Experiments on the Synthesis of Bz-*Substituted Indoles and Tryptophans. Part III.* The Synthesis of the Four* Bz-*Chloro-indoles and -tryptophans.*

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Syntheses of the four *Bz*-chloroindoles and the four *Bz*-chlorotryptophans are described.

The four *Bz*-chloroindoles and the derived *Bz*-chlorotryptophans were required for biochemical studies, in extension of earlier work on the corresponding methyl compounds (Fildes and Rydon, *Brit. J. Exp. Path.*, 1947, **28**, 211), and the synthesis of these compounds is described below; † the biochemical work will be reported elsewhere.

When our work began, neither the monochloroindoles nor the monochlorotryptophans were known, but, while it was in progress, Uhle (*J. Amer. Chem. Soc.*, 1949, **71**, 761) described the synthesis of 4-chloroindole and Fox and Bullock (*ibid.*, 1951, **73**, 2756) that of 6-chloroindole, although, in view of the prior publication of Rydon and Long (*Nature*, 1949, **164**, 575), the latter authors did not record an analysis; attention may also be drawn to the recent synthesis of the four *Bz*-fluoroindoles (Allen, Brunton, and Suschitzky, *J.*, 1955, 1283).

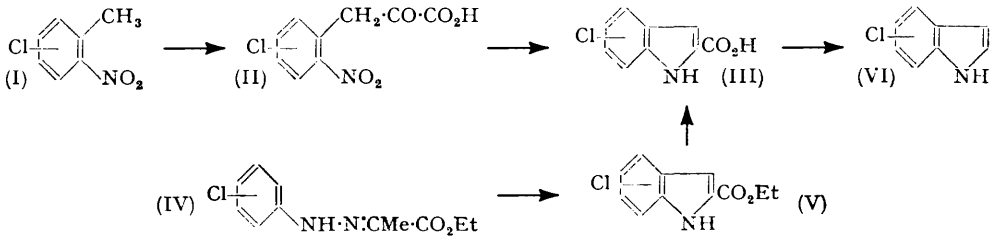
All four chloroindoles were prepared by way of the chloroindole-2-carboxylic acids (III). In the 4- and 6-chloro-series, these were prepared by Reissert's method (*Ber.*, 1897, **30**, 1030; cf. Blaikie and Perkin, *J.*, 1924, **125**, 296; Uhle, *loc. cit.*), the appropriate chloronitrotoluene (I) being condensed with ethyl oxalate; reductive cyclisation of the resulting chloronitrophenylpyruvic acids (II) gave the indole acids (III); potassium ethoxide was superior to sodium ethoxide in the condensation with ethyl oxalate, giving better, and

* Part II, Rydon and Siddappa, *J.*, 1951, 2462.

† All four *Bz*-chloroindoles and the derived chlorotryptophans were synthesised, during 1948—52, by Mr. C. A. Long, working in collaboration with one of us (H. N. R.) at Birkbeck College, London; unfortunately, however, apart from the small amount of work incorporated in the Experimental section, the detailed records of this work have been lost and the present study is virtually a complete re-investigation.

more consistent, yields of the pyruvic acid (II). For the preparation of 5- and 7-chloroindole, the ethyl pyruvate chlorophenylhydrazones (IV) were cyclised to the esters (V), which were then hydrolysed to the required acids (III); polyphosphoric acid (Snyder and Xerber, *J. Amer. Chem. Soc.*, 1950, **72**, 2962, 2965) was found to be greatly superior to other reagents for the cyclisation, giving better yields of purer products (cf. Kissman, Farnsworth, and Witkop, *ibid.*, 1952, **74**, 3948).

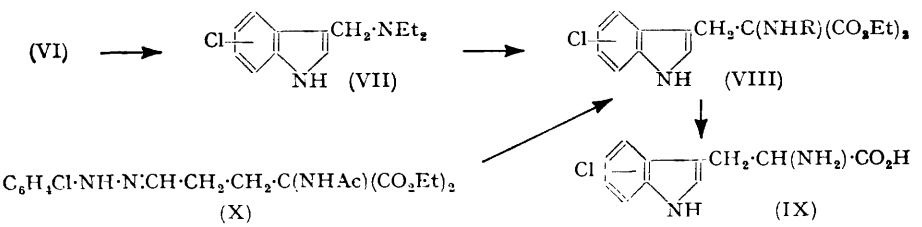
Both routes involve, as the final stage, the decarboxylation of the chloroindole-2-carboxylic acid (III). Uhle (*loc. cit.*) obtained a good yield of 4-chloroindole by heating the 4-chloro-acid (III) with cuprous chloride in quinoline and the same method was used



by Fox and Bullock (*loc. cit.*) for the preparation of 6-chloroindole, although no yield is recorded. In our hands this method was unsatisfactory, giving variable yields which were usually very low; Barltrop and Taylor (*J.*, 1954, 3399) experienced even greater difficulty in the decarboxylation of 4- and 6-bromoindole-2-carboxylic acid. Replacement of cuprous chloride by the chromite gave better, but still variable, yields; the variability was finally traced to the presence of small amounts of sulphate in the acid (III) and decarboxylation of the chloroindole-2-carboxylic acids (III), carefully freed from sulphate, by heating in quinoline in the presence of copper chromite has given the chloroindoles (VI) in consistent yields of 60—70%.

In this, as in the fluoro-series (Allen, Brunton, and Suschitzky, *loc. cit.*), the 4-halogenoindole is much lower-melting than its isomerides.

For the synthesis of 4- and 6-chlorotryptophan * (IX) we used Hellmann's modification (*Z. physiol. Chem.*, 1949, **284**, 163) of the gramine synthesis of tryptophan. The chloroindoles (VI) were condensed with formaldehyde and diethylamine, yielding the 3-diethylaminomethyl compounds (VII); condensation with formamidomalonic ester yielded the



(chloroindolylmethyl)formamidomalonic esters (VIII; R = CHO) which were smoothly hydrolysed and decarboxylated to the chlorotryptophans (IX). This route was much superior to the original gramine synthesis (Snyder and Smith, *J. Amer. Chem. Soc.*, 1944, **66**, 350; Albertson, Archer, and Suter, *ibid.*, p. 500; 1945, **67**, 36) used for the synthesis of the *Bz*-methyltryptophans (Rydon, *J.*, 1948, 705). 5- and 7-Chlorotryptophan were synthesised from the corresponding chlorophenylhydrazines, by way of the chlorophenylhydrazones (X), by the procedure of Warner and Moe (*J. Amer. Chem. Soc.*, 1948, **70**, 2763, 2765).

* While this paper was being prepared for publication, Hardegger and Corrodi (*Helv. Chim. Acta*, 1955, **38**, 468) described the synthesis of 4-chlorotryptophan by the same method; their results are in general agreement with ours.

Experimental

Chloroindoles.

Polyphosphoric acid was prepared by dissolving phosphoric oxide (360 g.) in commercial orthophosphoric acid, *d* 1·75 (200 g.).

4-*Chloroindole.*—A mixture of 2-chloro-6-nitrotoluene (100 g.) and ethyl oxalate (80 g.) was added during 10—15 min. to ethanolic potassium ethoxide (from potassium, 28 g., and anhydrous ethanol, 320 ml.), the temperature being kept at 15—20°. The mixture was then refluxed for 30 min. and the ethanol removed under reduced pressure. After dilution with water, unchanged starting material was removed by steam-distillation. Acidification of the filtered residue precipitated 2-chloro-6-nitrophenylpyruvic acid (II) (57·6 g., 41%); a specimen crystallised from benzene in needles, m. p. 116° (Uhle, *loc. cit.*, gives m. p. 114—115°).

This acid (40 g.) was reduced as described by Uhle (*loc. cit.*); the crude product, twice washed with water, was suspended in very dilute hydrochloric acid containing a little barium chloride and extracted with ether. Evaporation of the ether, after repeated washing with water until free from sulphate, left 4-chloroindole-2-carboxylic acid (III) (29 g., 90%), which crystallised from aqueous ethanol in long needles, m. p. 264° (decomp.) (Uhle, *loc. cit.*, gives m. p. 259—260°). An intimate mixture of the unrecrystallised, sulphate-free acid (20 g.) and copper chromite (2 g.) (Vogel, " Practical Organic Chemistry," Longmans, Green and Co., London, 2nd Edn., 1951, p. 808), suspended in redistilled quinoline (100 ml.), was heated to 215° (internal temp.) for 2 hr. The product was poured into water and repeatedly extracted with ether; the extract was washed (2N-hydrochloric acid, 2N-sodium hydrogen carbonate, water), dried (Na_2SO_4), and distilled, affording 4-chloroindole (VI) (10·3 g., 67%), b. p. 106—108°/0·6 mm., n_D^{20} 1·6278 (Uhle, *loc. cit.*, gives b. p. 143°/10 mm., n_D^{20} 1·6254; Fox and Bullock, *loc. cit.*, b. p. 150°/13 mm., n_D^{20} 1·6286).

5-*Chloroindole.*—A well-stirred mixture of ethyl α-methylacetoacetate (50 g.) and ethanol (250 ml.) was treated at 0° with 50% potassium hydroxide solution (130 g.); crushed ice (200 g.) and a diazonium solution, from *p*-chloroaniline (45 g.), 10N-hydrochloric acid (160m l.), and sodium nitrite (45 g.), were then added, with continued stirring. The brick-red solid which separated after 10 min. was collected and recrystallised from 50% aqueous ethanol (charcoal), affording ethyl pyruvate *p*-chlorophenylhydrazone (IV) (55 g., 65%), needles, m. p. 138° (Hewitt, *J.*, 1893, **63**, 868, gives m. p. 138°).

This hydrazone (10 g.) was dissolved, with stirring, in polyphosphoric acid (20 g.) and the viscous solution slowly heated, with continued stirring, in a metal-bath until a sudden rise in the internal temperature (from 150° to 180°) took place; the temperature of the mixture was maintained at 180° for a further 5 min. and then allowed to fall to 60°, whereupon water (100 ml.) was added. Extraction with ether, followed by evaporation of the extract, after washing with 5% sodium hydrogen carbonate solution and water, afforded *ethyl 5-chloroindole-2-carboxylate* (V) (5 g., 54%), which crystallised from ethanol in needles, m. p. 167—168° (Found: C, 59·35; H, 4·65; N, 6·3. $C_{11}H_{10}O_2NCl$ requires C, 59·1; H, 4·5; N, 6·3%). The crude ester (40 g.) was refluxed for 2 hr. with ethanolic potassium hydroxide (22 g. in 250 ml.); pouring the mixture into dilute hydrochloric acid precipitated *5-chloroindole-2-carboxylic acid* (III) (27·5 g., 79%) which, recrystallised from 50% aqueous ethanol, had m. p. 289—290° (decomp.) (Found: C, 55·2; H, 3·2; N, 7·1. $C_9H_6O_2NCl$ requires C, 55·3; H, 3·1; N, 7·15%).

This acid (4·2 g.) was decarboxylated at 215° for 2 hr. as described for the 4-isomer. The fraction, b. p. 120—130°/0·4 mm. (2.0 g., 62%), solidified (m. p. 66—68°) and was sufficiently pure for preparative purposes; recrystallisation from light petroleum (b. p. 40—60°) gave pure *5-chloroindole* (VI) as silvery plates, m. p. 71—72° (Found: C, 63·4; H, 4·05; N, 8·5. C_8H_6NCl requires C, 63·4; H, 3·95; N, 9·25%); the *picrate* crystallised from benzene in orange plates, m. p. 147° (Found: C, 44·5; H, 2·4; N, 15·1. $C_{14}H_9O_7N_4Cl$ requires C, 44·2; H, 2·35; N, 14·7%).

6-*Chloroindole.*—4-Chloro-2-nitrotoluene (22 g.) was condensed with ethyl oxalate (20·5 g.) in ethanolic potassium ethoxide (from potassium, 6·25 g., and anhydrous ethanol, 75 ml.), as described for 2-chloro-6-nitrotoluene; *4-chloro-2-nitrophenylpyruvic acid* (II) (13 g., 42%) crystallised from benzene in needles, m. p. 136° (Found: C, 44·6; H, 2·4; N, 5·8. $C_9H_6O_5NCl$ requires C, 44·4; H, 2·5; N, 5·75%).

This acid (40 g.) in dilute ammonia solution was added to a suspension in water (1 l.) of ferrous hydroxide, from ferrous sulphate heptahydrate (280 g.) and ammonia solution (*d* 0·880; 170 ml.), and the mixture boiled and stirred for 10 min. Ferric hydroxide was removed and

washed with dilute ammonia solution until the washings gave no precipitate on acidification. Acidification of the filtrate and washings with hydrochloric acid precipitated 6-chloroindole-2-carboxylic acid (III) (27·4 g., 85%), which crystallised from aqueous ethanol in granules, m. p. 242° (decomp.) (Found: C, 55·4; H, 3·1; N, 7·7. Calc. for $C_9H_6O_2NCl$: C, 55·3; H, 3·1; N, 7·2%) (Fox and Bullock, *loc. cit.*, give m. p. 242—244°).

This acid (10 g.), freed from sulphate as described for the 4-chloro-compound, was similarly decarboxylated at 210—220° for 3 hr., affording *6-chloroindole* * (VI) (5·1 g., 66%), b. p. 110°/0·2 mm., leaflets, m. p. 86—87° [from light petroleum (b. p. 60—80°)] (Found: C, 63·7; H, 3·8; N, 9·7. C_8H_6NCl requires C, 63·4; H, 3·95; N, 9·25%). (With C. A. Long) The *picrate* had m. p. 143—144° (Found: C, 44·0; H, 2·6; N, 15·4; Cl, 9·0. $C_{14}H_9O_7N_4Cl$ requires C, 44·2; H, 2·35; N, 14·7; Cl, 9·3%).

7-Chloroindole.—Pyruvic acid *o*-chlorophenylhydrazone (65 g.) (Hewitt, *J.*, 1891, **59**, 209) was esterified by passing dry hydrogen chloride through its ethanol solution for 4 hr.; the ester (IV) (55 g., 75%) crystallised from the mixture in needles, m. p. 71° (Hewitt, *J.*, 1893, **63**, 868, gives m. p. 68°). This ester (25 g.) was cyclised with polyphosphoric acid (40 g.) at 190°, as described for the 5-chloro-compound; *ethyl 7-chloroindole-2-carboxylate* (V) (12 g., 52%) crystallised from ethanol in needles, m. p. 105° (Found: C, 59·5; H, 4·3; N, 6·1. $C_{11}H_{10}O_2NCl$ requires C, 59·1; H, 4·5; N, 6·3%). Hydrolysis, as described for the 5-chloro-compound, afforded *7-chloroindole-2-carboxylic acid* (III) (91% yield) which, crystallised from 30% ethanol, had m. p. 234—236° (decomp.) (Found: C, 54·95; H, 3·1; N, 7·2. $C_9H_6O_2NCl$ requires C, 55·3; H, 3·1; N, 7·15%).

This acid (4·8 g.) was decarboxylated at 215° for 2 hr., as described for the 4-chloro-compound. Recrystallisation of the fraction, b. p. 90—95°/0·25 mm., m p. 54° (2·6 g., 70%), from light petroleum (b. p. 40—60°) yielded *7-chloroindole* (VI) as silvery plates, m. p. 57—58° (Found: C, 63·5; H, 4·3; N, 8·6. C_8H_6NCl requires C, 63·4; H, 3·95; N, 9·25%); the *picrate* crystallised from benzene in orange plates, m. p. 154—155° (Found: C, 44·2; H, 2·35; N, 14·8. $C_{14}H_9O_7N_4Cl$ requires C, 44·2; H, 2·35; N, 14·7%).

Chlorotryptophans.

4-Chlorotryptophan.—40% Aqueous formaldehyde (3·3 ml.) was added to a mixture of diethylamine (3·1 g.) and 60% aqueous acid (9 ml.), prepared at below 3°. This mixture was poured into 4-chloroindole (6·5 g.), which dissolved on warming to room temperature. After 2 hr. the mixture was poured into 2N-sodium hydroxide (150 ml.) and the white curdy precipitate immediately isolated by filtration; *4-chloro-3-diethylaminomethylindole* (VII) (10 g.; 99%) so prepared crystallised from acetone in prisms, m. p. 130° (Found: C, 65·7; H, 6·9; N, 11·8. $C_{13}H_{17}N_2Cl$ requires C, 66·0; H, 7·2; N, 11·85%). The amine (VII) (5·9 g.) and diethyl formamidomalonate (6 g.) (Galat, *J. Amer. Chem. Soc.*, 1947, **69**, 965) were added to a suspension of sodium hydroxide (0·35 g.) in boiling toluene (25 ml.); the mixture was heated under reflux at 130° in a stream of dry nitrogen for 30 min. After cooling to 0°, the semi-solid product was filtered off and washed with a little toluene; *diethyl (4-chloro-2-indolylmethyl)formamidomalonate* (VIII; R = CHO) (8·0 g., 88%) crystallised from ethanol in leaflets, m. p. 202° (Found: C, 56·2; H, 4·9; N, 7·3. $C_{17}H_{19}O_5N_2Cl$ requires C, 55·65; H, 5·2; N, 7·65%). This ester (4·5 g.) was heated under reflux in an oil-bath at 120° with sodium hydroxide (2·28 g.) in water (22 ml.) for 7 hr.; after cooling, glacial acetic acid (4 ml.) was added and the mixture heated for a further 2 hr. at 130°. *4-Chlorotryptophan* (IX) (1·8 g., 61%) separated overnight at 2° and recrystallised from glacial acetic acid as feathery clusters of plates, m. p. 298° (decomp.) (Found: C, 54·8; H, 4·35; N, 11·4. $C_{11}H_{11}O_2N_2Cl$ requires C, 55·3; H, 4·6; N, 11·7%).

Dimethyl sulphate (12·2 g.) was added during 5 min. to a solution of diethyl acetamidomalonate (10 g.) and 4-chlorogramine (9 g.) (Fox and Bullock, *loc. cit.*) in ethanolic sodium ethoxide (from sodium, 1·0 g., and anhydrous ethanol, 120 ml.). After the mixture had been kept at room temperature for 24 hr. it was filtered and the filtrate poured into water (500 ml.); the precipitated *diethyl (4-chloroindolylmethyl)acetamidomalonate* (VIII; R = Ac) (7·8 g., 47·5%) was collected and recrystallised from ethanol, forming laminæ, m. p. 162° (Found: C, 56·6; H, 5·3; N, 7·4. $C_{18}H_{21}O_5N_2Cl$ requires C, 56·8; H, 5·5; N, 7·35%).

5-Chlorotryptophan.—*p*-Chlorophenylhydrazine (30 g.) and glacial acetic acid (4·5 ml.) were added to a benzene solution of γ-acetamido-γγ-diethoxycarbonyl-*n*-butaldehyde (from acraldehyde, 17·1 ml., and diethyl acetamidomalonate, 5·5 g.; Warner and Moe, *loc. cit.*). The

* In a paper which appeared while our manuscript was in preparation, Plieninger *et al.* (*Chem. Ber.*, 1955, **88**, 370) record m. p. 78—80°.

mixture was warmed to 50° for 1 hr. and then kept at 2° for 24 hr. Evaporation to half volume under reduced pressure in an atmosphere of nitrogen, followed by addition of aqueous ethanol (70% v/v), precipitated *γ-acetamido-γγ-diethoxycarbonyl*-n-*butaldehyde* p-*chlorophenylhydrazone* (X) (60 g., 72%) which, crystallised from light petroleum (b. p. 60—80°), had m. p. 94—95° (Found: C, 54·7; H, 5·8; N, 10·7. $C_{18}H_{24}O_5N_3Cl$ requires C, 54·4; H, 6·0; N, 10·6%).

The crude hydrazone (50 g.) was refluxed under nitrogen with 5% sulphuric acid (200 ml.) for 5 hr. After the mixture had been kept overnight at 2°, the solidified cyclisation product (VIII; R = Ac) (theoretical yield) was collected; recrystallisation from aqueous ethanol gave a product, m. p. 149—150° not depressed on admixture with material prepared by the gramine route (see below). The crude product (5 g.) was refluxed for 6 hr. with 1·5N-hydrochloric acid (30 ml.); tar was removed by filtration and the filtrate brought to pH 6·5 with 2N-sodium hydroxide. *5-Chlorotryptophan* (IX) (1·02 g., 33%) separated slowly and was recrystallised from glacial acetic acid, forming lustrous plates, m. p. 278—279° (decomp.) (Found: C, 55·2; H, 4·5; N, 11·9%).

(With C. A. Long) Condensation of 5-chloroindole (1·8 g.) with formaldehyde and dimethylamine by the procedure described below for the 6-chloro-compound afforded *5-chloro-3-dimethylaminomethylindole* (2·1 g., 85%), which crystallised from ethyl acetate in needles, m. p. 150° (Found: N, 13·85, 13·1. $C_{11}H_{13}N_2Cl$ requires N, 13·4%). Condensation of this 5-chlorogramine with diethyl acetamidomalonate, as described below for the 6-chloro-compound, yielded *diethyl acetamido-(5-chloro-2-indolylmethyl)malonate* (VIII; R = Ac), m. p. 149—150° after recrystallisation from aqueous ethanol (Found: C, 56·5; H, 5·5; Cl, 9·3. $C_{18}H_{21}O_5N_2Cl$ requires C, 56·8; H, 5·5; Cl, 9·3%).

6-Chlorotryptophan.—6-Chloroindole (6·5 g.) was condensed with formaldehyde and diethylamine, as described for the 4-chloro-compound. The product, which separated as an oil in water, was extracted with ether. Evaporation of the dried extract afforded *6-chloro-3-diethylaminomethylindole* (VII) (6·6 g., 65%) which, crystallised from light petroleum (b. p. 60—80°), had m. p. 96° (Found: N, 12·0. $C_{13}H_{17}N_2Cl$ requires N, 11·85%). Condensation of this base (5·9 g.) with diethyl formamidomalonate (6 g.), as described for the 4-chloro-compound (time of heating, 1 hr.), afforded *diethyl (6-chloro-2-indolylmethyl)malonate* (VIII; R = CHO) (6·3 g., 69%), leaflets (from ethanol), m. p. 168° (Found: C, 55·9; H, 4·9; N, 7·9. $C_{17}H_{19}O_5N_2Cl$ requires C, 55·65; H, 5·2; N, 7·65%). This ester (4·5 g.), hydrolysed and decarboxylated as described for the 4-chloro-compound, afforded *6-chlorotryptophan* (IX) (2·5 g., 85%), plates (from water), m. p. 285—286° (decomp.) (Found: C, 54·8; H, 4·6; N, 12·0%).

Aqueous dimethylamine (33% w/v; 9 g.), cooled in a freezing mixture, was treated successively with glacial acetic acid (9 ml.) and 40% aqueous formaldehyde (9 ml.), the temperature being kept below −5°. The resulting mixture was poured on to 6-chloroindole (10 g.), which dissolved on warming to 20°. After 4·5 hr. at room temperature, the mixture was poured into an excess of 2N-sodium hydroxide, the temperature being kept below 0°. After 1 hr. in a freezing mixture, the precipitated *6-chloro-3-dimethylaminoethylindole* (11·4 g., 83%) was collected and recrystallised from aqueous ethanol, forming clusters of leaflets, m. p. 132° (Found: C, 63·3; H, 6·15; N, 13·2. $C_{11}H_{13}N_2Cl$ requires C, 63·3; H, 6·25; N, 13·4%). Crude 6-chlorogramine (9·5 g.) was condensed with diethyl acetamidomalonate (9·5 g.) as described for the 4-chloro-compound; the resulting *diethyl acetamido-(6-chloro-2-indolylmethyl)malonate* (VIII; R = Ac) (8·5 g., 49%) (from aqueous ethanol) had m. p. 197—199° (Found: C, 56·4; H, 5·4; N, 7·35. $C_{18}H_{21}O_5N_2Cl$ requires C, 56·8; H, 5·5; N, 7·35%).

7-Chlorotryptophan.—*γ-Acetamido-γγ-diethoxycarbonyl*-n-*butaldehyde* o-*chlorophenylhydrazone* (X), prepared in 66% yield (crude) from *o*-chlorophenylhydrazine as described for the *p*-compound and crystallised from light petroleum (b. p. 60—80°), had m. p. 98—100° (Found: C, 54·1; H, 5·7; N, 10·4. $C_{18}H_{24}O_5N_3Cl$ requires C, 54·4; H, 6·0; N, 10·6%). The crude material was cyclised and the crude cyclisation product hydrolysed and decarboxylated as described for the 5-chloro-compound. *7-Chlorotryptophan* (IX) (40% yield) so obtained crystallised from acetic acid in plates, m. p. 291—292° (Found: C, 55·8; H, 4·6; N, 11·1%).

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