225. *Studies in the Azole Series. Part XI. The Interaction of α-Amino-nitriles, Hydrogen Sulphide, and Ketones.*

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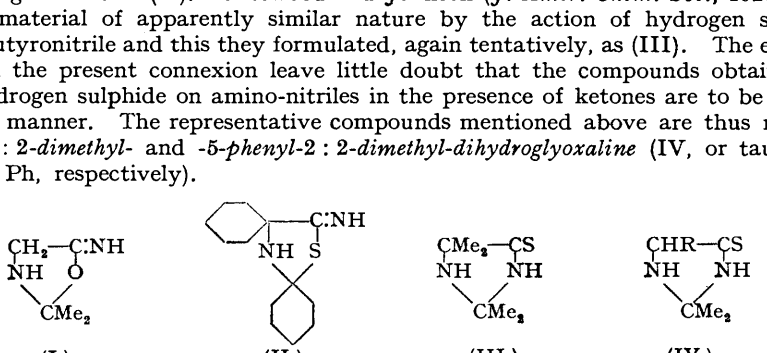
The interaction of aminoacetonitrile, acetone, and ethyl monothiobenzoate failed to give the expected 5-aminothiazole; instead, the monothio-ester appeared to provide the elements of hydrogen sulphide and the product was 4-*mercapto*-2 : 2-*dimethyldihydroglyoxaline* (IV; R = H). The same compound was obtained directly from aminoacetonitrile, acetone, and hydrogen sulphide. Analogous products were obtained from other combinations of α-amino-nitriles and ketones but not aldehydes.

Part I of this series (Cook, Heilbron, and Levy, *J.*, 1947, 1594) described the ready formation of 5-aminothiazoles which takes place when α-amino-nitriles are allowed to react with dithio-acids or their esters. The present work had its inception in attempts to replace the dithio-ester by a monothio-ester. On allowing ethereal solutions of ethyl monothiobenzoate and aminoacetonitrile or α-aminobenzyl cyanide to stand at 0° for several hours no reaction was observed, although these were the conditions which sufficed to give 5-aminothiazoles from ethyl phenyldithioacetate. Attempts to effect the reaction at high temperatures were also abortive. In cases where the preparation of the thiazoles described earlier had proved somewhat difficult, the Schiff's bases of these compounds were obtained comparatively easily by allowing the amino-nitrile and dithio-ester components to react in presence of the appropriate ketones. Accordingly, aminoacetonitrile and the above monothio-ester were allowed to react in acetone solution containing a catalytic amount of pyridine, and on prolonged cooling a crystalline material, soluble in both alkali and dilute hydrochloric acid, separated from the reaction mixture. It appeared to give a solid hydrochloride on treatment with alcoholic hydrogen chloride, the base being regenerated from the salt by treatment with ammonium hydrogen carbonate; these observations were clearly at variance with its formulation as a Schiff's base. Moreover, though the compound gave a monoacetyl derivative, attempts to diazotise it proved unavailing.

Finally, analysis conclusively showed that the product was not related to the expected 5-amino-thiazole, but seemed to indicate that it had been formed from acetone, hydrogen sulphide, and the amino-nitrile alone. The monothio-ester appeared merely to have contributed the elements of hydrogen sulphide, and it seemed worth while therefore to investigate the course of this reaction more closely. Accordingly, a study of the reaction was made with aminoacetonitrile and α-aminobenzyl cyanide on the one hand, and with acetone, methyl ethyl ketone, and acetophenone on the other. Ethereal solutions of the amino-nitriles were treated with an excess of the various ketones in presence of catalytic quantities of pyridine, and the mixtures then saturated with hydrogen sulphide. After several hours, the respective crystalline products separated in considerable yields. Of these, the compounds obtained from amino-acetonitrile and acetone, and from α-aminobenzyl cyanide and acetone, were selected for fuller study : the first product proved to be identical with the substance formed by use of ethyl monothiobenzoate, mentioned above. It had the composition $C_5H_{10}N_2S$, and the similar product from α-aminobenzyl cyanide had the formula $C_{11}H_{14}N_2S$. Both compounds were easily soluble in dilute acids and alkalis; the compound $C_{11}H_{14}N_2S$ yielded a *hydrochloride* from which it was regenerated by sodium hydrogen carbonate. The parent substances were further characterised as their *monoacetyl* derivatives. The latter were still soluble in dilute alkali without change and must be *N*-acetyl compounds. Pseudo-acidic groupings in these compounds were also evident from the formation of hydriodides of methyl derivatives on treating them with methyl iodide. Starting from α-aminobenzyl cyanide, the free methyl derivative was obtained from the salt on treatment with sodium hydrogen carbonate, and as it liberated methyl mercaptan on boiling with dilute sodium hydroxide, it must be an S-*methyl* derivative.

Acetone is known to condense with aminoacetonitrile in presence of a catalytic quantity of sodium methoxide to give a product which, as it affords aminoacetamide on treatment with water, has been formulated as (I) (Cook, Heilbron, and Levy, *J.*, 1948, 201). Bucherer and Brandt (*J. pr. Chem.*, 1934, **140**, 131) have obtained a product by heating *cyclo*hexanone cyanohydrin with ammonium sulphide which appears to be similar in behaviour to the new products under discussion. These authors observed that on dissolving the product in concentrated sulphuric acid and diluting the solution with water, a new material was obtained, evidently by replacement of an imino-group by oxygen, and for this reason they tentatively regarded it as (II). Gatewood and Johnson (*J. Amer. Chem. Soc.*, 1928, **50**, 1422) obtained a material of apparently similar nature by the action of hydrogen sulphide on α-amino*iso*butyronitrile and this they formulated, again tentatively, as (III). The experiments recounted in the present connexion leave little doubt that the compounds obtained by the action of hydrogen sulphide on amino-nitriles in the presence of ketones are to be formulated in the same manner. The representative compounds mentioned above are thus regarded as 4-*mercapto*-2 : 2-*dimethyl*- and -5-*phenyl*-2 : 2-*dimethyl-dihydroglyoxaline* (IV, or tautomerides; R = H and Ph, respectively).



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

If structure (IV) be accepted, it may well be that the cyclic compounds are preceded by the conversion of the α-amino-nitriles into α-amino-thioamides, and that the latter are the effective intermediates in the condensation with ketones. The thioamide of glycine could not be isolated after treating aminoacetonitrile with hydrogen sulphide (cf. Gatewood and Johnson, *loc. cit.*), but α-*aminophenylthioacetamide* was obtained from the corresponding nitrile by conducting the reaction in presence of a trace of pyridine, and was characterised as its *acetyl* derivative. This thioamide condensed spontaneously with acetone at room temperature to give (IV; R = Ph), identical with the material prepared earlier, and little doubt remains therefore of the course of the direct condensation between α-amino-nitriles, ketones, and hydrogen sulphide.

Experimental.

4-*Mercapto*-2 : 2-*dimethyldihydroglyoxaline*.—Aminoacetonitrile (11·2 g.) was suspended in ether (75 c.c.), and acetone (20 c.c.) added. After addition of a few drops of pyridine, hydrogen sulphide was passed in at 0° for 2 hours, and the solution kept at 5° for 12 hours. The solid (16·5 g.) which separated

was supplemented by a further crop (5·2 g.) obtained by evaporating the filtrate in a vacuum. The *thiol* crystallised from methanol as cubes, m. p. 154° (Found : C, 46·0; H, 7·8; N, 21·4. $C_5H_{10}N_2S$ requires C, 46·15; H, 7·7; N, 21·5%). It was soluble in ethanol, or hot water, and slightly soluble in ether or light petroleum. A solution of the substance in alcohol yielded on treatment with ethanolic hydrogen chloride, a crystalline hydrochloride which gave the parent compound on treatment with ammonium hydrogen carbonate. Recrystallisation from 95% ethanol converted it into what appeared to be *aminothioacetamide hydrochloride*, crystallising as glistening needles, m. p. 173° (decomp.) (Found : N, 22·0. $C_2H_7N_2ClS$ requires N, 22·1%). The compound also yielded a *picrate*, which crystallised from hot water as yellow needles, m. p. 143° (Found : N, 19·9; S, 8·9. $C_{11}H_{13}O_7N_5S$ requires N, 19·5; S, 8·9%).

The above compound (0·5 g.) was taken up in acetic anhydride (1 c.c.), and concentrated sulphuric acid (1 drop) added. Solution occurred, and the reaction was completed by a few minutes' heating under reflux. The solution was poured on ice, and the solid *acetyl* derivative recrystallised from toluene as beautiful leaflets, m. p. 204° (Found : C, 48·75; H, 6·8; S, 18·1. $C_7H_{12}ON_2S$ requires C, 48·8; H, 7·0; S, 18·6%).

The parent compound (0·5 g.) was dissolved in 2N-hydrochloric acid (10 c.c.). The solution was cooled in ice and treated slowly with stirring with a solution of sodium nitrite (0·5 g.) in water (1 c.c.). The solution became red and almost immediately a pale yellow precipitate appeared with vigorous effervescence. The reaction was completed by a few minutes' standing, and the precipitate (0·4 g.) crystallised on slow evaporation of its ethanol solution in very pale yellow needles. The *product* could be crystallised also from boiling water and then had m. p. 152° (decomp.) (Found : C, 37·8; H, 5·8; N, 21·6; S, 20·0. $C_{10}H_{19}O_3N_5S_2$ requires C, 37·4; H, 5·9; N, 21·8; S, 19·9%).

4-*Mercapto*-5-*phenyl*-2 : 2-*dimethyldihydroglyoxaline*.—α-Aminobenzyl cyanide (13·2 g.) in ether (120 c.c.) was treated with acetone (30 c.c.), and after addition of a few drops of pyridine, the solution was saturated with hydrogen sulphide for 2 hours while being kept at 0°. On allowing the mixture to stand at 5° for 48 hours, colourless prisms (17 g.) separated; these crystallised from 50% ethanol in colourless needles, m. p. 163° (Found : C, 64·1; H, 6·8; S, 15·5. $C_{11}H_{14}N_2S$ requires C, 63·9; H, 6·8; S, 15·2%). A solution of the *dihydroglyoxaline* in toluene yielded on treatment with ethanolic hydrogen chloride a *hydrochloride*, which recrystallised from ethanol as plates, m. p. 182° (Found : N, 11·6. $C_{12}H_{15}N_2ClS$ requires N, 11·6%). The picrate crystallised from hot water in reddish-yellow needles, m. p. 212° (darkening at 185°).

The above compound was taken up in acetic anhydride (2 c.c.), and concentrated sulphuric acid (1 drop) added. The clear solution was warmed to 90° for a few minutes and poured into ice-water; an oil separated which solidified on rubbing with ethanol. The *acetyl* derivative crystallised from ethyl acetate–light petroleum as colourless needles, m. p. 213—214° (Found : C, 62·8; H, 6·55. $C_{13}H_{16}ON_2S$ requires C, 62·9; H, 6·45%).

The above parent base (2 g.) was dissolved in concentrated hydrochloric acid (2 c.c.), diluted with water (15 c.c.), the solution cooled in ice, and treated with a solution of sodium nitrite (1 g.) in water (5 c.c.). There was immediate effervescence and a white solid separated. This was filtered off after the mixture had been kept in ice for 30 minutes, and the compound crystallised from toluene in needles, m. p. 157° (Found : C, 56·3; H, 4·9; N, 17·7%).

4-Mercapto-5-phenyl-2 : 2-dimethyldihydroglyoxaline (4 g.) was dissolved in ethanol (45 c.c.) and treated with excess of methyl iodide (2 c.c.). The solution was heated under reflux for 1 hour, cooled, diluted with light petroleum (100 c.c.), and kept at 5° for 24 hours. A glistening crystalline *hydriodide* (4 g.) was filtered off; it was easily soluble in water, and when recrystallised from ethanol–petroleum had m. p. 160° (decomp.) (Found : N, 7·7. $C_{12}H_{17}N_2IS$ requires N, 8·0%). Its aqueous solution was treated with excess of sodium hydrogen carbonate and kept at 0°. The solid was separated, and the mother-liquor extracted with ether. The combined ethereal extracts were evaporated to dryness in a vacuum, glistening plates (0·7 g.), m. p. 60°, being obtained. When recrystallised from a small quantity of ether (charcoal), 4-*methylthio*-5-*phenyl*-2 : 2-*dimethyldihydroglyoxaline* had m. p. 61° (Found : C, 65·5; H, 7·3; N, 12·7. $C_{12}H_{12}N_2S$ requires C, 65·4; H, 7·2; N, 12·4%). It was soluble in dilute acid but not in alkali.

4-Mercapto-5-phenyl-2 : 2-dihydroglyoxaline (5 g.) was dissolved in 5% aqueous sodium hydroxide (50 c.c.), and the solution heated under reflux for 2½ hours, ammonia being evolved. The solution was filtered and neutralised, whereupon a white precipitate (*ca.* 1·5 g.) separated. Recrystallisation gave phenylglycine, m. p. 250° (indefinite), the identity of which was proved by its conversion into mandelic acid by the action of nitrous acid.

4-Mercapto-5-phenyl-2 : 2-dimethyldihydroglyoxaline (1 g.) was dissolved in 5% sodium hydroxide (4 c.c.). Excess of benzoyl chloride (*ca.* 0·6 c.c.) was added, and the mixture shaken thoroughly for a few minutes, the liquid being kept alkaline by addition of aqueous sodium hydroxide. An oil separated, and the reaction was completed by warming to 90° for a few minutes. The gritty *benzoyl* derivative recrystallised from aqueous ethanol in clusters of needles, m. p. 236—237° (Found : C, 69·9; H, 5·8; N, 8·9. $C_{18}H_{18}ON_2S$ requires C, 69·8; H, 5·8; N, 9·0%).

4-Mercapto-5-phenyl-2 : 2-dimethyldihydroglyoxaline (2 g.) was dissolved in aniline (5 c.c.), and the solution heated under reflux for 1 hour. The clear solution was poured into dilute hydrochloric acid at 0°, the supernatant liquid decanted, and the oil solidified. This was crystallised repeatedly from aqueous acetone, from which the *compound* crystallised as pale yellow needles, m. p. 178° (Found : C, 64·55; H, 5·8; N, 13·45. $C_{22}H_{26}N_4S_2$ requires C, 64·4; H, 6·3; N, 13·6%).

The following were also prepared by saturating a solution of the appropriate amino-nitrile and ketone in ether containing a few drops of pyridine as catalyst with hydrogen sulphide (all three were crystallised from aqueous ethanol) : 4-*Mercapto*-2-*methyl*-2-*ethyldihydroglyoxaline*, prisms, m. p. 147° (Found : C, 50·6; H, 8·4. $C_6H_{12}N_2S$ requires C, 50·6; H, 8·3%); the 2-*phenyl*-2-*methyl* analogue, prisms, m. p. 157° (Found : C, 62·4; H, 6·7; N, 14·6. $C_{10}H_{12}N_2S$ requires C, 62·5; H, 6·25; N, 14·7%), and the 5-*phenyl*-2-*methyl*-2-*ethyl* analogue, prisms, m. p. 135° (Found : C, 65·4; H, 7·45; N, 12·4. $C_{12}H_{16}N_2S$ requires C, 65·5; H, 7·3; N, 12·7%).

α-Aminophenylthioacetamide.—A solution of α-aminobenzyl cyanide (3·3 g.) in ether (25 c.c.) containing a few drops of pyridine was saturated at 0° with hydrogen sulphide for 1 hour. The solution was kept at 0° for 24 hours, large colourless prisms (0·5 g.) then having separated. These crystallised as plates, m. p. 98°, from ethyl acetate–light petroleum. The *amide* was easily soluble in all common organic solvents (Found: C, 57·9; H, 6·2. $C_8H_{10}N_2S$ requires C, 57·8; H, 6·0%). The corresponding *α-acetamido*-compound was prepared by shaking an aqueous suspension of the preceding compound with excess of acetic anhydride; on standing, large prisms separated, and these recrystallised from water as plates, m. p. 130° (Found: N, 13·4. $C_{10}H_{12}ON_2S$ requires N, 13·5%).

A solution of the α-aminophenylthioacetamide in ethyl acetate was treated with excess of acetone and allowed to stand in the cold for 12 hours. Colourless prisms separated which were identified with 5-mercapto-4-phenyl-2 : 2-dimethyldihydroglyoxaline obtained above.

4-*Imino*-5-*phenyl*-2 : 2-*dimethyloxazolidine.*—α-Aminobenzyl cyanide (2 g.) was dissolved in dry acetone (15 c.c.) and treated with a solution of sodium ethoxide in ethanol to give a permanent turbidity. The solution was kept at 5° for 12 hours, and the colourless prisms (1·5 g.) which separated were recrystallised from dry acetone; m. p. 144° (Found: C, 69·9; H, 7·4; N, 15·2. $C_{11}H_{14}ON_2$ requires C, 69·5; H, 7·4; N, 14·7%). The *oxazolidine* dissolved in warm water, but on boiling its solution it was converted into α-aminophenylacetamide. The parent compound failed to yield 4-mercapto-5-phenyl-2 : 2-dimethyldihydroglyoxaline on treatment with hydrogen sulphide.

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