687. *The Synthesis and Properties of 2 : 4-Diaminothiazoles.*

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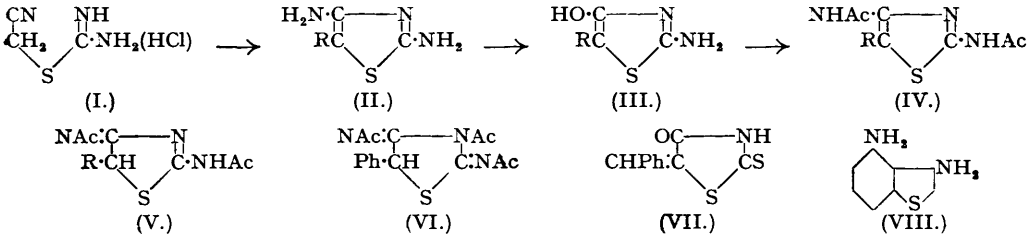
The reaction of thiourea with α-halogeno-nitriles to give the hydrohalide of 5-substituted 2 : 4-diaminothiazoles (II) is a general one. Similarly, chloroacetonitrile and selenourea give the hydrochloride of the selenium analogue of (II; R = H). The 4-amino-group of 2 : 4-diaminothiazoles is very easily hydrolysed by acid and 2 : 4-diaminothiazole itself seems devoid of aromatic character.

According to Miller, Kissinger, McBurney, and Sprague (*J. Amer. Chem. Soc.*, 1940, **62**, 2100, 2102), chloroacetonitrile and thiourea interact at room temperature in acetone to form *S*-(cyanomethyl)*iso*thiourea hydrochloride (I), m. p. 95—105° (decomp.). Zerweck and Schubert (D.R.-P. 729,853; *Chem. Zentr.*, 1943, I, 2033) claimed the production of the hydrochloride of (II) by the use of hot alcohol as solvent, but on repetition of the process Ganapathi and Venkataraman (*Proc. Indian Acad. Sci.*, 1945, **22**, *A*, 359) were unable to isolate the free base. Land, Ziegler, and Sprague (*J. Org. Chem.*, 1946, **11**, 622) then found that (I) was converted into the hydrochloride of (II) by means of hot alcohol. Meanwhile, the present authors had



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

(V.) (VI.) (VII.) (VIII.)

independently found that, when cold alcohol replaces acetone as solvent in the original condensation (Miller *et al.*, *loc. cit.*), the only product (which does not melt below 360°) is the hydrochloride of (II), into which the unstable (I) (prepared in acetone) is converted on attempted crystallisation. It is now found that the condensation of thiourea and α-halogeno-nitriles to form salts of 2 : 4-diaminothiazoles is a general reaction, which is, however, limited by the inactivity of the halogens in some substituted nitriles. The structure of the 2 : 4-diaminothiazole produced as above is proved by acid hydrolysis, which affords successively 2-amino-4-hydroxy- (III; R = H), and 2 : 4-dihydroxy-thiazole.

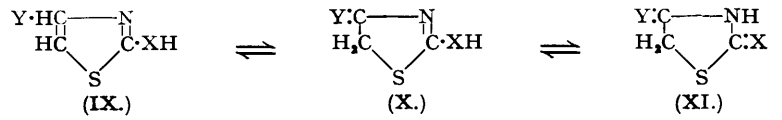
α-Bromobenzyl cyanide similarly gives the hydrobromide of 2 : 4-diamino-5-phenylthiazole (II; R = Ph), likewise converted stepwise by acid hydrolysis into the 2-amino-4-hydroxy- and the 2 : 4-dihydroxy-compound. The relatively inert α-chloropropionitrile reacts with alcoholic thiourea after the addition of sodium iodide, and yields the hydriodide of 2 : 4-diamino-5-methylthiazole (II; R = Me). However, attempts to condense α-bromo*iso*butyronitrile with thiourea have been unsuccessful. Although no reaction occurs between chloroacetonitrile and urea, which is less reactive in this sense than thiourea (Anderson, Faith, Marson, Winneck, and Roblin, *J. Amer. Chem. Soc.*, 1942, **64**, 2902), selenourea readily forms the hydrochloride of 2 : 4-diamino-1 : 3-selenazole (Se for S in II), the free base of which is too unstable to be isolated.

The 2 : 4-diaminothiazoles isolated are monoacid bases characterised as picrates, and their very soluble salts with halogen acids are stable to air for years. During the isolation of the free bases, especially (II; R = H), atmospheric oxidation readily produces tars and this may explain Ganapathi and Venkataraman's failure (*loc. cit.*, p. 360) to obtain the free base (II; R = H). These diaminothiazoles are almost completely devoid of aromatic character, for, unlike some 5-aminothiazoles, *e.g.*, 5-amino-2-mercapto-4-phenylthiazole (Cook, Heilbron, and Levy, *J.*, 1947, 1603), they neither form Schiff's bases with aldehydes nor undergo diazotisation. The 2 : 4-diaminothiazoles do not give the carbylamine reaction, which is, however, not a satisfactory test for amines in the thiazole series, since 2-aminothiazole also does not give this reaction under the usual conditions. Finally, both amino-groups are replaced by hydroxy-groups through acid hydrolysis, to which the 4-amino-group is extremely sensitive. This extreme activity accounts for the production of 4-hydroxy-2-anilinothiazole and not the expected diamine in the condensation of *N*-phenylthiourea with chloroacetonitrile.

An analogy is seen in the properties of 2 : 4-diaminothiazole and the so-called " isosteric " 2 : 6-diaminopyridine. Both these monoacid bases fail to form Schiff's bases (Schoeller and Schickh, D.R.-P. 563,132; " Friedlaender," XIX, 1128) or to undergo diazotisation (Titov,

Chem. Abs., 1939, **33**, 4248), and the structurally analogous 4- and 6-amino-groups are much more rapidly hydrolysed than the 2-amino-groups (Seide and Titov, *Ber.*, 1936, **69**, 1884). Similar lack of aromatic character is shown by some 2 : 4-disubstituted amino- or hydroxythiazoles such as 2-amino-4-hydroxythiazole (Culvenor, Davies, Maclaren, Nelson, and Savige, *J.*, 1949, 2573) and 2 : 4-dihydroxythiazole and related compounds, the properties of which indicate an imino- or " keto- " and a reactive methylene group. In general, compounds of this type including (II) react not so much in the aromatic form (IX) as in the partly saturated (X) and the completely saturated (XI) heterocyclic system. The introduction of an amino(or hydroxy)-group in other five-membered heterocyclic " aromatic " types is known to produce a similar effect. Thus the extremely labile 3- but not the 4-amino-group in 3 : 4-diaminothionaphthen (VIII) (Fries, Hemmecke, and Siebert, *Annalen*, 1937, **527**, 83) has no aromatic properties. Although in thiophen (Steinkopf, " Die Chemie des Thiophens," Leipzig, 1941, p. 59) and furan (*Ann. Reports*, 1939, **36**, 311) the presence of one amino-group causes a drastic weakening in aromatic character, yet three amino-groups are required to produce this effect in benzène (" Beilstein," Vol. 13, 294).

Acetylation of 2 : 4-diaminothiazole yields a diacetyl derivative (presumably IV or V; R = H), but 2 : 4-diamino-5-phenylthiazole yields in addition a triacetyl compound, probably (VI), from which the diacetyl compound is readily regenerated by hydrolysis. The structures (V) and (VI) take cognisance of the fact that the 4-amino-group in 2 : 4-diaminothiazoles seems,



(IX.) (X.) (XI.)

from its ready hydrolysis, to behave as a ketimino-group. Tautomerism of the 4-acetylimino- to the acetamido-group is still possible in both (V) and (VI), though no more acetyl groups can experimentally be introduced. The most easily hydrolysed acetyl group in (VI) is probably that in position 3, from analogy with the reactivity of the 3-sulphonylthiazoline derivatives (Hartman, Cueni, Druey, and Meyenburg, U.S.P. 2,386,852; *Chem. Abs.*, 1946, **40**, 5532).

It has been noticed that, when thioamides and related compounds can condense (Culvenor, Davies, and Heath, *J.*, 1949, 278) with ethylene oxides, they are also sufficiently reactive to condense with α-halogeno-nitriles. Since it was now found that ammonium dithiocarbamate forms 5-benzylidenerhodanine (VII) with ethyl phenylglycidate, it was expected that with α-chloroacetonitrile it would yield 4-amino-2-mercaptothiazole. The only products isolated, however, were ammonium chloride and sulphur-containing, indefinite liquids, which are also obtained when thioacetamide, benzyl dithiocarbamate, and *N*-allylthiourea are used. Also the expected synthesis of the hydrochloride of 2-amino-5 : 6-dihydro-4-imino-1 : 3-thiazine and its homologue from the condensation of thiourea with β-chloropropionitrile and with β-chloro-*iso*butyronitrile cannot be effected. Attention is directed to the structure of β-chloro*iso*-butyronitrile, Me·CH(CN)·CH_2Cl (prepared from acetone cyanohydrin and phosphorus pentachloride), since up to the work of Stevens (*J. Amer. Chem. Soc.*, 1948, **70**, 165) it had been recorded as the α-chloro-nitrile, $Me_2C(CN)Cl$.

2-Amino- and 2 : 4-diamino-thiazole have been reported (Shaw and Bentley, *Med. J. Australia*, 1949, **2**, 876) as having mild analeptic activity against morphine in the dog. Dr. Shaw (private communication) now reports that 2 : 4-diamino-5-phenylthiazole is a very potent analeptic, but 2 : 4-diamino-5-methylthiazole is without action.

Experimental.

2 : 4-*Diaminothiazole* (II; R = H).—The hydrochloride was produced almost quantitatively when chloroacetonitrile (1 mole) was added to a solution of thiourea (1 mole) in 15 times its weight of methyl alcohol, and the solution kept at room temperature for 3 weeks, or at 35° for one week. A larger proportion of ethyl alcohol was similarly used, and also refluxing of this solution for 4 hours gave a good yield of the hydrochloride. When acetone was used as solvent at room temperature (Miller *et al.*, *loc. cit.*), an oil gradually separated and slowly crystallised, and after several weeks at room temperature or a few minutes when boiled with 80% alcohol the product was again the above hydrochloride, which crystallised from 80% alcohol in short, fine needles very soluble in water; they darkened about 250° and melted above 360° (Found : C, 24·05; H, 4·0; Cl, 26·85; S, 20·8. Calc. for $C_3H_5N_3S$,HCl : C, 23·8; H, 4·0; Cl, 23·45; S, 21·1%). The free base was obtained when the hydrochloride (0·3 g.) was stirred with N-sodium hydroxide (2 c.c.), the solution acquiring a basic smell; the precipitate was filtered off, washed with a little water, and dried in a vacuum, and then crystallised from alcohol in colourless crystals (which gradually became pink and then brown in air), m. p. 143° (decomp.). Zerweck and Schubert (*loc. cit.*) report m. p. 145° (decomp.).

2 : 4-Diaminothiazole monopicrate was obtained by mixing an aqueous solution of the hydrochloride with an excess of picric acid solution, and separated from alcohol in yellow crystals, m. p. 223° (decomp.) (Found : S, 9·5. Calc. for $C_3H_5N_3S,C_6H_3O_7N_3$: S, 9·3%). Land *et al.* (*loc. cit.*) record m. p. >350°. Acetylation is also conveniently effected by use of the hydrochloride. To 2 : 4-diaminothiazole hydrochloride (3·04 g., 0·02 mole) in water (10 c.c.), sodium hydroxide solution (8 c.c.; 10%) was added, followed by acetic anhydride (4 c.c.). The mixture was shaken with cooling until one phase was obtained; subsequently, 2 : 4-*diacetamidothiazole* separated (2·3 g., 58%), and crystallised from aqueous alcohol in silky flakes, m. p. 240—241° (Found : C, 41·8; H, 5·1; N, 20·3. $C_7H_9O_2N_3S$ requires C, 42·2; H, 4·5; N, 21·1%). It was unchanged by boiling acetic anhydride and pyridine, and did not form a picrate.

2 : 4-*Diamino-5-phenylthiazole and Derivatives.*—Interaction of equimolar amounts of thiourea and α-bromobenzyl cyanide in alcohol at 35° (6 days) or on the water-bath (6 hours) gave 2 : 4-*diamino-5-phenylthiazole hydrobromide* in 83% yield after concentration of the alcoholic mother-liquor. It is very soluble in hot, moderately soluble in cold water, and crystallises from alcohol in prisms, m. p. >250° (decomp.) (Found : N, 15·8; S, 11·9. $C_9H_9N_3S,HBr$ requires N, 15·45; S, 11·8%). Its aqueous solution with a slight excess of sodium hydrogen carbonate or ammonia solution deposited 2 : 4-*diamino-5-phenylthiazole* (94% yield), flakes (from water or aqueous alcohol), m. p. 163—164° (decomp.), which slowly became yellow and then brown (Found : C, 56·7; H, 4·6. $C_9H_9N_3S$ requires C, 56·4; H, 4·7%). The *picrate*, yellow prisms from water, has m. p. 189—191° (decomp.) (Found : C, 43·15; H, 3·0; N, 20·15. $C_9H_9N_3S,C_6H_3O_7N_3$ requires C, 42·85; H, 2·85; N, 20·0%).

Diacetylation of 2 : 4-diamino-5-phenylthiazole was effected when the hydrobromide (2·7 g.) was warmed with pyridine (1 c.c.), cooled, mixed with acetic anhydride (10 c.c.), and kept at room temperature for 6 days. The precipitate was washed with water, and the crude 2 : 4-*diacetamido-5-phenylthiazole* (V; R = Ph) (1·9 g., 69%) then recrystallised from dioxan or alcohol in plates, m. p. 233—234° (Found : C, 56·8; H, 4·7; N, 15·2; S, 11·75. $C_{13}H_{13}O_2N_3S$ requires C, 56·7; H, 4·7; N, 15·25; S, 11·65%). With alcoholic picric acid it rapidly forms a *picrate*, yellow needles, m. p. 203—207° (decomp.), from alcohol (Found : N, 16·35; S, 6·5. $C_{13}H_{13}O_2N_3S,C_6H_3O_7N_3$ requires N, 16·7; S, 6·4%).

Triacetylation was effected under more vigorous conditions. 2 : 4-Diamino-5-phenylthiazole hydrobromide (5·4 g.), pyridine (2 c.c.), and acetic anhydride (20 c.c.) were boiled for one hour, cooled, and poured into water, and the crude 2 : 4-*diacetamido-3-acetyl-5-phenylthiazole* (VI) (5·8 g., 92%) recrystallised from benzene–acetic anhydride or from ethanol in prisms, m. p. 193—194·5° (Found : N, 12·90; O, 15·1; S, 10·2. $C_{15}H_{15}O_3N_3S$ requires N, 13·25; O, 15·1; S, 10·1%). It was also obtained when the diacetyl derivative (0·5 g.) was refluxed with acetic anhydride for one hour. The triacetyl derivative and alcoholic picric acid at ordinary temperatures slowly gave the picrate of the diacetyl compound (m. p. 203—207°), and the mother-liquor contained acetate ion. The tri- was also converted into the di-acetyl derivative when (*a*) it was refluxed in 20% alcohol for 6 hours, and (*b*) 0·34 g. in ethanol (8 c.c.) containing 10% sodium hydroxide (0·4 c.c., 0·33 mole) was kept at room temperature for 12 hours in a desiccator under reduced presure, which led to a gradual removal of the solvent.

Derivatives of 2 : 4-*Diamino-5-methylthiazole.*—Thiourea (3·8 g.) and α-chloropropionitrile (4·5 g.) did not interact in 96% alcohol (50 c.c.) at room temperature during 4 days, but at 40° the solution gradually became yellow, and in 10 weeks 2·63 g. of crystals were deposited. More was obtained by concentration of the mother-liquor and finally as the picrate, a total yield corresponding to 51% of 2 : 4-*diamino-5-methylthiazole hydrochloride* being obtained. This salt crystallised from 90% alcohol in prisms, m. p. 229—231° (decomp.) (Found : N, 25·45; Cl, 21·2. $C_4H_7N_3S,HCl$ requires N, 25·35; Cl, 21·4%). It was formed in 40% yield by refluxing of the alcoholic solution of the reactants for 20 hours. Molar quantities of thiourea, α-chloropropionitrile, and sodium iodide in 96% alcohol at room temperature gave in 3 months a 75% yield of 2 : 4-*diamino-5-methylthiazole hydriodide*, cream-coloured prisms, m. p. 225° (decomp.). During recrystallisation, rapid boiling of the alcohol is advisable to avoid separation of iodine (Found : N, 16·5. $C_4H_7N_3S,HI$ requires N, 16·35%). It was also formed in 72% yield by boiling an alcoholic solution of the reactants for 10 hours, followed by concentration of the solution on the water-bath at ordinary pressure. Attempts to prepare the free base from the chloride or iodide by means of the theoretical quantity of sodium hydroxide solution gave a pyridine-like smell, but the only derivative (also formed by the action of ammonia) was 2-amino-4-hydroxy-5-methylthiazole (III; R = Me), which was slowly deposited in the aqueous and not the ethereal layer used in extraction of the product. It formed long needles from water, sintered at 203°, and melted at 207—208° (decomp.) (Found : N, 21·55. Calc. for $C_4H_6O_2NS$: N, 21·55%). It was also made by refluxing α-chloropropionamide (2 g.) and thiourea (1·5 g.) in alcohol (25 c.c.) for 9 hours, the solution being evaporated to dryness after removal of ammonium chloride.

Unlike the other 2-amino-4-hydroxythiazoles, the 5-methyl derivative was recovered unchanged after being heated with concentrated hydrochloric acid on the water-bath; however, with 14N-sulphuric acid under similar conditions, the mixture gave off a strong mercaptan odour, and benzene-extraction yielded a colourless, alkali-soluble oil. This failed to crystallise, but is probably identical with 2 : 4-dihydroxy-5-methylthiazole, m. p. 46—47° (Wheeler and Barnes, *Amer. Chem. J.*, 1900, **24**, 78).

Although 2 : 4-diamino-5-methylthiazole is apparently too unstable to exist, the *monopicrate* readily formed orange needles (from water), m. p. 216—217° (Found : N, 23·15; S, 9·2. $C_4H_7N_3S,C_6H_3O_7N_3$ requires N, 23·45; S, 8·9%). 2 : 4-*Diacetamido-5-methylthiazole* was made by refluxing for 50 minutes a solution of 2 : 4-diamino-5-methylthiazole hydrochloride in acetic anhydride containing pyridine, followed by the evaporation of the water used to dilute the reaction product. It separated from water or alcohol–light petroleum in needles, m. p. 23° (Found : S, 14·95. $C_8H_{11}O_2N_3S$ requires S, 15·0%).

Miscellaneous Reactions.—No bromide ion was formed when α-bromo*iso*butyronitrile was refluxed with an alcoholic thiourea solution for 13 hours, but *N*-phenylthiourea and chloroacetonitrile reacted

when they were heated under reflux in alcohol for an hour and then kept at room temperature for 3 weeks. The alcoholic solution was decanted from a black tar and concentrated, water added, and the dark brown solid crystallised from aqueous alcohol, yielding a small amount of 4-hydroxy-2-anilinothiazole, plates, m. p. 177—179° (Wheeler and Johnston, *Amer. Chem. J.*, 1902, **28**, 144) record m. p. 178°. There was no depression in m. p. when it was mixed with a very pure specimen (m. p. 179—180°) obtained by refluxing for 2 hours 2-amino-4-hydroxythiazole (1·5 g.) and aniline (1 c.c.) in glacial acetic acid (15 c.c.) (compare Culvenor, Davies, Maclaren, Savige, and Nelson, *loc. cit.*).

Urea was unattacked when kept with alcoholic chloroacetonitrile at room temperature for a month, or at the b. p. for 16 hours. However, selenourea (1·3 g.) and chloroacetonitrile (0·7 g.) were refluxed in alcohol (20 c.c.) for 2½ hours, and the colourless precipitate (0·8 g.) was rapidly recrystallised from 80% alcohol in needles very soluble in water. Pure 2 : 4-*diamino*-1 : 3-*selenazole hydrochloride* (Found : N, 21·9. $C_3H_5N_3Se,HCl$ requires N, 21·2%), which did not melt below 250°, slowly deposited selenium from hot aqueous-alcoholic solution. Attempts to prepare the free base or to hydrolyse it to 2 : 4-dihydroxyselenazole resulted in the copious precipitation of selenium. 2 : 4-*Diaminoselenazole picrate*, formed by interaction of aqueous solutions of the diamine hydrochloride and sodium picrate, crystallised from water in golden needles, m. p. 220—225° (Found : N, 21·25. $C_3H_5N_3Se,C_6N_3O_7N_3$ requires N, 21·45%).

Hydrolysis of 2 : 4-*Diaminothiazole and its Derivatives.*—(i) 2 : 4-Diaminothiazole hydrochloride (0·5 g.) and water (7·5 c.c.) were heated under reflux for 6 hours, and the orange crystals (0·33 g., 85%) which separated recrystallised from water (charcoal) in colourless needles, m. p. 230—240° (decomp.), apparently identical with 2-amino-4-hydroxythiazole (Maly, *Ber.*, 1877, **10**, 1853) (Found : N, 24·3. Calc. for $C_3H_4ON_2S$: N, 24·15%). (ii) 2 : 4-Diaminothiazole hydrochloride (1·5 g.), water (10 c.c.), and concentrated hydrochloric acid (5 c.c.) were heated under reflux for 5 hours; the product formed on evaporation crystallised from water in needles, m. p. 125—126°, undepressed when mixed with authentic 2 : 4-dihydroxythiazole. (iii) Refluxing for 3 hours of a 5% aqueous solution of 2 : 4-diamino-5-phenylthiazole hydrobromide gave 2-*amino*-4-*hydroxy*-5-*phenylthiazole*, plates (from alcohol), m. p. 229—233° (depending on rate of heating) (Found : C, 56·2; H, 4·25; N, 14·65. $C_9H_8ON_2S$ requires C, 56·2; H, 4·15; N, 14·6%). It was also formed (mixed m. p.) in 58% yield by the interaction of α-bromophenylacetamide (5·6 g.) and thiourea (1·5 g.) in boiling alcohol (50 c.c.) for 2½ hours. The *picrate*, prepared in alcoholic solution, has m. p. 204° (Found : S, 7·7. $C_9H_8ON_2S,C_6H_3O_7N_3$ requires S, 7·6%). (iv) 2 : 4-Dihydroxy-5-phenylthiazole, prepared (time of boiling 2 hours) like 2 : 4-dihydroxythiazole (above), formed hair-like crystals, m. p. 130—131°. Wheeler (*Amer. Chem. J.*, 1901, **26**, 352) records m. p. 125—126° (Found : C, 56·4; H, 4·1. Calc. for $C_9H_7O_2NS$: C, 56·0; H, 3·65%). It was also formed when the di- and the tri-acetyl derivative of 2 : 4-diamino-5-phenylthiazole (1·0 g.) were boiled with dilute hydrochloric acid (10 c.c.; 6N.).

The unexpected formation of 2-amino-4-hydroxy-5-methyl- and 4-hydroxy-2-anilino-thiazole (above) instead of the expected free 2 : 4-diamino-derivatives affords further instances of the ready hydrolysis of the 4-amino-group.

5-*Benzylidenerhodanine.*—Ammonium dithiocarbamate (1·5 g.) and ethyl phenylglycidate (2·2 g.) in 75% alcohol (20 c.c.) were kept for a month at 35—40°, the sulphur was removed, and the filtrate concentrated under reduced pressure. The precipitated orange needles (0·1 g.), m. p. 203—204°, without recrystallisation, were identical (mixed m. p.) with 5-benzylidenerhodanine (VII) (Granacher, *Helv. Chim. Acta*, 1920, **3**, 152).

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