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Synthesis of Certain S-Substituted L-Cysteines

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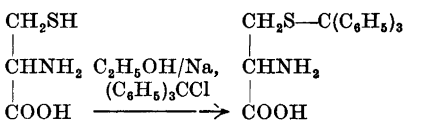
Twenty years ago du Vigneaud [1] introduced the benzylation of the thiol group of cysteine by adding benzyl chloride to the liquid ammonia solution of the sodium salt of cysteine. The S-benzyl group was reversibly split off by reduction with sodium in liquid ammonia. This method has played a fundamental role in the synthesis of various cysteinyl peptides and more recently in the dramatic synthesis of oxytocin [2].

Since the discovery by Weisberger and Levine [3] that leukaemic leukocytes have a high initial cystine-cysteine requirement, several S-cysteine analogues have been synthesized and tested as possible anticancer agents [4]. In most cases du Vigneaud's method has been employed with excellent results. Thus, S-dichlorovinyl-L-cysteine was prepared by McKinney [5] *et al.* in 60—70 % yield.

An alternative procedure for the synthesis of S-alkyl cysteines has been introduced by Zahn and Traumann [6]. Cysteine hydrochloride was treated with the appropriate alkyl bromide in a bicarbonate solution in the presence of nitrogen. Among the products thus produced, S-methyl-L-cysteine and S-ethyl-L-cysteine were obtained in 20 and 10 % yield, respectively. In a similar manner, but in alkaline solution with sodium hydroxide instead of bicarbonate, aminoethylcysteine[7] was synthesized.

In this respect it was found that treatment of cysteine in absolute ethanol with sodium, followed by addition of the appropriate alkyl or phenyl halide, results in the production of the desired S-derivative in excellent yield. Thus, S-benzyl-L-cysteine was synthesized in 70 % yield and its optical value shown to be identical to that reported. Excellent yields were also obtained in the cases of S-butyl-L-cysteine, S-ethyl-L-cysteine and S-methyl-L-cysteine. The thus obtained products were found to be homogeneous according to paper chromatography, as far as the method can detect. This finding suggests that the oxidation of cysteine to cystine is extremely limited or avoided under the experimental conditions described here. On the contrary, the diazonium salt procedure [8,9] for the preparation of S-aryl-L-cysteines gives products always contaminated with cystine, which is difficult to remove.

Treatment of cysteine hydrochloride with trityl chloride in a similar manner, produces S-trityl-L-cysteine in about 20 % yield.



A similar product has been synthesized by selective detritylation of S,N-ditrityl-L-cysteine [10], prepared by direct tritylation [11] of cysteine in the presence of diethylamine, but its reported optical value is entirely different to that described in this parer (see Experimental).

Experimental. S-Benzyl-L-cysteine. To a suspension of 1.75 g (0.01 mole) of L-cysteine hydrochloride monohydrate in 30 ml of absolute ethanol, 0.92 g (0.04 mole) of sodium was added within 10 min at room temperature. When the last piece of sodium was about to disappear, 1.26 g (0.01 mole) of benzyl chloride was added with stirring. After 2 min the reaction mixture was poured into 50 ml of water * and the solution acidified with acetic acid to pH 5—5.5. The desired product precipitated immediately. It was cooled in the refrigerator, filtered and washed successively with water and ethylether. Yield 1.5 g (71 %) m. p. 216—218° (decomp.), reported [1] 216—218° (decomp.),

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* Provided that all the sodium had disappeared.

$[\alpha]_D^{20}$ +21.9° (*c*, 2 in N NaOH), reported [1] $[\alpha]_D^{26.5}$ +23.5° (*c*, 1 in N NaOH).

S-Butyl-L-cysteine. It was prepared from cysteine hydrochloride and butyl bromide in a similar manner as described for the S-benzyl-cysteine derivative. Yield 1.6 g (94 %), m. p. 218—220° (decomp.), $[\alpha]_D^{20}$ —11.2° (*c*, 1 in 2 N HCl). (Found: N 7.50; S 17.82. Calc. for $C_7H_{15}O_2NS$: N 7.89; S 18.08.)

S-Ethyl-L-cysteine. This product was synthesized from L-cysteine hydrochloride and ethyl iodide as previously described, but the reaction mixture was diluted with no more than the necessary amount of water to form a clear solution. The desired product then precipitated upon acidification with acetic acid and cooling. Yield 1 g (82 %), m. p. 226—229° (decomp.), reported [6] m. p. 229°, $[\alpha]_D^{20}$ —27.9° (*c*, 2 in water), reported [6] $[\alpha]_D^{20}$ —25.8° (*c*, 5 in water). (Found: N 9.60; S 21.2. Calc. for $C_5H_{11}O_2NS$: N 9.39; S 21.40.)

S-Methyl-L-cysteine. Methyl iodide was used as the alkylating agent. The product being soluble in water was isolated in a similar manner as described for the S-ethylcysteine derivative. Yield 60 %, m. p. 245—250° (decomp.), reported [6] 251°, $[\alpha]_D^{20}$ —32.3° (*c*, 1 in water), reported [6] $[\alpha]_D^{20}$ —34.5° (*c*, 5 in water). (Found: N 10.15; S 23.20. Calc. for $C_4H_9O_2NS$: N 10.35; S 23.74.)

S-Trityl-L-cysteine. L-Cysteine hydrochloride monohydrate (1.75 g, 0.01 mole) was suspended in absolute ethanol and treated with sodium as described before. Trityl chloride (2.88 g, 0.01 mole) diluted in 6 ml of dry and freshly distilled tetrahydrofuran was added in 4—5 portions during 10 min with stirring. The reaction mixture was then acidified with acetic acid and diluted by addition of 100 ml of dry ether. Upon cooling for 1 h a white precipitate was deposited, which was filtered, washed well with water and finally with ethyl ether. Yield 0.8 g (20 %), m. p. 198—202° (decomp.), reported [10] 202—205° $[\alpha]_D^{20}$ —11.3° (*c*, 1 in 0.1 N NaOH), reported [10] $[\alpha]_D^{20}$ +19°± 1 (*c*, 2 in 0.1 N NaOH). (Found: N 3.5; S 8.6. Calc. for $C_{22}H_{21}I_2NS$: N 3.8; S 8.8.)

Foot note added in proof. Replacement of tetrahydrofuran by ethylether increased the yield in S-trityl-L-cysteine up to 60—70 %. It has also been found that the S-trityl group splits off by reduction with sodium in liquid ammonia at its boiling point. Thus, S-trityl-L-cysteine was converted to S-benzyl-L-cysteine and the optical rotation of the latter was in agreement with that reported above. However, the S-trityl group survives almost completely under the conditions used for the acidic hydrolysis of N-tritylamino acids and peptides [11].

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