Novel Reaction of Cysteine with Phenolic Amino-acids in Hydrobromic Acid: Reversible Formation of 3-Cystein-*S*-yltyrosine and Cystein-*S*-yldopas

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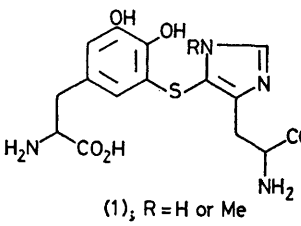
Summary Cystine reacts reversibly with tyrosine and dopa in hydrobromic acid to give 3-cystein-*S*-yltyrosine (**6**) and cystein-*S*-yldopas (**3**)—(**5**) in an electrophilic reaction involving $HO_2CCH(NH_2)CH_2S^+$, the sulphenyl ion from cysteine.

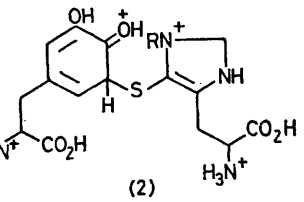
AROMATIC and heterocyclic amino-acids may be found in nature combined covalently with cysteine through a sulphide bond. Typical examples include tryptathionine[1] (2-cystein-*S*-yltryptophan) from the toxic peptides of *Amanita phalloides*,[2] the cysteinyldopa isomers (**3**) and (**4**) of the biosynthesis of phaeomelanins,[3] and a related metabolite, 2,5-dicystein-*S*-yldopa, isolated recently[4] from the eyes of fish. 2-Cysteine-*S*-ylhistidine betaine has also been postulated as an immediate precursor of ergothioneine.[5]

In the course of studies on some novel sulphide amino-acids, adenochromines and secoadenochromines,[6] derived from dopa and histidine-5-thiol, we found that heating of these compounds, *e.g.* (**1**), in 6 M HCl or conc. HBr in the presence of thioglycolic acid results in cleavage of sulphide bonds and formation of the parent amino-acids, presumably *via* elimination of a sulphenyl ion from a protonated species, *e.g.* (**2**). The reverse reaction, *viz.* formation of (**1**), was also observed when dopa was heated in 40% HBr containing an excess of bis(histidine-5-yl) disulphide, the latter probably acting as a source of the sulphenyl ion. These results prompted us to investigate an extension of the reaction to a more readily available and simple disulphide amino-acid, cystine, which is also reported to form $HO_2CCH(NH_2)CH_2S^+$ in strongly acidic solution by the equilibrium: Cys — Cys + $H^+ \rightleftharpoons Cys^+ + CysH$.[7]

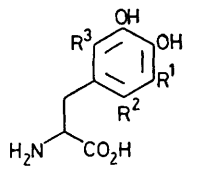
L-Dopa (2 mmol) was heated under reflux with L-cystine (8 mmol) in 40% HBr (40 ml) for 6 h. Fractionation of



(1); R = H or Me



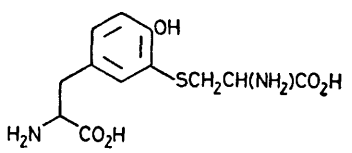
(2)



(3); $R^1 = -SCH_2CH(NH_2)CO_2H$, $R^2 = R^3 = H$

(4); $R^1 = R^2 = H$, $R^3 = -SCH_2CH(NH_2)CO_2H$

(5); $R^1 = R^3 = H$, $R^2 = -SCH_2CH(NH_2)CO_2H$



(6)

the reaction mixture by successive chromatography on Dowex 50W-X4 columns (eluent: 2 M HCl)[8] gave (**3**),[8,9] (**4**),[8,10] and 6-cystein-*S*-yldopa (**5**)[8] in yields of 6·1, 3·3, and 13·9%, respectively, based on dopa. A trace of various dicystein-*S*-yldopas was also formed. Heating for 24 h resulted in a considerable decrease in the yield of (**5**) with an increase in the yield of (**3**) and formation of yellow by-products.

L-Tyrosine reacted similarly with L-cysteine in 40% HBr (24 h) to give, besides 3,5-dicystein-*S*-yltyrosine (0·8%), the hitherto unknown 3-cystein-*S*-yltyrosine (**6**, 39%), m.p. 196° (decomp.), $C_{12}H_{16}N_2O_5S{\cdot}H_2O$ (elemental analysis); λ_{max} (0·1 M HCl) 290 and 253 nm (ϵ 3200 and 2980); δ (2 M DCl in D_2O) *ca.* 3·24 (2H, m, $ArCH_2$), 3·45 and 3·57 (2H, AB part of an ABX system, J_{AB} 15, J_{AX} 5, J_{BX} 5·5 Hz, SCH_2), 4·31 (1H, t, J 5·5 Hz, CH), *ca.* 4·40 (1H, m, CH), 7·01 (1H, d, J 8·5 Hz, H-5), 7·25 (1H, br d, J 8·5 Hz, H-6), and 7·47 (1H, br s, H-2).

Both phenylalanine and histidine failed to react with cystine in boiling 40% HBr. Under similar conditions (6 M HCl), tryptophan is known to give 3-oxindolylalanine,[11] the formation of which may well be explained as involving the intermediacy of 2-cystein-*S*-yltryptophan arising by the reaction of tryptophan with $HO_2CCH(NH_2)CH_2S^+$.

The results of this work are of theoretical and practical value in confirming the formation of $HO_2CCH(NH_2)CH_2S^+$ from cystine in strongly acidic solution,[7] and in providing an alternative entry for the synthesis of the cysteinyldopas[8] and related compounds.

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