## 71. *Pyrazine Derivatives. Part VIII. Synthesis of Acylamidopyrazines from Aminomethyl Ketones.*

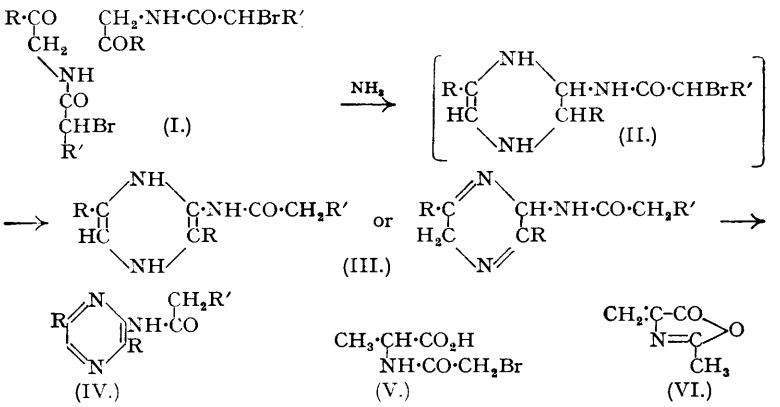
By G. T. Newbold, F. S. Spring, and Wilfred Sweeny.

The reaction described in Part V of this series whereby an α-bromopropionyl derivative of an aminomethyl ketone is converted into an acylamidopyrazine has been successfully extended to some corresponding phenylbromoacetyl derivatives. The mechanism of the reaction is discussed.

In Part V (*J.*, 1948, 1855) we have shown that treatment of an α-bromopropionyl derivative of an aminomethyl ketone (I; R′ = Me) with ammonia gives an α-propionamidopyrazine derivative (IV; R′ = Me) in high yield. Evidence concerning the mechanism of the reaction has been obtained by an examination of further cases. Our experience has hitherto been limited to α-bromopropionyl derivatives of different aminomethyl ketones (aminoacetone, 1-aminobutan-2-one, ω-aminoacetophenone), and it was considered desirable to extend this experience to other bromoacyl derivatives of aminomethyl ketones. Condensation of ω-aminoacetophenone with phenylbromoacetyl bromide gave ω-(*phenylbromoacetamido*)*acetophenone* (I; R = R′ = Ph); this on treatment with ammonia gave 3-*phenylacetamido*-2 : 5-*diphenylpyrazine* (IV; R = R′ = Ph), the structure of which was established by alkaline hydrolysis to 3-amino-2 : 5-diphenylpyrazine and phenylacetic acid.

Condensation of aminoacetone with phenylbromoacetyl bromide gave *phenylbromoacetamidoacetone* (I; R = Me, R′ = Ph), treatment of which with ammonia gave a compound, $C_{14}H_{17}ON_3$. This compound is 3-*phenylacetamido*-2 : 5-*dimethyldihydropyrazine*, since on standing in air or on oxidation under mild conditions with hydrogen peroxide it is converted into 3-*phenylacetamido*-2 : 5-*dimethylpyrazine* (IV; R = Me, R′ = Ph), the structure of which was established by alkaline hydrolysis to 3-amino-2 : 5-dimethylpyrazine and phenylacetic acid, and by its synthesis from 3-amino-2 : 5-dimethylpyrazine. If the reaction between ammonia and phenylbromoacetamidoacetone is carried out in an iron autoclave, 3-phenylacetamido-2 : 5-dimethylpyrazine is obtained and not the dihydro-derivative.

The isolation of a dihydropyrazine derivative is of some importance in a consideration of the mechanism of the general reaction. Condensation of two moles of a bromoacylamidomethyl ketone (I) with one mole of ammonia may give rise to a tetrahydropyrazine derivative such as



(II). The conversion of this tetrahydropyrazine into the aromatic pyrazine (IV) is most probably a two-stage process in which the dihydropyrazine (III) is an intermediate. Although a dihydropyrazine intermediate has been isolated in only one case of the general reaction, this is not surprising since dihydropyrazine derivatives, which are intermediates in numerous pyrazine syntheses, are readily oxidised to the corresponding aromatic pyrazine, and their isolation is either difficult or impossible. We believe that the tetrahydropyrazine (II) is oxidised to a dihydropyrazine by a simultaneous reductive dehalogenation of the bromoacyl group. In support of this view, we find that the general reaction is dependent upon the presence of a halogen atom in the acyl group, propionamidoacetone being recovered unchanged after treatment with ammonia.

The general reaction can now be formulated as shown at (I)—(IV). The step (II) ⟶ (III) bears a formal resemblance to the formation of azlactones such as (VI) from α′-halogenoacyl derivatives of α-amino-acids such as (V) (Bergmann and Stern, *Annalen*, 1926, **448**, 20; Bergmann, Kann, and Mieckley, *ibid.*, **449**, 135). The position of the double bonds in the dihydropyrazine (III) is an arbitrary choice; in the preparation of 3-phenylacetamido-2 : 5-dimethylpyrazine (IV; R = Me, R′ = Ph) the isolated intermediate dihydropyrazine does not exhibit selective absorption in the ultra-violet region of the spectrum and consequently it does not contain a conjugated system of double bonds.

## Experimental.

*ω-(Phenylbromoacetamido)acetophenone.*—A suspension of dry powdered ω-aminoacetophenone hydrochloride (10 g.) in dry chloroform (30 c.c.) was mixed with a solution of phenylbromoacetyl bromide (18 g.) in dry chloroform (30 c.c.). The mixture was rapidly stirred and treated at 0° with a solution of *N*-methylmorpholine (13·5 g.) in dry chloroform (30 c.c.) added dropwise during 1 hour. The mixture was stirred at room temperature for a further hour, and the chloroform solution washed successively with water, dilute hydrochloric acid, dilute sodium carbonate solution, and water. The dried ($Na_2SO_4$) solution was evaporated under reduced pressure. The crystalline solid was recrystallised from chloroform from which *ω-(phenylbromoacetamido)acetophenone* separated as prisms (yield 90%); for analysis it was recrystallised from light petroleum (b. p. 100—120°) from which it separated as needles, m. p. 119° (Found : C, 57·8; H, 4·3; N, 4·4. $C_{16}H_{14}O_2NBr$ requires C, 57·8; H, 4·2; N, 4·2%).

*Phenylbromoacetamidoacetone* was obtained in 85% yield from aminoacetone hydrochloride and phenylbromoacetyl bromide by the above procedure. It separated from benzene–light petroleum (b. p. 40—60°) as needles and from light petroleum (b. p. 100—120°) as plates, m. p. 108° (Found : C, 49·0; H, 4·3; N, 5·3. $C_{11}H_{12}O_2NBr$ requires C, 48·9; H, 4·4; N, 5·2%).

*3-Phenylacetamido-2 : 5-diphenylpyrazine.*—A solution of ω-(phenylbromoacetamido)acetophenone (6 g.) and ammonium iodide (1 g.) in liquid ammonia (200 c.c.) was kept in an autoclave at room temperature for 16 hours. Evaporation of the ammonia gave an oily residue which was extracted with boiling acetone (5 × 20 c.c.). The extract was concentrated, and on cooling deposited *3-phenylacetamido-2 : 5-diphenylpyrazine* as long needles, which, after recrystallisation from the same solvent, had m. p. 194° (yield, 25%) (Found : C, 79·2; H, 5·2; N, 11·4. $C_{24}H_{19}ON_3$ requires C, 78·9; H, 5·2; N, 11·5%).

*3-Amino-2 : 5-diphenylpyrazine.*—A suspension of 3-phenylacetamido-2 : 5-diphenylpyrazine (0·5 g.) in 0·1N-sodium hydroxide was refluxed for 3 days. The mixture was cooled, and the yellow solid collected by filtration and washed with water. Recrystallisation from ethanol gave 3-amino-2 : 5-diphenylpyrazine as yellow plates, m. p. 186° either alone or when mixed with an authentic specimen (yield,

quantitative). The alkaline filtrate from the reaction mixture was exactly neutralised with 0·1N-hydrochloric acid and evaporated to dryness under reduced pressure. The residue was extracted with ether, and the extract evaporated to give phenylacetic acid (0·11 g.), m. p. and mixed m. p. 74°. The acid was characterised by conversion into its amide by successive treatment with thionyl chloride and ammonia. Phenylacetamide was obtained from water as plates, m. p. 157° either alone or when mixed with an authentic specimen.

3-*Phenylacetamido*-2 : 5-*dimethyldihydropyrazine*.—Treatment of phenylbromoacetamidoacetone with liquid ammonia and ammonium iodide (using an autoclave fitted with a glass liner) as described above gave a product which was extracted with boiling benzene. Evaporation of the extract gave a crystalline solid which was recrystallised from benzene to give 3-*phenylacetamido*-2 : 5-*dimethyldihydropyrazine* as plates, m. p. 154° (yield, 60%). For analysis it was recrystallised from light petroleum (b. p. 100—120°) (Found : C, 69·9; H, 7·3; N, 17·1. $C_{14}H_{17}ON_3$ requires C, 69·1; H, 7·0; N, 17·3%). When the reaction was carried out in an iron autoclave without a glass liner, the product was 3-phenylacetamido-2 : 5-dimethylpyrazine, m. p. and mixed m. p. 130°.

The dihydropyrazine is unstable in air, the m. p. gradually falling. After 3 weeks the m. p. was less than 130°, after 3 months it was 116—124°, and a mixture with 3-phenylacetamido-2 : 5-dimethylpyrazine had an intermediate m. p.

3-*Phenylacetamido*-2 : 5-*dimethylpyrazine*.—A solution of 3-phenylacetamido-2 : 5-dimethyldihydropyrazine (0·14 g.) in methanol (2 c.c.) was treated with hydrogen peroxide solution (100 vol., 1 c.c.) and shaken overnight at room temperature. The solution was evaporated under reduced pressure to give 3-*phenylacetamido*-2 : 5-*dimethylpyrazine* (0·12 g.); this separated from light petroleum (b. p. 100—120°) as plates, m. p. 130° (Found : C, 69·7; H, 6·2; N, 17·3. $C_{14}H_{15}ON_3$ requires C, 69·7; H, 6·2; N, 17·4%).

3-*Amino*-2 : 5-*dimethylpyrazine*.—A solution of 3-phenylacetamido-2 : 5-dimethylpyrazine (0·5 g.) in 0·1N-sodium hydroxide (30 c.c.) was refluxed for 13 hours. The solution was cooled and extracted with ether. The ethereal solution was evaporated, and the residue crystallised from benzene to yield 3-amino-2 : 5-dimethylpyrazine (0·25 g.) as needles, m. p. 112°, undepressed when mixed with an authentic specimen. The picrate had m. p. 206° either alone or when mixed with 3-amino-2 : 5-dimethylpyrazine picrate. The aqueous alkaline phase from the ether extraction was acidified with dilute hydrochloric acid and evaporated to dryness under reduced pressure. Extraction of the residue with ether gave phenylacetic acid (0·2 g.), m. p. 69°, characterised by conversion into the amide which separated from water as plates, m. p. and mixed m. p. 157°.

3-Amino-2 : 5-dimethylpyrazine (50 mg.) was refluxed with phenylacetyl chloride (0·2 c.c.) in dry benzene (5 c.c.) for 3 hours. The mixture was cooled, and the solid collected and shaken with a mixture of 3N-sodium hydroxide (10 c.c.) and ether (100 c.c.). The ethereal layer was dried ($Na_2SO_4$) and evaporated. Recrystallisation of the residue from light petroleum (b. p. 100—120°) gave 3-phenylacetamido-2 : 5-dimethylpyrazine as plates, m. p. 130° either alone or when mixed with the specimen described above.

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