precipitate of the acid was filtered off after standing for three days at room temperature. It was purified through its sodium salt, and recrystallized from aqueous alcohol. The yield was 2.3 g. (23%).

Monoperphthalic Acid Oxidation.—The quinone (4.74 g.) was added to an excess of monoperphthalic acid in ether solution and the mixture was allowed to stand at room temperature for thirty hours. The precipitate of acid was filtered and the acid purified as before. The yield was 2.08 g. (31.2%).

The pure dicarboxylic acid melted at 186–190° (dec.) when the temperature of the block was raised 4° per minute.

Anal. Calcd. for $C_{11}H_{10}O_5$: C, 59.46; H, 4.54; neut. equiv., 111.3. Found: C, 59.32; H, 4.80; neut. equiv., 111.1.

DEPARTMENT OF CHEMISTRY
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A Peptide Derivative Related to Gramicidin

BY JOSEPH S. FRUTON

The studies of Hotchkiss[1] and of Gordon, *et al.*,[2] have shown that gramicidin is a cyclopeptide which is characterized by an unusually high content in D-leucine and L-tryptophan, these two components accounting for approximately one half of the total amino acids found after complete hydrolysis of gramicidin. In the course of our studies on the effect of peptides and peptide derivatives on bacterial growth, the substance D-leucyl-L-tryptophan diketopiperazine was synthesized. The synthesis involved the reaction of carbobenzoxy-D-leucyl azide with L-tryptophan methyl ester, followed by the catalytic hydrogenation of the coupling product. Treatment of the resulting dipeptide ester with ammonia gave the diketopiperazine.

If the antibacterial action of gramicidin were due solely to the presence of D-leucine or L-tryptophan residues, the synthetic diketopiperazine might have been expected to exhibit some inhibition of the growth of organisms affected by gramicidin. It has been found, however, that the diketopiperazine, when tested at concentration levels of 1 to 10 μg. per ml. of culture medium, shows no appreciable action on *Escherichia coli*, *Staphylococcus aureus*, *Clostridium welchii* or *Brucella abortus*, and only a slight antibacterial effect was noted with *Streptococcus hemolyticus*. Control experiments with gramicidin, at 1 and 5 μg. per ml., showed complete inhibition of the growth (in 12 hours) of *S. hemolyticus*. Further experiments on the antibacterial activity of peptide derivatives related to gramicidin and tyrocidine are in progress.

Experimental

N-Carbobenzoxy-D-leucyl-L-tryptophan Methyl Ester.—Three grams of carbobenzoxy-D-leucinhydrazide[3] was dissolved in a mixture of 25 ml. of water, 10 ml. of glacial acetic acid and 5 ml. of concentrated hydrochloric acid. The solution was chilled to 0° and, with shaking, there was added, in small portions, a solution of 0.7 g. of sodium nitrite in 10 ml. of water. The azide separated as an oil and was extracted with ether. The ethereal solution was washed successively with cold water, cold aqueous bicarbonate solution, and again with cold water. The ethereal layer (60 ml.) was dried briefly over sodium sulfate and added to a solution of 2.5 g. of L-tryptophan methyl ester[4] in 60 ml. of ether. The reaction mixture was left at room temperature for eighteen hours, and then washed successively with dilute hydrochloric acid, water, aqueous bicarbonate solution, and water. After being dried over sodium sulfate, the solution was concentrated to a small volume under reduced pressure. The careful addition of petroleum ether (30–60°) gave a sirup which crystallized readily. After recrystallization from ethyl acetate–petroleum ether, the substance (2.7 g.) melted at 125–127°.

Anal. Calcd. for $C_{26}H_{31}O_5N_3$: N, 9.0. Found: N, 9.2.

D-Leucyl-L-tryptophan Diketopiperazine.—One gram of the above carbobenzoxydipeptide ester was dissolved in a mixture of 15 ml. of methanol and 0.2 ml. of glacial acetic acid and was hydrogenated at atmospheric pressure in the presence of palladium black. The hydrogenation required two hours, after which time the catalyst was removed by filtration. The filtrate was added to 30 ml. of methanol which had previously been saturated with dry ammonia at 0°. The mixture was left at room temperature for two days, then concentrated under reduced pressure, and the resulting crystalline product was dissolved in 10 ml. of hot absolute alcohol. On chilling the alcoholic solution, 0.56 g. of the diketopiperazine crystallized; m. p. 218–219° (dec.).

Anal. Calcd. for $C_{17}H_{21}O_2N_3$: C, 68.2; H, 7.1; N, 14.0. Found: C, 67.9; H, 7.1; N, 14.0.

(1) Hotchkiss, *J. Biol. Chem.*, **141**, 171 (1941).
(2) Gordon, Martin and Synge, *Biochem. J.*, **37**, 86 (1943).
(3) This compound was prepared in the manner described for the L-form by Bergmann, *et al.*, *J. Biol. Chem.*, **109**, 325 (1935).
(4) Abderhalden and Kempe, *Z. physiol. Chem.*, **52**, 207 (1907).

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Indole from Formyl-toluidine

BY ALEXANDER GALAT AND HARRIS L. FRIEDMAN

Of the numerous methods of preparation of indole described in the literature, ring closure of *o*-formyltoluidine is the most direct and convenient. Tyson[1] has shown that yields up to 79% may be obtained with potassium alkoxides, whereas sodium alkoxides give little or no product. This is a peculiarity of the formyl group, for the higher acyl derivatives are readily dehydrated by sodium alkoxides.[2]

The use of potassium metal in the dehydration of *o*-formyltoluidine adds both expense and an element of danger to large scale preparations. It occurred to us that if the potassium *ion* had a catalytic effect in the reaction, it would be possible to use an inexpensive potassium salt with sodium alkoxide.

This possibility was tested as follows: sodium (4.6 g.) was dissolved in 100 ml. of anhydrous methanol and 27 g. of *o*-formyltoluidine was added. Complete solution resulted on warming.

(1) Tyson, THIS JOURNAL, **63**, 2024 (1941).
(2) Madelung, *Ber.*, **45**, 1130 (1912).

The potassium salt used was then added and methanol was distilled off with stirring to obtain a uniform dispersion. Complete removal of methanol was effected by applying reduced pressure (20–30 mm.) and the resulting solid was heated in a solder-bath between 300 and 350°. The reaction occurs at the internal temperature of 300–310° as evidenced by rapid distillation of toluidine. Reduced pressure (20–30 mm.) was applied toward the end of the reaction to remove all toluidine. The reaction mass was cooled, treated with water and the indole steam-distilled over. The product crystallized in the cooled distillate in the form of lustrous plates. Any trace of toluidine was removed by acidification and the indole was filtered, washed with water and dried; m. p. 50–51.5°.

Since half of the toluidine was recovered in every case, the yield was calculated on the basis of this recovery. The results obtained are contained in Table I.

TABLE I

Added salt, g.		K atoms	Yield, %	Observations
None		..	6.0	
17	Anhydrous K_2SO_4	1	14.5	No stirring used;
35	Anhydrous K_2SO_4	2	21.0	melt appears
70	Anhydrous K_2SO_4	4	14.5	heterogeneous
35	Anhydrous K_2SO_4	2	34.0	Mechanical stirring used
20	Anhydrous KOAc	1	27.0	Homogeneous
39	Anhydrous KOAc	2	37.5	fluid melt

Whether the potassium acts as a catalyst or as a reactant is open to question. The data show that a potassium salt does effect a marked increase in yield, the maximum effect being obtained apparently with two atoms of potassium.

Although the yield is not as high as when potassium metal is used, the procedure is safer and much less expensive.

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The Preparation of 2,2,2-Trifluoroethanol

BY HENRY GILMAN AND R. G. JONES

In connection with studies of compounds containing the trifluoromethyl group, we had need of trifluoroethanol. This substance had been described by Swarts[1] who prepared it by the catalytic reduction both of trifluoroacetic anhydride and of trifluoroacetamide. Since the former method afforded him a yield of only 23%, we attempted in vain its preparation from both ethyl and *n*-butyl trifluoroacetate by hydrogenation over copper chromite catalyst at pressures up to 3500 lb./sq. in. and temperatures up to 250°. No hydrogen was absorbed and we recovered unchanged 70% of the ethyl, and 32% of the butyl ester.

In view of this failure we resorted to the latter method of Swarts, who unfortunately gave no details of his procedure other than that he hydrogenated the ethereal solution under a pressure of 40 atmospheres.

Trifluoroethanol.—A solution of 113 g. (1.0 mole) of pure amide (m. p. 74.5–75.0°) in 100 cc. of anhydrous ether in a bomb of 490-cc. capacity with 3.5 g. of Adams catalyst was agitated with hydrogen at 1500 lb./sq. in. at 90° for seven hours, the pressure dropping to 670 lb./sq. in. To the cooled bomb 1.5 g. of fresh catalyst was added and agitation at the previous temperature and pressure was continued for four hours longer, the pressure then dropping to 1080 lb./sq. in. The contents of the cooled bomb with the ether washings was fractionated in a small packed column of about 10 equivalent plates, yielding a fraction weighing 76.5 g. (76.5%) and boiling at 75–77° (740 mm.). It was necessary to heat the distilling flask with a free flame in order to drive over the trifluoroethanol. Apparently the latter forms an unusually stable solvate with the unchanged trifluoroacetamide and ammonium trifluoroacetate present. The released hydrogen in each case was allowed to bubble through concentrated hydrochloric acid, whereby a total of 36 g. of ammonium chloride (66% yield), identified by analysis, was obtained.

The platinum catalyst seemed to quickly lose its activity. In all of the runs the rate of reduction became very slow after about four hours and it was necessary to add fresh catalyst.

From several preparations, the general reaction for which may be represented as

$$CF_3CONH_2 + 2H_2 \xrightarrow{Pt} CF_3CH_2OH + NH_3$$

none of the recently described[2] trifluoroethylamine was isolated. The only products were trifluoroethanol, ammonia, unchanged trifluoroacetamide, and ammonium trifluoroacetate. The small quantity of ammonium trifluoroacetate obtained may have resulted from hydrolysis of trifluoroacetamide.[3]

Trifluoroisopropanol.[4]—Seventy-five grams (0.67 mole) of trifluoroacetone,[5] 5 g. of Adams catalyst, and 3 cc. of water, were added to the bomb previously cooled to −15°, and the whole agitated at room temperature with hydrogen at 760 lb./sq. in. pressure. The absorption of hydrogen began at once and in three hours the pressure had dropped to 250 lb./sq. in. The bomb was then opened and the contents and ether washings were dried over calcium sulfate and

(1) Swarts, *Compt. rend.*, **197**, 1261 (1933); *Bull. soc. chim. Belg.*, **43**, 471 (1934) [*C. A.*, **29**, 729 (1935)].

(2) Gilman and Jones, THIS JOURNAL, **65**, 1458 (1943).

(3) Although care was taken to dry the reagents and the apparatus, sufficient water may have been formed from the catalyst [$PtO_2 \cdot H_2O$].

(4) Swarts, *Bull. soc. chim. Belg.*, **38**, 99 (1929) [*C. A.*, **23**, 4440 (1929)].

(5) Swarts, *Bull. classe. sci. Acad. roy. Belg.*, **13**, 175 (1927). [*C. A.*, **22**, 58 (1928)].