388. *The Addition of Hydrogen Sulphide to 2-Phenyl-Δ²-oxazoline and Benzoylethyleneimine: Attempted Synthesis of Fused Thiazolidine–Butyroazlactone Ring Systems.*

By Alan A. Goldberg and William Kelly.

2-Phenyl-Δ²-oxazoline reacts additively with hydrogen sulphide to yield N-(2-*hydroxyethyl*)*thiobenzamide*.

Addition of hydrogen sulphide to the isomeric benzoylethyleneimine yields 2-*benzamidoethylthiol*.

General observations of a quantitative nature have been made upon the thermal isomerisation of benzoylethyleneimine to 2-phenyl-Δ²-oxazoline and upon the stabilities of the oxazoline and ethyleneimine heterocycles towards additive reagents.

Use has been made of these observations to attempt the synthesis of compounds containing the fused thiazolidine–butyroazlactone ring system. Benzeneazoacetoacetyl chloride was converted into the corresponding ethyleneimide and the latter brought into reaction with hydrogen sulphide. Fission of the heterocycle with addition of hydrogen sulphide took place, followed by simultaneous cyclisation to a ketotetrahydro-1 : 4-thiazine.

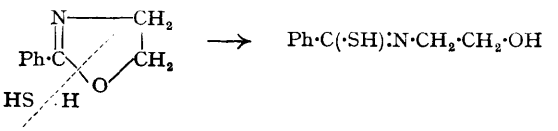
2-Acylamidoethylthiols were required for the synthesis of compounds containing the fused thiazolidine–butyroazlactone ring system for examination as bacterial inhibitors. 2-Benzamidoethylthiol, which was considered to be the most accessible of these compounds for model experiments, is unobtainable either by the action of alkali hydrogen sulphides on benz-2-bromoethylamide or by the benzoylation of 2-aminoethylthiol; accordingly, attention was turned to possible routes *via* the addition of hydrogen sulphide to benzoylethyleneimine and to 2-phenyl-Δ²-oxazoline. It is known that ethyleneimine reacts with water to yield ethanolamine (Gabriel and Stelzner, *Ber.*, 1895, **28**, 2929), with hydrogen sulphide to give 2-aminoethylthiol (Mills and Bogert, *J. Amer. Chem. Soc.*, 1940, **62**, 1177), and with sulphurous acid to yield taurine (Gabriel, *Ber.*, 1888, **21**, 2665); alternatively, 2-phenyloxazoline hydrochloride reacts with water to yield 2-aminoethyl benzoate and with concentrated hydrochloric acid to give benz-2-chloroethylamide (Gabriel and Heymann, *Ber.*, 1890, **23**, 2495). All these reactions constitute a scission of the heterocycle and addition of the other reactant.

It was found that hydrogen sulphide reacts additively with 2-phenyl-Δ²-oxazoline to yield a compound $C_9H_{11}ONS$, m. p. 96°, which gave no coloration with sodium nitroprusside and so did not appear to contain a thiol grouping. Treatment of the compound with sodium ethoxide and ethyl iodide effected immediate evolution of ethylthiol and formation of 2-phenyloxazoline; similarly, treatment with sodium ethoxide and benzyl chloride yielded benzylthiol and 2-phenyloxazoline. The elimination of thiol during the alkylation suggested the intermediate formation of an iminothioether, and the production of phenyloxazoline showed the presence of the Ph·C·N·CH_2·CH_2·O· complex in the original compound which was accordingly formulated as N-(2-*hydroxyethyl*)*thiobenzamide*. The proof of this structure was furnished by rational synthesis by a method developed from the work of Delépine (*Compt. rend.*, 1911, **153**, 281); ethyl thionbenzoate and ethanolamine condensed to yield a compound, m. p. 96°, identical with that obtained by the addition of hydrogen sulphide to phenyloxazoline.

2-Phenyloxazoline is an *ON*-ethylene-substituted benziminoether and accordingly would be expected to exhibit the general properties of an iminoether. Although the compound is remarkably stable towards cold water, it reacts at high temperatures to give benz-2-hydroxyethylamide; the addition could take place by rupture of, and addition of water to, either the 1 : 2- or the 1 : 5-oxygen–carbon bond of the heterocycle. 2-Phenyloxazoline monohydrochloride reacts with boiling water to yield 2-aminoethyl benzoate hydrochloride (Gabriel and Heymann, *loc. cit.*), a reaction which must take place by rupture of, and addition of water to, the 2 : 3-carbon–nitrogen double bond. These reactions resemble the well-known hydrolytic fission of iminoethers to amide and ester, respectively. Anhydrous phenyloxazoline

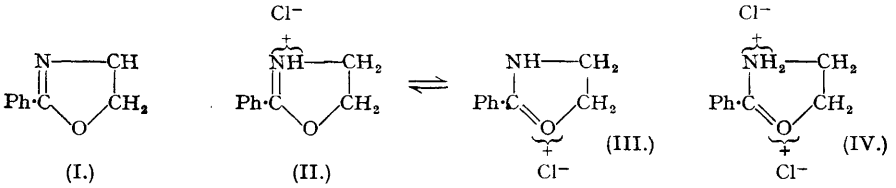
hydrochloride when heated to its melting point is rearranged quantitatively into benz-2-chloroethylamide (Wislicenus and Körber, *Ber.*, 1902, **35**, 164), a transformation completely comparable to the thermal degradation of an iminoether hydrochloride R·C(:NH)·OR_1,HCl into the amide R·CO·NH_2 and alkyl halide R_1Cl (Pinner, " Die Imidoaether ", 1892, p. 5); this degradtion must take place by rupture of the 1 : 5-oxygen–carbon bond. It has been found during the present work that concentrated anhydrous hydrogen chloride reacts with phenyloxazoline at 0° with almost quantitative formation of benz-2-chloroethylamide. Since these are conditions under which intramolecular rearrangements similar to those observed by Chapman (*J.*, 1925, **127**, 1992) would not take place, it must be deduced that the transformation is effected by rupture of, and addition of hydrogen chloride to, the 1 : 5-oxygen–carbon bond of the oxazoline.

It is evident that scission of the Δ^2-oxazoline heterocycle and addition of hydrogen sulphide can take place only by opening of the 1 : 2-oxygen–carbon bond, thus :

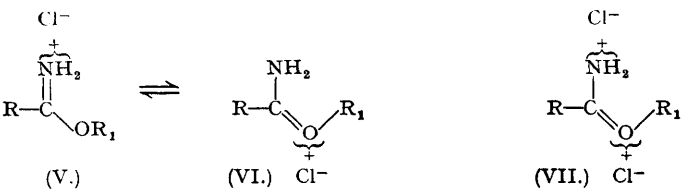


and by comparison it would seem reasonable to assume that formation of benz-2-hydroxyethylamide by addition of water to phenyloxazoline base takes place by rupture of the 1 : 2- and *not* the 1 : 5-oxygen–carbon bond. It is noteworthy that the 2 : 3-carbon–nitrogen bond of the oxazoline heterocycle is stable towards hydrogen sulphide, whereas benziminoether base readily condenses with hydrogen sulphide with elimination of ammonia to give high yields of ethyl thionbenzoate (Matsui, *Mem. Coll. Eng. Kyoto*, 1903—1908, **1**, 285; *Centr.*, 1909, II, 423; Delépine, *Bull. Soc. chim.*, 1911, **9**, 904).

The foregoing reactions of 2-phenyloxazoline may be rationalised by formulation of the monohydrochloride as a resonance hybrid of the ammonium and the oxonium form, (II) and (III), respectively. The existence of an ammonium–oxonium dihydrochloride (IV) may also be



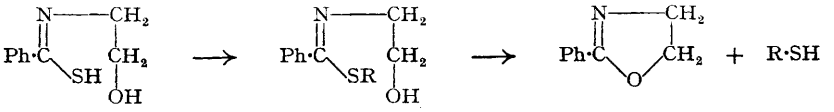
postulated but is not necessary. The position of opening of the oxazoline heterocycle would be expected to be governed by the internal conditions, *e.g.*, stereochemical or electromeric strain, and external influences such as proton availability or presence of solvent, which might stabilise either the ammonium or the oxonium phase of the monohydrochloride or promote formation of the ammonoum–oxonium dihydrochloride. It is easy to conceive that the ammonium form (II) would on hydrolysis yield 2-aminoethyl benzoate hydrochloride, that the oxonium form (III) on thermal decomposition would yield benz-2-chloroethylamide, and that the ammonium–oxonium dihydrochloride in the presence of concentrated hydrogen chloride would yield benz-2-chloroethylamide. It is of passing interest that iminoether hydrochlorides may in general be formulated upon the same lines, *i.e.*, as resonance hybrids of the ammonium and oxonium forms (V and VI), which would account for the hydrolytic degradation under different external conditions to ester R·CO_2R_1 or amide R·CO·NH_2 by rupture of the double bond attached



to the polarised focus of the ammonium or the oxonium phase, respectively. The influence of excess of hydrochloric acid, *i.e.*, effect of pH value, on the almost quantitative hydrolysis

of benziminoether hydrochloride into ethyl benzoate was observed by Schlesinger (*Amer. Chem. J.*, 1908, **39**, 719) and McCracken (*ibid.*, p. 586; compare also McKee, *ibid.*, 1901, **26**, 262) but, although formation of amide during the hydrolysis of iminoethers is well known, the literature does not appear to state the precise conditions which favour production of amide. It has now been shown that while benziminoether base on prolonged heating with water or aqueous alcohol at the pH value (8·0) created by the base itself gives a *ca.* 50% yield of benzamide, yet in the presence of sufficient benzyltrimethylammonium hydroxide to maintain a pH value of 11·0 the amount of benzamide is increased to *ca.* 60% of theory; apparently very little ethyl benzoate and a considerable amount of phenyl cyanide is formed at this pH value. In addition, if iminoether hydrochlorides in the solid phase are considered to exist in the oxonium form, the thermal degradation to amide $R{\cdot}CO{\cdot}NH_2$ and alkyl halide R_1Cl is more readily understandable. The unstable iminoether hydrochloride–hydrogen chloride complexes mentioned by Pinner (*op. cit.*, pp. 53, 55, 65) and assumed by him to be 1-chloro-1-aminoether hydrochlorides, $R{\cdot}CCl(NH_2){\cdot}OR_1,HCl$, are most probably dihydrochlorides of the ammonium–oxonium type (VII).

Alkylation of *N*-(2-hydroxyethyl)thiobenzamide apparently takes place thus:



the intermediate *N*-(2-hydroxyethyl)-*S*-alkylthiobenziminoether immediately undergoing cyclisation to phenyloxazoline with elimination of alkylthiol. That production of phenyloxazoline is a *direct* intramolecular cyclisation not involving the solvent (alcohol) is shown by the fact that benzylation of N-iso*propylthiobenzamide* in the presence of sodium ethoxide and alcohol gives a high yield of S-*benzyl*-N-iso*propylthiobenziminoether*, which is a remarkably stable compound (contrast the instability of unsubstituted iminothioether bases; Autenrieth and Brüning, *Ber.*, 1903, **36**, 3465; Bernthsen, *Annalen*, 1879, **197**, 350).

Gabriel and Stelzner (*loc. cit.*) obtained benzoylethyleneimine, m. p. 1°, by benzoylation of ethyleneimine and showed that the compound rearranged to phenyloxazoline on distillation at 240°/760 mm. It has now been found that benzoylation of ethyleneimine at 0° and isolation at a low temperature yields a product of m. p. 5°, this being raised to 8—9° by partial freezing and draining away of liquid. It is believed that this material represents pure benzoylethyleneimine substantially free from phenyloxazoline.

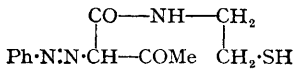
Action of Cold Dilute Hydrochloric Acid on Phenyloxazoline and Benzoylethyleneimine.—Phenyloxazoline is stable towards cold dilute hydrochloric acid; the base readily dissolves in the reagent and after standing at room temperature for 4 hours may be recovered by basification and ether extraction in 85% yield. On the other hand, on shaking the insoluble benzoylethyleneimine with cold dilute hydrochloric acid an immediate exothermic reaction develops with separation of benz-2-chloroethylamide. Since both the "crude" (m. p. 5°) and the "purified" (m. p. 8°) material give a *ca.* 75% yield of benzchloroethylamide it is believed that these represent benzoylethyleneimine, free from 2-phenyloxazoline, and that during the reaction *ca.* 25% of the former is converted by addition of water into the soluble benzhydroxyethylamide or by isomerisation into the oxazoline.

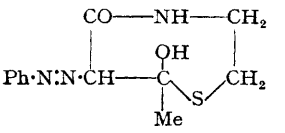
Although at 55° benzoylethyleneimine is stable for several hours, yet at 115° isomerisation into phenyloxazoline is considerable in 2 hours; at the b. p. 125°/12 mm. conversion into phenyloxazoline is very rapid, with distillation of liquid consisting of *ca.* 70% of phenyloxazoline and 30% of benzoylethyleneimine.

Addition of Hydrogen Sulphide to Benzoylethyleneimine.—In contrast with phenyloxazoline, benzoylethyleneimine reacts *rapidly* with hydrogen sulphide to yield 2-*benzamidoethylthiol*; this compound gives an intense coloration with sodium nitroprusside and on benzylation yields benzyl 2-benzamidoethyl sulphide. The latter was identified by hydrolysis to benzyl 2-aminoethyl sulphide, which on phthaloylation yielded benzyl 2-phthalimidoethyl sulphide identical with that obtained by the benzylation of 2-phthalimidoethylthiol (Michels, *Ber.*, 1892, **25**, 3050). It is noteworthy that benzyl 2-aminoethyl sulphide is most conveniently obtained by direct benzylation of 2-aminoethylthiol, thus eliminating the difficult hydrolysis of the phthalimido-derivative described by Michels.

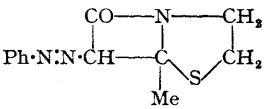
In order to utilise the foregoing reactions to obtain compounds potentially convertible into substances containing the fused thiazolidine–butyroazlactone ring system, it was necessary to prepare an acylamidoethylthiol containing a keto-group in the acyl residue; the benzeneazo-

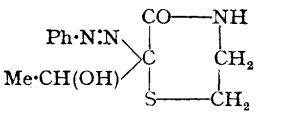
acetoacetyl grouping was selected as the most easily accessible acylating radical. Benzeneazoacetoacetic acid was converted into the acid chloride and this reacted with ethyleneimine under conditions known to yield the acylethyleneimide and not the oxazoline. It was thought that addition of hydrogen sulphide to the product would yield 2-(benzeneazoacetoacetamido)ethylthiol (VIII) which would undergo internal thiol–ketone condensation to give the seven-membered ring compound (IX) which might be dehydrated to yield the thiazolidine (X).

(VIII.) 



(IX.)

(X.) 



(XI.)

Benzeneazoacetoacetic acid was converted *via* its *acid chloride* into *benzeneazoacetoacetylethyleneimide*. The latter reacted exothermically with hydrogen sulphide—a reaction indicating an ethyleneimide and not an oxazoline—to yield a *compound* $C_{12}H_{15}O_2N_3S$. This was stable to alcoholic hydrogen chloride and to aqueous sodium hydroxide and gave no coloration with sodium nitroprusside. All attempts to effect dehydration were unsuccessful. The compound would therefore appear to be, not the expected thiol (VIII), but a condensate derived from the latter by a cyclisation involving the terminal thiol radical and (*a*) the keto-group (compound IX) or (*b*) the double bond of the enol form of the ketone (compound XI). The stability of the substance would lend support to the 3-keto-2 : 3 : 5 : 6-tetrahydro-1 : 4-thiazine formulation (XI).

Experimental.

2-Phenyloxazoline (cf. Gabriel and Heyman, *loc. cit.*).—Benz-2-bromoethylamide (87 g.; Goldberg, *J.*, 1945, 828) was suspended in 5N-sodium hydroxide (80 c.c.) and alcohol (150 c.c.), and the mixture heated with shaking to 40—45° and kept at room temperature for ½ hour. Water (1 l.) was added, and the precipitated oil extracted with ether (250 c.c.); the ethereal extract, after drying ($MgSO_4$) and distillation, yielded 2-phenyloxazoline as a colourless oil (40 g.), b. p. 122—124°/14 mm., m. p. 12° (Found, in redistilled sample: C, 73·5; H, 6·3; N, 9·7. Calc. for C_9H_9ON: C, 73·4; H, 6·1; N, 9·5%). The picrate separated from alcohol in stout yellow prisms, m. p. 186° (Found: N, 15·1. Calc. for $C_{15}H_{12}O_8N_4$: N, 14·9%).

Phenyloxazoline (13 g.) was also obtained as a colourless oil by refluxing benz-2-bromoethylamide (22·6 g.) in anhydrous methanol (150 c.c.) for 3 hours with anhydrous potassium cyanide (13 g.) and a trace of copper powder; none of the expected β-benzamidopropionitrile was obtained.

2-Phenyloxazoline is readily soluble in cold dilute hydrochloric acid. On addition of 1 mol. of hydrochloric acid to 1 mol. of phenyloxazoline suspended in water, the aqueous phase buffers between pH 4·0 and pH 3·0; a 15% solution of phenyloxazoline hydrochloride in water has pH 2·4—2·6.

2-Phenyloxazoline methiodide was obtained by refluxing the base (2 g.) and methyl iodide (2 c.c.) for ½ hour; it separated from alcohol–ether in slender cream needles, m. p. 116—117° (Found: N, 4·9; I, 43·5. $C_{10}H_{12}ONI$ requires N, 4·8; I, 43·9%). The methiodide was recovered unchanged after refluxing for 20 hours with excess of methyl iodide.

Benzoylation of 2-Phenyloxazoline in Aqueous Medium: 2-Benzamidoethyl Benzoate.—Benzoyl chloride (0·9 g.) was added portionwise to a stirred mixture of water (15 c.c.), 2-phenyloxazoline (1·0 g.), and sodium hydrogen carbonate (1·0 g.) at 10—15°. After 3 hours' stirring the precipitate (1·3 g., m. p. 76—82°) was collected and recrystallised from aqueous methyl alcohol, 2-benzamidoethyl benzoate being obtained, m. p. 88—89° alone and in admixture with material obtained by the benzoylation of ethanolamine (Knorr, *Ber.*, 1897, **30**, 909) (Found: C, 71·7; H, 5·6; N, 5·3. Calc. for $C_{16}H_{15}O_3N$: C, 71·4; H, 5·6; N, 5·2%). The same compound was obtained by addition of benzoyl chloride to a solution of phenyloxazoline in anhydrous pyridine and then pouring the mixture into water.

Stability of 2-Phenyloxazoline towards Cold Dilute Hydrochloric Acid.—A solution of 2-phenyloxazoline (10 g.) in water (50 c.c.) and 4·32N-hydrochloric acid (31·2 c.c.; 2 mols.) was kept at 15° for *x* hours. The solution was basified with 5N-sodium hydroxide, extracted with ether, and the dried ethereal extract distilled. The amount of 2-phenyloxazoline recovered was as follows:

Time (*x* hours)	1	4	48	192
Amount recovered, g.	9·0	8·5	4·5	(gum)

In each case the recovered phenyloxazoline had b. p. 122—124°/12 mm. and the picrate had m. p. 184—186° alone and in admixture with authentic material.

2-Phenyloxazoline Hydrochloride.—Anhydrous alcoholic hydrogen chloride (10%; 5 c.c.) was added to a solution of phenyloxazoline (2·0 g.) in dry ether (30 c.c.). The precipitate was collected immediately, washed with dry ether, and dried in a vacuum at room temperature; the hydrochloride was obtained as a white crystalline powder, m. p. 80—81°. When dissolved in water and the latter distilled off at 15°

at reduced pressure the salt was recovered unchanged, m. p. 80° (Found : N, 7·7; Cl, 19·1. Calc. for C_9H_9ON,HCl : N, 7·6; Cl, 19·3%).

Decomposition of Phenyloxazoline Hydrochloride by Water : 2-Aminoethyl Benzoate.—A solution of phenyloxazoline (10·2 g.) in water (70 c.c.) containing 1 equiv. of hydrochloric acid was refluxed for 1 hour and then evaporated to dryness on the water-bath during 6 hours. The solid residue of 2-aminoethyl benzoate hydrochloride was collected, washed with acetone, and dried at 15°; yield 10·8 g., m. p. 129—130° (Found : N, 7·2; Cl, 17·8. Calc. for $C_9H_{12}O_2NCl$: N, 7·0; Cl, 17·6%). The m. p. in admixture with 2-phenyloxazoline hydrochloride was 62—67°. The picrate, obtained by mixing hot aqueous solutions of the foregoing hydrochloride and picric acid, separated from water in yellow acicular plates, m. p. 202—204° alone and at 168—172° in admixture with phenyloxazoline picrate (Found : C, 46·1; H, 3·8; N, 14·5. Calc. for $C_{15}H_{14}O_9N_4$: C, 45·7; H, 3·6; N, 14·2%).

Decomposition of Phenyloxazoline Base by Water : Benz-2-hydroxyethylamide.—2-Phenyloxazoline (6·4 g.) was refluxed with water (25 c.c.) for 20 hours, and the resulting solution evaporated almost to dryness on the water-bath. The residual solid after draining on porous pot yielded crude benz-2-hydroxyethylamide (6·0 g.), m. p. 52—56°, which crystallised from ethyl acetate in white needles, m. p. 66° alone and in admixture with material obtained by partial hydrolysis of 2-benzamidoethyl benzoate (Fränkel and Cornelius, *Ber.*, 1918, **51**, 1657) (Found : N, 8·8. Calc. for $C_9H_{11}O_2N$: N, 8·5%).

Addition of Anhydrous Hydrogen Chloride to Phenyloxazoline : Benz-2-chloroethylamide.—A solution of redistilled 2-phenyloxazoline (5·0 g.) in anhydrous alcohol (20 c.c.) was saturated at 5° with anhydrous hydrogen chloride; a solid first separated which redissolved as more hydrogen chloride was passed in. After standing for 2 hours, the solvent was pumped off at 20°, and the residue (5·7 g.; m. p. 98°, softening at 70—80°) crystallised from aqueous methyl alcohol; benz-2-chloroethylamide separated in colourless prisms, m. p. 106° (Found : N, 7·5; Cl, 19·4. Calc. for $C_9H_{10}ONCl$: N, 7·6; Cl, 19·3%). A solution of 2-phenyloxazoline (5·0 g.) in anhydrous ether (50 c.c.) and anhydrous alcohol (3·0 c.c.), saturated with hydrogen chloride and kept for 5 hours at 4°, in the same manner gave 3·5 g. of recrystallised benz-2-chloroethylamide, m. p. 106—108°, with the same analytical figures.

Ethyleneimine (cf. Gabriel and Stelzner, *loc. cit.*).—2-Bromoethylamine hydrobromide (1100 g.) was added portionwise to a solution of potassium hydroxide (900 g.) in water (2 l.) stirred at < 10°. The stirred mixture was then heated to the b. p., and 550 c.c. of distillate collected; the latter was cooled and poured on to potassium hydroxide (200 g.), and the supernatant oil separated and dried overnight with fresh potassium hydroxide (100 g.). The ethyleneimine thus obtained was kept over sodium wire and then distilled from fresh sodium wire; yield 144 g., b. p. 55°.

Benzoylethyleneimine (cf. Gabriel and Stelzner, *loc. cit.*).—Ethyleneimine (10·3 g.) was added to ice-water (200 g.) and the solution stirred rapidly at < 0°. Sodium hydrogen carbonate (20 g.) was added, and then benzoyl chloride (23 g.) added portionwise during 30 minutes, the temperature of the mixture at no time being allowed to exceed 0°. Stirring at this temperature was continued for a further 1 hour, the mixture allowed to attain room temperature, and the layer of benzoylethyleneimine (24·5 g.) separated; this was an oil, f. p. 5° (Found : C, 72·9; H, 6·1; N, 9·3. Calc. for C_9H_9ON : C, 73·4; H, 6·1; N, 9·5%). By separating the solid from the partially frozen material the m. p. was raised to 8—9°; the m. p. of a mixture (50 : 50) of benzoylethyleneimine and 2-phenyloxazoline was < − 12°.

Reaction of Benzoylethyleneimine with Aqueous Hydrochloric Acid.—Benzoylethyleneimine (20 g.; m. p. 8°) was cooled in an ice-bath, ice-cold N-hydrochloric acid (300 c.c.) added, and the solution vigorously shaken; an immediate exothermic reaction developed with separation of benz-2-chloroethylamide. After 15 minutes this was collected, washed with water, and dried; yield 18·1 g. (72·5%), m. p. 102—104° (Found : N, 7·8; Cl, 19·0. Calc. for $C_9H_{10}ONCl$: N, 7·6; Cl, 19·3%). Crude benzoylethyleneimine, m. p. 5°, gave the same yield (72·5%) of the amide.

Thermal Isomerisation of Benzoylethyleneimine.—The crude product from the benzoylation of ethyleneimine was collected in ether, the ethereal extract dried ($MgSO_4$), the ether removed, and the residue distilled *as rapidly as possible*. The distillate, b. p. 128—129°/15 mm. (20 g.), could not be induced to crystallise in an ice–salt bath. Treatment with ice-cold hydrochloric acid in the above manner yielded only 5·9 g. of benz-2-chloroethylamide, m. p. 102—104° (23%); this distillate corresponds to a mixture of *ca.* 70% of phenyloxazoline and *ca.* 30% of benzoylethyleneimine.

Crude (m. p. 5°) benzoylethyleneimine was heated for x hours at the stated temperature and then treated in the same manner with N-hydrochloric acid. The yields of benz-2-chloroethylamide (y%) were :

Temp. 116°.

Time, x hrs.	0	½	1	1½	2	2½	3½
Yield, y %	75	70	64	58	42	28	(gum)

Temp. 55°.

Time, x hrs.	0	1	3	6	24	48	72
Yield, y %	73	72	71	69	66	48	29

Addition of Hydrogen Sulphide to 2-Phenyloxazoline : N-(2-Hydroxyethyl)thiobenzamide.—2-Phenyloxazoline (40 g.) was added to an alcoholic solution of ammonium sulphide (obtained by dissolution of 20 g. of ammonia and then 30 g. of hydrogen sulphide in 200 c.c. of methyl alcohol), and the solution kept in a closed bottle at 30° with occasional shaking for 8 days. The solvent was pumped off and water added to the residue; the solid was collected (51 g.; m. p. 88—92°) and recrystallised from aqueous methyl alcohol, N-(2-*hydroxyethyl*)*thiobenzamide* (38 g.) being obtained in colourless needles, m. p. 94°. For analysis a sample was recrystallised from the same solvent and obtained in slender colourless prisms, m. p. 96° [Found : C, 60·0; H, 6·2; N, 7·9; S, 17·8; *M* (Rast), 193. $C_9H_{11}ONS$ requires C, 59·7; H, 6·1; N, 7·7; S, 17·7%; *M*, 181]. The compound gave no coloration with sodium nitroprusside in dilute alcoholic solution and was insoluble in dilute hydrochloric acid.

Benzylation of N-(2-*Hydroxyethyl*)*thiobenzamide.*—The foregoing compound (40 g.; obtained from the

addition of hydrogen sulphide to 2-phenyloxazoline) was dissolved in a solution of sodium (6·0 g.) in anhydrous ethyl alcohol (250 c.c.), and then benzyl chloride (31·8 c.c.) added. After being kept for 1 hour at room temperature the solution was refluxed for a further 1 hour, alcohol (*ca.* 170 c.c.) distilled off, excess of water added, and the mixture extracted with ether. The ethereal extract (*A*) was shaken with 5N-sodium hydroxide, and the aqueous alkaline extract strongly acidified and shaken with ether; this ethereal extract after drying and distillation yielded benzylthiol (14 g.) as a colourless oil, b. p. 82°/13 mm. (Found: S, 25·9. Calc. for C_7H_8S: S, 25·8%), further identified by treatment with 2 : 4-dinitrochlorobenzene and conversion into 2 : 4-dinitrophenyl benzyl sulphide, m. p. 130° alone and in admixture with authentic material (Found: N, 9·8; S, 11·2. Calc. for $C_{13}H_{10}O_4N_2S$: N, 9·7; S, 11·0%). The ethereal layer remaining after extraction with alkali (*A*) was extracted with 5N-hydrochloric acid, the extract basified with sodium hydroxide, and the liberated oil collected in ether. Distillation of the ethereal solution yielded 2-phenyloxazoline (20 g.), b. p. 122—124°/13 mm., m. p. 12° (Found: N, 9·7. Calc.: N, 9·5%); the picrate had m. p. 186° alone and in admixture with authentic material (Found: C, 47·9; H, 3·4; N, 15·1. Calc. for $C_{15}H_{12}O_8N_4$: C, 47·9; H, 3·2; N, 14·9%). The base was further identified by benzoylation in aqueous sodium hydrogen carbonate solution and isolation of 2-benzamidoethyl benzoate; this had m. p. 88—89° alone and in admixture with material obtained by benzoylation of ethanolamine (Found: C, 71·6; H, 5·6; N, 5·3. Calc. for $C_{16}H_{15}O_3N$: C, 71·4; H, 5·6; N, 5·2%).

Ethylation of 2-Hydroxyethylthiobenzamide.—The amide (8·0 g.) was dissolved in a solution of sodium (1·22 g.) in anhydrous ethyl alcohol (50 c.c.), and the solution refluxed with ethyl iodide (7·2 c.c.) for 2 hours; during this time there was copious evolution of ethylthiol. The solvent was distilled off, water added, and the whole extracted with ether; the ethereal extract yielded 2-phenyloxazoline (4·8 g.), b. p. 120—124°/14 mm. (Found: N, 9·9. Calc. for C_9H_9ON: N, 9·5%). The picrate had m. p. 185—186° alone and mixed with authentic material (Found: N, 15·0. Calc. for $C_{15}H_{12}O_8N_4$: N, 14·9%).

Rational Synthesis of N-(2-*Hydroxyethyl*)*thiobenzamide.*—Ethyl thionbenzoate (Matsui, *loc. cit.*; Delépine, *loc. cit.*) (5·0 g.) and ethanolamine (20 g.) were heated together on the water-bath for ½ hour, the mixture diluted with water, and the precipitate (2·9 g.; m. p. 70—76°) collected. Recrystallisation twice from aqueous methyl alcohol yielded *N*-(2-hydroxyethyl)thiobenzamide in colourless needles, m. p. 94—96° alone and mixed with the material obtained by addition of hydrogen sulphide to phenyloxazoline (Found: N, 8·0; S, 17·8. Calc. for $C_9H_{11}ONS$: N, 7·7; S, 17·7%). This compound gave no coloration with sodium nitroprusside.

S-*Benzyl*-N-iso*propylthiobenzamide.*—This compound was prepared in order to determine the stability of an *NS*-disubstituted thioiminoether. Ethyl thionbenzoate (29·2 g.) was added to *iso*propylamine (41·5 g.) at < 0°, and the mixture gently heated on the water-bath for 1½ hours. Excess of amine was distilled off, water added to the residue, and the precipitated oil collected in ether; distillation of the product gave N-iso*propylthiobenzamide* (18·8 g.) as a viscid yellow oil, b. p. 182—186°/13 mm., which solidified on standing to a mass of yellow crystals, m. p. 53—55° (Found: N, 7·6; S, 18·1. $C_{10}H_{13}NS$ requires N, 7·8; S, 17·9%).

The foregoing thio-amide (18·6 g.) was added to a solution of sodium (2·4 g.) in anhydrous ethyl alcohol (50 c.c.); benzyl chloride (13·3 g.) was added, and the mixture refluxed on the water-bath for 4 hours. The alcohol was distilled away, the residue diluted with water, and the precipitated oil collected in ether. The ethereal solution (*X*) was extracted with dilute sodium hydroxide; acidification of the alkaline layer and ether extraction did not yield any benzylthiol. Distillation of the dried ethereal solution (*X*) gave S-*benzyl*-N-iso*propylthiobenzamide* (27·6 g.) as a viscous yellow oil, b. p. 196—202°/12 mm., which could not be induced to solidify (Found: N, 5·3; S, 11·9. $C_{17}H_{19}NS$ requires N, 5·2; S, 11·9%). The *picrate* crystallised from aqueous alcohol in yellow prisms, m. p. 112° (Found: N, 11·3; S, 6·2. $C_{23}H_{22}O_7N_4S$ requires N, 11·2; S, 6·4%).

S-Benzyl-*N*-*iso*propylthiobenzamide (2·0 g.) was refluxed with 2N-hydrochloric acid (20 c.c.) for 9 hours. The reaction mixture (*A*) was extracted with ether, and the ethereal extract (*B*) shaken with dilute sodium hydroxide; acidification of the aqueous alkaline layer and ether extraction yielded a small amount of benzylthiol (0·1 g.), identified by conversion into 2 : 4-dinitrophenyl benzyl sulphide, m. p. and mixed m. p. 130°. The ethereal solution (*B*) on drying and distillation of the ether left a residual oil (1·4 g.) which solidified on keeping; crystallisation of this from methyl alcohol yielded benzyl thiolbenzoate in colourless prisms, m. p. 42° alone and in admixture with authentic material obtained by benzoylation of benzylthiol (Found: C, 74·0; H, 5·6; S, 14·2. Calc. for $C_{14}H_{12}OS$: C, 73·7; H, 5·3; S, 14·0%). The aqueous acid liquors (*A*) were cooled, basified with 10N-sodium hydroxide, and extracted with benzene (5 c.c.). Addition of a hot benzene solution of picric acid to the dried benzene extract yielded *iso*propylamine picrate in yellow prisms, m. p. 150° alone and mixed with authentic material.

Benzyl-*N*-*iso*propylthiobenzamide (5·0 g.) was refluxed with alcohol (30 c.c.) and 5N-sodium hydroxide (10 c.c.) for 6 hours. After removal of the alcohol the product was collected in ether; removal of solvent yielded benzyl thiolbenzoate (2·0 g.), m. p. and mixed m. p. 40—42°.

S-Benzyl-*N*-*iso*propylthiobenzamide was recovered unchanged after refluxing for 10 hours with 0·5N-sodium hydroxide.

Addition of Hydrogen Sulphide to Benzoylethyleneimine: 2-Benzamidoethylthiol.—Benzoylethyleneimine (22 g.) was added to an alcoholic solution of ammonium sulphide (12 g. of ammonia and 18 g. of hydrogen sulphide dissolved in 150 c.c. of methyl alcohol). An immediate exothermic reaction developed (contrast the slow reaction with phenyloxazoline); after 20 hours at room temperature the solvent was removed under reduced pressure at 40°. Recrystallisation of the drained residue (15 g.; m. p. 66—70°) from benzene–ligroin gave 2-*benzamidoethylthiol* in colourless leaves, m. p. 70—71° [Found: C, 59·4; H, 6·0; N, 8·0; S, 17·8; *M* (Rast), 190. $C_9H_{11}ONS$ requires C, 59·7; H, 6·1; N, 7·7; S, 17·7%; *M*, 181]. The compound gave a powerful purple coloration with sodium nitroprusside; the mixed m. p. with *N*-(2-hydroxyethyl)thiobenzamide (m. p. 96°; obtained by addition of hydrogen sulphide to phenyloxazoline) was 36—44°.

Benzylation of 2-Benzamidoethylthiol: Benzyl 2-Benzamidoethyl Sulphide.—2-Benzamidoethylthiol (10·1 g.) was added to a solution of sodium (1·3 g.) in anhydrous ethyl alcohol (50 c.c.). After ½ hour,

benzyl chloride (7·0 g.) was added, the solution kept for 1 hour and refluxed for a further 1 hour, the solvent distilled off, and excess of water added. The precipitate was collected and recrystallised from aqueous methyl alcohol, benzyl 2-benzamidoethyl sulphide being obtained in colourless needles, m. p. 76—78°; these, after recrystallisation, had m. p. 79° alone and in admixture with authentic material prepared (see below) by benzylation and then benzoylation of 2-aminoethylthiol (Found: N, 5·4; S, 11·6. Calc. for $C_{16}H_{17}ONS$: N, 5·2; S, 11·8%).

Benzyl 2-Aminoethyl Sulphide.—This compound was prepared by Michels (*loc. cit.*) by the interaction of 2-phthalimidoethylthiol and benzyl chloride followed by hydrolysis; owing to the difficulty in removing the phthaloyl residue the following more convenient route was employed. 2-Aminoethylthiol (7·7 g.; Mills and Bogert, *loc. cit.*; cf. Gabriel, *Ber.*, 1897, **30**, 2497) was dissolved in a solution of sodium (2·3 g.) in anhydrous alcohol (60 c.c.), and then benzyl chloride (10 c.c.) added. After the abatement of the exothermic reaction the mixture was refluxed for 1 hour, the solvent distilled off, water added, and the whole extracted several times with ether. The ethereal solution was extracted with 5N-hydrochloric acid (3 × 25 c.c.), and the aqueous acid extract basified with ammonia and extracted with ether. Distillation of the latter yielded benzyl 2-aminoethyl sulphide as a colourless oil (10·2 g.), b. p. 150—152°/13 mm. (Found: N, 8·4. Calc. for $C_9H_{13}NS$: N, 8·4%). This (1·67 g.) was refluxed with phthalic anhydride (1·48 g.) and glacial acetic acid (10 c.c.) for ¾ hour, and the boiling solution diluted to incipient crystallisation with hot water; benzyl 2-phthalimidoethyl sulphide separated in colourless glittering plates (1·65 g.), m. p. 76—78° alone and in admixture with authentic material obtained by benzylation of 2-phthalimidoethylthiol (Michels, *loc. cit.*) (Found: N, 4·8; S, 10·8. Calc. for $C_{17}H_{15}O_2NS$: N, 4·7; S, 10·8%). Benzoylation of the amine in presence of aqueous sodium hydrogen carbonate yielded benzyl 2-benzamidoethyl sulphide in colourless needles, m. p. 79° alone and in admixture with the material obtained by the benzylation of 2-benzamidoethylthiol (see above) (Found: N, 5·5; S, 11·5. Calc. for $C_{16}H_{17}ONS$: N, 5·2; S, 11·8%).

2-(*Acetylsulphanilamido*)*ethyl Bromide.*—Sodium carbonate (7·0 g.) was added to an ice-cold stirred solution of 2-bromoethylamine hydrobromide (10 g.) in water (25 c.c.) and acetone (40 c.c.), and then acetylsulphanilyl chloride (11·0 g.) was added portionwise. Stirring was continued for a further ½ hour, water (50 c.c.) added, and the precipitate (13·1 g.) collected; recrystallisation from aqueous methyl alcohol yielded 2-(*acetylsulphanilamido*)*ethyl bromide* in colourless needles, m. p. 168—170° (Found: N, 9·0; Br, 24·9; S, 10·4. $C_{10}H_{13}O_3N_2BrS$ requires N, 8·7; Br, 24·9; S, 10·0%).

Acetylsulphanilylethyleneimide.—A solution of the foregoing compound (31·7 g.) in water (200 c.c.) and 5N-sodium hydroxide (100 c.c.) was kept at 20° for ½ hour, by which time a heavy precipitate (19 g.) had separated. The *imide* was collected, washed with water, and dried in a vacuum; a sample crystallised from water in colourless needles, m. p. 116—118° (Found: N, 11·7; S, 13·0. $C_{10}H_{12}O_3N_2S$ requires N, 11·7; S, 13·3%).

2-(*Acetylsulphanilamido*)*ethylthiol.*—Acetylsulphanilylethyleneimide (19 g.) was added to a methanolic solution of ammonium sulphide (10 g. ammonia, 16 g. hydrogen sulphide in 120 c.c. methyl alcohol), and the solution kept at room temperature for 48 hours. The solvent was pumped off, water added, and the solid (17 g.; m. p. 120°) collected; crystallisation from aqueous methyl alcohol yielded 2-(*acetylsulphanilamido*)*ethylthiol* in pale pink prisms, m. p. 126—128° (Found: N, 10·5; S, 23·5. $C_{10}H_{14}O_3N_2S_2$ requires N, 10·2; S, 23·4%). The compound gave an intense purple coloration with sodium nitroprusside.

2-*Sulphanilamidoethylthiol Hydrochloride.*—A solution of the foregoing acetyl compound (4·0 g.) in alcohol (40 c.c.) and 10% w/w alcoholic hydrogen chloride (60 c.c.) was refluxed for 1½ hours. After the solvent had been pumped off, 2-*sulphanilamidoethylthiol hydrochloride* (2·6 g.) separated in small colourless prisms, m. p. 210—212° (Found: N, 10·6; Cl, 13·5; S, 23·5. $C_8H_{12}O_2N_2S_2$,HCl requires N, 10·4; Cl, 13·2; S, 23·8%). The free base was an oil which could not be induced to crystallise.

Benzeneazoacetoacetic Acid (cf. Bulöw and Neber, *Ber.*, 1912, **45**, 3732).—A solution of aniline (91 c.c.) in 5N-hydrochloric acid (500 c.c.) was diazotised at 0—5° with a solution of sodium nitrite (73 g.) in water (250 c.c.); after a further 10 minutes' stirring, saturated sodium acetate solution was added until the solution was no longer acid to Congo-red. This solution was added slowly to a stirred solution of ethyl acetoacetate (127 c.c.) and sodium acetate (120 g.) in water (200 c.c.) and alcohol (750 c.c.), the temperature being kept below 10°. After the addition, the reaction mixture was stirred for a further ½ hour at 5—10° and then for 1½ hours at room temperature, diluted with water (1000 c.c.), and the ethyl benzeneazoacetoacetate (229 g.), m. p. 76—78°, filtered off and dried at 20°.

5N-Sodium hydroxide (120 c.c.; 0·6 mol.) was added to a solution of the foregoing ester (50 g.; 0·21 mol.) in alcohol (500 c.c.), and the mixture kept at room temperature for 20 hours. The yellow felted needles of sodium benzeneazoacetoacetate, m. p. 210—222°, which separated were collected and washed with alcohol (Found, in material dried at 120°: Na, 9·8. Calc. for $C_{10}H_9O_3N_2Na$: Na, 10·1%). The sodium salt was dissolved in boiling water (1 l.), and the solution acidified with hydrochloric acid, benzeneazoacetoacetic acid (37 g.) separating in fine yellow needles, m. p. 164° (cf. Bülow, *Ber.*, 1899, **32**, 197).

Benzeneazoacetoacetylethyleneimide.—Benzeneazoacetoacetic acid (20 g.) was dissolved in chloroform (60 c.c.), the solution cooled in an ice-bath, and powdered phosphorus pentachloride (25 g.) added portionwise. After standing at room temperature overnight, the solvent was pumped off at 20°, xylene (40 c.c.) added, and this pumped off at 30°. The residue was boiled with benzene (100 c.c.) and the filtered solution chilled; *benzeneazoacetoacetyl chloride* (12 g.) separated in golden brown plates, m. p. 122—124°. A sample crystallised from benzene–ligroin in golden plates, m. p. 125° (Found: N, 12·8; Cl, 16·0. $C_{10}H_9O_2N_2Cl$ requires N, 12·5; Cl, 15·8%).

The foregoing acid chloride (17·2 g.) was added portionwise to a stirred solution of ethyleneimine (17 c.c.) in water (80 c.c.) at 10°. After stirring at this temperature for a further ¼ hour the *benzeneazoacetoacetylethyleneimide* (9·3 g.; m. p. 88—90°) was collected and washed with water; a sample separated from benzene–ligroin in golden needles with the same m. p. (Found: C, 61·9; H, 5·6; N, 18·4. $C_{12}H_{13}O_2N_3$ requires C, 62·3; H, 5·6; N, 18·2%).

Addition of Hydrogen Sulphide to Benzeneazoacetoacetylethyleneimide: Formation of (IX) *or* (XI).—The foregoing imide (11·1 g.) was added to an alcoholic solution of ammonium sulphide (7 g. of ammonia

and 14 g. of hydrogen sulphide in 100 c.c. of methyl alcohol); after the initial exothermic reaction had subsided (compare reaction with benzoylethyleneimine and contrast reaction with phenyloxazoline) the mixture was kept at room temperature for 24 hours and the crystalline precipitate (7·5 g.; m. p. 146—150°) collected. Recrystallisation from chloroform–methanol yielded a *compound* (6·0 g.) in fine yellow needles, m. p. 164—166°, which gave no coloration with sodium nitroprusside (Found: C, 54·5; H, 5·4; N, 16·0; S, 12·3. $C_{12}H_{15}O_2N_3S$ requires C, 54·3; H, 5·7; N, 15·85; S, 12·1%). The substance was insoluble in cold alcoholic sodium hydroxide. It was recovered unchanged (m. p. and mixed m. p.) after refluxing with dilute alcoholic sodium hydroxide and after standing for 30 days with 12% alcoholic hydrogen chloride or 5N-alcoholic ammonia.

WARD, BLENKINSOP & CO. LTD., RESEARCH LABORATORIES,
SHEPTON MALLET, SOMERSET.
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