Before starting a run, qualitative tests were made to see that the explosive product was being formed. To do this, the cap was removed from bottle E, and stopcock M was closed. Stopper I was inserted into the neck of bottle E and the gas was passed through the glass trap J, which was cooled at the bottom to −183°. After gas had passed for a measured time of four to eight minutes, tube J was disconnected at L and it was placed in an explosion shield made of sheet iron. Copper wire K was inserted as shown. After waiting for about 100 seconds to allow the product to vaporize, a spark producing "leak tester" was touched to wire K. If this caused a sharp explosion to occur, the apparatus was known to be producing the desired substance. The flow rates given below yielded enough material in four minutes to explode with a sharp report but not with enough energy to shatter the glass tube.

The role of water vapor in the reaction is not clear. Usually the product could be obtained without adding water. However, in the case of the last cylinder of fluorine used in the study, almost none of the explosive substance was formed unless water vapor was added.

The run which finally resulted in identification of the compound involved the following flow rates: F_2 from 0.97 to 0.83 g. per hour, trifluoroacetic acid at 2.1 g. per hour, water vapor at 0.1 g. per hour and nitrogen at 9.0 liters per hour. The reaction vessels were held at 25 ± 1° and the reaction was allowed to continue for three hours while the product was condensed in trap W. At the end of this time fluorine was swept from the system by a stream of dry nitrogen; then stopcock M was closed and the glass system was pumped out for about 10 minutes with a pump connected at X. After closing stopcock X, the product was distilled from trap W to the 10-ml. bulb U. Dry nitrogen at atmospheric pressure was then admitted to the glass apparatus and the system was left open to the atmosphere. Bulb U was then allowed to warm slowly to about −60°, being kept there by the near proximity of Dry Ice held in a suitable container, leaving only a few drops of liquid in the bulb. Stopcock S was then closed and gas was pumped from all of the glass system except bulb U. Stopcocks Y, O and M were closed and bulb U was immersed in a bath of acetone and solid carbon dioxide. Stopcock S was then opened and after a few seconds was closed. The pressure of gas in the system was measured on mercury manometer Z. An unsuccessful attempt was made to explode the gas in the system using the spark producing "leak tester" held outside the manometer tube at a point about 1 cm. above the mercury meniscus. The non-reacting gas was pumped from the system through stopcocks Y and X; then another sample of gas was allowed to escape from bulb U. With stopcock S closed another attempt was made to explode the gas in the line. The fourth trial of this sort and all succeeding trials resulted in explosions. This procedure removed impurities more volatile than trifluoroacetyl hypofluorite and finally resulted in what appeared to be the nearly pure compound being the gas escaping from bulb U. Repeated sampling of this sort showed the vapor pressure of the hypofluorite at −78.5° to be about 27 mm. When the gas at this pressure was exploded, the products had a pressure of about 57 mm. A 45.4 ml. (measured at 0°, 760 mm.) sample of the explosion product was found upon a rather crude analysis to contain about 13.5 ml. of COF_2, 12.6 ml. of CO_2, 15.3 ml. of CF_4 and 4.0 ml. of a mixture of gases remaining uncondensed when bulb R was cooled to −183°. When this uncondensed mixture was examined using the mass spectrometer it was found to contain CF_4, SiF_4, CO_2, O_2 and N_2. Some carbon monoxide may also have been present.

Two low pressure samples of the unexploded gas were collected in bulbs of the type shown at R. These samples had densities corresponding to molecular weights of 137 and 136 (theoretical for CF_3COOF = 132). The total fluorine content was found to be 57.0 ± 1.0% (theoretical 57.6%).

When the gas was allowed to stand at room temperature it decomposed slowly as shown by a gradual increase in pressure. Within a few hours the decomposition was complete.

Upon contact with a solution of potassium iodide the substance was found to explode. When diluted with much nitrogen it did not explode, but it did react rapidly liberation iodine.

When the reflux condenser T was cooled by solid carbon dioxide, and trifluoroacetyl hypofluorite was then boiled in bulb U under a pressure of one atmosphere, the temperature indicated by a thermocouple in well V was −21.5 ± 1°. This is an approximate value for the normal boiling point.

As far as could be told from the small samples observed, the substance was colorless. Its odor was irritating and similar to that of fluorine and the other compounds containing an -O-F bond.

The total weight of the purified compound obtained in the above run from 2.11 g. of trifluoroacetic acid was 0.33 g. Even though a part of the material was lost during the purification process, the total yield must have been less than 25% of theoretical.

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5-Benzyloxyindole

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The recent elucidation of structure[2] and synthesis[3,4] of 5-hydroxytryptamine, a naturally occurring vasoconstrictor substance of serum and tissue fluids,[5] has prompted the investigation of a more convenient preparation of 5-benzyloxyindole, an intermediate in two of the reported syntheses.[3] Burton and Stoves[6] have described the reduction and cyclization of 2-nitro-5-benzyloxyphenylpyruvic acid in the presence of ferrous hydroxide and alkali to yield 70% 5-benzyloxyindole-2-carboxylic acid. Decarboxylation in glycerol at 210° afforded a 24% yield of benzyloxyindole.

Application of the Japp–Klingemann reaction[7] with 4-benzyloxybenzenediazonium chloride and ethyl methylacetoacetate followed by cyclization of the phenylhydrazone in absolute ethanolic hydrogen chloride yielded 46–49% ethyl 5-benzyloxyindole-2-carboxylate. Alkaline saponification of the ester (84–95%) and decarboxylation of the resulting 5-benzyloxyindole-2-carboxylic acid gave 65% crystallized 5-benzyloxyindole.

Experimental[8]

4-Benzyloxyaniline.—To a solution of 23 g. (1 mole) of sodium in 1 l. of absolute ethanol was added 151 g. (1 mole) of 4-acetylaminophenol and 127 g. (1 mole) of benzyl chloride. The mixture was refluxed with stirring for 1.5 hr., about 750 ml. of solvent removed by distillation, and the residue poured into 2 l. of cold water. The 4-benzyloxyacetanilide which precipitated as fine almost colorless needles was filtered off and washed with water. The damp filtercake was then refluxed for 15 hr. with a solution of 280 g. (5 moles) of potassium hydroxide in 2 l. of 90% ethanol. Most of the solvent was again removed by distillation. The residue partially crystallized on cooling. The crude product was taken up in ether and the extracts were dried superficially by filtration through a layer of anhydrous magnesium sulfate. Distillation yielded 167–170 g. (84–85%) of a

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(8) Analyses by S. Alpert.

light yellow oil which solidified on cooling to large almost colorless rectangular plates, b.p. 161–164° (0.25 mm.), m.p. 51–53°. For analysis a sample was crystallized from hexane, m.p. 54–55° (lit. 56°).[9]

Ethyl 5-Benzyloxyindole-2-carboxylate.—4-Benzyloxyaniline (116 g., 0.583 mole) was dissolved in 250 ml. of boiling ethanol. The hydrochloride was precipitated in a finely divided form by the rapid addition with vigorous stirring of a solution of 233 ml. of concentrated hydrochloric acid in 360 ml. of water followed by the addition of 1 kg. of ice. A solution of 47.7 g. (0.68 mole) of sodium nitrite in 110 ml. of water was run in below the surface of the cream-colored slurry and stirring was continued until a clear solution resulted (*ca.* 20 min.).

Ethyl methylacetoacetate (92 g., 0.64 mole) was dissolved in 600 ml. of ethanol. To this solution was added 100 g. of potassium hydroxide dissolved in 100 ml. of water followed by 1 kg. of ice. The diazonium solution was then added in one portion with stirring. The red oil which separated was taken up in benzene, the benzene extracts dried superficially by filtration through anhydrous potassium carbonate, and the solvent removed under vacuum on the steam-bath. The crude red liquid phenylhydrazone was dissolved in 450 ml. of absolute ethanol and a rapid stream of dry hydrogen chloride was passed into the solution until a precipitate formed (*ca.* 20 min.). The introduction of hydrogen chloride was then continued for 10 min. longer. When the spontaneous exothermic reaction subsided (*ca.* 15 min.) the mixture was allowed to stand overnight in the refrigerator. The product was filtered off, washed with several small portions of ice-cold ethanol and then with water until the washings were substantially free of chloride ion. The air-dried yellow prisms weighed 110–117.5 g. (46–49%), m.p. 161–163°. A sample recrystallized from carbon tetrachloride for analysis melted at 162–164°.

Anal. Calcd. for $C_{18}H_{17}NO_3$: N, 4.74. Found: N, 4.69, 4.75.

5-Benzyloxyindole-2-carboxylic Acid.—Ethyl 5-benzyloxyindole-2-carboxylate (117.5 g., 0.4 mole) was dissolved in 3 l. of boiling ethanol. With stirring a solution of 237 g. (3 moles) of potassium hydroxide in 400 ml. of water was added rapidly. Crystallization of the potassium salt began in a few minutes. The suspension was refluxed 1 hr., acidified with acetic acid, and poured into 10 l. of cold water. The solid was filtered off, washed well with water, and crystallized from aqueous acetic acid. The yield of light tan crystals was 89–101 g. (84–95%), m.p. 194.5–195.5° (dec.) (lit. m.p. 193–194°[10]).

5-Benzyloxyindole.—5-Benzyloxyindole-2-carboxylic acid (45.0 g., 0.169 mole) was heated for 1.5 hr. in a Claisen flask at a bath temperature of 210–220°. The dark brown melt was distilled in vacuum yielding 27.5 g. of an almost colorless liquid which solidified on cooling, b.p. 176–190° (0.1 mm.). Redistillation of the crude product (26.0 g., b.p. 182–188° (0.1 mm.), m.p. 81–86°) and crystallization from toluene–hexane gave 24.3 g. (65%) of fine colorless needles, m.p. 94–96° (lit. m.p. 96–97°[6]).

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Improvements in the Synthesis of DL-Carnitine[1]

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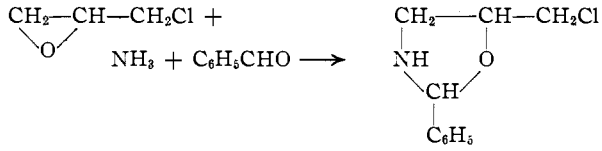
In the course of studies on the biochemistry of (−)-carnitine (β-hydroxy-γ-butyrobetaine) we had occasion to synthesize a quantity of the racemic form. Several crystalline salts of DL-carnitine have been prepared but the substance itself has been obtained only as a hygroscopic gum. The present note describes the preparation of crystalline DL-carnitine by a modified procedure giving considerably better yields than those obtained by Bergmann, *et al.*[2] It was discovered that a key intermediate—2-phenyl-5-chloromethyloxazolidine—could be obtained in one step (instead of three) by the direct condensation of epichlorohydrin, ammonia and benzaldehyde (yield 70–80%).



Subsequent reactions leading to β-hydroxy-γ-aminobutyric acid were carried out as previously described.[2]

Methylation of β-hydroxy-γ-aminobutyric acid was effected by a slight modification of the procedure of Tomita[3] and the product was purified by extraction into phenol from an aqueous solution. This extraction procedure has been used to advantage in the isolation of (−)-carnitine from natural sources.[4] The yield of crystalline DL-carnitine in this step was 75–78% and the over-all yield was 20–25% (compared to the 5–7% yield obtained according to methods previously described). In view of the recent identification of (−)-carnitine as an essential growth factor for *Tenebrio molitor*[5] it seemed worthwhile to make available these modifications in the synthesis of DL-carnitine.

Experimental

2-Phenyl-5-chloromethyloxazolidine.—To a solution of 212 g. of benzaldehyde in 1000 ml. of ethanol was added with stirring 200 ml. of concentrated aqueous ammonium hydroxide (29% NH_3). This solution was stirred continually while 185 g. of epichlorhydrin was added in a thin stream. The reaction mixture warmed spontaneously to 40–45° over a 2-hour period. It was allowed to stand overnight at room temperature and was then heated on the steam-bath for 20 minutes to complete the reaction. The alcohol and ammonia were removed on the water pump and the residual yellow sirup was poured into 200 ml. of ice-water. The mixture was cooled in an ice-bath and stirred from time to time. Over a 4-hour period the entire mass solidified. The solid residue was filtered and sucked dry on the filter giving 345 g. of crude material. Recrystallization of this material from 4800 ml. of hot hexane gave 271 g. (69% yield) of pure 2-phenyl-5-chloromethyloxazolidine melting at 81–83°. The mother liquor was cooled overnight at −11° giving 42 g. of less pure material.

Conversion of β-Hydroxy-γ-aminobutyric Acid to DL-Carnitine.—A solution of 7 g. of methyl iodide in 50 ml. of methanol was added to a solution of 1.0 g. of β-hydroxy-γ-aminobutyric acid and 2.0 g. of potassium hydroxide in 5 ml. of water. The mixture was refluxed slowly under an efficient condenser for 36 hours (*p*H of solution about 5.5). The reaction mixture was evaporated to dryness on the water pump and the residue was dissolved in 50 ml. of water. The solution was extracted with three 50-ml. portions of phenol saturated with water. The three phenol extracts were washed countercurrently with two 50-ml. portions of water. The phenol extracts were then combined and poured into 450 ml. of ether in a separatory funnel. The aqueous layer was separated and the ether–phenol layer was washed with three 50-ml. portions of water. The combined aqueous extracts were washed with 450 ml. of ether and passed through a column containing 100 ml. of Amberlite IRA 45 in the hydroxyl phase. The column was washed with 500 ml. of

(1) The authors are happy to acknowledge a research grant from Merck and Co., Inc., in support of this work.

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