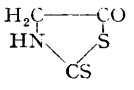
58. *New Syntheses of* DL-*Tryptophan. Part II.* A Synthesis from Indole and 2-Thio-5-thiazolidone.*

By D. O. Holland and J. H. C. Nayler.

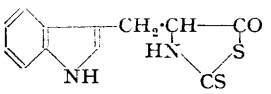
A number of possible routes to tryptophan involving the use of 2-thio-5-thiazolidone have been examined, one of them succeeding in an indirect manner.

In contrast to the numerous successful syntheses of DL-tryptophan in which 3-dialkylaminomethylindoles have been condensed with suitable acyclic intermediates (cf. Part I *), similar investigations with cyclic compounds have been confined to the observations by Howe, Zambito, Snyder, and Tishler (*J. Amer. Chem. Soc.*, 1945, **67**, 38) that gramine does not condense with hydantoin or diketopiperazine. Condensation of gramine with 2-thio-5-thiazolidone (I) was therefore investigated, this intermediate having proved of value for the synthesis of other amino-acids (Billimoria and Cook, "Studies in the Azole Series," Part XIX, *J.*, 1949, 2323, and other Parts in the series).

Attempts to condense gramine with 2-thio-5-thiazolidone in boiling toluene or xylene under nitrogen in the presence or absence of potassium carbonate (conditions similar to those used by Howe *et al.*, *loc. cit.*, for the condensation with acetamidomalonic ester) gave only gramine and an insoluble material which resembled the polymer produced when 2-thio-5-thiazolidone is heated in pyridine (Cook and Levy, *J.*, 1950, 637). Evidently 2-thio-5-thiazolidone is too sensitive to bases to undergo condensation with a tertiary amine such as gramine.



(I)



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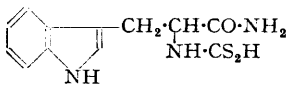


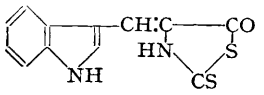
(III)

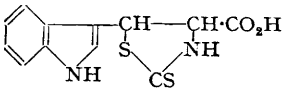
For comparison 4-3′-indolylmethyl-2-thio-5-thiazolidone (II) was prepared from DL-tryptophan amide and carbon disulphide. Attempts to isolate either the triethylamine or the tryptophan amide salts of the intermediate dithiocarbamic acid (III) were abandoned owing to their deliquescent nature and the reaction mixture was acidified to yield the thiazolidone directly. Although the ring closure of such intermediates is normally best carried out at 0°, this reaction proceeded satisfactorily only at a slightly higher temperature. The crude product obtained by acidification at or below room temperature had no reproducible melting point, could not be purified, gradually developed an odour of carbon disulphide, and when heated with picric acid in alcohol yielded a small amount of tryptophan amide picrate. These facts, supported by analytical results for the crude product, suggest that it may have been a mixture of the required thiazolidone (II) and the presumably unstable dithiocarbamic acid (III). 4-3′-Indolylmethyl-2-thio-5-thiazolidone was readily

* Part I, preceding paper.

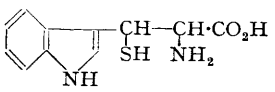
converted into tryptophan methyl ester hydrochloride by treatment with sodium methoxide followed by methanolic hydrogen chloride.

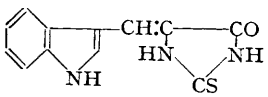
Next, 4-3′-indolylmethylene-2-thio-5-thiazolidone (IV) was prepared, without difficulty,

(IV) 

 (V)

from 2-thio-5-thiazolidone and indole-3-aldehyde, but reaction of indole with 4-ethoxymethylene-2-thio-5-thiazolidone (Cook, Heilbron, and Levy, *J.*, 1948, 201), afforded a more convenient route to it. Attempts to reduce (IV) to (II) by reagents such as zinc and acetic acid, zinc and dry hydrogen chloride in alcohol or dioxan, phosphorus and iodine in moist acetic acid, or sodium in liquid ammonia were unsuccessful. Then (IV) was converted into 5-3′-indolyl-2-thiothiazolidine-4-carboxylic acid (V) by the ring-turning reaction of Chatterjee, Cook, Heilbron, and Levy (*J.*, 1948, 1337), but attempts to prepare tryptophan therefrom by

(VI) 

 (VII)

way of β-3-indolylcysteine (VI) failed. Finally 4-3′-indolylmethylene-2-thio-5-thiazolidone (IV) was smoothly converted by concentrated aqueous ammonia into 5-3′-indolylmethylene-2-thiohydantoin (VII), the structure being proved by conversion into the known 5-3′-indolylmethylenehydantoin by chloroacetic acid in a modification of the general method of Johnson, Pfau, and Hodge (*J. Amer. Chem. Soc.*, 1912, **34**, 1041). [The action of ammonia on 4-alkylidene- or -arylidene-2-thio-5-thiazolidones may lead to 2-thiohydantoins or to ring-turning with the formation of 5-substituted-2-thiothiazolidine-4-carboxyamides, while in certain cases both products are formed (Cook, Hunter, and Pollock, *J.*, 1950, 1892); but (VII) was our sole product.] Since the hydantoin is readily converted into tryptophan by reduction and hydrolysis (cf. Elks, Elliot and Hems, *J.*, 1944, 629) the present reactions provide a novel, though circuitous, route to tryptophan.

Experimental

M.p.s are uncorrected

DL-*Tryptophan Methyl Ester Hydrochloride.*—DL-Tryptophan was esterified essentially by Abderhalden and Kempe's method (*Z. physiol. Chem.*, 1907, **52**, 207) for L-tryptophan. The product, obtained in 94% yield, crystallised from methanol–ether in needles, m. p. 225 (decomp.) (softening at 221°) (Found: C, 56·5; H, 6·2; N, 11·2; Cl, 13·7. Calc. for $C_{12}H_{15}O_2N_2Cl$: C, 56·6; H, 5·9; N, 11·0; Cl, 13·9%). Brenner, Sailer, and Kocher (*Helv. Chim. Acta*, 1948, **31**, 1908) give m. p. 216°, but it is not clear if this refers to a pure specimen.

DL-*Tryptophan Amide.*—DL-Tryptophan methyl ester hydrochloride (13 g.) was suspended in methanol (50 ml.), neutralised to phenolphthalein by sodium methoxide in methanol, and filtered to remove sodium chloride. The filtrate was cautiously saturated with gaseous ammonia, the temperature being kept at >0°, and, after 6 days at room temperature, evaporated *in vacuo*. Trituration with chloroform and crystallisation from this solvent afforded the *amide* (8·58 g.) as needles, m. p. 120—121° (Found: C, 63·5; H, 6·4; N, 20·4. $C_{11}H_{13}ON_3$,0·25H_2O requires C, 63·6; H, 6·55; N, 20·2%). Drying (P_2O_5) at 80°/0·4 mm. for 5 hours did not change the m. p. or analysis. Bauguess and Berg (*J. Biol. Chem.*, 1934, **106**, 615) prepared L-tryptophan amide, m. p. 167—170°, from the acid chloride hydrochloride and ammonia, but gave inadequate details. The present product was characterised as the *picrate* which separated from alcohol in excellent yield as orange-red needles and after recrystallisation from the same solvent had m. p. 241° (decomp.) (shrinking and becoming dark from 224°) (Found: C, 47·4; H, 4·0; N, 19·2. $C_{11}H_{13}ON_3$,$C_6H_3O_7N_3$ requires C, 47·2; H, 3·7; N, 19·4%).

4-3′-*Indolylmethyl-2-thio-5-thiazolidone* (II).—A solution of tryptophan amide (0·5 g.) in alcohol (10 ml.) was kept with concentrated aqueous ammonia (*d* 0·88; 0·5 ml.) and carbon disulphide (0·5 ml.) at room temperature for 2 hours. The solution was then heated to 40°, acidified with concentrated hydrochloric acid (2 ml.), and kept at 35—40° for 30 minutes. On

dilution with water (20 ml.) ammonium chloride redissolved and a very pale cream-coloured flocculent precipitate separated (0·27 g.). 4-3′-*Indolylmethyl-2-thio-5-thiazolidone* crystallised from acetone–water or chloroform–light petroleum as fine very pale cream-coloured needles, m. p. 188—191° (decomp., after shrinking at 180°) (heating from 160° at 5°/min.; slower heating resulted in indefinite decomposition above 220°) (Found: C, 55·0; H, 4·1; N, 10·7. $C_{12}H_{10}ON_2S_2$ requires C, 54·9; H, 3·8; N, 10·7%).

4-3′-Indolylmethyl-2-thio-5-thiazolidone (0·2 g.) was dissolved in a solution of sodium (0·05 g.) in methanol (5 ml.) and kept at room temperature for 2 hours. The yellow solution was acidified with methanolic hydrogen chloride, filtered from sodium chloride, and evaporated *in vacuo* to leave a yellow powder. Recrystallisation from methanol–ether gave tryptophan methyl ester hydrochloride (0·16 g.), m. p. 225° (decomp.) (softening 221°) not depressed by admixture with an authentic specimen.

4-3′-*Indolylmethylene-2-thio-5-thiazolidone* (IV).—(*a*) Indole-3-aldehyde (Elks, Elliot, and Hems, *loc. cit.*) (0·5 g.), 2-thio-5-thiazolidone (0·45 g.), and zinc chloride (0·5 g.) were refluxed in ethyl acetate (15 ml.) for 15 minutes. After cooling to 0° the solid was collected and washed with acetone and then with water. A small second crop obtained by concentration of the ethyl acetate filtrate brought the total yield of 4-3′-*indolylmethylene-2-thio-5-thiazolidone* to 0·48 g. (54%), the product crystallising from acetone–water in fine orange needles, m. p. 279° (decomp.).

(*b*) 4-Ethoxymethylene-2-thio-5-thiazolidone (18·9 g.) was dissolved in hot acetic acid (500 ml.). Indole (11·7 g.) was added and the resulting red solution refluxed for 6 hours, during which an orange-brown solid gradually separated. After cooling to room temperature the product (20·9 g., 80%) was collected. It was only very sparingly soluble in most solvents, and was purified by dissolution in a large volume of boiling acetone and dilution with water, separating as orange needles, m. p. 279° (decomp.), identical with the product from method (*a*) (Found: C, 55·5; H, 3·35; N, 10·6; S, 24·1. $C_{12}H_8ON_2S_2$ requires C, 55·4; H, 3·1; N, 10·8; S, 24·6%).

5-3′-*Indolyl-2-thiothiazolidine-4-carboxylic Acid* (V).—4-3′-Indolylmethylene-2-thio-5-thiazolidone (10 g.) was dissolved in a solution of potassium hydroxide (4·5 g.) in methanol (150 ml.) and kept at room temperature for 5 days, during which the colour gradually faded from very dark to light red. Evaporation *in vacuo* left a red gum which was dissolved in water (50 ml.) and acidified with concentrated hydrochloric acid (10 ml.), the product separating as a red-brown plastic mass. Partial purification was effected by dissolution in aqueous sodium hydrogen carbonate, acidification of the filtered solution yielding an orange gum which solidified in the refrigerator overnight to a buff powder (8·36 g.), m. p. 169—170° (decomp.). 5-3′-*Indolyl-2-thiothiazolidine-4-carboxylic acid* crystallised from acetone–chloroform in colourless needles, m. p. 187—188° (decomp.) (Found: C, 51·7; H, 3·7; N, 10·1; S, 23·3. $C_{12}H_{10}O_2N_2S_2$ requires C, 51·8; H, 3·6; N, 10·1; S, 23·0%).

5-3′-*Indolylmethylene-2-thiohydantoin* (VII).—4-3′-Indolylmethylene-2-thio-5-thiazolidone (10 g.) was dissolved in aqueous ammonia (*d* 0·88; 100 ml.) and the blood-red solution heated on the steam-bath for 3 hours, during which orange crystals separated. The mixture was diluted with water (100 ml.), cooled, and filtered, and the crude product (5·73 g.) washed with water. 5-3′-*Indolylmethylene-2-thiohydantoin* crystallised from acetic acid as orange needles, decomp. 310—315° (Found: C, 55·7; H, 4·35; N, 13·8; S, 10·5. $C_{12}H_9ON_3S,C_2H_4O_2$ requires C, 55·4; H, 4·3; N, 13·9; S, 10·6%).

5-3′-*Indolylmethylenehydantoin.*—A suspension of the crude thiohydantoin (2 g.) in acetic acid (300 ml.), chloroacetic acid (50 g.) and water (100 ml.) was refluxed for 5½ hours, a clear orange-red solution being obtained after 7 minutes' boiling. On cooling to room temperature a first crop of 5-3′-indolylmethylenehydantoin (1·44 g.) separated and concentration of the filtrate to about 100 ml. gave a further 0·27 g. Recrystallisation from acetic acid gave the hydantoin as a lemon-yellow powder, m. p. 334° (slight darkening from 331°) (Found: N, 18·6. Calc. for $C_{12}H_9O_2N_3$: N, 18·5%), identical with an authentic specimen of 5-3′-indolylmethylenehydantoin prepared by the condensation of indole-3-aldehyde and hydantoin in boiling piperidine (Shabica, Howe, Ziegler, and Tishler, *J. Amer. Chem. Soc.*, 1946, **68**, 1156).

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