255. *Synthesis of the 2-ω-Aminoalkyl and 2-ω-Sulphanilamidoalkyl Derivatives of Thiazole and Pyrimidine.*

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4 : 6-Dimethyl-2-aminomethylpyrimidine and a series of 4-methyl-2-ω-aminoalkylthiazoles have been synthesised from the acylamidoalkyl cyanides described in the previous communication. From these new bases homologues of 2-sulphanilamido-4-methylthiazole and 2-sulphanilamido-4 : 6-dimethylpyrimidine have been prepared for examination as bacterial inhibitors.

Homologues of sulphanilamide containing the homologising methylene chain between the amino-group and the benzene ring and between the latter and the sulphonamide residue have previously been reported (Miller, Sprague, Kissinger, and McBurney, *J. Amer. Chem. Soc.*, 1940, **62**, 2099; G.P. 726382; Klarer, *Die Chemie*, 1943, **56**, 10; Bergeim and Braker, *J. Amer. Chem. Soc.*, 1944, **66**, 1459). In addition, similar homologues of 2-sulphanilamidothiazole (sulphathiazole) and 2-sulphanilamido-4 : 6-dimethylpyrimidine (sulphadimethylpyrimidine) have been prepared (Bergeim and Braker, *loc. cit.*) and shown to possess activities of a rather lower order against experimental *Cl. perfringens* infections than α-aminotoluene-*p*-sulphonamide (marfanil) (Hamre *et alii*, *Proc. Soc. Exp. Biol. Med.*, 1944, **55**, 170; compare also Maclennan, *Lancet*, 1943, **265**, 123; Schreus and Peltzer, *Klin. Wochenschr.*, 1941, **20**, 1233, 1250; Schreus, *ibid.*, 1942, **21**, 14; Domagk, *ibid.*, p. 448; Klöse and Schrober, *Zentr. Bakt.*, 1942, **149**, 15). It was accordingly of interest to synthesise a series of homologues of sulphathiazole and sulphadimethylpyrimidine in which the homologising chain occupies a position between the sulphonamido-residue and the heterocycle for examination as bacterial inhibitors.

Two methods were employed which would appear to be of general application for the preparation of this type of homosulphathiazole. Conversion of the ω-benzamidoalkyl or ω-phthalimidoalkyl cyanide into the corresponding thioamide, formation of the thiazole ring by condensation with an α-halogeno-aldehyde or -ketone, and hydrolysis of the product readily yielded the 2-(ω-aminoalkyl)thiazole; this was converted by the normal route into the 2-(ω-sulphanilamidoalkyl)thiazole. Alternatively, the ω-acetylsulphanilamidoalkyl cyanide was transformed into the thioamide, the latter treated with the α-halogeno-aldehyde or -ketone, and the resulting 2-(ω-acetylsulphanilamidoalkyl)thiazole deacetylated with aqueous alkali. The overall yields of the 2-aminoalkylthiazoles and 2-(ω-sulphanilamidoalkyl)thiazoles were of a high order with the lower members and also with the highest member of the series. With 5-acylamidoamyl cyanide, however, the normal procedure of hydrogen sulphide addition in the presence of ammonium sulphide gave the corresponding thioamide in yields of the order of only 25%; use of ethanolamine (Yuoh-Fong Chi, *J. Amer. Chem. Soc.*, 1942, **64**, 90) and alkali ethoxide as catalysts (Erlenmeyer, *Helv. Chim. Acta*, 1944, **27**, 412) failed to effect improvement. The α-halogeno-ketones employed were chloroacetone, ethyl α-chloroacetoacetate, ethyl γ-bromoacetoacetate, and ethyl bromopyruvate. It is of interest that a sample of ethyl α-chloroacetoacetate obtained by the action of sulphuryl chloride on ethyl acetoacetate after standing in diffused daylight in a closed bottle for 12 months gave the same high yield of ethyl 4-methyl-2-benzamidomethylthiazole-5-carboxylate on condensation with benzamidothioacetamide as did the freshly prepared compound, whereas Epprecht (*Annalen*, 1894, **278**, 79) states that ethyl α-bromoacetoacetate is not stable and on standing for several weeks isomerises in part to the γ-bromo-compound.

The 4-methyl-2-aminoalkylthiazoles are stable, distillable oils, very soluble in dilute acid; the 4-methyl-2-sulphanilamidoalkylthiazoles are well-crystallised compounds with much lower melting points than sulphathiazole and with considerably more solubility than the latter in water and dilute organic acids. The displacement of the thiazole ring from its adjacence to the sulphonamido-residue allows the basic function of the heterocycle, masked in 2-acetylsulphanilamidothiazole, to reappear; for example, the 2-acetylsulphanilamidoalkylthiazoles are easily soluble in cold aqueous mineral acid, whereas 2-acetylsulphanilamidothiazole is completely insoluble.

Less success was obtained in the case of the attempted preparation of a range of homosulphamethazines. Both benzamidomethyl cyanide and acetylsulphanilamidomethyl cyanide readily yielded the corresponding imino-ethers and amidines and these condensed with acetylacetone to give 4 : 6-*dimethyl-2-benzamidomethyl-* and *-2-acetylsulphanilamidomethylpyrimidine*; hydrolysis of the former with acid and the latter with dilute alkali gave respectively 4 : 6-*dimethyl-2-aminomethylpyrimidine* and 4 : 6-*dimethyl-2-sulphanilamidomethylpyrimidine*. Benzamidoacetamidine reacted readily with ethyl cyanoacetate but failed to give the expected

pyrimidine derivative; elimination of ammonia from the amidine residue and the reactive methylene group of the ester occurred with formation of *ethyl* (1-*amino*-2-*benzamidoethylidene*)-*cyanoacetate* in good yield. With malononitrile, benzamidoacetamidine reacted in the same manner with production of 1-*amino*-2-*benzamidoethylidenemalononitrile*; compare the similar condensation of ethyl cyanoacetate with formamidine and with benzamidine in the absence of alkali (Kenner *et alii*, *J.*, 1943, 388). The higher homologues of benzamidoacetamidine could not be induced to condense with acetylacetone under any of the varied reaction conditions employed.

Antibacterial Activities.—Infections of medium and low density with *Streptococcus hæmolyticus* (Aronson) were induced in mice by intraperitoneal inoculation of 0·5 c.c. of a 1 : 2000 dilution of a 24-hours old broth subculture of organisms of different virulence; the M.L.D. of the standard organism was 0·5 c.c. of a 1 : 32,000 dilution of the 24-hour old subculture, while the other organism used had been attenuated until the M.L.D. of the 24-hour old subculture was 0·5 c.c. of a 1 : 8000 dilution. Oral administration of daily divided doses of 200—300 mg./kg. of the 4-methyl-2-sulphanilamidoalkylthiazoles, Nos. **1423**, **1424**, **1432**, **1433**, **1323**, and of the sulphanilamidomethyl-4 : 6-dimethylpyrimidine, No. **1427**, failed to give complete protection to the mice; in the controls daily administration of 100 mg./kg. of sulphathiazole or sulphadiazine or 150 mg./kg. of sulphanilamide effected complete protection. All the compounds showed a small but nevertheless definite activity in daily doses of 400 mg./kg.

The activity of these homosulphonamides against *Cl. perfringens* infections in mice will be reported elsewhere.

Experimental.

(The acylamidoalkyl cyanides used are described in the previous paper.)

Benzamidothioacetamide.—Ammonia was passed into methyl alcohol (200 c.c.) until the increase in weight was 20 g., followed by hydrogen sulphide until 40 g. had been absorbed. Benzamidomethyl cyanide (50 g.) was added, and the resulting solution kept in a closed vessel at room temperature for 36—48 hours with occasional shaking. After the addition of water (500 c.c.) and standing for 12 hours, *benzamidothioacetamide* (40 g.; m. p. 152—154°) separated in small crystals. For analysis a sample was recrystallised from aqueous methyl alcohol and obtained in stout colourless prisms, m. p. 154° (Found : N, 14·7; S, 16·6. $C_9H_{10}ON_2S$ requires N, 14·4; S, 16·5%).

4-*Methyl*-2-*benzamidomethylthiazole.*—A solution of the foregoing thioamide (31 g.) in methyl alcohol (300 c.c.) and pyridine (25 c.c.) was refluxed with chloroacetone (23 c.c.) for 2 hours. The methyl alcohol was distilled off, water (200 c.c.) added, and the precipitated 4-*methyl*-2-*benzamidomethylthiazole* collected (35 g.; m. p. 108°). A sample separated from aqueous methyl alcohol in pale cream needles, m. p. 114—116° (Found : N, 12·3; S, 13·5. $C_{12}H_{12}ON_2S$ requires N, 12·1; S, 13·8%).

4-*Methyl*-2-*aminomethylthiazole.*—A solution of 4-methyl-2-benzamidomethylthiazole (35 g.) in 5N-hydrochloric acid (225 c.c.) was refluxed for 3 hours, cooled, the precipitate of benzoic acid removed, and the filtrate evaporated to small volume at reduced pressure. The residue was strongly basified with 10N-sodium hydroxide and extracted with ether (3 × 100 c.c.); after drying over potassium carbonate and distillation, the ethereal extract yielded 4-*methyl*-2-*aminomethylthiazole* (13·5 g.) as a colourless oil, b. p. 82—84°/5 mm. (Found : N, 22·1; S, 24·7. $C_5H_8N_2S$ requires N, 21·8; S, 25·0%).

4-*Methyl*-2-*sulphanilamidomethylthiazole* (No. 1423).—4-Methyl-2-aminomethylthiazole (2·5 g.) was heated on the water-bath for ½ hour with a solution of acetylsulphanilyl chloride (4·7 g.) in anhydrous pyridine (10 c.c.). The mixture was cooled, diluted with water, and the precipitated 4-*methyl*-2-*acetylsulphanilamidomethylthiazole* (4·9 g.) collected; this crystallised from aqueous alcohol in cream leaves, m. p. 176° (Found : N, 13·1; S, 19·3. $C_{13}H_{15}O_3N_3S_2$ requires N, 12·9; S, 19·7%).

The foregoing acetamido-compound (4·0 g.) was heated with 2·5N-sodium hydroxide (32 c.c.) at 100° for 1 hour, the solution diluted with water, partly neutralised with acetic acid, the filtered solution (charcoal) acidified with acetic acid, and the precipitate collected. Recrystallisation from aqueous alcohol yielded 4-*methyl*-2-*sulphanilamidomethylthiazole* (3·1 g.) in colourless plates, m. p. 124—126° (Found : N, 14·6; S, 23·0. $C_{11}H_{13}O_2N_3S_2$ requires N, 14·8; S, 22·6%).

4-*Methyl*-2-*aminomethylthiazole*-5-*carboxylic Acid.*—A solution of β-benzamidothioacetamide (19·4 g.) in anhydrous methyl alcohol (225 c.c.) and anhydrous pyridine (12 c.c.) was refluxed with ethyl α-chloroacetoacetate (18 c.c.; Dey, *J.*, 1915, **107**, 1646) for 5 hours. The solvent was distilled off to incipient crystallisation, and the solution (70 c.c.) chilled, *ethyl* 4-*methyl*-2-*benzamidomethylthiazole*-5-*carboxylate* (25 g.; m. p. 140°) separating in long colourless needles; by evaporation of the filtrate a further crop (1·5 g.) was obtained (Found, in recrystallised material, m. p. 140—142° : N, 8·9; S, 10·4. $C_{15}H_{16}O_3N_2S$ requires N, 9·2; S, 10·5%).

A solution of the foregoing benzamido-compound (6·1 g.) in methyl alcohol (50 c.c.) was refluxed with 5N-sodium hydroxide (10 c.c.) for 1 hour. After standing overnight at 20° the alcohol was distilled away at reduced pressure, the residue dissolved in water (70 c.c.), filtered (charcoal), and the solution adjusted to pH 4 with hydrochloric acid; 4-*methyl*-2-*benzamidomethylthiazole*-5-*carboxylic acid* (5·0 g.) separated as a microcrystalline precipitate. The acid crystallised from 50% alcohol in glittering white tablets, m. p. 252—254° (decomp.) (Found : N, 10·3; S, 11·7. $C_{13}H_{12}O_3N_2S$ requires N, 10·2; S, 11·6%).

A solution of crude ethyl 4-methyl-2-benzamidomethylthiazole-5-carboxylate (15 g.) in methyl alcohol (200 c.c.) was refluxed with 10N-hydrochloric acid (100 c.c.) for 14 hours. The solution was distilled in a current of steam to remove alcohol and benzoic acid and, after the addition of more hydrochloric acid, evaporated to very small volume; on cooling, 4-*methyl*-2-*aminomethylthiazole*-5-*carboxylic acid hydrochloride* separated in small prisms (6 g.), m. p. 248—250° (decomp.) (Found, in material dried at 120°/1 mm. over phosphoric oxide : N, 13·7; Cl, 16·8. $C_6H_8O_2N_2S,HCl$ requires N, 13·5; Cl, 16·9%).

The foregoing hydrochloride (5 g.) was dissolved in water (12 c.c.) and the solution adjusted to pH 3·5—4·0 by addition of 5N-sodium hydroxide (*ca.* 6 c.c.). When the resulting solution was kept on ice, *4-methyl-2-aminomethylthiazole-5-carboxylic acid* (2·8 g.) separated in white plates; these crystallised from 50% alcohol in stellate clusters of colourless feathers, m. p. 282—284° (Found: N, 16·4; S, 18·5. $C_6H_8O_2N_2S$ requires N, 16·3; S, 18·6%).

2-Benzamidomethyl-4-thiazolylacetic Acid.—A solution of benzamidomethylthioacetamide (9·7 g.) in anhydrous methyl alcohol (150 c.c.) and anhydrous pyridine (6 c.c.) was refluxed with ethyl γ-bromoacetoacetate (8·5 c.c.; Epprecht, *loc. cit.*) for 4½ hours. The solvent was distilled away at reduced pressure, the residual oil dissolved in warm 1·5N-hydrochloric acid (200 c.c.), and the solution filtered (charcoal) and adjusted to pH 7 with dilute sodium hydroxide; *ethyl 2-benzamidomethyl-4-thiazolylacetate* (12·5 g.) separated, which crystallised from benzene–ligroin in glittering plates, m. p. 86—88° (Found: N, 9·6; S, 10·9. $C_{15}H_{16}O_3N_2S$ requires N, 9·7; S, 11·0%).

A solution of the foregoing crude benzamido-compound (6 g.) in methyl alcohol (60 c.c.) and 5N-sodium hydroxide (10 c.c.) was refluxed for 1 hour. The solvent was removed at reduced pressure, the residue dissolved in a small volume of water, and the filtered solution adjusted to pH 4 with hydrochloric acid; *2-benzamidomethyl-4-thiazolylacetic acid* (3 g.) separated in colourless plates, which crystallised from dilute alcohol in glittering plates, m. p. 184—186° (Found: N, 10·3; S, 11·6. $C_{13}H_{12}O_3N_2S$ requires N, 10·2; S, 11·6%).

2-Benzamidomethylthiazole-4-carboxylic Acid.—A solution of freshly prepared and redistilled pyruvic acid (75 g.; 60 c.c.) and toluenesulphonic acid (6 g.) in ethyl alcohol (1250 c.c.) and benzene (300 c.c.) was refluxed under a 12″ Widmer column with a 10 : 1 reflux ratio and solvent removed at the rate of 100 c.c./hour. After 5 hours a further quantity of benzene (300 c.c.) was added and the distillation continued for another 4 hours, solvent being removed at the rate of 240—250 c.c./hour. After standing overnight the residual oil was distilled through a 6″ Vigreux column, the solvent being removed first at 760 mm. up to 80° to avoid loss of ester; redistillation of the fraction, b. p. 50—65°/20 mm. (75 g.), yielded 68 g. of ethyl pyruvate as a colourless oil, b. p. 54—60°/20 mm. A solution of dry bromine (25 c.c.) in dry carbon tetrachloride (25 c.c.) was added dropwise during ½ hr. to a refluxing solution of ethyl pyruvate (58 g.) in carbon tetrachloride (100 c.c.). After standing for 3 hours, the oil was distilled and yielded a fraction (82 g.), b. p. 96—100°/10 mm., which on redistillation gave ethyl bromopyruvate (70 g.), b. p. 90—94°/8 mm.

A solution of benzamidothioacetamide (9·7 g.) in dioxan (110 c.c.) and benzene (40 c.c.) was heated on the water-bath with ethyl bromopyruvate (8 c.c.) for 2 hours. The solvent was *rapidly* distilled away at reduced pressure, the residual oil dissolved in 1·7N-hydrochloric acid (300 c.c.), and the solution filtered (charcoal), adjusted at 20° with stirring to pH 7·6 by addition of 5N-sodium hydroxide, and the precipitate of *ethyl 2-benzamidomethylthiazole-4-carboxylate* (5·0 g.; m. p. 76—80°) collected. Adjustment of the filtrate to pH 2·8—3·0 with hydrochloric acid effected precipitation of *2-benzamidomethylthiazole-4-carboxylic acid* (5·8 g.; m. p. 176—180°). The ester crystallised from benzene–ligroin in colourless plates, m. p. 82—84° (Found: N, 9·7; S, 10·9. $C_{14}H_{14}O_3N_2S$ requires N, 9·7; S, 11·0%); the acid separated from dilute alcohol in glittering colourless leaves, m. p. 180—182° (Found: N, 10·4; S, 11·9. $C_{12}H_{10}O_3N_2S$ requires N, 10·7; S, 12·2%). Interaction of the thioamide and ethyl bromopyruvate in alcoholic solution in the presence of pyridine yielded a dark gum.

Benzamidoacetamidine Hydrochloride.—A mixture of benzamidomethyl cyanide (40 g.), anhydrous chloroform (300 c.c.), and anhydrous ethyl alcohol (59 c.c.) was saturated at 5° with dry hydrogen chloride; the cyanide dissolved as the hydrogen chloride was passed in and then set to a crystalline mass which redissolved as the solution became saturated. After standing at 4° for 16—20 hours, the chloroform was pumped off at room temperature, and the crystalline residue (53 g.; m. p. 144—146°) of *benzamidoacetiminoether hydrochloride*, containing ammonium chloride as impurity, was washed with a little dry chloroform and dried in a vacuum (Found: N, 12·2; Cl, 15·8. $C_{11}H_{14}O_2N_2$,HCl requires N, 11·5; Cl, 14·6%). This was added to alcohol (300 c.c.; lime-dried), which had been previously saturated with dry ammonia at 5°, and the mixture swirled at room temperature until solution was obtained and then allowed to stand in a closed vessel at *ca.* 4° for 24 hours. After addition of absolute ether (200 c.c.), the crystalline precipitate of *benzamidoacetamidine hydrochloride* (44 g.), m. p. 184—186°, was collected and dried in a vacuum over sulphuric acid; from alcohol–ether a sample separated in colourless nacreous plates, m. p. 187° (Found: N, 20·1; Cl, 17·1. $C_9H_{11}ON_3$,HCl requires N, 19·7; Cl, 16·6%). The free amidine, m. p. 132—134°, precipitated by the addition of 5N-sodium hydroxide to a cold 20% aqueous solution of the hydrochloride, was unstable and rapidly became converted into benzamidoacetamide, which crystallised from boiling water in large colourless prisms, m. p. 186° (Found: C, 60·8; H, 5·8; N, 16·1. Calc. for $C_9H_{10}O_2N_2$: C, 60·6; H, 5·7; N, 15·7%).

4 : 6-Dimethyl-2-benzamidomethylpyrimidine.—A solution of benzamidoacetamidine hydrochloride (30 g.) in alcohol (150 c.c.) was refluxed with anhydrous potassium carbonate (20 g.) and acetylacetone (18 g.) for 4 hours. The alcohol was distilled off, water added to the residue, and the precipitated oil, which slowly solidified to a dark gum, lixiviated with warm dilute hydrochloric acid and, after chilling, the insoluble benzamidoacetamide removed. Basification of the filtrate with 5N-sodium hydroxide precipitated *4 : 6-dimethyl-2-benzamidomethylpyrimidine* (8·7 g.; m. p. 192—194°), which crystallised from aqueous methyl alcohol (charcoal) in slender colourless needles, m. p. 200° (Found: C, 69·6; H, 6·3; N, 17·8. $C_{14}H_{15}ON_3$ requires C, 69·7; H, 6·3; N, 17·4%). Many modifications of the above procedure failed to increase the yield.

4 : 6-Dimethyl-2-aminomethylpyrimidine.—A solution of crude 4 : 6-dimethyl-2-benzamidopyrimidine (36·5 g.) in 5N-hydrochloric acid (225 c.c.) was refluxed for 4 hours, cooled, the precipitate of benzoic acid removed, and the filtrate evaporated to dryness under reduced pressure. The residual hydrochloride was dissolved in warm water (200 c.c.), filtered (charcoal), evaporated under reduced pressure to small volume (100 c.c.), chilled, and strongly basified with 5N-sodium hydroxide. After standing, the precipitate was collected (22 g.; m. p. 152—156°), drained, boiled with water (250 c.c.), the unchanged benzamido-compound (4·0 g.) removed, and the filtered solution allowed to cool; *4 : 6-dimethyl-2-aminomethylpyrimidine* (17 g.) separated in colourless, hydrated, felted needles which on drying at 100° yielded an

anhydrous white powder, m. p. 168° (Found: C, 61·4; H, 8·1; N, 30·9. $C_7H_{11}N_3$ requires C, 61·3; H, 8·1; N, 30·6%). The *monohydrochloride* separated from methyl alcohol–ether in slender white needles, m. p. 244—246° (Found: N, 24·3. $C_7H_{11}N_3$,HCl requires N, 24·2%).

Acetylsulphanilamidoacetamidine Hydrochloride.—A mixture of acetylsulphanilamidomethyl cyanide (14·6 g.), dry chloroform (100 c.c.), and absolute ethyl alcohol (13·7 c.c.) was saturated with dry hydrogen chloride at 5° and then kept at *ca.* 4° for 7 days with occasional shaking. The solvents were pumped off at room temperature, the residue mixed with anhydrous alcohol (100 c.c.) which had previously been saturated with dry ammonia, and the solution, which rapidly crystallised, allowed to stand at room temperature for 16 hours. The solvent was pumped off, and the crystalline residue (16 g.; m. p. 160°) of *acetylsulphanilamidoacetamidine hydrochloride* washed with ether. For analysis a sample was recrystallised from alcohol–ether and obtained in white needles, m. p. 164—166° (Found: N, 19·0; Cl, 12·0. $C_{10}H_{14}O_3N_4S$,HCl requires N, 18·5; Cl, 11·8%). The free amidine was precipitated from the concentrated aqueous solution of the hydrochloride by 5N-sodium hydroxide but rapidly decomposed to *acetylsulphanilamidoacetamide*, which crystallised from boiling water in colourless rectangular prisms, m. p. 218—220° (Found: C, 44·1; H, 5·0; N, 16·0. $C_{10}H_{13}O_4N_3S$ requires C, 44·2; H, 4·8; N, 15·9%).

4 : 6-*Dimethyl-2-sulphanilamidomethylpyrimidine* (No. 1427).—Acetylsulphanilamidoacetamidine hydrochloride (10 g.), acetylacetone (6·0 c.c.), pyridine (14 c.c.), and water (6 c.c.) were heated together at 100° for 4 hours. Water (20 c.c.) was added, and the precipitate (4·8 g.; m. p. 256°) collected and recrystallised from aqueous alcohol, 4 : 6-*dimethyl-2-acetylsulphanilamidomethylpyrimidine* being obtained in slender cream needles, m. p. 260—262° (Found: C, 53·7; H, 5·3; N, 17·2. $C_{15}H_{18}O_3N_4S$ requires C, 53·9; H, 5·4; N, 16·9%).

The foregoing acetamido-compound (7·8 g.) was dissolved in 2·5N-sodium hydroxide (62 c.c.), and the solution heated on the water-bath for 1 hour, cooled, partly neutralised with dilute hydrochloric acid, and filtered (charcoal). Adjustment of the filtrate to pH 7·0 effected separation of 4 : 6-*dimethyl-2-sulphanilamidomethylpyrimidine* (6·6 g.) in microscopic needles, m. p. 230—232°, which after a further crystallisation from aqueous alcohol had m. p. 232—234° (Found: N, 19·4; S, 11·0. $C_{13}H_{16}O_2N_4S$ requires N, 19·2; S, 10·6%).

The compound was also obtained by the following route. Acetylsulphanilyl chloride (3 g.) was added to a solution of 4 : 6-dimethyl-2-aminomethylpyrimidine (2 g.) and sodium hydrogen carbonate (2 g.) in 60% acetone (50 c.c.). After being warmed on the water-bath for a short time, the mixture was diluted with water, and the precipitate collected. Crystallisation from aqueous alcohol yielded 4 : 6-dimethyl-2-acetylsulphanilamidomethylpyrimidine in cream needles, m. p. 261—262°, alone and in admixture with a sample prepared as above described.

Condensation of Benzamidoacetamidine with Malononitrile: 1-Amino-2-benzamidoethylidenemalononitrile.—A solution of benzamidoacetamidine hydrochloride (21·3 g.) in anhydrous alcohol (150 c.c.) was converted into the free amidine base by addition of a solution of sodium (2·3 g.) in alcohol (50 c.c.). Malononitrile (7·5 c.c.) was added, and the solution allowed to stand at 40—45°; the mixture rapidly turned orange and in 2 hours developed an ammoniacal odour and began depositing crystals. After 48 hours at this temperature the mixture was chilled, and the crystalline, almost colourless precipitate of 1-*amino-2-benzamidoethylidenemalononitrile* (25·5 g.; m. p. 206°) collected. A sample crystallised from dilute alcohol in colourless, glistening leaves, m. p. 220—222° (decomp.) with softening at 210° (Found, in material dried at 80°/2 mm. over phosphoric oxide: C, 63·6; H, 4·5; N, 24·9, 25·0. $C_{12}H_{10}ON_4$ requires C, 63·8; H, 4·4; N, 24·8%).

Condensation of Benzamidoacetamidine with Ethyl Cyanoacetate: Ethyl 1-Amino-2-benzamidoethylidenecyanoacetate.—A mixture of ethyl cyanoacetate (12·4 g.) and an anhydrous alcoholic solution of benzamidoacetamidine (prepared as in the foregoing example from 21·3 g. of benzamidoacetamidine hydrochloride in 150 c.c. alcohol and 2·3 g. of sodium in 50 c.c. alcohol) was kept for 48 hours at 40°; crystals rapidly separated with development of an ammoniacal odour. The mixture was chilled, and the crystalline precipitate of *ethyl 1-amino-2-benzamidoethylidenecyanoacetate* (24 g.; m. p. 196°) collected. A sample separated from dilute alcohol in colourless felted leaves, m. p. 198—200° (Found: C, 61·3; H, 5·4; N, 15·6, 15·5. $C_{14}H_{15}O_3N_3$ requires C, 61·5; H, 5·5; N, 15·4%).

α-Benzamidothiopropionamide.—α-Benzamidopropionitrile (11·2 g.) was added to freshly prepared methanolic ammonium sulphide (obtained by dissolution of 6 g. of ammonia and then 6 g. of hydrogen sulphide in 75 c.c. of methyl alcohol) and the solution kept in a sealed bottle at room temperature for 16 hours. On dilution with water *α-benzamidothiopropionamide* (7·6 g.) slowly separated; this crystallised from aqueous methyl alcohol in colourless needles, m. p. 146° (Found: N, 13·8; S, 15·4. $C_{10}H_{12}ON_2S$ requires N, 13·5; S, 15·4%).

4-Methyl-2-(1'-aminoethyl)thiazole.—A solution of the foregoing amide (50 g.) in methyl alcohol (200 c.c.) and pyridine (38 c.c.) was refluxed with chloroacetone (24 c.c.) for 2 hours, and the alcohol then distilled off. Addition of water to the residue precipitated *4-methyl-2-(1'-benzamidoethyl)thiazole* (50 g.), which crystallised from aqueous methyl alcohol in colourless needles, m. p. 112° (Found: N, 11·6; S, 13·4. $C_{13}H_{14}ON_2S$ requires N, 11·4; S, 13·0%).

A solution of the foregoing crude compound (50 g.) in 5N-hydrochloric acid (400 c.c.) was refluxed for 7 hours, cooled, the benzoic acid removed, and the filtrate evaporated almost to dryness at reduced pressure. Water (300 c.c.) was added, and the solution evaporated to very small volume, cooled, strongly basified with 10N-sodium hydroxide, and extracted with chloroform (2 × 50 c.c.). After drying and distillation, the chloroform extracts yielded *4-methyl-2-(1'-aminoethyl)thiazole* as a colourless oil (21 g.), b. p. 98—100°/12 mm. (Found: N, 20·0; S, 22·5. $C_6H_{10}N_2S$ requires N, 19·7; S, 22·6%).

α-Acetylsulphanilamidothiopropionamide.—α-Acetylsulphanilamidopropionitrile (9·2 g.) was added to freshly prepared methanolic ammonium sulphide (5 g. of ammonia and 5 g. of hydrogen sulphide in 100 c.c. of methyl alcohol), and the mixture kept at 20° with frequent shaking for 24 hours. Addition of water (150 c.c.) caused the *thio-amide* (6·6 g.) slowly to separate in colourless prisms, m. p. 220; these crystallised from aqueous methyl alcohol in stout prisms, m. p. 226° (Found: N, 14·2; S, 21·1. $C_{11}H_{15}O_3N_3S_2$ requires N, 14·0; S, 21·3%).

4-Methyl-2-(1'-sulphanilamidoethyl)thiazole (No. 1424).—A solution of the foregoing amide (5·0 g.) in

alcohol (50 c.c.), water (5 c.c.), and pyridine (4 c.c.) was refluxed with chloroacetone (2·4 g.) for 2 hours, and the alcohol then distilled off. Addition of water (50 c.c.) precipitated 4-*methyl*-2-(1′-*acetylsulphanilamidoethyl*)*thiazole* (5·2 g.; m. p. 172°) which crystallised from aqueous alcohol in pale cream needles, m. p. 180—182° (Found: N, 12·3; S, 18·6. $C_{14}H_{17}O_3N_3S_2$ requires N, 12·4; S, 18·9%).

Hydrolysis of the foregoing compound (4·2 g.) with 2·5N-sodium hydroxide at 100° for 1 hour yielded 4-*methyl*-2-(1′-*sulphanilamidoethyl*)*thiazole* (2·4 g.), which separated from dilute alcohol in colourless prisms, m. p. 168° (Found: N, 14·5; S, 21·3. $C_{12}H_{15}O_2N_3S_2$ requires N, 14·2; S, 21·6%).

β-Benzamidothiopropionamide.—A solution of β-benzamidopropionitrile (42 g.) in 96% alcohol (325 c.c.) containing 3·3% w/w ammonia was saturated with hydrogen sulphide and kept at *ca.* 40° for 5 days, more hydrogen sulphide being added each day. Solvent was pumped off from the semi-solid mixture, ether in excess added, and the precipitate collected. This was dissolved in 90% methyl alcohol (500 c.c.), the sulphur removed, and the filtrate evaporated to incipient crystallisation (vol. 250 c.c.); on standing in the ice chest, *β-benzamidothiopropionamide* (30 g.) separated in glittering colourless rhombs, m. p. 160—162°. A further quantity of less pure material was separated from the mother-liquor (Found: N, 13·6; S, 15·2. $C_{10}H_{12}ON_2S$ requires N, 13·5; S, 15·2%). The compound was obtained in similar yield by saturating the cold methyl-alcoholic solution of the nitrile with ammonia and then with hydrogen sulphide and keeping it in a sealed vessel at 40° for 5 days.

4-*Methyl*-2-(2′-*benzamidoethyl*)*thiazole.*—A solution of the foregoing amide (41·6 g.) in anhydrous methyl alcohol (600 c.c.) was refluxed with chloroacetone (24 c.c.) and anhydrous pyridine (32 c.c.) for 4½ hours. After standing overnight the solvent was distilled off, and the oil which separated dissolved in warm N-hydrochloric acid (300 c.c.), the solution filtered (charcoal), and the filtrate adjusted to pH 7·0 with ammonia; 4-*methyl*-2-(2′-*benzamidoethyl*)*thiazole* (40 g.) separated as an oil which solidified on scratching and freezing. The compound was obtained in slender colourless needles, m. p. 74—76°, by dissolution in warm benzene–ligroin and allowing the solvent to evaporate slowly in a current of cold filtered air (Found: C, 64·0; H, 5·9; N, 11·8; S, 13·6. $C_{13}H_{14}ON_2S$ requires C, 63·5; H, 5·7; N, 11·4; S, 13·0%).

4-*Methyl*-2-(2′-*aminoethyl*)*thiazole.*—The foregoing crude benzamido-compound (32 g.) was refluxed for 4 hours with 5N-hydrochloric acid (260 c.c.), the solution chilled, and the precipitated benzoic acid removed. The filtrate was evaporated to small volume, chilled, strongly basified with 10N-sodium hydroxide, and extracted several times with ether; the ethereal solution after drying over potassium carbonate yielded 4-*methyl*-2-(2′-*aminoethyl*)*thiazole* (15 g.) as a colourless oil, b. p. 102—104°/10 mm. (Found: N, 19·6; S, 22·2. $C_6H_{10}N_2S$ requires N, 19·7; S, 22·5%).

4-*Methyl*-2-(2′-*sulphanilamidoethyl*)*thiazole* (No. 1323).—A solution of acetylsulphanilyl chloride (17 g.) in acetone (50 c.c.) was added dropwise during 45 minutes to a mixture of 4-methyl-2-(2′-aminoethyl)-thiazole (10 g.), sodium hydrogen carbonate (10 g.), water (150 c.c.), and acetone (20 c.c.) stirred at 10—15°. Stirring was continued at 20° for a further 4 hours, water (150 c.c.) added, and the precipitate of 4-*methyl*-2-(2′-*acetylsulphanilamidoethyl*)*thiazole* (26 g.; m. p. 110°) collected and washed with water. The compound is insoluble in cold water but easily soluble in cold dilute hydrochloric acid and dilute sodium hydroxide. A sample crystallised from dilute alcohol in colourless needles, m. p. 116—118° (Found, in material dried at 1 mm. over phosphoric oxide: N, 12·3; S, 18·7. $C_{14}H_{17}O_3N_3S_2$ requires N, 12·4; S, 18·9%).

A solution of the foregoing crude acetamido-compound (20 g.) in 2·5N-sodium hydroxide (200 c.c.) was heated on the water-bath for 75 minutes. 10N-Hydrochloric acid (70 c.c.) was added, the solution filtered (charcoal), cooled, and adjusted with simultaneous scratching to pH 6·6—7·0 with dilute sodium hydroxide; 4-*methyl*-2-(2′-*sulphanilamidoethyl*)*thiazole* separated in small colourless crystals (15·8 g.; m. p. 92°), which crystallised from dilute methyl alcohol in elongated needles, m. p. 98—100° (Found, in material dried over phosphoric oxide at 1 mm.: N, 14·4; S, 21·4. $C_{12}H_{15}O_2N_3S_2$ requires N, 14·2; S, 21·6%). The compound is considerably more soluble in cold 5% lactic acid than is sulphathiazole.

β-Benzamidopropionamidine Hydrochloride.—A solution of β-benzamidopropionitrile (35 g.) in anhydrous chloroform (300 c.c.) and anhydrous ethyl alcohol (46 c.c.) was saturated at 5° with dry hydrogen chloride and set aside for 18—24 hours at 0—4°. The solvent was completely pumped off at 20°, and the glittering crystalline residue of β-benzamidopropionimino-ether hydrochloride was mixed with cold anhydrous ethyl alcohol (400 c.c.) and saturated with dry ammonia at 5°. The clear solution which resulted was allowed to stand at 5° for 24—30 hours, the ammonia pumped off at 20°, the volume made up to 400 c.c. with lime-dried alcohol, and the solution filtered at the b. p. to remove ammonium chloride and kept on ice; *β-benzamidopropionamidine hydrochloride* separated in large colourless transparent cubes (34 g.; m. p. 174—180°) which were collected and dried in a vacuum. From the mother-liquors a further 7 g. (m. p. 178—180°) was obtained by evaporation. A sample recrystallised from anhydrous ethyl alcohol had m. p. 178—180° (Found: N, 18·4; Cl, 16·4. $C_{10}H_{14}ON_3Cl$ requires N, 18·4; Cl, 15·6%).

All attempts to condense this amidine with acetylacetone (i) in dilute alcohol in presence of sodium carbonate at the b. p., (ii) in refluxing anhydrous alcohol in presence of sodium carbonate, (iii) in warm (40°) and in refluxing anhydrous alcohol in presence of 1 mol. or 2 mols. of sodium ethoxide failed to yield any of the required pyrimidine. In (i) a quantitative yield of *β-benzamidopropionamide* was obtained which crystallised from boiling water in heavy colourless prisms, m. p. 174—176° (Found: C, 62·2; H, 6·3; N, 14·6. $C_{10}H_{12}O_2N_2$ requires C, 62·6; H, 6·3; N, 14·6%).

γ-Phthalimidothiobutyramide.—A mixture of 3-phthalimidopropyl cyanide (20 g.) and freshly prepared methanolic ammonium sulphide (5 g. of ammonia and 12 g. of hydrogen sulphide in 120 c.c. of methyl alcohol) was kept at 40° in a closed vessel with frequent shaking for 48 hours. The mixture was chilled, and the precipitated *amide* (11·5 g.; m. p. 184°) collected; on re-heating the filtrate to 40—45° for 5 days, a further quantity (2 g.) separated. For analysis a sample was recrystallised from alcohol and obtained in colourless needles, m. p. 186° (Found: N, 11·3; S, 13·2. $C_{12}H_{12}O_2N_2S$ requires N, 11·3; S, 12·9%).

4-*Methyl*-2-(3′-*aminopropyl*)*thiazole.*—The above amide (10 g.), chloroacetone (5·6 g.), pyridine (6·5 c.c.), and methyl alcohol (70 c.c.) were refluxed together for 2 hours, the solvent distilled off, and the residue diluted with water. The oil which separated slowly solidified to a crystalline mass (11·2 g.) of

4-methyl-2-(3′-phthalimidopropyl)thiazole, which crystallised from aqueous methyl alcohol in colourless prisms, m. p. 80° (Found: N, 10·0; S, 11·4. $C_{15}H_{14}O_2N_2S$ requires N, 9·8; S, 11·2%).

The foregoing compound (45 g.) was refluxed with 10N-hydrochloric acid (340 c.c.) for 8 hours, the mixture chilled, the phthalic acid removed, and the filtrate evaporated almost to dryness at reduced pressure. Basification of the residue with 10N-sodium hydroxide and extraction with chloroform yielded *4-methyl-2-(3′-aminopropyl)thiazole*, which distilled as a colourless oil (19·5 g.), b. p. 120—122°/12 mm. (Found, in redistilled sample: N, 17·8; S, 21·2. $C_7H_{12}N_2S$ requires N, 17·9; S, 20·5%).

4-Methyl-2-(3′-sulphanilamidopropyl)thiazole (No. 1432).—Acetylsulphanilyl chloride (5 g.) was added to a rapidly stirred solution of 4-methyl-2-(3′-aminopropyl)thiazole (3 g.) and sodium hydrogen carbonate (3 g.) in 50% aqueous acetone (25 c.c.), and the mixture stirred for ½ hour at room temperature and then for a further ½ hour at 50—60°. Addition of water precipitated *4-methyl-2-(3′-acetylsulphanilamidopropyl)thiazole* (6·2 g.), which crystallised from aqueous methyl alcohol in colourless prisms, m. p. 91° (Found: N, 11·8; S, 17·3. $C_{15}H_{19}O_3N_3S_2$ requires N, 11·9; S, 16·9%). Deacetylation with 2·5N-sodium hydroxide at 100° for 1 hour yielded *4-methyl-2-(3′-sulphanilamidopropyl)thiazole*, which separated from aqueous methyl alcohol in colourless needles, m. p. 130—132° (Found: N, 13·8; S, 20·5. $C_{13}H_{17}O_2N_3S_2$ requires N, 13·5; S, 20·6%).

γ-Phthalimidobutyramidine Hydrochloride.—A solution of 3-phthalimidopropyl cyanide (20 g.) in dry chloroform (100 c.c.) and anhydrous alcohol (22 c.c.) was saturated at 5° with dry hydrogen chloride and kept overnight at 5°. The solvent was completely removed at 30° under reduced pressure, anhydrous alcohol (120 c.c.) added, and the solution saturated at 5° with dry ammonia. After standing at 0—5° for 72 hours, the solvent and excess ammonia were distilled away at < 30°; crystallisation of the residue from a small volume of water yielded *γ-phthalimidobutyramidine hydrochloride* (12 g.) in colourless nacreous plates, m. p. 180—182°; for analysis a sample was recrystallised from alcohol–ether and obtained in colourless plates, m. p. 186° (Found: N, 16·1; Cl, 14·0. $C_{12}H_{13}O_2N_3$,HCl requires N, 15·7; C., 13·3%). Attempts to condense this compound with acetylacetone failed to yield any of the desired pyrimidine.

5-Benzamidothiohexoamide.—A solution of 5-benzamido-*n*-amyl cyanide (4 g.) in methyl alcohol (24 c.c.) was saturated with ammonia and then with hydrogen sulphide at 0° and kept in a closed vessel at 50° for 72 hours. Addition of a small amount of water effected separation of the *hexoamide* (1·25 g.; m. p. 90°), which crystallised from aqueous methyl alcohol in colourless leaves, m. p. 94—96° (Found: N, 11·4; S, 12·4. $C_{13}H_{18}ON_2S$ requires N, 11·2; S, 12·8%).

Use of ethanolamine or of sodium or potassium ethoxide as catalyst failed to improve the yield, and accordingly the attempt to prepare the corresponding thiazole derivative was abandoned.

5-Benzamido-n-hexoamidine Hydrochloride.—A solution of 5-benzamido-*n*-amyl cyanide (10 g.) in chloroform (60 c.c.) and ethyl alcohol (10 c.c.) was saturated at 5° with dry hydrogen chloride, kept at 5° for 24 hours, and evaporated to dryness at *ca.* 20°, and anhydrous alcohol (50 c.c.), which had previously been saturated at 0° with ammonia, was added. After standing at 5° for 72 hours and then for a further 24 hours at room temperature, a portion of the alcohol was distilled off at reduced pressure, and the residue diluted with dry ether. The oil which separated slowly solidified to a crystalline mass of the *hydrochloride* (11·5 g.; m. p. 130°); crystallisation from alcohol–ether yielded white prisms, m. p. 132° (Found: N, 15·1; Cl, 13·7. $C_{13}H_{19}ON_3$,HCl requires N, 15·6; Cl, 13·2%). All attempts to obtain a pyrimidine derivative by condensation with acetylacetone were unsuccessful.

11-Benzamidothioundecoamide.—Hydrogen sulphide was passed into a solution of 10-benzamidodecyl cyanide (25 g.) in methyl alcohol (125 c.c.) and aqueous ammonia (*d* 0·880; 20 c.c.) until an increase in weight of 10 g. was obtained. The solution was heated in a closed vessel for 7 days at 35°, water (100 c.c.) added, and the precipitate collected and recrystallised from aqueous methyl alcohol, *11-benzamidothioundecoamide* (10·5 g.) separating in pale cream needles, m. p. 112° (Found: N, 8·9; S, 10·0. $C_{18}H_{28}ON_2S$ requires N, 8·7; S, 10·0%).

4-Methyl-2-(ω-aminodecyl)thiazole.—A solution of the foregoing amide (10·5 g.) in methyl alcohol (75 c.c.) and pyridine (5·4 c.c.) was refluxed with chloroacetone (4·0 c.c.) for 3 hours. The excess of solvent was distilled off, water (100 c.c.) added to the residue, and the *4-methyl-2-(ω-benzamidodecyl)thiazole* (11·5 g.; m. p. 54°) collected; this recrystallised from aqueous methyl alcohol in white plates, m. p. 58—60° (Found: C, 70·1; H, 8·5; N, 7·8; S, 8·6. $C_{21}H_{30}ON_2S$ requires C, 70·4; H, 8·4; N, 7·8; S, 9·0%).

The foregoing crude benzamido-compound (27·3 g.) was refluxed with 10N-hydrochloric acid (273 c.c.) for 12 hours, the mixture chilled, and the benzoic acid filtered off. The filtrate was evaporated to small volume at reduced pressure, diluted with water (200 c.c.), and evaporated to dryness. Addition of 5N-sodium hydroxide to the residue, followed by chloroform extraction and distillation, yielded *4-methyl-2-(ω-aminodecyl)thiazole* as a pale yellow oil (10 g.), b. p. 166—170°/0·5 mm. (Found: N, 11·0; S, 12·8. $C_{14}H_{26}N_2S$ requires N, 11·0; S, 12·6%).

4-Methyl-2-(ω-sulphanilamidodecyl)thiazole (No. 1433).—Acetylsulphanilyl chloride (3·2 g.) was added to a stirred mixture of the foregoing base (3·0 g.), sodium hydrogen carbonate (2·0 g.), and 50% aqueous acetone (20 c.c.). After being stirred for ½ hour at room temperature, the mixture was heated on the water-bath for ¼ hour, diluted with water (100 c.c.), and the precipitate (5·2 g.; m. p. 102°) collected. Recrystallisation from aqueous methyl alcohol yielded *4-methyl-2-(ω-acetylsulphanilamidodecyl)thiazole* in white needles, m. p. 102—104° (Found: N, 8·9; S, 14·2. $C_{22}H_{35}O_3N_3S_2$ requires N, 9·3; S, 14·2%). Deacetylation with 2·5N-sodium hydroxide in 50% aqueous alcohol at the reflux for 1½ hours gave *4-methyl-2-(ω-sulphanilamidodecyl)thiazole*, which separated from aqueous methyl alcohol in pale cream prisms, m. p. 108° (Found: N, 10·4; S, 15·8. $C_{20}H_{31}O_2N_3S_2$ requires N, 10·3; S, 15·7%).

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