A McFadyen-Stevens Reaction of Thiosemicarbazides

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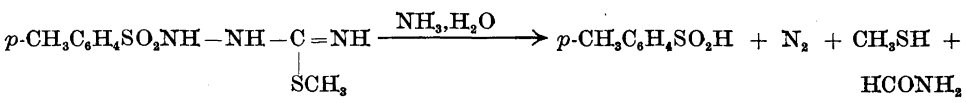
During attempts to prepare *p*-toluenesulfonylaminoguanidine from S-methyl-*p*-toluenesulfonylisothiosemicarbazide (I) and ammonia we obtained instead *p*-toluene sulfinic acid in 80–90 % yield [1]. It was assumed that a McFadyen-Stevens reaction had taken place (the acyl group being methylmercaptocarbimidoyl, $CH_3S-\underset{|}{C}=NH$):



I

Such a reaction is rather surprising, both because Greer and Smith [2] have prepared sulfanilamido-methylguanidine from the corresponding S-methylthiosemicarbazide and methylamine, and because McFadyen-Stevens reactions seem only to have been observed with hydrazides containing a cyclic acyl group [3].

A closer examination of this reaction has, however, shown that it proceeds as assumed with the formation of formamide. It proved difficult to isolate pure formamide from the reaction mixture, but it was definitely identified through its xanthydrol derivative. The reaction seems to be quite general for compounds of this type. From the S-methyl derivatives of 1-*p*-toluenesulfonyl-4-methylthiosemicarbazide and 1-*p*-toluenesulfonyl-4-phenylthiosemicarbazide, N-methylformamide and formanilide were obtained. The former, which has properties similar to formamide, could only be identified by its infrared spectrum, but formanilide was isolated in a crystalline state; its melting point showed no depression on admixture with an authentic sample of formanilide and the infrared spectrum of the reaction product was in all details identical with the spectrum of formanilide. *p*-Toluenesulfinic acid was in both cases isolated in high yield.

Experimental. 1-p-Toluenesulfonyl-4-methylthiosemicarbazide (II; p-$CH_3C_6H_4SO_2NHNH$-CS-$NHCH_3$). A mixture of *p*-toluenesulfonylhydrazine (37.2 g; 0.2 mole), methylisothiocyanate (14.6 g; 0.2 mole) and benzene (350 ml) was boiled for 30 min. Generally the reactants passed into solution and then the thiosemicarbazide began to precipitate in the boiling solution. After cooling, the precipitate was filtered and washed with a little benzene and ether. Yield 40 g = 77 %. M.p. after three recrystallisations from abs. ethanol 199–202°C (decomp.). (Found: N 16.15. Calc for $C_9H_{13}N_3O_2S_2$: N 16.21).

1-p-Toluenesulfonyl-3,4-dimethylisothiosemicarbazide (III; p-$CH_3C_6H_4SO_2NHNH$-C(=NCH_3)-SCH_3). A suspension of II (38.8 g; 0.15 mole) in methyl iodide (21.3 g; 0.15 mole) and abs. ethanol (500 ml) was boiled until all had dissolved and then for a further 10 min. The ethanol was distilled off *in vacuo;* the residue was stirred with hot water and the solution was neutralised with sodium hydroxide. The solid was filtered off and washed with water. Yield 38 g = 91 %. M.p. 172.5–173°C after recrystallisation from ethanol. (Found: N 15.33. Calc. for $C_{10}H_{15}N_3O_2S_2$: N 15.38).

In the same way were prepared: *1-p-Toluenesulfonyl-4-phenylthiosemicarbazide* (IV; p-$CH_3C_6H_4SO_2NHNH$-CS-NHC_6H_5). Yield 94 %. M.p. 197–199°C (decomp.) after recrystallisation from ethanol. (Found: N 13.22. Calc. for $C_{14}H_{15}N_3O_2S_2$: N 13.08).

1-p-Toluenesulfonyl-3-methyl-4-phenylisothiosemicarbazide (V; p-$CH_3C_6H_4SO_2NHNH$-C(=NC_6H_5)-SCH_3). Yield 86 %. M.p. 169.5–170°C after recrystallisation from propanol/water. (Found: N 12.67. Calc. for $C_{15}H_{17}N_3O_2S_2$: N 12.53).

Decomposition of the isothiosemicarbazides by ammonia. (*a*) 13 g of I (0.05 mole) was boiled with 300 ml of aqueous ammonia. All went into solution with the evolution of methanethiol in the course of ½ h. The solution was boiled for 2 h with the addition of 20 ml conc. aqueous ammonia every ½ h. The solution was evaporated *in vacuo* and the residue

first extracted with ether (the ether solution left no residue on evaporation) and then with acetone. The acetone solution was dried with Na_2SO_4 and evaporated *in vacuo;* it left 1.6 g of a yellowish oil, *i.e.* 72 % calculated on formamide. After treatment with active carbon the infrared spectrum of the oil, sandwiched between two KBr discs, was recorded on a Perkin Elmer model 21 spectrophotometer. The spectrum left little doubt that the oil was formamide, although in an impure state.

The xanthydrol derivative of formamide was prepared in the following way: Xanthydrol (0.5 g) was dissolved in acetic acid (7 ml) and dure formamide (0.5 g) was added. The solution was heated for ½ h on a steam bath; after addition of water to begin crystallisation the solution was cooled and yielded a crystalline substance which was filtered off and recrystallised from dioxan/water. M.p. 187–89°C (lit.[4] 184°C). When the above-mentioned impure formamide was added to a xanthydrol solution a small amount of a solid separated at once. It was filtered off and found to be a nitrogen-free substance. The filtrate was heated on a steam bath as above and yielded on dilution with water the xanthydrol derivative of formamide. M.p. after recrystallisation from dioxan/water 184–87°C, no depression occurring on admixture with the authentic xanthydrol derivative.

The crystalline residue from the acetone extraction was almost pure ammonium *p*-toluenesulfinate (equiv. weight by titration of the ammonia 174, calc. 173). Yield 7.7 g = 89 %. On dissolution in water and addition of hydrochloric acid it yielded *p*-toluenesulfinic acid with m.p. 83–86°C.

(*b*) The isothiosemicarbazide III (9.1 g; 0.033 mole) was treated with aqueous ammonia as sub (*a*), except for the washing with ether, but the boiling was extended to 7 h. The acetone solution left on evaporation 1.3 g of a yellowish oil, *i.e.* 65 % calculated as N-methylformamide. (Found: C 40.66; H 8.53. Calc. for C_2H_4NO: C 41.70; H 7.90). The infrared spectrum showed all the bands of N-methylformamide, but in addition 4 weak bands due to impurities.

The residue from the acetone extraction was almost pure ammonium *p*-toluenesulfinate (equiv. weight by titration of the ammonia 171, calc. 173). Yield 5.2 g = 93 %. On dissolution in water and addition of hydrochloric acid it yielded *p*-toluenesulfinic acid with m.p. 84–86°C.

(*c*) The isothiosemicarbazide V (6.7 g; 0.02 mole) was treated with aqueous ammonia as above for 7 h. The residue, left after evaporation of the solution *in vacuo*, was extracted with ether, which dissolved the formanilide. The ether solution, dried with Na_2SO_4, left 1.2 g (66 %) of an oil which crystallised on seeding with formanilide. The crude product melted at 44°C, sintering beginning some degrees lower; after recrystallisation from light petroleum the m.p. was 45°C (lit. 47.5). The infrared spectrum of this sample was identical with a spectrum of pure formanilide.

The crystalline residue from the ether extraction was almost pure ammonium *p*-toluenesulfinate (equiv. weight by titration of the ammonia 171, calc. 173). Yield 2.9 g = 84 %. On dissolution in water and addition of hydrochloric acid it yielded *p*-toluenesulfinic acid with m.p. 83–85°C.

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2. Greer, A. H. and Smith, G. B. L. *J. Am. Chem. Soc.* **76** (1954) 1141.
3. Mosettig, E. *Org. Reactions*, **8** (1954) 218.
4. Phillips, R. F. and Pitt, B. M. *J. Am. Chem. Soc.* **65** 1355 (1943).

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