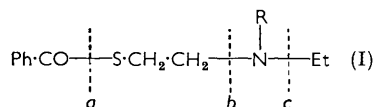


**913. Thiol-esters. Part II.<sup>1</sup> The Chlorination of 2-Diethylaminoethyl Thiolbenzoate and the Rearrangement of 2-Alkylaminoethyl Thiolbenzoates.**

By C. J. M. STIRLING.

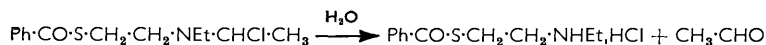
Chlorination of 2-diethylaminoethyl thiolbenzoate causes *N*-dealkylation; the subsequent reactions have been traced in a study of the stability of a series of 2-alkylaminoethyl thiolbenzoates. These esters rearrange to benzamido-thiols which then undergo intermolecular self-benzoylation.

CRANE, FORREST, STEPHENSON, AND WATERS<sup>2</sup> showed that aqueous chlorination of tertiary amines caused dealkylation at the nitrogen atom by successive  $\alpha$ -chlorination and hydrolysis. *N*-Chloroamides were used to trace the systematic breakdown of the tertiary bases by successive chlorination of the alkyl groups. In the present work, 2-diethylaminoethyl thiolbenzoate (I; R = Et) reacted rapidly with an excess of aqueous chlorine in acid solution, to give a quantitative yield of benzoic acid together with *NN*-diethyltaurine. As observed previously,<sup>2</sup> chlorine does not attack protonated amino-groups, and with the thiol-ester carbonyl-sulphur fission occurs exclusively. In alkaline hypochlorite, reaction with the ester occurs both at the amino-group and at the sulphur atom. The products are benzoic acid, diethylamine, and acetaldehyde (together with the product of further chlorination, chloroform). These products are derived respectively from cleavages at (a), (b), and (c). In addition, a chloramine, which on reduction gave only neutral material, was obtained. This chloramine could not be purified but was probably the ester (I; R = Cl). Neither of the products resulting from cleavages at (b) and (c), namely, 2-(benzoylthio)ethanal and 2-ethylaminoethyl thiolbenzoate (I; R = H), was found, and no pure taurine derivative was isolated.



An attempt to obtain 2-ethylaminoethyl thiolbenzoate from 2-ethylaminoethyl chloride hydrochloride and potassium thiolbenzoate gave only a neutral compound, C<sub>18</sub>H<sub>19</sub>O<sub>2</sub>NS. Its infrared spectrum, which was closely similar to that of the neutral material obtained from the reduction of the *N*-chloro-amine, showed carbonyl bands at 1668 and 1630 cm.<sup>-1</sup>, the latter that of a tertiary amide, together with a strong band at 911 cm.<sup>-1</sup>. Alkaline hydrolysis gave benzoic acid and a thiol (C<sub>12</sub>H<sub>15</sub>ONS), from whose spectrum the bands at 1668 and 911 cm.<sup>-1</sup> were absent. Comparison with the spectra of other thiol-esters considered in this investigation has shown that these bands are to be associated with the thiolcarboxylic group. On this evidence the original compound was considered to be *NS*-dibenzoyl-2-ethylaminoethanethiol (II; R = Et) and the thiol, therefore, to be *N*-benzoyl-2-ethylaminoethanethiol (IV; R = Et). This was confirmed by synthesis (see scheme p. 4525).

Attention was turned to anhydrous chlorination of the ester; *NN'*-dichloro-*NN'*-di-(2 : 4 : 6-trichlorophenyl)urea reacted rapidly with 2-diethylaminoethyl thiolbenzoate to give benzoyl chloride, diethylamine, *NS*-dibenzoyl-2-ethylaminoethanethiol, and 2-ethylaminoethyl thiolbenzoate hydrochloride. The last product resulted from hydrolysis of the  $\alpha$ -chloro-amine:

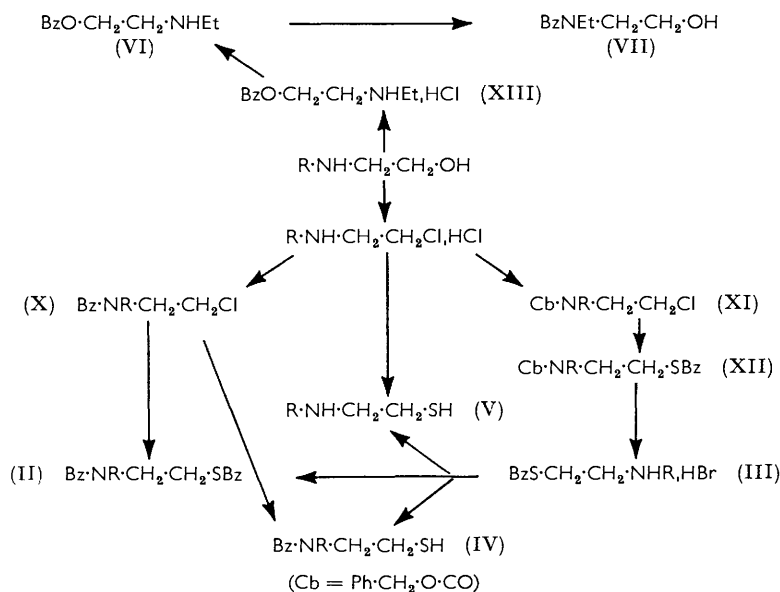


No free secondary amino-ester was isolated.

<sup>1</sup> The paper by Stirling, *J.*, 1957, 3597, is regarded as Part I.

<sup>2</sup> Crane, Forrest, Stephenson, and Waters, *J.*, 1946, 827.

Of the products obtained in reactions with both chlorine and the chloro-amide, only *NS*-dibenzoyl-2-ethylaminoethanethiol could not be accounted for as a product of  $\alpha$ -chlorination of the *N*-substituent or of carbonyl-sulphur fission. This, together with the failure to isolate 2-ethylaminoethyl thiolbenzoate, prompted an investigation of the stability of 2-alkylaminoethyl thiolbenzoates. Alkylaminoalkyl carboxylic esters undergo <sup>3,4</sup>  $O \rightarrow N$  acyl migration to give amides, but  $\beta$ -amino-thiol-esters have been less investigated. Two methods <sup>5,6</sup> for the synthesis of 2-acylaminoethanethiols involve the assumption that an amino-thiol-ester is initially formed, but in neither instance was it isolated. Wieland and Hornig <sup>7</sup> have obtained  $\omega$ -aminoalkyl thiolcarboxylic esters as the hydrochlorides and have measured the rates of rearrangement of the free bases without isolation of the products. In no case was formation of *NS*-diacylated compounds reported. 2-Ethylaminoethyl thiolbenzoate hydrobromide (III; R = Et) was obtained as outlined in the scheme below. Liberation of the base gave not only the expected product of  $S \rightarrow N$  migration, *N*-benzoyl-2-ethylaminoethanethiol (IV; R = Et), but also *NS*-dibenzoyl-2-ethylaminoethanethiol (II; R = Et). No basic product was obtained. Similarly, 2-aminoethyl thiolbenzoate hydrobromide (III; R = H) gave a mixture of 2-benzamidoethanethiol (IV; R = H) (cf. Kuhn and Quadbeck <sup>5</sup>) and *NS*-dibenzoyl-2-



aminoethanethiol (II; R = H). This showed that 2-alkylaminoethyl thiolbenzoates undergo rapid  $S \rightarrow N$  benzoyl migration which is followed by benzoylation of the resulting thiol. The formation of dibenzoylated compounds in these reactions must be accompanied by elimination of a 2-alkylaminoethanethiol (V). Attempts to isolate this thiol (R = H or Et) failed, but from 2-cyclohexylaminoethyl thiolbenzoate hydrobromide (III; R = cyclohexyl) all three compounds (II, IV, and V; R = cyclohexyl) were obtained. Rearrangement of the thiol-esters was much faster than that of the oxygen analogue (VI) which only slowly rearranged to the amido-alcohol (VII). No corresponding *NO*-dibenzoyl compound could be isolated.

<sup>3</sup> Phillips and Baltzly, *J. Amer. Chem. Soc.*, 1947, **69**, 200.

<sup>4</sup> Cope and Hancock, *ibid.*, 1944, **66**, 1453, and references there cited.

<sup>5</sup> Kuhn and Quadbeck, *G.P.* 893,795.

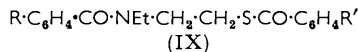
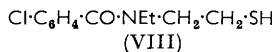
<sup>6</sup> McQuillin and Stewart, *J.*, 1955, 2966.

<sup>7</sup> Wieland and Hornig, *Annalen*, 1956, **600**, 12.

In principle, the *NS*-dibenzoyl compound obtained from the thiol-ester may arise in two ways:

(i) Intermolecular aminolysis, *i.e.*, displacement of 2-alkylaminoethanethiol by attack of the secondary amino-group at the carbonyl group of the second molecule. This, however, is unlikely, as the  $S \rightarrow N$  migration is rapid whereas aminolysis of thiol-esters is slow. 2-Diethylaminoethyl thiolbenzoate and di-*n*-butylamine, for example, required 1 hr. at 170° for 20% reaction.

(ii) Transesterification. Reaction of the amido-thiol (IV), the product of rearrangement, with free amino-ester would account for the formation of the *NS*-dibenzoyl compounds. Transesterification of thiol-esters has been reported<sup>8</sup> and, to test this possibility, 2-ethylaminoethyl thiolbenzoate was liberated from the hydrobromide in the presence of *N-p*-chlorobenzoyl-2-ethylaminoethanethiol (VIII). The higher-boiling fraction contain-



ing *NS*-dibenzoyl compounds was found to contain chlorine, showing that the substituted thiol had reacted. The infrared spectrum of this fraction, however, contained a band at 719  $\text{cm}^{-1}$  which was present in neither the spectrum of *NS*-dibenzoyl-2-ethylaminoethanethiol nor that of the expected chlorine-containing product, *S*-benzoyl-*N-p*-chlorobenzoyl-2-ethylaminoethanethiol (IX; R = Cl, R' = H). This band was, however, present in the spectra of the compounds (IX; R = H or Cl, R' = Cl). This suggested that the substituted thiol had reacted with itself, and later examination of the residue from the distillation of this thiol (VIII) showed it to be *NS*-di-*p*-chlorobenzoyl-2-ethylaminoethanethiol (IX; R = R' = Cl). Tests of the stability of the other amido-thiols considered above showed that *S*-benzoylation occurred during distillation and that therefore postulation of transesterification was unnecessary. The reaction must involve displacement of amino-thiol (V) from the amido-thiol (IV) and resembles the high-temperature alcoholysis of amides<sup>9</sup> and the reaction of thiols with thioamides to give esters of dithio-acids.<sup>10</sup>

In spite of the observation that *NS*-dibenzoyl-2-alkylaminoethanethiols arise directly from 2-alkylaminoethyl thiolbenzoates, the failure to isolate the thiol (IV; R = Et) from the partial chlorination of 2-diethylaminoethyl thiolbenzoate suggests that the formation of *NS*-dibenzoyl-2-ethylaminoethanethiol is probably not due to the decomposition of amido-thiol. Instead, benzoylation of the amido-thiol (or possibly of unrearranged secondary amino-ester) by benzoyl chloride simultaneously produced in the chlorination, must be regarded as more probable.

### EXPERIMENTAL

Extracts were dried over  $\text{MgSO}_4$ . The light petroleum used had b. p. 40—60° unless otherwise stated. *NN'*-Dichloro-*NN'*-di-(2 : 4 : 6-trichlorophenyl)urea<sup>11</sup> had m. p. 175° (decomp.) (Found: Available chlorine, 14.7. Calc. for  $\text{C}_{13}\text{H}_4\text{ON}_2\text{Cl}_8$ : 14.6%).

*2-Diethylaminoethyl Thiolbenzoate*.—Potassium thiolbenzoate (41 g.) and 2-diethylaminoethyl chloride hydrochloride (48 g.) in water (200 ml.) were kept at 100° for 1 hr. The solution was basified with sodium hydroxide and extraction with chloroform gave the ester (60 g.), b. p. 112°/0.1 mm.,  $n_D^{25}$  1.5465 (Found: C, 65.5; H, 8.3. Calc. for  $\text{C}_{13}\text{H}_{19}\text{ONS}$ : C, 65.8; H, 8.0%). The hydrochloride had m. p. 139—140° (Found: N, 5.1. Calc. for  $\text{C}_{13}\text{H}_{20}\text{ONClS}$ : N, 5.0%). Clinton, Salvador, and Laskowski<sup>12</sup> give m. p. 137—138.5°.

<sup>8</sup> Sasin, Schaeffer, and Sasin, *J. Org. Chem.*, 1957, **22**, 1183.

<sup>9</sup> Taylor and Baker, "Sidgwick's Organic Chemistry of Nitrogen," Oxford University Press, 1937, p. 145.

<sup>10</sup> Reid, Orig. Comm. 8th Internat. Congr. Appl. Chem. (Appendix), Vol. 25, p. 423; *Chem. Abs.*, 1913, **7**, 2190.

<sup>11</sup> Chattaway and Orton, *Ber.*, 1901, **34**, 1073.

<sup>12</sup> Clinton, Salvador, and Laskowski, *J. Amer. Chem. Soc.*, 1949, **71**, 3366.

*NN-Diethyltaurine*.—The following method is superior to James's.<sup>13</sup> Sodium 2-bromoethane-sulphonate<sup>14</sup> (10 g.), diethylamine (50 g.), and water (50 ml.) were heated at 150° (autoclave) for 1 hr. The mixture was evaporated to dryness and a solution of the residue (13 g.), in ethanol (50 ml.), was saturated with hydrogen chloride. Sodium chloride was centrifuged off and the mother-liquors gave the amino-acid (6 g.), m. p. 161—162° (Found: N, 7.6. Calc. for C<sub>6</sub>H<sub>15</sub>O<sub>3</sub>NS: N, 7.7%).

*Aqueous Chlorination of 2-Diethylaminoethyl Thiolbenzoate*.—(a) *In acid*. A solution of the ester (5 g.) in 0.1N-hydrochloric acid (200 ml.) was saturated with chlorine. After removal of excess of chlorine in air, the solution was saturated with sodium chloride and extracted with methylene chloride. Evaporation of the dried extracts gave benzoic acid (2.5 g.), m. p. and mixed m. p. 121°. The aqueous solution was basified with sodium hydroxide and extracted with chloroform. Evaporation of the extracts gave no residue. The aqueous solution was then acidified, neutralised with sodium carbonate, and evaporated to dryness. The residue was extracted with hot absolute ethanol, and the extracts were saturated with hydrogen chloride and filtered. Evaporation of the filtrates gave *NN*-diethyltaurine (3 g.), m. p. and mixed m. p. 158—162°.

(b) *In alkali*. The ester (20 g.) was vigorously stirred with saturated aqueous sodium hydrogen carbonate (180 ml.), and a solution of sodium hypochlorite (8.7% available chlorine; 140 ml.; 2 atom-equivs.). When the aqueous layer gave no starch-iodide reaction the layers were separated.

The aqueous layer was acidified and extraction with ether gave benzoic acid (1.4 g.), m. p. and mixed m. p. 119—120°. The aqueous extracts, which gave a strong positive potassium hydroxide-pyridine test for chloroform, were distilled under reduced pressure. Acetaldehyde was obtained from a portion of the distillate as the 2 : 4-dinitrophenylhydrazone which, after chromatography on alumina, had m. p. and mixed m. p. 167°. No other carbonyl compound was detected. The residual aqueous solution, which did not give a derivative on treatment with aqueous 2 : 4-dinitrophenylhydrazine hydrochloride, was basified with sodium hydroxide and extracted with chloroform. The extracts, after being saturated with hydrogen chloride, were evaporated and treatment of the crystalline residue with toluene-*p*-sulphonyl chloride and aqueous sodium hydroxide gave *NN*-diethyltoluene-*p*-sulphonamide, m. p. and mixed m. p. 60—61°. The aqueous extracts were treated as described above for the isolation of taurine derivatives but no pure material was obtained.

The oil was washed with ice-cold 2N-hydrochloric acid. The washings were basified with sodium hydroxide and extracted with chloroform. Evaporation of the extracts and treatment of an ethereal solution of the residue with hydrogen chloride gave recovered ester hydrochloride (10.8 g.), m. p. and mixed m. p. 139—140°. The remainder of the oil was treated with an excess of potassium iodide and sodium thiosulphate in aqueous acetic acid. After 30 min. the solution was basified with sodium hydroxide and extracted with chloroform. Evaporation of the extracts gave a small neutral residue which did not give a 2 : 4-dinitrophenylhydrazone. The nitroprusside test was negative until the material had been treated with hot alcoholic sodium hydroxide. Attempts to obtain sufficient of the compound for purification failed but the infrared spectrum was closely similar to that of *NS*-dibenzoyl-2-ethylaminoethanethiol (below).

*Reaction of Potassium Thiolbenzoate with 2-Ethylaminoethyl Chloride Hydrochloride*.—2-Ethylaminoethyl chloride hydrochloride<sup>15</sup> (16 g.) and potassium thiolbenzoate (19.6 g.) were heated in water (100 ml.) at 95°. After 15 min. an oil separated and hydrogen sulphide was evolved. After 1½ hr. the solution was extracted with ether, and the extracts were washed with hydrochloric acid. No basic product was obtained. Evaporation of the ethereal solution and distillation of the residue gave *NS*-dibenzoyl-2-ethylaminoethanethiol (13.5 g.), b. p. 200°/0.2 mm.,  $n_D^{25}$  1.5961 (Found: C, 68.3; H, 6.3. C<sub>18</sub>H<sub>19</sub>O<sub>2</sub>NS requires C, 69.0; H, 6.1%). Hydrolysis (of 4.7 g.) with sodium hydroxide in aqueous acetone gave: (i) benzoic acid (1.7 g.), m. p. and mixed m. p. 119—121°; and (ii) slightly impure *N*-benzoyl-2-ethylaminoethanethiol (1.8 g.), b. p. 133°/0.1 mm.,  $n_D^{25}$  1.5612 (Found: C, 62.3; H, 7.6. C<sub>11</sub>H<sub>15</sub>ONS requires C, 63.1; H, 7.2%). The infrared spectra of the compounds were identical with those of authentic specimens (below). Starting material (0.6 g.) was recovered from the hydrolysis.

<sup>13</sup> James, *J.*, 1885, **47**, 367.

<sup>14</sup> Marvel and Sparberg, *Org. Synth.*, 1930, **10**, 96.

<sup>15</sup> Lasselle and Sundet, *J. Amer. Chem. Soc.*, 1941, **63**, 2374.

*N*-Benzoyl-2-ethylaminoethyl Chloride (X; R = Et).—2-Ethylaminoethyl chloride hydrochloride (5 g.) was treated with benzoyl chloride (4 ml.) and 5% aqueous sodium hydroxide (50 ml.). Extraction of the product with ether and subsequent distillation gave the *chloride* (5 g.), b. p. 115°/0.2 mm.,  $n_D^{25}$  1.5395 (Found: C, 62.0; H, 6.8.  $C_{11}H_{14}ONCl$  requires C, 62.4; H, 6.6%).

*NS*-Dibenzoyl-2-ethylaminoethanethiol (II; R = Et).—The chloride (5.7 g.) and potassium thiolbenzoate (4.8 g.) were heated under reflux in ethanol (30 ml.) for 1½ hr. Water (250 ml.) was added and the product was extracted with ether. Distillation gave the ester (6.9 g.), b. p. 220°/0.3 mm.,  $n_D^{25}$  1.5965, m. p. 49—50° (Found: C, 69.1; H, 6.4%).

*S*-(*N*-Benzoyl-2-ethylaminoethyl)thiuronium Hydrochloride.—The salt (16 g.), from thiourea (6.4 g.) and *N*-benzoyl-2-ethylaminoethyl chloride (20 g.), had m. p. 145° (from acetone-ethanol) (Found: Cl, 12.3.  $C_{12}H_{18}ON_3ClS$  requires Cl, 12.3%).

*N*-Benzoyl-2-ethylaminoethanethiol (IV; R = Et).—Hydrolysis of the thiuronium salt (11 g.) with 5% aqueous sodium hydroxide and extraction of the product with chloroform, gave the thiol (6.2 g.), b. p. 125°/0.04 mm.,  $n_D^{25}$  1.5606 (Found: C, 63.0; H, 7.4%).

*Anhydrous Chlorination of 2-Diethylaminoethyl Thiolbenzoate*.—The ester (20 g.) was added to a solution of the octachlorodiphenylurea (40 g.) in anhydrous ( $P_2O_5$ ) ethanol-free ( $CaCl_2$ ) chloroform (300 ml.). After 15 hr. the precipitate of hexachlorodiphenylurea (31.3 g.), m. p. 316°,<sup>11</sup> was filtered off. Solvent was removed from the filtrate and addition of anhydrous ether (250 ml.) to the residue precipitated 2-diethylaminoethyl thiolbenzoate hydrochloride which, after being washed with acetone, had m. p. 130—133° (11 g.). The ethereal solution, after extraction with 2*N*-hydrochloric acid and 10% aqueous sodium carbonate, was washed with water and dried. While being dried, the ethereal solution gave a further precipitate (1.4 g.), m. p. 163° raised to 165° on crystallisation from acetone-ethanol. The infrared spectrum of the compound was closely similar to that of 2-ethylaminoethyl thiolbenzoate hydrobromide (below) and analysis showed it to be 2-ethylaminoethyl thiolbenzoate hydrochloride (Found: C, 54.1; H, 6.7.  $C_{11}H_{16}ONClS$  requires C, 53.8; H, 6.6%). Treatment of a saturated aqueous solution with saturated aqueous potassium bromide precipitated the *hydrobromide*, m. p. 169—170° (from acetone-ethanol) both alone and mixed with an authentic specimen (below). The residual ethereal solution was evaporated and the residue was fractionally distilled, giving: (i) benzoyl chloride (0.6 g.), b. p. 65°/14 mm.,  $n_D^{25}$  1.4923 (benzanilide, m. p. and mixed m. p. 161—162°); (ii) (0.4 g.), b. p. 80—140°/0.1 mm., which was not identified but whose spectrum did not contain bands at 1630 or 2500  $cm^{-1}$  and was therefore not the amido-thiol (IV; R = Et); and (iii) *NS*-dibenzoyl-2-ethylaminoethanethiol (2.8 g.), b. p. 200°/0.2 mm.,  $n_D^{25}$  1.5967 (the spectrum was the same as that of an authentic specimen).

The aqueous alkaline extracts yielded only a trace of dark material. The acid extracts were basified with sodium hydroxide and extracted with chloroform. The dried extracts were distilled, diethylamine being isolated from the distillates as previously described, and saturation of an ethereal solution of the residue with hydrogen chloride precipitated recovered ester hydrochloride (0.4 g.) m. p. and mixed m. p. 136°.

*Reactions of 2-Alkylaminoethyl Thiolbenzoates*. (a) *Series R = Et (see scheme)*.—(a) *N*-Benzoyloxycarbonyl-2-ethylaminoethyl chloride (XI). 2-Ethylaminoethyl chloride hydrochloride (15 g.) was treated with benzyl chloroformate (15 g.) and 5% aqueous sodium hydroxide (150 ml.). Extraction of the product with ether gave the *chloride* (19 g.), b. p. 112°/0.05 mm.,  $n_D^{25}$  1.5157 (Found: C, 59.8; H, 7.0.  $C_{12}H_{16}O_2NCl$  requires C, 59.6; H, 6.6%).

*N*-Benzoyloxycarbonyl-2-ethylaminoethyl thiolbenzoate (XII). The preceding chloride (16 g.) and potassium thiolbenzoate (11 g.), in ethanol (50 ml.), were heated under reflux for 3 hr. Water (200 ml.) was added and extraction of the product with chloroform gave the *ester* (10.5 g.), b. p. 200°/0.05 mm.,  $n_D^{25}$  1.5760 (Found: C, 66.0; H, 6.3.  $C_{19}H_{21}O_3NS$  requires C, 66.5; H, 6.1%).

2-Ethylaminoethyl thiolbenzoate hydrobromide (III). The ester (10 g.), in dry acetic acid (10 ml.), was treated with 20% w/w hydrobromic-acetic acid (25 g.). After 1 hr. addition of anhydrous ether (200 ml.) precipitated the *ester hydrobromide* (8.3 g.), m. p. 169—170° (Found: C, 45.5; H, 5.8; Br, 27.6.  $C_{11}H_{16}ONBrS$  requires C, 45.5; H, 5.5 Br, 27.5%).

*Rearrangement of 2-ethylaminoethyl thiolbenzoate*. The hydrobromide (8 g.), in oxygen-free water (200 ml.), was treated with sodium hydroxide (2.2 g.). The mixture was extracted with chloroform and then acidified and re-extracted. Distillation of the extracts gave: (i) *N*-benzoyl-2-ethylaminoethanethiol (3.5 g.), b. p. 132°/0.1 mm.,  $n_D^{25}$  1.5605; and (ii) *NS*-dibenzoyl-2-ethylaminoethanethiol (1.5 g.), b. p. 196°/0.1 mm.,  $n_D^{25}$  1.5493, m. p. and mixed m. p. 46—47°.

(b) Series R = H.—(Except where otherwise stated, the methods in this and the following series, R = cyclohexyl, were the same as in the series R = Et. Yields at each stage are based on the preceding compound).

*S*-2-Benzamidoethylthiuronium hydrochloride. The salt (80%) (from 2-chloroethylbenzamide<sup>16</sup>) had m. p. 175° (from ethanol-acetone) (Found: Cl, 13.6. C<sub>10</sub>H<sub>14</sub>ON<sub>3</sub>ClS requires Cl, 13.7%).

2-Benzamidoethanethiol (IV). The product (88%) had m. p. 70° (from benzene-light petroleum). Kuhn and Quadbeck<sup>5</sup> give m. p. 71°.

2-Benzamidoethyl thiolbenzoate (II). Benzoylation (Schotten-Baumann) of the thiol gave the ester, m. p. 96—97° (from benzene-light petroleum) (Found: C, 67.3 H, 5.5. C<sub>16</sub>H<sub>15</sub>O<sub>2</sub>NS requires C, 67.3; H, 5.3%).

2-*N*-Benzoyloxycarbonylaminoethyl thiolbenzoate (XII). The ester (82%) (from 2-*N*-benzyloxycarbonylaminoethyl bromide<sup>17</sup>) had m. p. 77° (from chloroform-light petroleum) (Found: C, 64.8; H, 5.7. C<sub>17</sub>H<sub>17</sub>O<sub>3</sub>NS requires C, 64.8; H, 5.4%).

2-Aminoethyl thiolbenzoate hydrobromide (III). The salt (76%) had m. p. 192—193° (from acetone-ethanol) (Found: C, 41.3; H, 4.8. C<sub>9</sub>H<sub>12</sub>ONBrS requires C, 41.2; H, 4.6%).

Rearrangement of 2-aminoethyl thiolbenzoate. The hydrobromide (9 g.) gave: (i) 2-benzamidoethanethiol (4.6 g.), b. p. 138°/0.05 mm., m. p. and mixed m. p. 68.5—70°; and (ii) 2-benzamidoethyl thiolbenzoate (1.0 g.), b. p. 200°/0.05 mm., m. p. and mixed m. p. 90—91°.

(c) Series R = cycloHexyl.—*N*-Benzoyloxycarbonyl-2-cyclohexylaminoethyl chloride (XI). The chloride (63%) (from 2-cyclohexylaminoethyl chloride hydrochloride<sup>18, 19</sup>) had m. p. 53—54° (from light petroleum) (Found: C, 64.6; H, 7.6. C<sub>16</sub>H<sub>22</sub>O<sub>2</sub>NCl requires C, 65.0; H, 7.5%).

*N*-Benzoyloxycarbonyl-2-cyclohexylaminoethyl thiolbenzoate (XII). The chloride (25 g.), potassium thiolbenzoate (20 g.), and potassium iodide (2 g.), heated in boiling ethanol for 3 hr., gave the ester (8.2 g.), b. p. 200°/0.05 mm.,  $n_D^{25}$  1.5749 (Found: C, 69.6; H, 7.1. C<sub>23</sub>H<sub>27</sub>O<sub>3</sub>NS requires C, 69.5; H, 6.9%).

2-cycloHexylaminoethyl thiolbenzoate hydrobromide (III). The salt (98%) had m. p. 206—207° (from ethanol) (Found: C, 52.2; H, 6.6. C<sub>15</sub>H<sub>22</sub>ONBrS requires C, 52.3; H, 6.4%).

*S*-2-cycloHexylaminoethylthiuronium hydrochloride. 2-cycloHexylaminoethyl chloride hydrochloride (10 g.) and thiourea (3.8 g.) gave the salt (7 g.), m. p. 245° (from methanol) (Found: Cl, 25.7. C<sub>9</sub>H<sub>20</sub>N<sub>3</sub>ClS requires Cl, 25.9%).

2-cycloHexylaminoethanethiol (V). Hydrolysis of the salt (5 g.) gave the thiol (1.4 g.), b. p. 112°/14 mm.,  $n_D^{25}$  1.5045 (Found: C, 60.4; H, 11.0. C<sub>8</sub>H<sub>17</sub>NS requires C, 60.3; H, 10.8%). The urea thiolcarbamate, obtained with  $\alpha$ -naphthyl isocyanate, had m. p. 207—208° (from chloroform-light petroleum) (Found: N, 8.2. C<sub>30</sub>H<sub>31</sub>O<sub>2</sub>N<sub>3</sub>S requires N, 8.4%).

*N*-Benzoyl-2-cyclohexylaminoethyl chloride (X). The chloride (55%) (from 2-cyclohexylaminoethyl chloride hydrochloride) had b. p. 145°/0.05 mm.,  $n_D^{25}$  1.5437 (Found: C, 67.9; H, 8.0. C<sub>15</sub>H<sub>20</sub>ONCl requires C, 67.8; H, 7.6%).

*S*-(*N*-Benzoyl-2-cyclohexylaminoethyl)thiuronium hydrochloride. The salt (96%) had m. p. 207° (from acetone-ethanol) (Found: Cl, 10.3. C<sub>16</sub>H<sub>24</sub>ONClS requires Cl, 10.4%).

*N*-Benzoyl-2-cyclohexylaminoethanethiol (IV). Pure thiol could not be obtained from the hydrolysis of the thiuronium salt but treatment of the product, b. p. 148°/0.05 mm., with  $\alpha$ -naphthyl isocyanate gave the thiolcarbamate, m. p. 180° (from benzene-light petroleum) (Found: C, 72.5; H, 6.7. C<sub>26</sub>H<sub>28</sub>O<sub>2</sub>N<sub>2</sub>S requires C, 72.2; H, 6.5%).

*NS*-Dibenzoyl-2-cyclohexylaminoethanethiol (II). Benzoylation (Schotten-Baumann) of the crude thiol gave the ester, m. p. 100° (from benzene-light petroleum) (Found: C, 71.8; H, 7.1. C<sub>22</sub>H<sub>25</sub>O<sub>2</sub>NS requires C, 71.9; H, 6.9%).

Rearrangement of 2-cycloHexylaminoethyl thiolbenzoate. Distillation of the products gave fractions: (i) b. p. 40—50°/0.05 mm., which on treatment with  $\alpha$ -naphthyl isocyanate gave a derivative, m. p. 205—206° alone or mixed with that obtained from 2-cyclohexylaminoethanethiol; and (ii) b. p. 145°/0.05 mm., which with  $\alpha$ -naphthyl isocyanate gave a derivative, m. p. 178—179° alone or mixed with that obtained from *N*-benzoyl-2-cyclohexylaminoethanethiol. The residue, after crystallisation from ethanol, had m. p. 96° alone or mixed with *NS*-dibenzoyl-2-cyclohexylaminoethanethiol.

<sup>16</sup> Fry, *J. Org. Chem.*, 1949, **14**, 887.

<sup>17</sup> Katchalski and Ben-Ishai, *ibid.*, 1950, **15**, 1067.

<sup>18</sup> Wedekind and Bruch, *Annalen*, 1929, **471**, 73.

<sup>19</sup> Cheney, Smith, and Binkley, *J. Amer. Chem. Soc.*, 1949, **71**, 60.

**2-Ethylaminoethyl Benzoate Hydrochloride (XIII).**—2-Ethylaminoethanol hydrochloride<sup>15</sup> was heated with benzoyl chloride at 100° until no further hydrogen chloride was evolved. Addition of ether precipitated the salt, m. p. 164—165° (Found: C, 57.4; H, 7.4; Cl, 15.4. C<sub>11</sub>H<sub>16</sub>O<sub>2</sub>NCl requires C, 57.5; H, 7.0; Cl, 15.4%).

**Rearrangement of the Amino-ester.**—The preceding hydrochloride (5 g.) was treated as before and distillation of the products gave fractions: (i) (1.9 g.) 2-ethylaminoethyl benzoate, b. p. 87°/0.05 mm.,  $n_D^{25}$  1.5109 (Found: N, 7.4. C<sub>11</sub>H<sub>15</sub>O<sub>2</sub>N requires N, 7.3%); (ii) (1.8 g.) N-benzoyl-2-ethylaminoethanol, b. p. 138°/0.05 mm.,  $n_D^{25}$  1.5428 (Found: N, 7.4%). Fraction (i) with ethereal hydrogen chloride gave the ester hydrochloride, m. p. and mixed m. p. 164°, and with  $\alpha$ -naphthyl isocyanate gave the  $\alpha$ -naphthylurea, m. p. 115—116° (from benzene-light petroleum) (Found: N, 7.8. C<sub>22</sub>H<sub>22</sub>O<sub>3</sub>N<sub>2</sub> requires N, 7.7%). The infrared spectrum showed a C=O band at 1715 cm.<sup>-1</sup>. Fraction (ii) was neutral, showed C=O 1611 cm.<sup>-1</sup>, and with  $\alpha$ -naphthyl isocyanate gave the  $\alpha$ -naphthylcarbamate, m. p. 102° (from benzene-light petroleum) (Found: N, 7.7%). The refractive index and infrared spectrum of the amino-ester (i) slowly changed to that of the amido-alcohol (ii).

**Test of Aminolysis.**—2-Diethylaminoethyl thiolbenzoate (5 g.) and di-*n*-butylamine (10 g.) were heated at 170° for 1 hr. The neutral product (0.7 g.), b. p. 122°/0.3 mm., had a C=O band at 1620 cm.<sup>-1</sup>.

**N-*p*-Chlorobenzoyl-2-ethylaminoethyl Chloride.**—The chloride (59%) (from *p*-chlorobenzoyl chloride and 2-ethylaminoethyl chloride) had b. p. 140°/0.05 mm.,  $n_D^{25}$  1.5504 (Found: C, 53.7; H, 5.6. C<sub>11</sub>H<sub>13</sub>ONCl<sub>2</sub> requires C, 53.7; H, 5.3%).

**S-(N-*p*-Chlorobenzoyl-2-ethylaminoethyl)thiuronium Hydrochloride.**—The chloride with thiourea gave the salt (92%), m. p. 200—201° (from ethanol) (Found: C, 44.5; H, 5.7; N, 12.5. C<sub>12</sub>H<sub>17</sub>ON<sub>3</sub>Cl<sub>2</sub>S requires C, 44.7; H, 5.3; N, 13.0%).

**N-*p*-Chlorobenzoyl-2-ethylaminoethanethiol (VIII).**—The salt (21 g.) was hydrolysed with 5% aqueous sodium hydroxide (200 ml.). Extraction of the product with chloroform and subsequent distillation gave the thiol (4.7 g.), b. p. 154°/0.1 mm.,  $n_D^{25}$  1.5708 (Found: C, 54.2; H, 6.2. C<sub>11</sub>H<sub>14</sub>ONClS requires C, 54.2; H, 5.8%). The residue, m. p. 83—84°, after crystallisation from benzene-light petroleum (b. p. 80—100°), had m. p. 88—89° alone or mixed with an authentic specimen of NS-*di-p*-chlorobenzoyl-2-ethylaminoethanethiol (IX; R = R' = Cl) (below).

**Reaction of 2-Ethylaminoethyl Thiolbenzoate with N-*p*-Chlorobenzoyl-2-ethylaminoethanethiol.**—The ester hydrobromide (8 g.) was treated with a solution of the thiol (3.6 g.) in 3% aqueous sodium hydroxide (100 ml.). Distillation of the chloroform extracts gave fractions: (i) (4.3 g.), b. p. 130—180°/0.15 mm.,  $n_D^{25}$  1.5634 (Found: Cl, 3.7%); and (ii) (3.3 g.), b. p. 206—218°/0.15 mm.,  $n_D^{25}$  1.5997 (Found: Cl, 8.5%). The infrared spectra of the two fractions have been referred to above.

**S-Benzoyl-N-*p*-chlorobenzoyl-2-ethylaminoethanethiol (IX; R = Cl, R' = H).**—The ester (70%) (from *N-p*-chlorobenzoyl-2-ethylaminoethyl chloride and potassium thiolbenzoate) had b. p. 206—208°/0.08 mm.,  $n_D^{25}$  1.6006 (Found: C, 62.0; H, 5.5; Cl, 9.9. C<sub>18</sub>H<sub>18</sub>O<sub>2</sub>NCIS requires C, 62.2; H, 5.2; Cl, 10.2%).

**N-Benzoyl-S-*p*-chlorobenzoyl-2-ethylaminoethanethiol (IX; R = H, R' = Cl).**—Treatment of the thiol (IV; R = Et) with *p*-chlorobenzoyl chloride in pyridine gave the ester, b. p. 196°/0.02 mm., m. p. 63—64° (from benzene-light petroleum) (Found: C, 61.6; H, 5.3%).

**NS-*Di-p*-chlorobenzoyl-2-ethylaminoethanethiol (IX; R = R' = Cl).**—Treatment of the thiol (VIII) with *p*-chlorobenzoyl chloride in pyridine gave the ester, m. p. 88—89° (from benzene-light petroleum) (Found: C, 56.5; H, 4.8. C<sub>18</sub>H<sub>17</sub>O<sub>2</sub>NCl<sub>2</sub>S requires C, 56.6; H, 4.5%).

**Self-benzoylation of Amido-thiols (IV).**—In view of the observation that *N-p*-chlorobenzoyl-2-ethylaminoethanethiol underwent thermal self-benzoylation, the thermal stability of the other amido-thiols that have been considered in this investigation was tested. In each case, prolonged heating of the thiol at 140° gave the NS-dibenzoyl compound, and in the case of the *N-cyclohexyl* compound, the amino-thiol (V) was also isolated.

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