The sulfonic anhydride did not react at elevated temperatures with potassium chloride. When the anhydride, 40 g. (0.044 mole), and aluminum chloride, 10 g. (0.075 mole), were strongly heated in a 100-ml. distilling flask, volatile products were collected which, upon fractional distillation, gave 12.8 g. (60%) of 4-$C_2F_5C_6F_{10}SO_2Cl$, b.p. 184°, $n^{25}D$ 1.3516. The same product was obtained in slightly better yield, *ca.* 75%, when an equivalent amount of freshly fused zinc chloride was substituted for the aluminum chloride. A limitation, despite the relatively good yields, is that half of the sulfonic anhydride molecule is unavailable in these reactions.

Perfluoro-(4-methylcyclohexane)sulfonic anhydride was made in exactly similar fashion, except that only half as much sulfonic acid had been employed. The excess phosphorus pentachloride was driven off with heating and clogged the apparatus; handling losses resulted and the yield (63%) was not truly representative. The sulfonic anhydride was isolated by fractional distillation. Despite the excess of phosphorus pentachloride used here, none of the corresponding sulfonyl chloride could be detected in any fraction by infrared spectroscopy.

Anal. Calcd. for $C_{14}F_{26}O_5S_2$: C, 20.86; F, 61.27. Found: C, 21.0; F, 61.0. The piperidide prepared as above, had m.p. 89–99° (isomer mixture).

Anal. Calcd. for $C_{12}H_{10}F_{13}NO_2S$: N, 2.92. Found: N, 2.80.

A similar reaction of perfluoro(*n*-octane)sulfonic anhydride[4] with piperidine yielded the piperidide, m.p. 77.5–78.5° (lit., m.p. 75–76.5°[2]; 77°[4]). The anhydride had been prepared from the acid by reaction with phosphorus pentachloride (mole ratio 2:1), about a 10% yield of sulfonyl chloride also having been produced.

Perfluoro(4-methylcyclohexane)sulfonyl Fluoride.—In a 25-ml. flask fitted with a 10-cm. fractionating column filled with $^1/_{16}$-in. "Helipak" (reg. t.m., Podbielniak Co.), was placed 20.8 g. (0.026 mole) of perfluoro(4-methylcyclohexane)sulfonic anhydride and 4.2 g. (0.10 mole) of sodium fluoride. The flask was slowly heated to 220° over a period of 10 hr. (more rapid heating should not be harmful), and refluxing volatile materials were taken off occasionally. The product, 8.5 g. (80%), boiled at 131–132° and had $n^{25}D$ 1.3172, in excellent agreement with reported data.[2]

Anal. Calcd. for $C_7F_{14}O_2S$: C, 20.30; F, 64.23. Found: C, 20.1; F, 64.2.

Perfluoroöctanesulfonyl Chloride.—Dried potassium perfluorooctanesulfonate, 240 g. (0.45 mole) was heated with $PCl_5 \cdot 2ZnCl_2$, 274 g. (0.57 mole of phosphorus pentachloride) and 156 g. of zinc chloride (1.14 moles) in a 1-l. distilling flask at 100 mm. until no more volatiles were collected. The distillate was fractionally distilled at reduced pressure and yielded, in two experiments, 201 g. (87%) and 192 g. (83%) of *n*-$C_8F_{17}SO_2Cl$, b.p. 121° (100 mm.), m.p. 36.5–7.5°.

Anal. Calcd. for $C_8ClF_{17}O_2S$: Cl, 6.84. Found: Cl, 6.95. Higher-boiling residues, *ca.* 6–8%, were shown by infrared analysis to be virtually pure perfluoöctanesulfonic anhydride.

When instead $PCl_5 \cdot 2ZnCl_2$ was used, the yield of sulfonyl chloride fell to 73–78%, much larger amounts of anhydride, *ca.* 18%, being recovered. The pasty, viscous condition of the reaction mixture may have been responsible for the lower yield, since less zinc chloride was present to establish a liquid phase; presumably some of the undissolved sulfonate salt reacted with sulfonyl chloride to give the anhydride.

Perfluoro(4-ethylcyclohexane)sulfonyl Chloride.—In a similar fashion 12.0 g. (0.024 mole) of dried potassium perfluoro(4-ethylcyclohexane)sulfonate reacted with 12.9 g. (0.027 mole) of $PCl_5 \cdot 2ZnCl_2$. Upon fractional distillation there was obtained 5.1 g. (53%) of 4-$C_2F_5C_6F_{10}SO_2Cl$, b.p. 118° (100 mm.).

Anal. Calcd. for $C_8ClF_{15}O_2S$: C, 19.99; F, 59.30; Cl, 7.38. Found: C, 20.0; F, 59.4; Cl, 7.48. Difficulties were encountered in the mixing of the reagents which would have been alleviated by use of $PCl_5 \cdot 4ZnCl_2$, and the 17% yield of anhydride might have been reduced appreciably also.

Trifluoromethanesulfonyl Chloride.—Dried zinc trifluoromethanesulfonate, 250 g. (0.69 mole), reacted with $PCl_5 \cdot 2ZnCl_2$, 928 g. (1.93 mole), by heating to 260° for 8 hr. at atmospheric pressure in a stirred 2-l. distilling flask. Upon fractional distillation of the volatile products, 220.1 g. (94%), of highly pure CF_3SO_2Cl, b.p. 32°, $n^{25}D$ 1.3315, was obtained. When the potassium salt was used instead, the sulfonyl chloride was obtained in somewhat lower yield, 80–85%, but equal purity.

Acknowledgment.—The author thanks Ray A. Malzahn for assistance with some of the sulfonyl chloride preparations, and Dr. J. J. McBrady for infrared analyses which greatly benefitted the research.

3-Indoleacetic Acid

HERBERT E. JOHNSON AND DONALD G. CROSBY

Research Department, Union Carbide Chemicals Company, South Charleston 3, West Virginia

Received September 1, 1961

The synthesis of indoleacetic acid in high yield by the reaction of indole with potassium glycolate at 250° is described. Selected methylated indoles also undergo this reaction as do salts of other α-hydroxy acids. The probable mechanism of the reaction is discussed.

3-Indoleacetic acid, its higher homologs, and their simple derivatives have been, over a period of the last twenty-five years, the subject of extensive investigation regarding their plant-growth regulating properties. A great many useful effects have been discovered, especially with the acetic and butyric acids, but the synthetic effort required to prepare these materials has precluded any practical agricultural applications. This communication describes a method by which indoleacetic acid may be readily prepared, namely by the direct reaction of indole with potassium glycolate.

Numerous examples of the reaction of simple primary and secondary alcohols with various indoles are known. For example, benzyl alcohol, hexahydrobenzyl alcohol, butanol, cyclohexanol, and others react with indole in the presence of a base and a nickel catalyst at 145–185° to give the corresponding 3-alkylated indoles.[1] At 210–220°, indole and alcohols react similarly in the presence of alkoxide and without a nickel catalyst, as do 2- and 7-methylindoles.[2,3] 2-Carboxyindole, however, reacts only with primary alcohols giving the 3-derivatives with concomitant loss of the carboxyl group.[2] Ethylene glycol and 2-ethoxyethanol gave 3-ethylindole under these conditions, while ethanolamine and *N,N*-diethylethanolamine gave no tryptamine derivatives or other characterizable products.[2] The reaction of other complex alcohols with indole apparently has not been reported.

Initial experiments in which indole and butyl glycolate were allowed to react together at 185° with a nickel catalyst, as described by Pratt and Botimer,[1] provided only traces of the desired ester. Further investigation led to heating indole with potassium

---

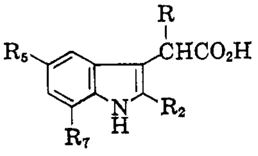
[1] E. F. Pratt and L. W. Botimer, *J. Am. Chem. Soc.*, **79**, 5248 (1957).

[2] R. H. Cornforth and R. Robinson, *J. Chem. Soc.*, **1942**, 680.

[3] B. Oddo and C. Alberti, *Gazz. chim. ital.*, **63**, 236 (1933); *Chem. Abstr.*, **27**, 3933 (1933).

TABLE I

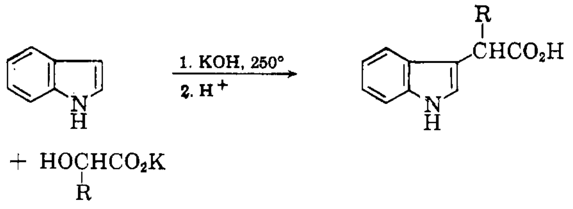
INDOLEACETIC ACIDS



R	R_2	R_5	R_7	Yield, %	M.p., °C.	Conditions		
H	H	H	H	90	164-166	70% Glycolic acid[e]	250°	22 hr.
H	H	H	H	54	164-166	18% Glycolic acid	250°	19 hr.
H	CH_3	H	H	87	197-199[a]	16% Glycolic acid	250°	17 hr.
H	CH_3	CH_3	H	43	169-171[b]	22% Glycolic acid	250°	17 hr.
H	CH_3	H	CH_3	29	164-166[c]	7% Glycolic acid	250°	16 hr.
CH_3	H	H	H	80	105-110[d]	85% Lactic acid	250°	21 hr.
$CH(C_2H_5)_2$	H	H	H	10	131-133	See Experimental		

[a] Reported[6] 195-200°. [b] Reported[7] 172-173°. [c] Reported[8] 164-165°. [d] Reported[7,9] 102°, 111-112°. [e] Aqueous.

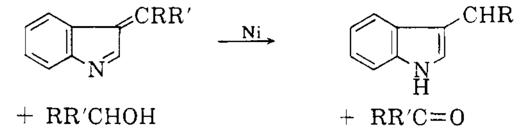
glycolate at 250° in the presence of potassium hydroxide which produced a 90% yield of indoleacetic acid, after dilution and acidification of the reaction mixture. Under similar conditions potassium lactate led to 2-(3'-indolyl)propionic acid in 80% yield, and potassium 2-hydroxy-3-ethylpentanoate the expected 2-(3'-indolyl)-3-ethylpentanoic acid in 10% yield. From the pentanoate there was also formed considerable amounts of 1-(3'-indolyl)-2-ethylbutane, the structure of which was established by synthesis from indole and 2-ethylbutanol. 2-Hydroxy-3-methylpropionic acid, as anticipated from mechanistic considerations (see below), failed to yield any of the corresponding indole derivative.



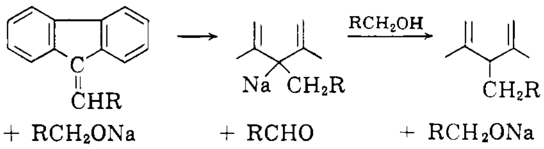
R = H, CH_3, $CH(C_2H_5)_2$

2-Methyl-, 2,5-dimethyl-, and 2,7-dimethylindole also reacted with potassium glycolate to yield the corresponding acetic acids (Table I). Only relatively small amounts of these starting indoles were available thus limiting the efficiency of agitation and resulting in low yields of the desired products. This difficulty was partially solved by the addition of sufficient water to the reaction vessel to allow proper mixing. However, control experiments with indole and potassium glycolate indicate that this procedure can, in itself, be detrimental to the yield of indole acid formed. 1,2-Dimethylindole, when treated with potassium glycolate, failed to give any of the 3-acetic acid; the 1,2-dimethylindole was recovered unchanged.

The formation of indoleacetic acids by the present method is only partially explained by either (A) the mechanism of Pratt and Botimer[1] for the 3-alkylation of indole or (B) that of Shoen and Becker[4] for the 9-alkylation of fluorene. The essential features of both mechanisms involve an initial oxidation of a small amount of the alcohol to an aldehyde or ketone which condenses at the nucleophilic site with loss of water to give an indolenine or fulvene intermediate. These intermediates are reduced by the alcohol or alkoxide



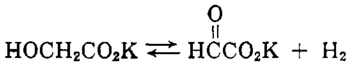
(A)



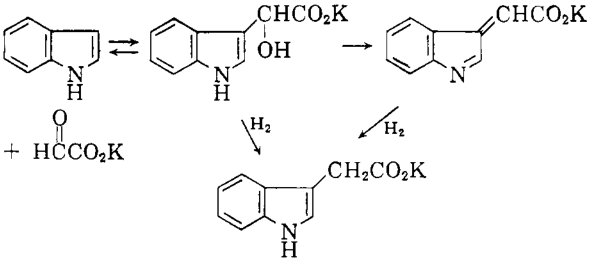
(B)

present, thereby regenerating the carbonyl function and producing product.

In order for the condensation of glycolic acid with indole to take place, it seems reasonable that the glycolate salt must be dehydrogenated to a glyoxalate intermediate. Reaction of this aldehyde with indole gives indolegycolic acid[5] which undergoes hydrogenolysis directly to product or dehydrates to an indolenine which is subsequently reduced.



$$HOCH_2CO_2K \rightleftharpoons H\overset{\overset{O}{\|}}{C}CO_2K + H_2$$



During the reaction at 250° the atmosphere of the reactor is abundant in hydrogen, and, if this hydrogen is released, the yield of indoleacetic acid is proportionately lowered. Also, the reaction cannot be successfully performed in an open system since at about 250° an exothermic reaction takes place with gas evolution and marked loss of product. These observations indicate that the reduction of indolenine or glycolate intermediates is a discrete step and is not affected by any direct interaction with potassium glycolate as in the previously described mechanisms.[1,4] Alternatively,

---

(4) K. L. Shoen and E. I. Becker, *J. Am. Chem. Soc.*, **77**, 6030 (1955).

(5) J. B. Greenberg, A. W. Galston, K. N. F. Shaw, and M. D. Armstrong, *Science*, **125**, 992 (1957).

(6) E. Fischer, *Ann.*, **236**, 149 (1886).

(7) F. Kögl and D. G. F. R. Kostermans, *Z. physiol. chem.*, **235**, 201 (1935).

(8) M. W. Bullock and J. J. Hand, *J. Am. Chem. Soc.*, **78**, 5852 (1956).

(9) H. Erdtmann and A. Jönsson, *Acta Chem. Scand.*, **8**, 119 (1954).

it is possible that dehydrogenation of glycolate occurs much more readily than does the reduction of the intermediates *via* reaction with glycolate. However, since the reaction is conducted in stainless steel equipment, it is likely that the metal surface catalyzes the reaction of hydrogen with the indolenine or indole glycolate. Conditions employing lower reaction temperatures (100–150°) in the presence of added Raney nickel, however, were ineffective in producing indoleacetic acid, although traces detectable by paper chromatography were formed at temperatures as low as 100°.

The fact that 1,2-dimethylindole is unreactive towards potassium glycolate and is recovered unchanged under the present reaction conditions is of interest. With this isomer, an indolenine cannot form and it is attractive to suggest that the reaction must proceed through reduction of this intermediate as opposed to hydrogenolysis of an indoleglycolate. However, the 1-substituent may, more simply, prevent the formation of an indole anion thus precluding the initial condensation of glyoxalate. This inertness does establish in the present case and in examples of other 3-alkylations[1–3] that the reaction does not involve 1-alkylation as part of the reaction sequence.

Experimental[10]

3-Indoleacetic Acid.—A 3-l. stainless steel rocker autoclave was charged with 270 g. (4.1 moles) of 85% potassium hydroxide and 351 g. (3.0 moles) of indole followed by the gradual addition of 360 g. (3.3 moles) of 70% aqueous glycolic acid. The mixture was then heated at 250° under autogenous pressure for 14–22 hr., cooled to 90°, and 1 l. of water added to dissolve the crude potassium indoleacetate. Additional water was added to give a total volume of 3 l. and the solution extracted with ether to remove any neutral material present. The aqueous phase was acidified with concd. hydrochloric acid keeping the temperature 20–30° and finally cooling to 10°. The precipitated product was collected, washed with copious amounts of cold water, and dried. A 90% yield (475 g.) of light cream product was obtained, m.p. 163–165° dec. Crystallization of a sample from water (Darco) gave nearly colorless needles, m.p. 164–166° dec.; reported,[11] m.p. 165°.

Indoleacetamide was prepared *via* the acid chloride by the method of Shaw and Woolley[12] and obtained as colorless needles after crystallization from water, m.p. 149–150°; reported[13] m.p. 150–151°.

Methylated Indoleacetic Acids. General Procedure.—For these preparations (Table I), 75- and 300-ml. stainless steel autoclaves were used in a Magne-Dash apparatus.[14] The reactions were conducted as described for the preparation of indoleacetic acid, except that, in cases where the quantity of starting indole was limited (5–10 g.), water was added in a quantity sufficient to give a level above the dash mechanism. Some of the indole always sublimed into the dash mechanism thereby resulting in decreased yields.

Reaction of Indole with Potassium 2-Hydroxy-3-ethylpentanoate.—In the manner described for the preparation of indoleacetic acid, 100 g. (0.85 mole) of indole, 75 g. (1.14 moles) of 85% potassium hydroxide, and 146 g. (1.0 mole) of 2-hydroxy-3-ethylpentanoic acid[15] were heated at 260° for 20 hr. The crude reaction mixture contained a considerable quantity of a neutral oil which was removed by extraction with ether. Acidification of the aqueous phase gave 22 g. (9.5%) of a red sticky solid. Several crystallizations from cyclohexane afforded pure (2-3′-indolyl)-3-ethylpentanoic acid as slightly reddish needles, m.p. 131–133°.

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.68; H, 7.59; N, 5.77.

Distillation of the ether extracts afforded 20 g. (20%) of indole, b.p. 118° (1.0 mm.), and 60 g. of a fraction, b.p. 136–150° (1.0 mm.), $n^{30}\mathrm{D}$ 1.5563–1.5570. Redistillation afforded 36 g. of nearly colorless 1-(3′-indolyl)-2-ethylbutane; a center fraction boiled at 124° (0.12 mm.), $n^{30}\mathrm{D}$ 1.5553. The infrared spectrum of this material was identical to the spectrum of an authentic sample as prepared below.

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.83; H, 9.33; N, 6.79.

1-(3′-Indolyl)-2-ethylbutane.—A mixture of 60 g. (0.51 mole) of indole, 20 g. of 85% potassium hydroxide, and 500 ml. of 2-ethylbutanol was charged to a 3-l. stainless steel rocking autoclave and heated at 260° for 21 hr. The reactor was cooled and the contents washed out with ether. After washing the ether solution several times with water, it was distilled yielding 89 g. (87%) of product, b.p. 132–136° (0.6 mm.), $n^{30}\mathrm{D}$ 1.5513. A sample was redistilled, b.p. 161° (3.0 mm.), $n^{30}\mathrm{D}$ 1.5525, for examination of its infrared spectrum.

Acknowledgment.—The authors are grateful to C. R. McClure for capable assistance and to Q. Quick and his associates for microanalyses and spectral data.

---

[10] Melting points are corrected and boiling points are uncorrected. Infrared spectra were recorded by a Perkin-Elmer, Model 21, spectrophotometer.

[11] A. Ellinger, *Ber.*, **37**, 1801 (1904).

[12] E. Shaw and D. W. Woolley, *J. Biol. Chem.*, **203**, 979 (1953).

[13] R. Majima and T. Hoshino, *Ber.*, **58**, 2046 (1925).

[14] Autoclave Engineers, Erie, Pa.

[15] Geneoursly supplied by R. W. Kiefer of this laboratory.

Cotton Effects of α,β-Unsaturated Carboxylic Acids[1]

ULRICH WEISS AND HERMAN ZIFFER

National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U. S. Public Health Service, Department of Health, Education and Welfare, Bethesda, Maryland

Received December 26, 1962

Several α,β-unsaturated carboxylic acids show anomalous rotatory dispersion and circular dichroism at relatively long wave lengths (~250–270 mμ). This finding necessitates the assumption that hitherto undetected very weak bands exist in the absorption spectra of these compounds; one such band is actually observed in the vapor spectrum of β,β-dimethylacrylic acid. Similar Cotton effects are also given by the sodium salt of one of the acids, and by several α,β-unsaturated lactones. In the case of shikimic acid (I), the expected circular dichroism is found, but the corresponding anomalous rotatory dispersion is completely obscured by background effects.

Recently, the study of rotatory dispersion, which has been applied so successfully to ketonic compounds,[2] has been extended increasingly to substances having other chromophores. As a contribution to this field, we wish here to call attention to Cotton effects occurring at unexpectedly long wave lengths in the rotatory dispersion curves of α,β-unsaturated carboxylic acids having asymmetric carbon atoms adjacent to the chromo-

---

[1] This paper is dedicated to the memory of our friend, Dr. Erich Mosettig.

[2] C. Djerassi, "Optical Rotatory Dispersion: Applications to Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1960.