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The Preparation of 3-Halopropyl Isothiocyanates and 5,6-Dihydro-2-sulphanilamido-4*H*-1,3-thiazine

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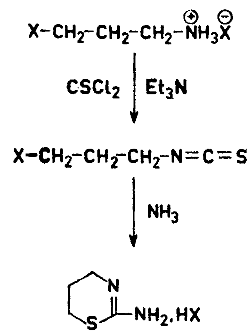
In connection with other work in this laboratory it became of interest to prepare the previously unknown 3-chloro- and 3-bromo-propyl isothiocyanates (II, X = Cl or Br). Both were readily obtained by reaction of the corresponding amine salt (I, X = Cl or Br) with thiocarbonyl chloride and triethylamine, conditions commonly utilized in isothiocyanate synthesis.

Upon treatment with methanolic ammonia, both isothiocyanates (II) cyclized as expected to the corresponding salts of 2-amino-5,6-dihydro-4*H*-1,3-thiazine (III, X = Cl or Br). Recently, Schöberl *et al.*[1,2] synthesized the hydrobromide (III, X = Br) by a cyanide-induced cyclization of 3-aminopropyl thiocyanate hydrobromide, whereas the hydrochloride (III, X = Cl) was produced from the hydrobromide *via* the free amine. The same authors also de-

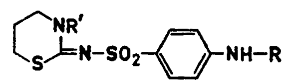


I

II

III

monstrated that the reaction of 3-bromopropylamine with thiocyanate does not afford the cyclic compound (III, X = Br) as originally proposed by Gabriel and Lauer,[3] but rather 3-aminopropyl thiocyanate hydrobromide.[2]



IVa, R = Ac; R' = (p)-AcNHC$_6$H$_4$SO$_2$.
IVb, R = R' = H
IVc, R = Ac; R' = H

Upon reaction with *p*-acetamidobenzenesulphonyl chloride in pyridine the hydrobromide (III, X = Br) was transformed into the bis-derivative (IVa) which on acid hydrolysis was further converted into 5,6-dihydro-2-sulphanilamido-4*H*-1,3-thiazine (IVb, or the tautomeric form). Acetylation of the latter afforded the N-acetyl derivative (IVc).

We consider this to be the first synthesis of authentic specimens of these sulphonamides. Jensen and Possing[4] correctly interpreted the product obtained from the reaction between *p*-acetamidobenzenesulphonyl chloride and '2-amino-dihydrothiazine hydrobromide', followed by acid hydrolysis, as bis-3-sulphanilylaminopropyldisulphide. However, these authors, as well as others,[5,6] were obviously misled by the fact that their starting material, Gabriel and Lauer's 'Trimethylen-ψ-thioharnstoff'[3] in fact consisted of 3-aminopropyl thiocyanate hydrobromide.[2]

The sulphonamide (IVb) is presently being investigated for bacteriostatic activity.

Experimental. Melting points are uncorrected and were determined in capillary tubes in an Anschütz-Hershberg apparatus. Infra-red spectra were determined in KBr-pellets on a Perkin-Elmer Infracord-137 instrument. Analytical specimens were dried *in vacuo* over calcium chloride at room temperature. Microanalyses were performed by Mr. G. Cornali and his staff.

3-Chloropropyl isothiocyanate (II, X = Cl). To a cooled and stirred solution of 3-chloropropylamine hydrochloride (I, X = Cl) * (22 g) and thiocarbonyl chloride (19.6 g) in chloroform (80 ml), triethylamine (51.6 g) was dropwise added. The organic layer was washed with 1 N HCl, 1 N NaOH, and water, and the chloroform was removed. A gaschromatographically pure fraction of the mustard oil distilled at 43–48°/0.1–0.3 mm (12.2 g), n_D^{25} 1.5398. (Found: C 35.86; H 4.62; N 10.24; S 23.45. Calc. for C_4H_6NSCl: C 35.43; H 4.46; N 10.33; S 23.64). The IR-spectrum (film between two KBr-pellets) exhibited conspicuous bands at: 2960 (m); 2900 (sh); 2190 (vs); 2100 (vs); 1500 (w); 1450 (s); 1430 (sh); 1370 (m); 1350 (s); 1295 (s); 1250 (w); 1205 (w); 1160 (w); 1095 (w); 1065 (w); 1020 (w); 990 (w); 970 (w); 870 (m); 780–800 (m); 730 cm^{-1} (w).

3-Bromopropyl isothiocyanate (II, X = Br) was prepared in the same way from the hydrobromide (I, X = Br)[2] (11 g), b.p. 64°/0.2 mm (6.4 g), n_D^{25} 1.5712. Before analysis, a minor contamination was removed by preparative gas chromatography. (Found: C 26.51; H 3.43; N 7.76; S 17.61. Calc. for C_4H_6NSBr: C 26.69; H 3.36; N 7.78; S 17.81). The IR-spectrum exhibited prominent bands at: 2900 (m); 2850 (sh); 2170 (vs); 2090 (vs); 1440 (s); 1425 (sh); 1360 (m); 1340 (s): 1290 (sh); 1280 (m); 1250 (s); 1210 (m); 1195 (m); 1085 (w); 1060 (w); 1005 (w); 970 (w)· 942 (m); 862 (m); 833 (w); 775 cm^{-1} (m).

*2-Amino-5,6-dihydro-4*H*-1,3-thiazine hydrochloride* (III, X = Cl). The isothiocyanate (II, X = Cl) (157 mg) was dissolved in methanol saturated with ammonia (25 ml) and kept at room temperature for a few hours. The solid residue (160 mg) was recrystallized twice from ethanol and ether to give an analytically pure specimen, m.p. 153–154°. (Found: C 30.83; H 6.41; N 18.24; S 21.28. Calc. for $C_4H_9N_2SCl$: C 31.48; H 5.94; N 18.36; S 21.01). Previously reported:[2] m.p. 144° (closed tube).* UV-spectrum: $\lambda_{max}^{96\ \%\ EtOH}$ 214 mμ (ε 9900); IR-spectrum: 3400 (sh); 3240 (vs); 3100 (vs); 1640 (vs); 1490 (s); 1455 (m); 1440 (m); 1390 (s); 1320 (s); 1285 (m); 1265 (m); 1195 (m); 1180 (w); 1055 (w); 980 (m); 945 (m); 880 (w); 859 (w); 765 (w); 740 (m); 695 cm^{-1} (m). This spectrum was superimposable on that of a specimen furnished by Prof. Schöberl.

*2-Amino-5,6-dihydro-4*H*-1,3-thiazine hydrobromide* (III, X = Br). The isothiocyanate (II, X = Br) (230 mg) was treated with methanolic ammonia as above. Recrystallization of the product from 2-propanol gave a sample with m.p. 144–145°.

A larger portion (21.2 g) was prepared by ring closure of 3-aminopropyl thiocyanate hydrobromide (39 g) with KCN (13.5 g) in water (3.2 l) as described by Schöberl *et al.*[2], m.p. 146–147,° alone or in admixture with a specimen obtained from Prof. Schöberl. The picrate was prepared, m.p. 233–234.5° (Ref. 2, 234°). UV-spectrum of the hydrobromide: $\lambda_{max}^{96\ \%\ EtOH}$ 211 mμ (ε 11 600), differing significantly from the reported data: λ_{max}^{MeOH} 224 mμ (ε 678), 255 mμ (ε 652).[2] However, IR-spectra of the two preparations from this laboratory and that of the specimen from Prof. Schöberl were identical and exhibited significant bands at: 3400 (sh); 3220 (vs); 3200 (vs); 3120 (vs); 3050 (vs); 2950 (sh); 1650 (vs); 1505 (m); 1470 (m); 1450 (w); 1435 (w); 1430 (sh); 1380 (s); 1335 (m); 1280 (m); 1275 (w); 1215 (w); 1190 (s); 1180 (w); 988 (m); 945 (m); 885 (w); 860 (w); 739 (m); 695 cm^{-1} (m).

*2-(N⁴-Acetylsulphanilamido)-3-acetylsulphanilyl-5,6-dihydro-4*H*-1,3-thiazine* (IV a). A solution of (III, X = Br) (9.85 g) in anhydrous pyridine (90 ml) was heated with N-acetylsulphanilyl chloride (11.7 g) at 75° for 15 min. The reaction mixture was poured onto ice (600 g) when a yellowish solid separated (8.6 g). On recrystallization, once from 50 % ethanol and twice from 96 % ethanol, flat needles separated, m.p. 196–197.5°. An analytical speci-

* The author is grateful to Dr. K. Rubinstein, A/S Pharmacia, Copenhagen, for a generous gift of this salt.

* Reference specimens of the salts (III, X = Cl and Br), synthesized by different procedures,[2] were kindly supplied by Professor A. Schöberl, Department of Chemistry, The Veterinary College, Hannover, Germany. Determined under identical conditions the reference hydrochloride was found in this laboratory to melt at 154°.

men was produced by two additional recrystallizations from ethanol, m.p. 198–198.5°. (Found: C 45.93; H 4.72; N 10.81; S 18.13; 1.96 % H_2O. Calc. for $C_{20}H_{24}O_6N_4S_3$,0.5 H_2O: C 46.06; H 4.83; N 10.74; S 18.44; 1.73 % H_2O). An additional recrystallization from 80 % ethanol and subsequent drying over calcium chloride *in vacuo* for 27 h did not change the melting point or the analytical composition.

*5,6-Dihydro-2-sulphanilamido-4*H*-1,3-thiazine* (IV b). The acetylated compound (IV a) (2.3 g) was hydrolyzed on heating for 2 h in 0.25 N HCl (160 ml). The mixture was adjusted to pH 8 with conc. NaOH, and after cooling the precipitate was filtered off. Three recrystallizations from 50 % ethanol, with the use of a little charcoal, afforded a pure specimen of (IV b) (718 mg), m.p. 209–209.5°. (Found: C 44.45; H 4.96; N 15.57; S 23.53. Calc. for $C_{10}H_{13}N_3O_2S_2$: C 44.27; H 4.83; N 15.49; S 23.63). The IR-spectrum displayed strong bands at: 3400 (vs); 3300 (s); 3250 (s); 3200 (s); 2900 (w) with shoulders at 2960 and 2860; 1640 (s); 1600 (vs); 1570 (vs); 1500 (s); 1470 (m); 1435 (m); 1370 (vs); 1335 (sh); 1325 (s); 1305 (vs); 1300 (sh); 1280 (s); 1270 (vs); 1180 (m); 1140 (vs); 1100 (s); 1080 (vs); 1045 (w); 1015 (s); 955 (m); 880 (m); 850 (s); 835 (m); 827 (s); 820 (s); 745 (s); 725 (m); 680 cm^{-1} (s).

*2-(N^4-Acetylsulphanilamido)-5,6-dihydro-4*H*-1,3-thiazine* (IV c). A solution of (IV b) (55 mg) and acetic anhydride (0.1 ml) in 25 % ethanol (13 ml) was left for 24 h at room temperature and then briefly heated to a boil. The residue (41 mg), m.p. 211–211.7°, was recrystallized from 50 % ethanol to give colourless crystals, m.p. 211–212°. (Found: C 45.58; H 4.99; N 13.55; S 20.17. Calc. for $C_{12}H_{15}N_3O_3S_2$: C 45.98; H 4.82; N 13.41; S 20.46).

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Reductions with Potassium Graphitate

I. Preparation of Nickel(0) Complexes of Trialkyl Phosphites

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It was already noted during our investigations of nickel complexes of trialkyl phosphines [1-4] that trialkyl phosphites form similar red to violet nickel(II) complexes. In contrast to the phosphine complexes, which crystallise readily; the phosphite complexes are low melting substances which are extremely soluble in inert organic solvents so it has not been possible to isolate them in the pure state. Analyses indicate, however, that they are analogous to the phosphine complexes, *i.e.* of the type $[NiX_2(P(OR)_3)_2]$.

During some attempts to use potassium graphitate as reducing agent it was noted that the red or violet solutions of these compounds in benzene were slowly decolourized at room temperature. When the solutions contained excess trialkyl phosphite, completely colourless solutions could be obtained from which colourless nickel (0) complexes with the general formula $[Ni(P(OR)_3)_4]$ were isolated. They are formed according to the equation:

$$NiX_2(P(OR)_3)_2 + 2\ P(OR)_3 + 2C_8K \rightarrow Ni(P(OR)_3)_4 + \text{graphite} + 2KX$$
$$(X = Cl,\ Br,\ I)$$

Some reduction also took place by heating with finely dispersed potassium in toluene or xylene. However, it has not been possible to prepare pure compounds in this way.

As expected for compounds based on the configuration d^{10} of the metal these compounds were found to be diamagnetic. Their infrared spectra in the NaCl range are almost identical with the spectra of the phosphite ligands (*cf.* the infrared spectra of the corresponding phosphine complexes [3]), especially the establishment of a bond between phosphorus and nickel