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The Addition of Hydrogen Sulphide to Some Unsaturated Aliphatic Nitriles and Carboxylic Acids

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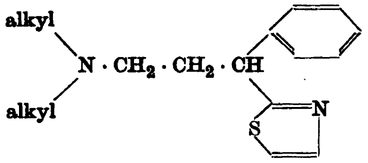
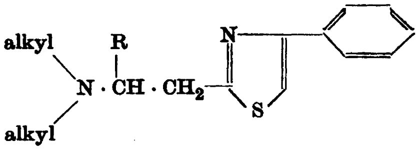
In a previous communication[1] the syntheses of a number of aminoalkyl derivatives of 2-benzylthiazole, of the type I, were described. In connection with this work it was desired to prepare a series of 2-aminoalkyl-4-phenylthiazoles, II.



I

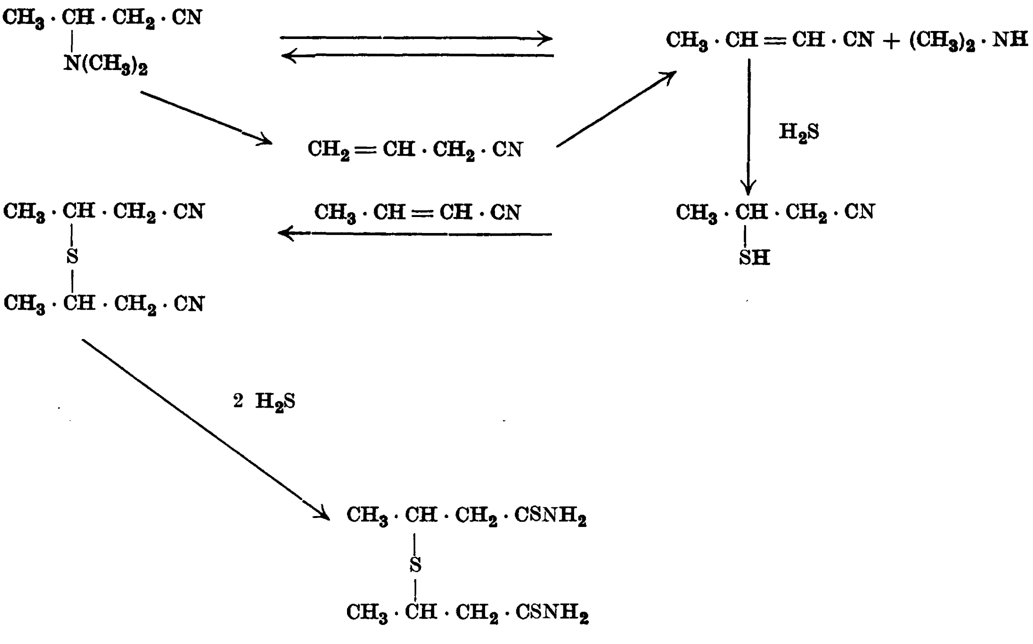


$R = H$ or CH_3

II

As starting materials for these syntheses β-dialkylaminosubstituted thiobutyramides and thiopropionamides were required, and attempts were made initially to prepare β-dimethylaminothiobutyramide by the addition of hydrogen sulphide to β-dimethylaminobutyronitrile in ethanolic solution at 70° using sodium ethoxide as a catalyst. A crystalline product melting at 169—170° was obtained, but this, however, did not have the properties of the expected thioamide. It was insoluble in acids, and analyses showed that it had the composition $C_8H_{16}N_2S_3$. Two thioamide groups were present as one mole of the substance reacted with two moles of ω-bromoacetophenone or ω,*p*-dibromoacetophenone to give thiazoles of the compositions $C_{24}H_{24}N_2S_3$ and $C_{24}H_{22}Br_2N_2S_3$ respectively. The former thiazole was oxidised by treatment with hydrogen peroxide in acetic acid to a compound having the composition $C_{24}H_{24}N_2OS_3$, and it was thus probable, that the third sulphur atom in the molecule was present as a sulphide group. The thioamide yielded, on hydrolysis with concentrated hydrochloric acid, an acid having equivalent weight 103, and melting at 84—84.5°. These constants agree with those recorded for the higher melting form of β,β′-thiodibutyric acid, prepared by Lovén and Johansson[2] and later shown by Johansson[3] to be the racemic form of the acid. The product obtained from the hydrolysis of the thioamide gave no melting point depression with an authentic sample of acid synthesised by the method of Lovén and Johansson[2], and the corresponding sulphones obtained from the thio acids by oxidation with potassium permanganate or bromine were also identical. It was thus evident that the reaction between β-dimethylaminobutyronitrile and hydrogen sulphide yielded *dl*-β,β′-thiodi-(thiobutyramide), if it be assumed that no inversion occurred during the hydrolysis.

The formation of this compound can be accounted for by the following reaction sequence



The first step is assumed to be the decomposition of β-dimethylaminobutyronitrile into dimethylamine and crotononitrile or possibly allyl cyanide, a type of reaction which has been reported[4,5] to take place with other β-dialkylaminonitriles on heating. This reaction is probably reversible but proceeds largely to completion owing to the removal of the crotononitrile by reaction with hydrogen sulphide. If allyl cyanide is the primary decomposition product, it would be expected to isomerise into crotononitrile almost instantaneously under conditions employed.

The second decomposition product, dimethylamine, acts as a catalyst for the addition of the hydrogen sulphide to crotononitrile, for the addition of β-mercaptobutyronitrile to another mole of crotononitrile, and for the formation of the thioamide. It is of course not impossible that the reactions occur in a different order. The sodium ethoxide added initially as a catalyst is of no importance, as the same reaction product is obtained in its absence.

In order to investigate the unexpected formation of β,β'-thiodi-(thiobutyramide) somewhat more closely, some other β-dialkylaminosubstituted or unsaturated nitriles were treated with hydrogen sulphide under similar conditions. β-Diethylaminobutyronitrile, allyl cyanide, and crotononitrile all yielded β,β'-thiodi-(thiobutyramide). If a very large excess (10 moles) of diethylamine, or better triethylamine, was used, excellent yields were obtained. It should be noted that acetyl and benzoyl derivatives of β-amino- and β-methylaminobutyronitrile are quite stable under the same conditions and give the expected β-acetylamino- and β-benzoylaminothiobutyramides[6]. The fact that allyl cyanide and crotononitrile give the same product is due to the rapid base catalysed isomerisation of the former compound. This isomerisation has been thorougly studied[4, 7–10], the resonance between the double bond and the cyanide group being the cause of the stability of crotononitrile. When sodium ethoxide alone was used as catalyst, allyl cyanide was isomerised to crotononitrile, and no reaction with hydrogen sulphide could be detected.

β-Dialkylaminosubstituted propionitriles seem to behave in an analogous manner to the butyronitriles. β-Diethylaminopropionitrile or acrylonitrile yielded a compound of m.p. 94—95° and having the composition $C_6H_{12}N_2S_3$, which was shown to be β,β'-thiodi-(thiopropionamide). Hydrolysis of this product gave an acid of m.p. 130—131° and equivalent weight 89, which proved to be identical with an authentic sample of β,β'-thiodipropionic acid.

When sodium ethoxide was used as catalyst, acrylonitrile added on ethanol forming β-ethoxypropionitrile, and no reaction with hydrogen sulphide could be detected. It is of interest to note, that in this case, the sodium ethoxide failed to catalyse the addition of hydrogen sulphide to the cyanide group, though it is usually considered to be superior to amines in this respect[11].

A related reaction has been reported by Gershbein and Hurd[12], who obtained β,β'-thiodipropionitrile from acrylonitrile and hydrogen sulphide using sodium methoxide or "Triton B" (trimethylbenzylammonium hydroxide) as catalyst by carrying out the reaction in the absence of solvent at 70° at atmospheric pressure. The same compound was obtained by Lieser and Kemmner[13] using acetone as solvent, and sodium sulphide as catalyst at room temperature. The formation of β,β′-thiodipropionitrile under these conditions, which are somewhat milder than those employed in the present investigation, is, however, evidence for the validity of the reaction sequence outlined above.

On the other hand, when γ-piperidinobutyronitrile was treated with hydrogen sulphide under the usual conditions, γ-piperidinothiobutyramide was smoothly formed.

In the hope of finding an easy route to β,β′-thiodibutyric acid, crotonic acid was treated with hydrogen sulphide in ethanolic solution in the presence of diethylamine. However, the only product was β-mercaptobutyric acid identified by conversion into β-benzylsulphonylbutyric acid. Vinylacetic acid, which is easily isomerised by bases to crotonic acid[8,14] gave the same product.

Acrylic acid when treated in this manner yielded β-mercaptopropionic acid together with β,β′-dithiodipropionic acid, apparently formed by oxidation of the mercapto acid.

A similar synthesis of a mercapto acid has recently been reported by Földi and Kollonitsch[15], who prepared β-mercapto-α-carboxy*iso*valeric acid by the addition of hydrogen sulphide to *iso*propylidenemalonic acid in ethanol solution and with triethylamine as catalyst.

EXPERIMENTAL

β-Dimethylaminobutyronitrile and hydrogen sulphide

β,β′-Thiodi-(thiobutyramide). β-Dimethylaminobutyronitrile (20 g, prepared according to Bruylants[4]) was dissolved in absolute ethanol (200 ml) in which sodium (0.5 g) had been dissolved. The mixture was saturated with hydrogen sulphide at — 20°, and then kept at 70° in a sealed glass bottle for sixteen hours. After cooling, the solvent was evaporated at reduced pressure, and the solid residue washed thoroughly with water and collected. The crude product (12.4 g) which melted at 149—153° was recrystallised three times from ethanol, giving white prisms, m. p. 169—170° (dec.).

$C_8H_{16}N_2S_3$ (236.4)	Calc.	C 40.7	H 6.82	N 11.9	S 40.7
	Found	» 41.0	» 6.84	» 11.7	» 40.9

In another experiment under the same conditions but with the omission of sodium, 4.1 g of crude product was obtained from 5.6 g of β-dimethylaminobutyronitrile. The purified thioamide was identical with the thioamide obtained above.

Hydrolysis of β,β′-thiodi-(thiobutyramide) to dl-*β,β′-thiodibutyric acid.* The thioamide (1.0 g) was refluxed with concentrated hydrochloric acid (10 ml) until hydrogen sulphide was no longer evolved (2 hours). The solution was extracted with ether (5 × 20 ml), the ether extract dried, and the solvent evaporated. The crystalline residue (0.9 g) was recrystallised twice from benzene — light petroleum, from which it separated in white plates, m. p. 84—84.5°, undepressed by an authentic specimen of *dl*-β,β'-thiodibutyric acid prepared by the method of Lovén and Johansson [8]. Titration of the product with 0.1 *N* sodium hydroxide gave an equivalent weight of 103.5 (calc. for β,β'-thiodibutyric acid 103.1).

Oxidation of dl-β,β'*-thiodibutyric acid to* dl-β,β'*-sulphonyldibutyric acid.* The thio acid (100 mg) was dissolved in water (1 ml) and a slight excess of bromine was added. After a few minutes the sulphone began to separate as white plates (86 mg). After recrystallisation from acetone — light petroleum the compound had m.p. 170—171° undepressed by an authentic sample of β,β'-sulphonyldibutyric acid prepared by the method of Lovén and Johansson [8] by the oxidation of the thio acid with potassium permanganate. Equivalent weight: found 118.8, calcd. 119.1.

β,β'*-Di-[4-(*p*-bromophenyl)-thiazolyl-2]-di*iso*propyl sulphide.* In order to show the presence of two thioamide groups, β,β'-thiodi-(thiobutyramide) (2.0 g, 8.5 millimoles) and ω,p-dibromoacetophenone (4.85 g, 17.5 millimoles) were refluxed in ethanol (15 ml) for half an hour. The precipitate which formed on cooling was collected, suspended in dilute ammonia, and the mixture shaken for an hour at room temperature. The solid (4.65 g) was collected and recrystallised twice from ethanol-acetone (4 : 1) forming white leaflets, m.p. 132—133°.

$C_{24}H_{22}Br_2N_2S_3$ (594.5)	Calc.	C	48.5	H	3.73	S	16.2
	Found	»	47.9	»	3.64	»	16.3

β,β'*-Di-(4-phenylthiazolyl-2)-di*iso*propyl sulphide* was prepared from the thioamide (2.5 g) and ω-bromoacetophenone (4.65 g) in the same manner as above. The crude product (4.0 g) was crystallised twice from light petroleum and then melted at 66—67°.

$C_{24}H_{24}N_2S_3$ (436.6)	Calc.	C	66.0	H	5.54	S	22.0
	Found	»	66.3	»	5.52	»	21.8

β,β'*-Di-(4-phenylthiazolyl-2)-di*iso*propyl sulphoxide.* The thiazole compound (250 mg) obtained above was dissolved in glacial acetic acid (5 ml), and 30 % hydrogen peroxide (0.3 ml) was added. The solution was kept at room temperature for a week and was then poured into excess of water. The precipitated oil solidified after a few days, giving white crystals (210 mg), melting at 89.5—90° after recrystallisation twice from acetone — light petroleum.

$C_{24}H_{24}N_2OS_3$ (452.6)	Calc.	C	63.7	H	5.35	N	6.19
	Found	»	63.9	»	5.58	»	6.13

γ,γ'*-Thiodi-(thiobutyramide).* As a comparison with the β,β'-compound, this thioamide was prepared from γ,γ'-thiodibutyronitrile [16] (8.0 g) and diethylamine (70 g) in ethanol (100 ml) under the usual conditions. The crude thioamide (7.4 g) was recrystallised twice from methanol and then melted at 88—90°.

$C_8H_{16}N_2S_3$ (236.4)	Calc.	N	11.9	S	40.7
	Found	»	11.6	»	40.0

γ,γ′-Di-(4-phenylthiazolyl-2)-dipropyl sulphide. For further characterization, γ,γ′,-thiodi-(thiobutyramide) (0.6 g) was converted to the thiazole by refluxing it in ethanol (6 ml) with ω-bromoacetophenone (1.1 g) for one hour. Working up in the usual way gave a semi-solid product, which was dissolved in a boiling mixture of ethanol and light petroleum. On cooling, white crystals (0.5 g) were deposited. After one more recrystallisation the thiazole compound melted at 49—50°.

$C_{24}H_{24}N_2S_3$ (436.6)	Calc.	C	66.0	H	5.54
	Found	»	65.8	»	5.59

β-Diethylaminobutyronitrile and hydrogen sulphide

β-Diethylaminobutyronitrile. This compound, which was required as a starting material, has not been described in the literature. Bruylants[4] stated that attempts to add diethylamine to allyl cyanide in a manner analogous to the preparation of β-dimethylaminobutyronitrile, only resulted in the rearrangement of the allyl cyanide to crotononitrile. It has now been found, however, that if distillation of the crude product at atmospheric pressure was avoided, β-diethylaminobutyronitrile could be obtained in good yield (79 %) by this method. Allyl cyanide (20 g) and 33 % diethylamine (90 g) were mixed with cooling and set aside at room temperature for three days, during which time the mixture separated into two phases. The mixture was saturated with potassium carbonate, and the top layer separated and fractionated, yielding 33 g of product, b. p. 83—85°/11 mm, n_D^{20} 1.4388.

$C_8H_{16}N_2$ (140.2)	Calc.	N	20.0	Eq. wt.	140.2
	Found	»	19.9	»	139.5
				(Mixed indicator: bromo-cresol green-methyl red)	

β-Diethylaminobutyronitrile (5 g) when treated under the usual conditions with hydrogen sulphide in ethanol (50 ml) to which sodium (0.15 g) had been added yielded 1.55 g of crude product, which after purification was identical with β,β′-thiodi-(thiobutyramide). If, instead of sodium, diethylamine (26 g) was used as catalyst, a higher yield (3.65 g) was obtained.

Allyl cyanide and hydrogen sulphide

Allyl cyanide was prepared from allyl bromide[17], or from allyl alcohol by the excellent method of Breckpot[18], which was more convenient.

Allyl cyanide (5.0 g, 0.075 mole) was treated with hydrogen sulphide in ethanol (50 ml) in the usual way, various amounts of different catalysts being used. With diethylamine (55 g, 0.75 mole), 6.2 g of crude crystalline product was obtained: triethylamine (75.8 g, 0.75 mole) gave a still better yield (8.7 g). The products proved after purification to be identical with β,β′-thiodi-(thiobutyramide). In some experiments when only small amounts of amine (0.02 mole) were used viscous oils were obtained, from which no identifiable products could be isolated. If the amine was replaced by sodium (0.115 g, 0.005 mole) the allyl cyanide was isomerised to crotononitrile (3.4 g), b.p. 114—116°, n_D^{20} 1.4204, together with a tarry destillation residue.

Crotononitrile and hydrogen sulphide

Crotononitrile (mixture of *cis*- and *trans*-form) was prepared by shaking allyl cyanide with *N* sodium hydroxide for 12 hours, as described by Letch and Linstead [10]. Treatment of the nitrile (5.0 g) in ethanol (50 ml) with hydrogen sulphide in the presence of diethylamine (55 g) yielded 7.5 g of crude β,β′-thiodi-(thiobutyramide).

β-Diethylaminopropionitrile and hydrogen sulphide

β,β′-Thiodi-(thiopropionamide). β-Diethylaminopropionitrile [5] (10 g) and diethylamine (29 g), dissolved in ethanol (50 ml), were allowed to react with hydrogen sulphide under the usual conditions. The crystalline compound obtained (6.85 g) melted at 94.5—95.5° after three recrystallisations from acetone — light petroleum.

$C_6H_{12}N_2S_3$ (208.4)	Calc.	C	34.6	H	5.81	S	46.2
	Found	»	35.1	»	5.86	»	46.0

Hydrolysis of β,β′-thiodi-(thiopropionamide) to β,β′-thiodipropionic acid. β,β′-Thiodi-(thiopropionamide) (0.7 g) was refluxed with concentrated hydrochloric acid (10 ml) for two hours. The solution was extracted with ether (5 × 20 ml), and evaporation of the ether gave a crystalline residue (0.6 g), which, after recrystallisation from ethyl acetate-light petroleum, melted at 130—131°. Titration with alkali gave an equivalent weight of 89.3, in good agreement with the value of 89.1 for β,β′-thiodipropionic acid and no depression in m.p. was obtained on admixture with an authentic specimen of this acid.

Bromine oxidation of the acid yielded β,β′-sulphonyldipropionic acid; eq. wt. 105.4 (calc. 105.1). After recrystallisation from ethanol the compound melted at 223—225° in agreement with the values recorded by Holmberg [19] (220—222°) and by Larsson [20] (225°), but at variance with the value of 210° first reported by Lovén [21].

β,β′-Di-(4-phenylthiazolyl-2)-diethyl sulphide. This compound was prepared by refluxing β,β′-thiodi-(thiopropionamide) (0.4 g) and ω-bromoacetophenone (0.84 g) in ethanol (5 ml) for one hour. The crude thiazole (0.7 g), which was isolated as previous thiazoles, was recrystallised twice from ethanol and then melted at 68—69°.

$C_{22}H_{20}N_2S_3$ (408.6)	Calc.	C	64.7	H	4.94	N	6.86
	Found	»	64.5	»	4.89	»	6.99

Acrylonitrile and hydrogen sulphide

Acrylonitrile (6.1 g) when heated with diethylamine (42 g) in ethanol (50 ml) and hydrogen sulphide following the usual procedure, yielded 11 g of crude β,β′-thiodi-(thiopropionamide).

In another experiment, acrylonitrile (15 g) was treated with hydrogen sulphide in ethanol (75 ml) to which sodium (0.2 g) had been added. The product was an oil which boiled at 169—170° (11.2 g), apparently consisting of β-ethoxypropionitrile, formed by the addition of ethanol to the acrylonitrile [22].

γ-Piperidinobutyronitrile and hydrogen sulphide

γ-Piperidinothiobutyramide. γ-Piperidinobutyronitrile[5] (4.0 g) and diethylamine (19 g) were dissolved in ethanol (50 ml) and treated with hydrogen sulphide in the usual way. After removal of the solvent at reduced pressure, a dark viscous oil was obtained, which crystallised on trituration with ethanolic hydrogen chloride giving white crystals (3.4 g), which melted at 155—156° after recrystallisation twice from ethanol.

$C_9H_{18}N_2S \cdot HCl$ (222.8)	Calc.	C	48.5	H	8.59	N	12.6
	Found	»	47.9	»	8.44	»	12.6

Crotonic acid and hydrogen sulphide

A mixture of solid crotonic acid (10.0 g), diethylamine (87.5 g), and ethanol (100 ml) was saturated with hydrogen sulphide at — 20°, and heated at 70° overnight in a sealed vessel. The solvent was removed at reduced pressure, and the residue acidified with hydrochloric acid and extracted with ether (5 × 50 ml). After evaporation of the ether, the oily residue was distilled *in vacuo* giving 7.1 g of product, b.p. 70°/0.15 mm, n_D^{20} 1.4781. The compound was titrated with alkali and with iodine giving the equivalent weights 120.8 and 119.2, respectively (calc. for β-mercaptobutyric acid 120.1). Holmberg and Schjånberg[23] record n_D^{20} 1.4782 for β-mercaptobutyric acid.

The acid was identified by benzylating it following the directions of Holmberg and Schjånberg[23]. Bromine oxidation of the oily β-benzylthiobutyric acid in aqueous solution gave a product which was recrystallised twice from water, forming prisms of m. p. 130.5—131° undepressed on admixture with an authentic specimen of β-benzylsulphonylbutyric acid. Eq. wt.: found 242.2, calc. 242.2.

Vinylacetic acid and hydrogen sulphide

Vinylacetic acid[24] (10 g) yielded under the conditions of above experiment 5.4 g of β-mercaptobutyric acid, identified as the benzylsulphonyl derivative.

Acrylic acid and hydrogen sulphide

Acrylic acid (4.3 g) was treated with hydrogen sulphide in ethanol (50 ml) in the presence of diethylamine (44 g) in the usual manner. Distillation of the reaction product *in vacuo* gave an oil (2.3 g), b.p. 65°/0.2 mm. Titrations with alkali and iodine gave the equivalent weights 107.1 and 104.8, respectively (calc. for β-mercaptopropionic acid 106.1). The mercapto acid was dissolved in water and oxidised with iodine giving crystals of m.p. 154—155°, undepressed by an authentic specimen of β,β'-dithiodipropionic acid. Extraction of the distillation residue with ethyl acetate gave a further 0.9 g of the same material.

SUMMARY

Hydrogen sulphide reacts with β-diethylamino- and β-dimethylaminobutyronitrile in ethanol at 70° to form β,β'-thiodi-(thiobutyramide). The same product is obtained from allyl cyanide or crotononitrile in the presence of diethylamine or triethylamine.

Under similar conditions β-diethylaminopropionitrile and acrylonitrile give β,β′-thiodi-(thiopropionamide).

Crotonic acid and vinylacetic acid add hydrogen sulphide under the same conditions to give β-mercaptobutyric acid, while acrylic acid yields β-mercaptopropionic acid.

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