247. *The Synthesis of ωω′-Bis-2′-amino-4′-thiazolylalkanes and N⁴-2′-Thiazolylsulphanilamides.*

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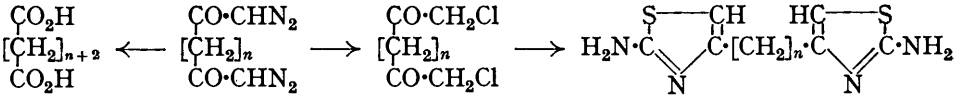
ωω′-Bischloroacetylalkanes react with thiourea with quantitative formation of the *dihydrochlorides* of *ωω′-bis-2′-amino-4′-thiazolylalkanes*. The Arndt–Eistert method for the homologation of carboxylic acids is applicable to the bis-homologation of dibasic acids. Two *N⁴-2′-thiazolylsulphanilamides* have been obtained by the condensation of p-*sulphonamidophenylthiourea* with the appropriate α-halogeno-ketones.

TRAUMANN (*Annalen*, 1889, **249**, 31) showed that derivatives of 2-aminothiazole were readily accessible by the condensation of α-halogeno-ketones with thiourea, and this reaction has now been extended to a number of ωω′-bischloroacetylalkanes (I) with the production of ωω′-bis-2′-amino-4′-thiazolylalkanes (II), which were of theoretical interest in relation to recent developments in the chemotherapy of trypanosomiasis (for brief review, *vide* Yorke, *Trans. R. Soc. trop. Med. Hyg.*, 1940, **33**, 463). The *dihydrochlorides* of 1 : 4-*bis*-2′-*amino*-4′-*thiazolyl*-n-*butane* (II; $n = 4$), 1 : 6-*bis*-2′-*amino*-4′-*thiazolyl*-n-*hexane* (II; $n = 6$), 1 : 8-*bis*-2′-*amino*-4′-*thiazolyl*-n-*octane* (II; $n = 8$), and 1 : 10-*bis*-2′-*amino*-4′-*thiazolyl*-n-*decane* (II; $n = 10$) were obtained in practically quantitative yield by the Traumann reaction from thiourea and 1 : 4-*bischloroacetyl*-n-*butane* (I; $n = 4$), 1 : 6-*bischloroacetyl*-n-*hexane* (I; $n = 6$), 1 : 8-bischloroacetyl-*n*-octane (I; $n = 8$), and 1 : 10-bischloroacetyl-*n*-decane (I; $n = 10$) respectively. These salts were somewhat sparingly soluble in water at room temperature and their saturated aqueous solutions had a p_H of the order of 5. The free bases also were isolated and are described below. The necessary ωω′-bischloroacetylalkanes (I) were obtained from the chlorides of the corresponding aliphatic dibasic acids containing two fewer carbon atoms by treatment with diazomethane, followed by decomposition of the resulting ωω′-bisdiazoacetylalkanes (III) with hydrogen chloride.



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

While ωω′-bisdiazoacetylalkanes (III) were being handled the opportunity was taken to see whether the Arndt–Eistert homologation process (*Ber.*, 1935, **68**, 200) would be applicable to the bis-homologation of dibasic acids, (III) ⟶ (IV), and this was found to be the case. Adipic acid and sebacic acid were readily bis-homologated in this way to suberic acid and decane-1 : 10-dicarboxylic acid respectively and it was found preferable to use the ammoniacal silver reagent and then to hydrolyse the resulting amides to the free acids. Arndt and Eistert (*loc. cit.*) also found this procedure preferable to attempting the direct preparation of the homologous acid or of its ester, although the direct conversion of 1 : 8-bisdiazoacetyl-*n*-octane (III; $n = 8$), prepared from sebacic acid, into decane-1 : 10-dicarboxylic acid (IV; $n = 8$) was also found to be a facile process.

In another connection the synthesis of the two *N*-2′-thiazolylsulphanilamides containing the thiazole moiety characteristic of vitamin B_1 was undertaken in the anticipation that these might be of interest in infections due to organisms requiring vitamin B_1 as a growth factor, and these experiments were already in progress when Fildes (*Lancet*, 1940, i, 955; cf. *Chem. and Ind.*, 1940, **59**, 133) published his thesis of a "rational approach" to chemotherapy, which embodied this idea. Much of the synthetic work projected and undertaken has, however, been recently anticipated (May and Baker, Newbery and Viaud, Brit. Pat. 517,272) and further work along these lines has therefore been suspended. The two *N⁴*-derivatives, *N⁴-4′-methyl-2′-thiazolylsulphanilamide* (V; R = H) and *N⁴-5′-β-hydroxyethyl-4′-methyl-2′-thiazolylsulphanilamide* (V; R = CH_2·CH_2·OH), resulted from

the condensation of 4-*sulphonamidophenylthiourea* (VI) with chloroacetone and methyl α-bromo-γ-acetoxypropyl ketone respectively.

Experimental.

The Preparation of Diazomethane.—In agreement with Owen, Ramage, and Simonsen (J., 1938, 1211) diazomethane has been found to be very economically accessible from nitrosomethylurea prepared, not according to Arndt (*Organic Syntheses*, **15**, 48), but from acetamide and bromine (Hofmann, *Ber.*, 1881, **14**, 2725, 2734; Werner, J., 1919, **115**, 1096). In addition, however, the precautions recommended by Odenwald (*Annalen*, 1918, **416**, 228; 1918, **418**, 317) should be observed if the maximum yields of the intermediate acetylmethylurea are to be obtained.

1 : 4-*Bisdiazoacetyl*-n-*butane* (III; $n = 4$).—Adipoyl chloride (9·1 g.) in dry ether (50 c.c.) was added dropwise to a dried (potassium hydroxide) solution of diazomethane (9·25 g.; estimated by titration against N/20-ethereal benzoic acid; cf. Marshall and Acree, *Ber.*, 1910, **43**, 2323) in ether (700 c.c.). A brisk effervescence took place and a crystalline separation occurred within a few minutes. The mixture was left overnight at room temperature and then concentrated to small bulk and chilled. The yellow crystalline product was collected (7·32 g.; m. p. 69—71°) and washed with a small amount of cold ether; it was free from chlorine. The mother-liquors on further concentration yielded a further small quantity (0·94 g.) of less pure product which contained traces of chlorine. The *compound* separated from benzene–ligroin (1 : 2) in lemon-yellow plates, m. p. 69—71°, *i.e.*, the main product as obtained initially was pure (Found: C, 49·9; H, 4·9; N, 28·1. $C_8H_{10}O_2N_4$ requires C, 49·5; H, 5·1; N, 28·9%).

1 : 4-*Bischloroacetyl*-n-*butane* (I; $n = 4$).—The foregoing compound in ether–chloroform (to increase solubility) was treated with dry hydrogen chloride until the yellow colour was discharged (5—10 minutes). Part of the product crystallised directly and the remainder was obtained by evaporation of the solvent under reduced pressure (yield, quantitative). The *substance* was readily soluble in the common organic solvents, but recrystallisation from ether afforded thin colourless rods, m. p. 81—82° (Found: C, 45·4; H, 5·6; Cl, 33·5. $C_8H_{12}O_2Cl_2$ requires C, 45·5; H, 5·7; Cl, 33·7%).

1 : 4-*Bis*-2'-*amino*-4'-*thiazolyl*-n-*butane* (II; $n = 4$) *Dihydrochloride*.—1 : 4-Bischloroacetylbutane (2·11 g.; 1 mol.) and thiourea (1·52 g.; 2 mols.) were dissolved in 66% aqueous alcohol (21 c.c.) and warmed on the water-bath. A microcrystalline solid separated after about 15 minutes and the mixture was left on the steam-bath for about 2 hours. After chilling in the ice-chest the colourless solid (2·64 g., m. p. 281—284°) was collected and a further quantity (0·53 g.) was obtained by concentrating the mother-liquors to small bulk (total yield, 97%). The *dihydrochloride* separated from hot water in small cubes with frequent twinning, m. p. 284—285° (efferv.) after darkening (Found: C, 37·1; H, 5·2; N, 17·2; S, 20·1; Cl, 21·3. $C_{10}H_{14}N_4S_2,2HCl$ requires C, 36·7; H, 4·9; N, 17·1; S, 19·6; Cl, 21·7%).

The free *base* was precipitated from a hot aqueous solution of the dihydrochloride by the addition of an excess of sodium bicarbonate solution. It separated from 50% aqueous alcohol in small, colourless, elongated, rhombic octahedra, m. p. 220—221° (Found: C, 47·7; H, 5·3. $C_{10}H_{14}N_4S_2$ requires C, 47·2; H, 5·5%).

1 : 6-*Bischloroacetyl*-n-*hexane* (I; $n = 6$).—Suberic acid (3·5 g.) was converted into the acid chloride with thionyl chloride (6 c.c.) and the crude chloride, freed from the excess of thionyl chloride, was added dropwise in ethereal solution (25 c.c.) to an excess of ethereal diazomethane (from 20 g. of nitrosomethylurea). After 12 hours chloroform was added to dissolve the bis-diazoacetylhexane which had crystallised and the solution was set aside for 30 minutes after saturation with hydrogen chloride. Evaporation of the ether–chloroform yielded the crude product in theoretical yield as a light brown solid. The *substance* separated from 60% aqueous methyl alcohol as a voluminous mass of small colourless plates, m. p. 85—86° (Found: C, 50·2; H, 6·6; Cl, 29·7. $C_{10}H_{16}O_2Cl_2$ requires C, 50·2; H, 6·7; Cl, 29·7%).

1 : 6-*Bis*-2'-*amino*-4'-*thiazolyl*-n-*hexane* (II; $n = 6$) *Dihydrochloride*.—1 : 6-Bischloroacetylhexane (1·2 g.; 1 mol.) and thiourea (0·76 g.; 2 mols.) were refluxed in 60% aqueous alcohol (25 c.c.) for 1½ hours and the resulting solution was filtered hot. On cooling, short stout prisms

separated: these (1·3 g., m. p. 306—308°) were collected and a further quantity (0·44 g.) was obtained after concentrating the mother-liquors to small bulk (total yield, 98%). Recrystallisation from hot water afforded short, stout, faintly cream-coloured prisms of the *dihydrochloride*, m. p. 308—310° after darkening (Found: C, 40·8; H, 5·8; N, 15·8. $C_{12}H_{18}N_4S_2$,2HCl requires C, 40·6; H, 5·6; N, 15·8%).

The free *base*, liberated by means of sodium bicarbonate solution, separated from 75% aqueous alcohol in microscopic bipyramids, m. p. 204—205° (Found: C, 51·1; H, 6·4; N, 19·8. $C_{12}H_{18}N_4S_2$ requires C, 51·0; H, 6·4; N, 19·8%).

1 : 8-*Bis*-2'-*amino*-4'-*thiazolyl*-n-*octane* (II; $n = 8$) *Dihydrochloride*.—1 : 8-Bischloroacetyloctane (2·67 g.; 1 mol.) (Work, this vol., p. 1318) and thiourea (1·52 g.; 2 mols.) were condensed in aqueous alcohol as in the examples already recorded; much of the product crystallised at the b. p. of the solution. The *dihydrochloride*, obtained in practically quantitative yield, separated from hot water in microscopic stout rhombs, m. p. 309—311° (efferv.) after darkening (Found: C, 44·1; H, 6·0; N, 14·3; S, 16·6; Cl, 18·2. $C_{14}H_{22}N_4S_2$,2HCl requires C, 43·9; H, 6·3; N, 14·6; S, 16·7; Cl, 18·5%).

The free *base*, isolated in the usual way, separated from 95% alcohol in lance-shaped prisms, m. p. 180—181° (Found: C, 54·4; H, 6·9. $C_{14}H_{22}N_4S_2$ requires C, 54·2; H, 7·1%).

1 : 10-*Bis*-2'-*amino*-4'-*thiazolyl*-n-*decane* (II; $n = 10$) *Dihydrochloride*.—1 : 10-Bischloroacetyldecane (2·95 g.; 1 mol.) (Work, *loc. cit.*) and thiourea (1·52 g.; 2 mols.) gave a quantitative yield of the *dihydrochloride* (m. p. 270—272°). Recrystallisation from hot water afforded colourless microscopic cubes, m. p. 274—276° after darkening (Found: C, 47·1; H, 6·6; N, 13·2; S, 15·4; Cl, 17·1. $C_{16}H_{26}N_4S_2$,2HCl requires C, 46·7; H, 6·8; N, 13·6; S, 15·6; Cl, 17·3%).

The free *base* separated from 70% aqueous alcohol in short stout prisms with pointed ends, m. p. 168—171° (Found: C, 56·9; H, 7·7. $C_{16}H_{26}N_4S_2$ requires C, 56·8; H, 7·7%).

Bis-homologation of Sebacic Acid. Decane-1 : 10-*dicarboxylic Acid*.—(A) 1 : 8-Bisdiazoacetyloctane (6·8 g.) (Work, *loc. cit.*), prepared from sebacoyl chloride, in warm dioxan (100 c.c.) was added to a suspension of freshly prepared silver oxide (7 g.) in water (250 c.c.) containing sodium thiosulphate (11 g.), stirred throughout at 75°. A fairly brisk effervescence took place and after 1½ hours at 75° the liquid was filtered from the black silver residue. Acidification of the clear, almost colourless filtrate with nitric acid yielded a gelatinous precipitate, which proved exceedingly difficult to filter; the product was therefore isolated by ether extraction. Evaporation of the dried extract afforded a white microcrystalline solid (4·5 g., 72%), m. p. 115—117°. Recrystallisation from 20% aqueous acetic acid raised the m. p. to 127—128°, undepressed on admixture with authentic decane-1 : 10-dicarboxylic acid (m. p. 126—127°) but depressed (108—113°) on admixture with sebacic acid [Found: C, 62·9; H, 9·4; equiv., 116. Calc. for $C_{12}H_{22}O_4$: C, 62·6; H, 9·5%; equiv. (dibasic acid), 115]. In another experiment a considerable bulk of the bisdiazoacetyloctane was precipitated in a crystalline condition when its dioxan solution was added to the aqueous mixture. It was recovered by extracting the silver residue with acetone and the following procedure was found to be an improvement.

(B) 1 : 8-Bisdiazoacetyloctane (3·9 g.) in warm dioxan (50 c.c.) was treated with 20% aqueous ammonia (15 c.c.) and 10% aqueous silver nitrate (3 c.c.) under reflux in a roomy flask on the water-bath. There was a gentle effervescence for a few minutes, terminated by a violent reaction in which the clear yellow colour of the solution disappeared and the mixture became dark brown and opaque. The solution, after remaining for ½ hour on the water-bath, was filtered hot; on cooling, it deposited the amide of decanedicarboxylic acid as a colourless microcrystalline solid (3·1 g., 87%), m. p. 181—184°, and 184—185° after recrystallisation from 25% aqueous acetic acid (Found: C, 62·8; H, 10·3; N, 12·1. Calc. for $C_{12}H_{24}O_2N_2$: C, 63·1; H, 10·5; N, 12·3%). Barnicoat (J., 1927, 2928) records m. p. 189°.

The diamide (1 mol.) was refluxed for *ca.* 2½ hours with 3N-potassium hydroxide (4 mols.); the acid, recovered quantitatively, separated from 20% aqueous acetic acid in large, thin, transparent plates, m. p. 127—128°, undepressed on admixture either with the specimen prepared in (A) (above) or with an authentic specimen.

Bis-homologation of Adipic Acid. Suberic Acid.—1 : 4-Bisdiazoacetylbutane (6 g.) (prepared from adipoyl chloride) in warm dioxan (60 c.c.) was treated with a mixture of 20% aqueous ammonia (25 c.c.) and 10% aqueous silver nitrate (4 c.c.). As in the preceding experiment, a moderate effervescence for a minute or two reached a climax in a violent effervescence and darkening. The mixture was left on the water-bath for ½ hour, and the reduced silver coagulated. The clear yellow solution was filtered and chilled and the solid (2·83 g.) which separated was collected. Concentration of the mother-liquor yielded a further quantity

(1·21 g.). The crude suberamide (5·43 g.) was directly hydrolysed to the more readily purified free acid by alkaline hydrolysis as in the analogous case described above. The crude acid (5·4 g.; overall yield, 75%) had m. p. 137—139°, which was raised to that (141°) of pure suberic acid by recrystallisation from water (Found: C, 55·3; H, 8·3. Calc. for $C_8H_{14}O_4$: C, 55·1; H, 8·0%).

4-Sulphonamidophenylthiourea (VI).—Sulphanilamide (17·2 g.) and ammonium thiocyanate (8 g.) were dissolved in N-hydrochloric acid (100 c.c.) and the solution was evaporated to dryness on the water-bath. The solid residue was triturated with water (100 c.c.) and again taken to dryness; this process was repeated a second time. The solid crystalline residue finally obtained was triturated with 3N-hydrochloric acid and washed with water; it then gave no diazo-reaction and unchanged sulphanilamide (2·55 g.) was recovered from the acid washings. The crude product (16·7 g.; net yield 85%), m. p. 205—206°, was readily purified by recrystallisation from hot water and the pure *compound* formed thin flat prisms with pointed ends, m. p. 209° (Found: C, 36·4; H, 4·3; N, 17·7; S, 27·1. $C_7H_9O_2N_3S_2$ requires C, 36·4; H, 3·9; N, 18·2; S, 27·6%).

N^4-*4′-Methyl-2′-thiazolylsulphanilamide* (V; R = H).—4-Sulphonamidophenylthiourea (2·31 g.) was dissolved in hot water (150 c.c.) and treated with freshly distilled chloroacetone (0·9 c.c.; 10% excess). The solution was left on the water-bath for 2 hours; on cooling, a solid (0·86 g.) separated, m. p. 228—229°. The remainder of the product was precipitated as a microcrystalline solid by the addition of an excess of sodium bicarbonate solution (total yield, 2·47 g.; 92%). The *compound* separated from 50% aqueous alcohol in colourless, thin, square plates, m. p. 234—235° (Found: C, 45·0; H, 4·1; N, 15·6; S, 23·6. $C_{10}H_{11}O_2N_3S_2$ requires C, 44·6; H, 4·1; N, 15·6; S, 23·9%).

N^4-*5′-β-Hydroxyethyl-4′-methyl-2′-thiazolylsulphanilamide* (V; R = $CH_2{\cdot}CH_2{\cdot}OH$).—4-Sulphonamidophenylthiourea (4·62 g.) and methyl α-bromo-γ-acetoxypropyl ketone (4·46 g.) were dissolved in warm 50% alcohol (60 c.c.) and left on the water-bath for 2 hours. The alcohol was then distilled off, and the resulting aqueous solution cooled, but no separation of solid took place until an excess of sodium bicarbonate solution was added. The resulting precipitate (6 g., 80%) was collected and dried. In the expectation that the solid would consist of incompletely deacetylated material it was dissolved in 3N-hydrochloric acid (*ca.* 70 c.c.) and kept overnight at 37°. A crystalline separation, presumably of a hydrochloride, took place. The mixture was diluted with water and treated with an excess of sodium bicarbonate solution and the precipitated solid was collected, washed with water, and dried. The *compound* separated from 50% aqueous alcohol either in stout tetrahedral wedges or in fine colourless needles depending upon whether the hot solution was cooled slowly or rapidly, m. p. 211—212°, depressed (188—194°) on admixture with 4-sulphonamidophenylthiourea (Found: C, 45·6; H, 4·9; N, 13·4. $C_{12}H_{15}O_3N_3S_2$ requires C, 46·0; H, 4·8; N, 13·4%).

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