 : 6-trisubstituted 2-hydroxypyrazines (III) in which a 2-(α-bromoacylamido)ketone (II) is treated with ammonia. The preparation of the α-bromoacyl derivative (II) of the unstable 2-amino-ketone (I) was effected by adding an aqueous solution of the hydrochloride of the amino-ketone to a suspension of calcium carbonate in chloroform and immediately

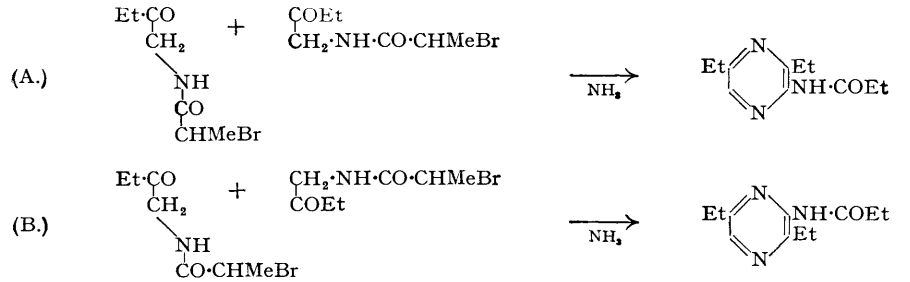
treating this mixture with a chloroform solution of the α-bromoacyl bromide. Using this method, Tota and Elderfield have prepared 2-hydroxy-5 : 6-dimethylpyrazine (III; R = R′ = Me, R″ = H), 2-hydroxy-5-phenyl-6-methylpyrazine (III; R = Ph, R′ = Me, R″ = H), 2-hydroxy-5-phenyl-6-methyl-3-ethylpyrazine (III; R = Ph, R′ = Me, R″ = Et), and 2-hydroxy-5-methyl-6-(2-hydroxyethyl)pyrazine (III; R = Me, R′ = HO·$[CH_2]_2$, R″ = H), and Newbold and Spring (*J.*, 1947, 373) have used it to prepare 2-hydroxy-3 : 5 : 6-trimethylpyrazine (III; R = R′ = R″ = Me).

In a general study of methods for the synthesis of hydroxypyrazines in connection with an examination of the antibacterial substance aspergillic acid, we have attempted to use the Tota and Elderfield method to prepare 2-hydroxy-3 : 5-dialkyl-substituted pyrazines. In the preparation of 2-(α-bromoacylamido)ketones, we find that considerable improvement in yield results (in the cases examined by us) if *N*-methylmorpholine is used instead of calcium carbonate, and the reaction is carried out under anhydrous conditions. Using this modified procedure, condensation of α-bromopropionyl bromide with the hydrochloride of 1-aminobutan-2-one (I; R = Et, R′ = H) gave the expected 1-(*α-bromopropionamido*)*butan-2-one* (II; R = Et,



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

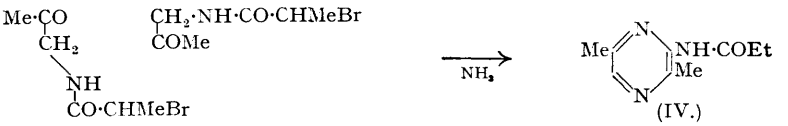
R″ = Me, R′ = H) in high yield. When treated with ammonia, this bromoacylamido-ketone gave a crystalline compound, $C_{11}H_{17}ON_3$, m. p. 98°, and not the expected 2-hydroxy-3-methyl-5-ethylpyrazine. The compound $C_{11}H_{17}ON_3$ does not show the characteristic properties of a hydroxypyrazine; it does not possess acidic properties, and its absorption spectrum exhibits maxima at 2260 A. and 2790 A., whereas alkyl-substituted hydroxypyrazines exhibit maxima at approximately 2280 A. and 3250 A. (Newbold and Spring *loc. cit.*). When heated with sodium hydroxide solution, the compound $C_{11}H_{17}ON_3$ gives a hygroscopic base, m. p. 42°, characterised as its *picrate*. Analysis of the picrate established the molecular formula $C_8H_{13}N_3$ for the parent base. A comparison of the absorption spectrum of this base with that of 2-amino-3 : 6-dimethylpyrazine (Baxter, Newbold, and Spring, this vol., p. 370) suggested that the former is an aminopyrazine and this was confirmed by treatment of the base with nitrous acid, whereby a hydroxypyrazine, m. p. 135°, was obtained, characterised by its ultra-violet absorption spectrum which exhibits maxima at 2270 A. and 3220 A. The relationship of the base and the compound $C_{11}H_{17}ON_3$ was established by treatment of the former with propionic anhydride, whereupon a propionyl derivative was obtained which proved to be identical with the compound $C_{11}H_{17}ON_3$. The compound $C_{11}H_{17}ON_3$ would thus appear to be a 2-propionamidodiethylpyrazine, and the base, $C_8H_{13}N_3$, a 2-aminodiethylpyrazine, and the reaction between ammonia and 1-(α-bromopropionamido)butan-2-one can be represented by one of the two expressions, (A) and (B).



If one of the expressions (A) and (B) is a true representation of the reaction, the formation of a propionamidopyrazine from an α-bromopropionamido-ketone and ammonia can only proceed if the parent amino-ketone is an aminomethyl ketone, *i.e.*, if the parent amino-ketone contains the grouping NH_2·CH_2·COR. The cases previously examined by Tota and Elderfield and by us before this investigation all employed substituted aminomethyl ketones of the type NH_2·CHR′·COR, and the products were all hydroxy-pyrazines. In such cases, reactions (A) and (B) are excluded since the necessary aromatisation involved in these reactions cannot occur.

In order to obtain general confirmation of these deductions, the reaction between ammonia and α-bromopropionyl derivatives of some other aminomethyl ketones has been examined.

Condensation of aminoacetone (I; R = Me, R′ = H) with α-bromopropionyl bromide in the presence of *N*-methylmorpholine gave *α-bromopropionamidoacetone* (II; R = R″ = Me, R′ = H) which, on treatment with ammonia, yielded a compound $C_9H_{13}ON_3$, m. p. 106—108°, and not a hydroxypyrazine. Hydrolysis of the compound, m. p. 106—108°, gave 2-amino-3 : 6-dimethylpyrazine, characterised by its picrate and by conversion into 2-hydroxy-3 : 6-dimethylpyrazine. Treatment of 2-amino-3 : 6-dimethylpyrazine with propionic anhydride gave 2-*propionamido*-3 : 6-*dimethylpyrazine* (IV), which was identical with the compound, m. p. 106—108°. The reaction in this case is represented by the expression



(IV.)

By analogy, expression (B) is preferred for the reaction between ammonia and 1-(α-bromopropionamido)butan-2-one leading to the formulation of the compound $C_{11}H_{17}ON_3$ as 2-*propionamido*-3 : 6-*diethylpyrazine*, the base $C_8H_{13}N_3$ as 2-*amino*-3 : 6-*diethylpyrazine*, and the corresponding hydroxypyrazine, m. p. 135°, as 2-*hydroxy*-3 : 6-*diethylpyrazine*. Confirmation of the structure of the compound has been obtained by its synthesis using a different route (Sharp and Spring, this vol., p. 1862).

Condensation of ω-aminoacetophenone with α-bromopropionyl bromide gave ω-(α-*bromopropionamido*)*acetophenone* (II; R = Ph, R′ = H, R″ = Me) which, on treatment with ammonia, yielded 2-*propionamido*-3 : 6-*diphenylpyrazine*, alkaline hydrolysis of which yielded 2-*amino*-3 : 6-*diphenylpyrazine*. The ultra-violet absorption spectra of the 2-propionamidopyrazines and the corresponding aminopyrazines described in this paper are shown in the table.

This remarkable cyclisation reaction appears to be of general application. Whilst, as mentioned previously, the inability of an α-bromoacyl derivative of a 2-amino-ketone of the type R·CO·CHR·NH_2 to yield a 2-acylamido-3 : 6-disubstituted pyrazine is readily understood, it is difficult to suggest a reason for the obvious reluctance of α-bromoacylamidomethyl ketones to yield 2-hydroxy-3 : 5-disubstituted pyrazines. Methods for the synthesis of the latter class of pyrazine derivative are being examined.

Ultra-violet absorption spectra.

	Maxima, A.	ε, max.
1. 2-Propionamido-3 : 6-dimethylpyrazine	(1) 2260; 2805	6,400; 6,800
	(2) 2250; 2810	6,000; 6,500
2. 2-Propionamido-3 : 6-diethylpyrazine	(1) 2260; 2790	6,100; 6,600
	(2) 2250; 2800	5,800; 6,000
3. 2-Propionamido-3 : 6-diphenylpyrazine	(1) 2780; 3295	13,200; 16,800
	(2) 2770; 3290	12,600; 16,000
4. 2-Amino-3 : 6-dimethylpyrazine	(3) 2340; 3190	12,000; 7,500
	(4) 2350; 3195	11,500; 7,300
5. 2-Amino-3 : 6-diethylpyrazine	(4) 2360; 3190	12,200; 8,000
6. 2-Amino-3 : 6-diphenylpyrazine	(4) 2640; 3560	12,500; 24,000

(1) Specimen obtained by the action of ammonia on a bromopropionamido-ketone.
(2) Specimen obtained by propionylation of the corresponding aminopyrazine.
(3) Specimen prepared as described by Baxter, Newbold, and Spring, *loc. cit.*
(4) Specimen obtained by hydrolysis of corresponding propionyl derivative (1).

Experimental.

α-Bromopropionamidoacetone.—A suspension of aminoacetone hydrochloride (11 g.) in dry chloroform (35 c.c.) was treated with a solution of α-bromopropionyl bromide (27 g.) in dry chloroform (25 c.c.). The mixture was cooled in ice and treated dropwise during 15 minutes with a solution of *N*-methylmorpholine (23 g.) in dry chloroform (30 c.c.), the mixture being vigorously stirred. Stirring was continued at 0° for 15 minutes, and during the next hour the mixture was allowed to attain room temperature. After being washed with water, dilute hydrochloric acid, saturated aqueous sodium carbonate, and water, the chloroform solution was dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a crystalline residue, m. p. 74—77° (14·1 g.), which was washed with light petroleum (b. p. 40—60°). Recrystallisation from benzene–light petroleum (b. p. 40—60°) gave *α-bromopropionamidoacetone* as needles, m. p. 80° (Found: C, 34·7; H, 4·7; N, 6·5. $C_6H_{10}O_2NBr$ requires C, 34·6; H, 4·8; N, 6·7%).

α-Bromopropionamidomethyl ethyl ketone was obtained in 63% yield by the same procedure from 1-aminobutan-2-one hydrochloride and α-bromopropionyl bromide. It separated from benzene–light

petroleum (b. p. 40—60°) as needles, m. p. 77° (Found : C, 37·9; H, 5·3; N, 6·3. $C_7H_{12}O_2NBr$ requires C, 37·8; H, 5·4; N, 6·3%).

ω-(α-Bromopropionamido)acetophenone was obtained in 66% yield from ω-aminoacetophenone hydrochloride and α-bromopropionyl bromide. It separated as needles, m. p. 90°, from benzene–light petroleum (b. p. 40—60°) (Found : C, 48·6; H, 4·75; N, 5·5; Br, 30·2. $C_{11}H_{12}O_2NBr$ requires C, 48·9; H, 4·4; N, 5·2; Br, 29·6%).

2-*Propionamido*-3 : 6-*dimethylpyrazine*.—A solution of α-bromopropionamidoacetone (2·6 g.) and ammonium iodide (0·5 g.) in liquid ammonia (50 c.c.) was kept at room temperature in an autoclave for 16 hours. After evaporation of the ammonia, the residue was extracted with boiling benzene (4 × 25 c.c.). The solution was filtered through a column of alumina (75 × 16 mm.), and the column washed with benzene (250 c.c.). Removal of the solvent from the filtrate yielded a colourless crystalline residue, recrystallisation of which from benzene–light petroleum (b. p. 40—60°) gave 2-*propionamido*-3 : 6-*dimethylpyrazine* (0·9 g.) as blades, m. p. 106—108°; it is very soluble in water and in the common alcohols and is extracted by ether from an aqueous alkaline solution. For analysis, it was sublimed at 100°/0·005 mm. (Found : C, 60·6, 60·6; H, 7·4, 7·2; N, 23·3, 23·2. $C_9H_{13}ON_3$ requires C, 60·3; H, 7·2; N, 23·5%).

2-*Amino*-3 : 6-*dimethylpyrazine*.—2-Propionamido-3 : 6-dimethylpyrazine (0·2 g.) was heated under reflux for 4 hours with 10% aqueous potassium hydroxide (4 c.c.). The solution was exactly neutralised with 10% hydrochloric acid, and the mixture evaporated to dryness under reduced pressure. The residue was extracted with boiling benzene, and the dried extract evaporated to dryness. The crystalline solid was recrystallised from benzene, from which 2-amino-3 : 6-dimethylpyrazine separated as needles, m. p. 111°, showing no depression when mixed with a specimen prepared by the method of Joiner and Spoerri (*J. Amer. Chem. Soc.*, 1941, **63**, 1929). For analysis, a specimen was sublimed at 70°/1 mm. (Found : C, 55·0; H, 7·6; N, 31·6. $C_6H_9N_3,\frac{1}{2}H_2O$ requires C, 54·6; H, 7·6; N, 31·8%).

The picrate separated from ethanol as needles, m. p. 205°, either alone or when mixed with a specimen prepared from authentic 2-amino-3 : 6-dimethylpyrazine. Tschitschibabin and Shukina (*J. Russ. Phys. Chem. Soc.*, 1930, **62**, 1189) give m. p. 205° for the picrate of 2-amino-3 : 6-dimethylpyrazine.

2-Amino-3 : 6-dimethylpyrazine (0·22 g.) was heated to 90° with propionic anhydride (5 c.c.) for 15 minutes. The solution was poured into water, and the excess propionic anhydride decomposed by warming the mixture. The mixture was neutralised by addition of aqueous sodium hydrogen carbonate and evaporated to dryness under reduced pressure. The residual solid was extracted with boiling benzene (3 × 10 c.c.), the filtered extract evaporated to dryness, and the residue crystallised from benzene, from which 2-propionamido-3 : 6-dimethylpyrazine (0·2 g.) separated as needles, m. p. 107° either alone or when mixed with the specimen described above; a mixture with 2-amino-3 : 6-dimethyl pyrazine had m. p. 98—100°. 2-Hydroxy-3 : 6-dimethylpyrazine (60% yield), m. p. and mixed m. p. 211°, was obtained from this specimen of 2-amino-3 : 6-dimethylpyrazine by using the method described by Baxter, Newbold, and Spring (*loc. cit.*).

2-*Propionamido*-3 : 6-*diethylpyrazine*.—Treatment of α-bromopropionamidomethyl ethyl ketone with liquid ammonia was carried out as described in the preparation of the dimethyl homologue with the difference that the filtration of the benzene extract through a column of alumina was omitted. The benzene extract was evaporated to dryness, and the solid crystallised from benzene–light petroleum (b. p. 40—60°), from which 2-*propionamido*-3 : 6-*diethylpyrazine* separated as needles (yield 62%), m. p. 98°; it was soluble in water and most organic solvents and sublimed readily at 70°/0·5 mm. (Found : C, 63·9, 64·1; H, 8·0, 8·0. $C_{11}H_{17}ON_3$ requires C, 63·8; H, 8·2%).

2-*Amino*-3 : 6-*diethylpyrazine*.—A solution of 2-propionamido-3 : 6-diethylpyrazine (0·2 g.) in N-sodium hydroxide solution (10 c.c.) was heated under reflux. After 1 hour, an oil began to separate, and after 3 hours the mixture was cooled, whereupon the oil crystallised. The solid was isolated by means of ether, evaporation of the dried ethereal solution giving 2-*amino*-3 : 5-*diethylpyrazine* as long needles, m. p. 42°. It is extremely soluble in water and the common organic solvents and this property precluded efficient crystallisation. For analysis, it was sublimed at 35°/10^{-4} mm., being obtained as hygroscopic needles, m. p. 42° (Found : C, 60·2, 60·5; H, 8·2, 8·8; N, 25·9, 26·0. $C_8H_{13}N_3,\frac{1}{2}H_2O$ requires C, 60·0; H, 8·7; N, 26·2%). Its *picrate* separated as needles from ethanol, m. p. 157° (Found : C, 44·7; H, 4·2; N, 22·2. $C_{14}H_{16}O_7N_6$ requires C, 44·4; H, 4·2; N, 22·1%).

A mixture of 2-amino-3 : 6-diethylpyrazine (0·2 g.) and propionic anhydride (5 c.c.) was kept at 90° for 15 minutes, solution then being complete. The cold solution was treated with water (10 c.c.), and the mixture warmed on the steam-bath to decompose the excess of anhydride. The mixture was neutralised by the addition of sodium hydrogen carbonate and evaporated to dryness under reduced pressure. The residue was extracted with boiling benzene, and the dried extract evaporated to dryness. The crystalline residue was recrystallised from benzene–light petroleum (b. p. 40—60°), from which 2-*propionamido*-3 : 6-*diethylpyrazine* (0·2 g.) separated as needles, m. p. 98° not depressed when mixed with the specimen prepared as described above (Found : N, 20·3. $C_{11}H_{17}ON_3$ requires N, 20·3%).

2-*Hydroxy*-3 : 6-*diethylpyrazine*.—A solution of 2-amino-3 : 6-diethylpyrazine (0·2 g.) in N-hydrochloric acid (10 c.c.) at 0° was treated with sodium nitrite (0·2 g.) added in small quantities during 10 minutes with stirring. The solution was kept at 0° for 15 minutes and then allowed to attain room temperature, kept at this temperature for 3 hours, neutralised with sodium hydrogen carbonate, and extracted with chloroform. The dried (Na_2SO_4) extract was evaporated, and the crystalline residue recrystallised from light petroleum, from which 2-*hydroxy*-3 : 6-*diethylpyrazine* (0·1 g.) separated in needles, m. p. 135°. Light absorption in alcohol : Maxima at 2270 A., $\epsilon = 6800$, and 3220 A., $\epsilon = 8100$. For analysis, it was sublimed at 100°/10^{-3} mm. (Found : C, 63·7; H, 8·0; N, 18·2. $C_8H_{12}ON_2$ requires C, 63·2; H, 7·9; N, 18·4%).

2-*Propionamido*-3 : 6-*diphenylpyrazine*.—*ω*-(α-Bromopropionamido)acetophenone was treated with liquid ammonia as described for the preparation of 2-propionamido-3 : 6-dimethylpyrazine. After evaporation of the ammonia, the solid residue was extracted with boiling chloroform. The dried extract was evaporated, and the residue crystallised from ethanol, from which 2-*propionamido*-3 : 6-*diphenylpyrazine* separated as needles, m. p. 212·5°; yield 60%. It sublimed readily at 120°/10^{-3} mm. and was

insoluble in water and aqueous sodium hydroxide solution (Found: C, 75·0; H, 5·7; N, 14·0, 14·1. $C_{19}H_{17}ON_3$ requires C, 75·2; H, 5·6; N, 13·9%).

2-*Amino*-3 : 6-*diphenylpyrazine*.—A suspension of 2-propionamido-3 : 6-diphenylpyrazine (3·0 g.) in N-sodium hydroxide solution (25 c.c.) and ethanol (0·5 c.c.) was refluxed for 5 hours. The mixture was cooled, and the yellow solid collected. Crystallisation from ethanol gave 2-*amino*-3 : 6-*diphenylpyrazine* as yellow plates, m. p. 186°; yield 90%. Solutions of this base in the common organic solvents show a blue fluorescence. It was only weakly basic, solutions in concentrated hydrochloric acid depositing an orange-coloured hydrochloride which is decomposed by water with regeneration of the parent base. 2-Amino-3 : 6-diphenylpyrazine gave a positive carbylamine reaction; it did not yield a picrate under normal reaction conditions (Found : C, 78·0; H, 5·2; N, 16·8. $C_{16}H_{13}N_3$ requires C, 77·7; H, 5·3; N, 17·0%).

Treatment of 2-amino-3 : 6-diphenylpyrazine with propionic anhydride as described in the case of the diethyl homologue gave 2-propionamido-3 : 6-diphenylpyrazine as needles from ethanol, m. p. 212·5°, not depressed when mixed with the specimen described above (yield, quantitative) (Found : C, 75·6; H, 5·6; N, 13·9%).

The *diacetyl* derivative of 2-amino-3 : 6-diphenylpyrazine was obtained by heating the base (0·2 g.) under reflux with acetic anhydride (10 c.c.) for 15 minutes. The mixture was poured on ice, and the crystalline precipitate collected and crystallised from methanol, from which the diacetyl derivative separated as needles, m. p. 117° (Found : C, 72·3; H, 5·3. $C_{20}H_{17}O_2N_3$ requires C, 72·3; H, 5·4%).

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