sium carbonate, 1.0 g. of copper bronze, 2.7 g. (0.011 mole) of iodine, and 250 ml. of nitrobenzene was refluxed for 24 hr. The product was steam distilled and the residue extracted with hot benzene. The cooled extract deposited 5 g. of white solid which yielded, after repeated alternate recrystallizations from benzene or toluene and extractions with hot ethanol, 3.2 g. (13%) of transparent crystals, m.p. 282.5–284°. The infrared spectrum indicated both *ortho-* and *para*-disubstituted benzene rings.

Anal. Calcd. for $C_{36}H_{24}N_2$: C, 89.00; H, 5.10. Found: C, 89.13, 89.04; H, 5.18, 5.45.

9-2'-Pyridylcarbazole. A mixture of 8.35 g. (0.05 mole) of carbazole, 7.25 ml. (11.8 g., 0.075 mole) of 2-bromopyridine, 10.4 g. (0.075 mole) of potassium carbonate, 1.0 g. of copper bronze, 1.9 g. (0.0075 mole) of iodine, and 200 ml. of petroleum ether (b.p. 190–210°) was stirred and refluxed for 24 hr. The product was steam distilled and the residue extracted with hot benzene. The cooled extract was evaporated in an air stream to give a heterogeneous solid which was recrystallized twice from ethanol and three times from petroleum ether (b.p. 60–70°) to yield 1.5 g. (13%) of colorless crystals, m.p. 93–95°. The infrared spectrum has a C=N band and lacks a N—H band.

Anal. Calcd. for $C_{17}H_{12}N_2$: N, 11.47. Found: N, 11.36, 11.51.

9-2'-Quinolylcarbazole. Refluxing a mixture of 16.7 g. (0.1 mole) of carbazole, 24.5 g. (0.15 mole) of 2-chloroquinoline, 20.7 g. (0.15 mole) of potassium carbonate, 2.0 g. of copper bronze, and 3.8 g. (0.015 mole) of iodine for 48 hr. yielded a dark product which was extracted with hot benzene. Evaporation of the extract, dissolution of the residue in hot ethanol (Norit-A), filtration, and cooling gave a dark tar and a yellow solution. The solution was decanted into an equal volume of cold water. The resulting oil slowly crystallized. Successive recrystallizations from ethanol, petroleum ether (b.p. 77–115°) and petroleum ether (b.p. 60–70°) yielded 1.5 g. (10%) of colorless crystals, m.p. 93–94°. This compound, in contrast to the pyridyl analog, showed a very troublesome tendency to form an oil at every stage of purification. The infrared spectrum indicated the presence of a C=N bond and an absence of a N—H bond.

Anal. Calcd. for $C_{21}H_{14}N_2$: C, 85.56; H, 4.79. Found: C, 85.52, 85.38; H, 4.97, 5.07.

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New Synthesis of Trichocereine

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During the course of investigation of the alkaloids present in *Trichocereous terscheckii* (Parmentier), Reti[3] isolated a new phenethylamine base, trichocereine, which is peculiar to this species of cactus. The structure of trichocereine was shown by degradation to be N,N-dimethyl-3,4,5-trimethoxy-β-phenethylamine. Reti gives a cursory description of his synthesis of the base, in unstated yield, from the reaction of 3,4,5-trimethoxy-β-phenethyl chloride with dimethylamine; the phenethyl chloride was obtained by subjecting an aqueous solution of mescaline hydrochloride to the action of nitrous acid. Banholzer, Campbell, and Schmid[4] describe the synthesis of trichocereine (28% yield as the picrate) from 3,4,5-trimethoxybenzoyl chloride *via* the diazo ketone.

A more direct route has been found for the synthesis of trichocereine hydrochloride from 3,4,5-trimethoxyphenylacetic acid[5] in an over-all yield of 47%. The acid was converted to 3,4,5-trimethoxyphenylacetyl chloride by treatment with thionyl chloride in the presence of catalytic amounts of pyridine. Reaction of the resulting acid chloride with dimethylamine afforded N,N-dimethyl-3,4,5-trimethoxyphenylacetamide, which was subsequently reduced to trichocereine with lithium aluminum hydride.

EXPERIMENTAL

N,N-Dimethyl-3,4,5-trimethoxyphenylacetamide. A slurry of 3,4,5-trimethoxyphenylacetic acid (11.3 g.) in 50 ml. of dry ether was treated with 7.3 ml. of thionyl chloride and then 2 drops of dry pyridine were added to the mixture. After standing at room temperature overnight, the ethereal solution of the acid chloride was filtered free of suspended pyridine hydrochloride and the ether removed at diminished pressure. The residual acid chloride was purified by distillation; b.p. 150–152°/1.5 mm.; yield, 9.1 g. (74%).

A solution of 3,4,5-trimethoxyphenylacetyl chloride (9.1 g.) in 20 ml. of dry ether was first cooled and then slowly added to an ice-cold ethereal solution of 7 ml. of dimethylamine in 30 ml. of dry ether. After the vigorous reaction had subsided, the reaction mixture was filtered free of the precipitated dimethylamine hydrochloride and the clear filtrate evaporated to an oily residue at reduced pressure. Distillation of the residue *in vacuo* afforded 6.7 g. (72%) of N,N-dimethyl-3,4,5-trimethoxyphenylacetamide, b.p. 173–175°/0.4 mm. as a light yellow oil. The amide was crystallized by cooling an ether-petroleum ether solution in a dry-ice bath; colorless prisms, m.p. 49–50.5°. Literature,[4] m.p. 50–51°.

Trichocereine Hydrochloride. Reduction of 8.2 g. of N,N-dimethyl-3,4,5-trimethoxyphenylacetamide was carried out with 1.3 g. of lithium aluminum hydride in 100 ml. of dry ether. The resulting ethereal suspension of the intermediate complex was hydrolyzed by the careful addition of water, and the ether solution was decanted from the solid lithium *meta* aluminate. The ether solution of the reaction product was dried over anhydrous magnesium sulphate, filtered, and treated with a slight excess of an ice-cold solution of hydrogen chloride in dry ether. The crude trichocereine hydrochloride which precipitated was collected and washed with additional dry ether; yield 7.8 g. (88%); m.p. 199–201°. Recrystallization from ethanol containing a small amount of dry ether gave the pure base hydrochloride (6.4 g.) as colorless prisms; m.p. 207–208°. Literature,[3] m.p. 205°.

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(5) This compound is available from the Aldrich Chemical Company, Milwaukee, Wis.

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Improved Synthesis of DL-Carnitine Hydrochloride[1]

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We have recently been interested in studying the radiation sensitivity of DL-carnitine hydrochloride, $[(CH_3)_3NCH_2CH(OH)CH_2CO_2H]^+Cl^-$. The first synthetic route to carnitine, involving a Gabriel-type synthesis, was described by Tomita[3]—however, the yields were poor. Another synthesis, based on an oxazolidine intermediate of Bergmann's,[4] has been described by Carter.[5] A final procedure, recently published by Strack, Röhnert and Lorenz[6] involves the preparation of the mononitrile from $ClCH_2CH(OH)CH_2Cl$, followed by treating the chloronitrile with trimethylamine, and finally hydrolyzing the cyano group to carboxyl. This latter procedure was of little interest to us as the over-all yields were also low and because we wished to introduce C^{14} into the carnitine molecule, via $C^{14}H_3I$, at the last step of a reaction sequence. We therefore turned our attention to the Bergmann-Carter synthesis. It is carried out in six steps: (1) epichlorohydrin is treated with benzaldehyde and ammonia to give 5-chloromethyl-2-phenyloxazolidine; (2) the product is treated successively with benzoyl chloride and concentrated HCl to form 3-benzoylamino-1-chloro-2-hydroxypropane; (3) the chloro group is converted to cyano by reaction with KCN to give the corresponding benzoylaminonitrile; (4) the nitrile is hydrolyzed and esterified to the benzoylamino ethyl ester; (5) the ester and benzoylamino groups are simultaneously hydrolyzed to give the free amino acid; and (6) carnitine is formed by quaternization with methyl iodide and KOH.

We have found that this reaction sequence can be simplified by going directly from the benzoylamino-nitrile to the amino acid in a single step.[7] The final step in the sequence, the methylation of the amino acid, is very troublesome. The best methylation procedure now available[5] is hard to apply, particularly for a small-scale preparation with C^{14}, because it involves successive extractions with phenol, countercurrent washings with water, and final washings of aqueous extracts with ether. Our experiments have shown that the use of barium hydroxide as the base in the methylation, removal of barium with H_2SO_4, and exchange of other anions for hydroxide on an ion exchange column, leads to an 88% yield of recrystallized DL-carnitine hydrochloride from the amino acid. The experimental conditions for the improved synthesis are described below. (All melting points are uncorrected.)

EXPERIMENTAL

5-Chloromethyl-2-phenyloxazolidine. The directions given by Carter[5] were followed. It is desirable to use freshly purified benzaldehyde and epichlorohydrin, and to add the epichlorohydrin very slowly (to decrease polymerization). We have obtained a yield of 85% of impure 5-chloromethyl-2-phenyloxazolidine by this procedure and, after crystallization, the analytically pure compound was obtained in 76% yield; m.p. 71°.

3-Benzoylamino-1-chloro-2-hydroxypropane. This is a modification of the procedure given by Bergmann, Randt and Brand.[8] To a solution of 40 g. (0.2 mole) of the pure oxazolidine in 150 ml. of chloroform was added 16 g. (0.2 mole) of pyridine. The solution was cooled to −40° in a dry ice-isopropyl alcohol bath, removed from the bath, and 28 g. (0.2 mole) of benzoyl chloride was added dropwise, with stirring. During this addition the temperature of the reaction mixture reached a maximum of 0°. The mixture was then left overnight at room temperature; however, another experiment indicated that the overnight standing was unnecessary.

Concentrated HCl (200 ml.) was then added and the mixture stirred for 5 min. Finally, 500 ml. of water and 500 ml. of petroleum ether (b.p. 60–70°) were added and the flask was placed in a refrigerator. Crystals soon appeared in the upper (pet. ether) phase and the crystallization was complete in 1–2 hours. The yield of crystallized benzoylamino chlorohydroxypropane was 26.8 g. (yield 79%); m.p. 108°.

3-Benzoylamino-1-cyano-2-hydroxypropane. Ten grams (0.047 mole) of crystallized benzoylaminochlorohydroxypropane was dissolved in 60 ml. of 67% ethanol and 5 g. (0.077 mole) of KCN and 50 mg. of KI were added. The solution was left at room temperature for 72 hr. The alcohol and water were removed by evaporation at reduced pressure, and the crystalline residue was washed with ice water, filtered, re-washed with ice water, and dried. It was recrystallized from acetone-petroleum ether giving 7.7 g. (yield 80%) of pure nitrile, m.p. 126°.

γ-Amino-β-hydroxybutyric acid. The cyano group was hydrolyzed to carboxyl, and the benzoyl group was simultaneously removed, as follows:

To 1.60 g. (7.8 mmoles) of the pure benzoylaminonitrile was added 10 ml. of reagent-grade 48% aqueous HBr and the solution was refluxed for 45 min.; shorter (10, 20 or 30 min.) and longer (1 or 3 hr.) times led to lesser yields. The benzoic acid freed by the hydrolysis was filtered off, washed

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(2) U. S. Foreign Operations Administration Fellow, 1954–1956.

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(7) We are grateful to Dr. P. K. Bhattacharyya of the National Chemical Laboratory, Poona, India, for suggesting this possibility.

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