3-Indolepropionic Acid. Some Reactions of Indole with Salts of Acrylic and Methacrylic Acids[1]

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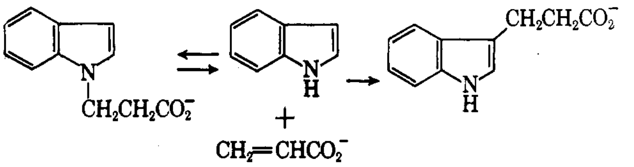
Indole and sodium acrylate react at 250° to give high yields of 3-indolepropionic acid. Methacrylate salts react similarly. The probable mechanism, origin of by-products, and limitations of this novel reaction are discussed.

The formation of 1-indolepropionic acid is reported[2,3] to proceed in high yield *via* the reaction of indole with sodium acrylate in aqueous solution at about 180°. Analogous to other reactions of amines with α,β-unsaturated esters and nitriles,[4] this reaction may be reversible. In contrast, 3-indolepropionate salts might be expected to be more stable. Therefore, by considering the 1-addition of sodium acrylate reversible and the 3-addition, if it occurs at all, irreversible reaction conditions should be possible to allow the formation of 3-indolepropionic acid from these reagents. This communication describes the syntheses of various 3-indolepropionic acid derivatives by the reaction of indole with salts of α,β-unsaturated acids at temperatures from 225–300°.



Experiments in which indole, potassium acrylate, and a catalytic quantity of potassium hydroxide were allowed to react at 250° for seventeen hours provided a 60% yield of 3-indolepropionic acid. Although an exhaustive study of the reaction conditions was not made, it was determined that reaction times from two to twenty-one hours were about equally effective in producing the desired product. The reaction temperature, wever, was more critical: at 225° mixtures (approxtely 1:1) of 1- and 3-indolepropionic acids were served and at 300° some degradation of the indole nucleus was noted.[5] Best results were obtained by performing the reaction in the presence of sodium hydroxide at 260° for about seventeen hours and employing indole–acrylic acid–sodium hydroxide in a ratio of 1:0.90:1.35. In this manner there was obtained a 69% yield (based on indole charged) of light tan 3-indolepropionic acid having a melting point less than 5° below that of pure material. As 21% of the starting indole could be recovered, a 90% efficiency based on this reactant was realized. A small amount (≤ 5%) of acidic impurities persist in the reaction product and most probably consist of acrylate polymers. These materials are difficultly removable by crystallization techniques; consequently, esterification followed by distillation was used to purify the reaction product. No β-(1-indolyl)propionate could be detected in the distillate.

Several variations in the reaction conditions produced results of interest. In particular, the reaction of indole, acrylic acid, and triethylamine at 260°, and in a mole ratio of 1:1:1.5, deserves mention. From this reaction was isolated, *inter alia*, N,N-diethylpropionamide (7%), 3-ethylindole (15%), **1,2,3,4-tetrahydrocarbazole** (5%), N,N-diethyl-β-(1-indolyl)propionamide (9%), N,N-diethyl-β-(3-indolyl)propionamide (8%), and considerable nonvolatile intractable residue. With the exception of the 1-propionamide, all of the reaction products were identified by comparison of a purified sample with authentic material. As this amide could not be obtained in a pure state its presence can only be inferred by comparison of the infrared spectrum of this fraction and the g.l.c. retention time of the major component to those of an authentic crystalline sample. Hydrolysis to β-(1-indolyl)propionic acid by prolonged heating with 40% aqueous potassium hydroxide was not successful; the 3-isomer behaved similarly.

A triethylacylammonium hydroxide may be an intermediate in the formation of 3-ethylindole and the diethylamides, as this base could be expected to decompose to an ethyl fragment (ethanol or ethylene) thus, producing the observed amides and 3-ethylindole. As indole and ethanol do not react at 250° in the presence of triethylamine, and indole and ethylene are unreactive in the presence of aqueous sodium hydroxide at temperatures to 250°, it is possible that the triethylacylammonium hydroxide catalyzes the reaction of indole and ethanol[6,7] as well as the acrylate additions.

The origin of 1,2,3,4-tetrahydrocarbazole remains obscure. However, methacrylic acid, when treated with indole and triethylamine under similar conditions, produced some 1-methyl-1,2,3,4-tetrahydrocarbazole, establishing that the presence of an acrylate is necessary for the formation of these carbazoles. The structure of this carbazole derivative was inferred by its n.m.r. spectrum and established by dehydrogenation to 1-methycarbazole.[8]

Large amounts of water added to the reaction mixture were found to be deleterious to the formation of 3-indolepropionic acid. Esterification of the crude acidic product, obtained as an oil, enabled the reaction products to be characterized as being predominantly 1-indolepropionic acid. Some 3,3-diindolylmethane was also formed and probably is derived from the base-catalyzed reaction of indole with formaldehyde.[9] Hy-

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[1] Paper III in a series of Reactions of Indole. Papers by H. E. Johnson and D. G. Crosby, *J. Org. Chem.*, **25**, 569 (1960), and **28**, 1246 (1963), to be considered I and II of this series.

[2] W. Reppe and H. Ufer, U. S. Patent 2,195,974.

[3] W. Reppe and H. Ufer, German Patent 698,273.

[4] H. A. Bruson, Organic Reactions, Vol. 5, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 79.

[5] R. Weissgerber and C. Seidler, *Ber.*, **60**, 2090 (1927).

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

[7] R. H. Cornforth and R. Robinson, *J. Chem. Soc.*, 680 (1942).

[8] F. Ullman, *Ann.*, **332**, 82 (1904).

[9] J. Thesing, S. Klussendorf, P. Ballach, and H. Meyer, *Chem. Ber.*, **88**, 1295 (1955).

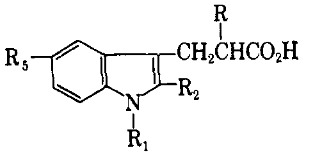
dration of acrylic acid followed by a reverse aldol condensation possibly accounts for the presence of formaldehyde.

It is worth noting that the reaction of methacrylate salts with indole at 300° produced appreciable amounts of 3-*n*-propylindole and *o*-toluidine,[5] in addition to considerable quantities of the 3-acid derivative. At 280°, crotonate salts yielded some 3-ethylindole. Although no β-(3-indolyl)butyric acid was ever observed among the reaction products, at 250° some β-(1-indolyl)butyric acid could be isolated (*via* esterification of the crude acidic product).

The use of 2-methyl- and 2,5-dimethylindole produced the corresponding 3-propionic acids in 30 and 48% yields, respectively. 1,2-Dimethylindole, under the present conditions, was not reactive, presumably due to its inability to form a reactive anion. As expected, methacrylate salts and indole reacted to give α-methyl-β-(3-indolyl)propionic acid in 60–70% yield. The structure of this acid was substantiated by its identity to an acid prepared by the reaction of indole with methacrylic acid in the presence of acetic anhydride.[10] Crotonic, itaconic, maleic, and fumaric acids did not react noticeably with the 3-position of indole, employing the present reaction conditions. The indole acids prepared by this method are shown in Table I.

TABLE I

INDOLEPROPIONIC ACIDS



R	R1	R2	R5	Yield, %	M.p.; °C.	Other
H	H	H	H	70	134–136	Reported[a] m.p. 135–136°
CH_3	H	H	H	60	129–130	See Experimental
H	H	CH_3	H	30	135–136	Reported[b] m.p. 137–138°
H	H	CH_3	CH_3	48	169–170	*Anal.* Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.82; H, 7.17; N, 6.38.
H	CH_3	CH_3	H	No reaction		

[a] See ref. 11. [b] See ref. 12.

Experimental

Melting points are corrected and boiling points are uncorrected. Infrared spectra were recorded by a Perkin-Elmer Model 21 spectrophotometer, ultraviolet spectra by a Cary Model 21 spectrophotometer, and nuclear magnetic resonance spectra by a Varian Associates Model A-60 spectrometer. G.l.c. analyses were performed at 200–250° with a 5-ft. column containing Apiezon-L supported on Fluoropak.

3-Indolepropionic Acid.—To a 3-l. stainless steel rocker autoclave was added 234 g. (2.0 moles) of indole, 144 g. (2.0 moles) of acrylic acid, and 180 g. (2.7 moles) of 85% potassium hydroxide. The reaction mixture was heated under autogenous pressure with rocking at 275° for 20 hr. and then cooled to about 100°. Eight hundred milliliters of water was added to dissolve the reaction product and, after cooling the mixture further, it was extracted with ether to remove unchanged indole and other neutral materials. Acidification of the aqueous phase followed by filtration and drying afforded 229 g. (61%) of light tan 3-indolepropionic acid, m.p. 121–125°. Repeated crystallization of a sample from water raised the m.p. to 134–136° (lit.[11] m.p. 135–136°), undepressed when mixed with an authentic sample. The nature of the acidic impurity in the crude reaction product is unknown and is difficultly removable by crystallization. A more satisfactory method for the purification of the crude reaction product consists of the preparation of the ethyl ester followed by fractional distillation and saponification, as described later for ethyl α-methyl-β-(3-indolyl)propionate.

In another experiment using 234 g. (2.0 moles) of indole, 130 g. (1.8 moles) of acrylic acid, and 108 g. (2.7 moles) of sodium hydroxide, 260 g. (76% based on acrylic acid, 69% based on indole) of very light tan 3-indolepropionic acid was obtained, m.p. 127–131°. Distillation of the neutral material recovered from the reaction mixture afforded 49 g. (21%) of indole. Increasing the amount of acrylic acid in the reaction mixture led to higher yields of reaction products; the quality, however, was poorer.

α-Methyl-β-(3-indolyl)propionic Acid. (a) By the Reaction of Indole with Potassium Methacrylate.—In the manner described before for preparation of 3-indolepropionic acid, 234 g. (2.0 moles) of indole, 172 g. (2.0 moles) of methacrylic acid, and 180 g. (2.7 moles) of 85% potassium hydroxide reacted at 280° for 19 hr. to give 244 g. (60%) of light brown product, m.p. 109–119°. Several crystallizations from water afforded an analytical sample as short off-white needles, m.p. 127–129°.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.88; H, 6.38; N, 6.80.

From a similar experiment in which the reaction temperature was 300°, 250 g. (61%) of dark brown acid was obtained, m.p. 112–117°, and 101 g. of neutral material, b.p. 76–130° (3.0 mm.). Fractional distillation of this product afforded 6 g. of pure *o*-toluidine, b.p. 61° (3.0 mm.), $n^{30}D$ 1.5675; 58 g. (25%) of indole; and 10 g. of 3-(*n*-propyl)indole, b.p. 116° (1.25 mm.), $n^{30}D$ 1.5762, m.p. 26–27° (lit.[13] m.p. 29° and as an oil[7]). The infrared spectra of the toluidine and propylindole were identical in detail to the respective spectra of authentic samples and a mixture melting point of the two indole samples was undepressed.

(b) By the Reaction of Indole with Methacrylic Acid in the Presence of Acetic Anhydride and Sodium Acetate.[10]—A mixture of 240 g. (2.04 moles) of indole, 344 g. (4.0 moles) of methacrylic acid, 816 g. (8.0 moles) of acetic anhydride, 128 g. (1.56 moles) of sodium acetate, and 960 ml. of acetic acid was heated under reflux for 5 hr. All volatile material was removed quickly *in vacuo* and the remaining 853 g. of residue added to 360 g. of sodium hydroxide in 1.2 l. of water. Considerable nonacidic oil was present and was removed by extraction with ether. The aqueous phase was acidified with concentrated hydrochloric acid to give, after collection by filtering and drying, 129 g. (31%) of dark brown product, m.p. 118–125°. Crystallization from water raised the m.p. to 129–130°, which was undepressed when mixed with the acid as prepared in method a.

Ethyl α-Methyl-β-(3-indolyl)propionate.—A solution of 519 g. (2.54 moles) of α-methyl-β-(3-indolyl)propionic acid in 2 l. of ethanol containing 25 g. of *p*-toluenesulfonic acid monohydrate was prepared and heated under reflux for a total of 18 hr. The ethanol was removed by distillation under reduced pressure and the remaining residue dissolved in 1 l. of ether. After washing the ether solution successively with 5% sodium hydroxide solution and water, the ether was evaporated and the residue distilled. A total of 471 g. (80%) of slightly yellow distillate was obtained, b.p. 182–185° (1.5 mm.), $n^{30}D$ 1.5492. A portion was redistilled and analyzed, b.p. 165° (0.75 mm.), $n^{30}D$ 1.5504.

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.47; H, 7.41; N, 5.99.

The Reaction of Indole with Sodium Crotonate.—As described for the preparation of 3-indolepropionic acid, 234 g. (2.0 moles) of indole, 155 g. (1.8 moles) of crotonic acid, and 80 g. (2.0 moles) of sodium hydroxide were heated at 250° for 21 hr. Acidification of the crude reaction mixture produced a thick oil that would not solidify. Ether extraction followed by evaporation led to 144 g. of acidic product which was esterified by treatment with ethanol and *p*-toluenesulfonic acid. From this reaction was obtained 66 g. of product, b.p. 123–160° (2.0 mm.). Fractional distillation provided 35 g. of colorless ester, b.p. 167° (4.0 mm.), $n^{30}D$ 1.5452. The analytical data, lack of an NH absorption at about 3 μ, and boiling point are consistent with ethyl β-(1-indolyl)butyrate.

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.55; H, 7.51; N, 6.22.

The Reaction of Indole with Acrylic Acid in the Presence of Triethylamine.—A mixture of 234 g. (2.0 moles) of indole, 144 g.

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(10) H. E. Johnson and D. G. Crosby, *J. Org. Chem.*, **25**, 569 (1960).

(11) A. Ellinger, *Ber.*, **38**, 2884 (1905).

(12) J. Harley-Mason, *J. Chem. Soc.*, 2433 (1952).

(13) G. F. Smith and A. E. Waters, *ibid.*, 940 (1961).

(2.0 moles) of acrylic acid, and 303 g. (3.0 moles) of triethylamine was prepared and heated, with agitation, at 260° in a 3-l. stainless steel autoclave. After 21 hr. the reaction mixture was cooled, diluted with 1 l. of water, and extracted with ether. Acidification of the aqueous phase provided only a trace of acidic material, which was not investigated further. Distillation of the ether extracts gave 227 g. of a mixture of reaction products, b.p. to 243° (1.0 mm.), and 140 g. of nonvolatile intractable residue. Fractional distillation of the volatile reaction products using a 3-ft. spinning band column produced the following major fractions: (A) 28 g., b.p. to 82° (1.0 mm.); (B) 46 g., b.p. 82–88° (1.0 mm.); (C) 30 g., b.p. 88–112° (1.0 mm.); (D) 11 g., b.p. 145–147° (1.0 mm.); (E) 44 g., b.p. 180–183° (1.0 mm.); (F) 37 g., b.p. 220–229° (1.0 mm.); and (G) 34 g. residue and mid-fractions.

Fraction A consisted of a multitude of products of which indole was found in minor amounts. No indoline was present. Further fractionation of this mixture afforded a pure sample of N,N-diethylpropionamide, b.p. 46° (1.85 mm.). Its infrared spectrum was found to be identical to the spectrum of an authentic sample, b.p. 62° (2.0 mm.), $n^{30}\mathrm{D}$ 1.4351.

Fraction B was redistilled and identified as being predominantly indole from its g.l.c. retention time and physical constants, b.p. 82° (1.0 mm.) and m.p. 51–52°. Approximately 10% of a mixture of lower boiling materials also was present.

Fraction C contained 7.5% of lower boiling unidentified material, 17% of indole, 0.5% of skatole (by retention time only), and 75% of 3-ethylindole. Additional fractionation afforded pure 3-ethylindole as a colorless solid, m.p. 36–37°, undepressed when mixed with an authentic sample (lit.[7] m.p. 37°).

Fraction D solidified and was purified further by repeated crystallizations from hexane, m.p. 117–118°. Elemental analysis suggested a $C_{12}H_{13}N$ formula; infrared, ultraviolet, and n.m.r. spectra indicated the material to be 1,2,3,4-tetrahydrocarbazole. A mixture melting point with an authentic sample[14] of m.p. 118–119° was undepressed.

Fraction E was redistilled and a constant-boiling fraction was collected at 164° (0.06 mm.). G.l.c. indicated a purity of 82%; the material could not be induced to solidify. Further purification by chromatography on alumina resulted in an oily fraction, about 90% pure, which still would not crystallize, even when seeded with N,N-diethyl-β-(1-indolyl)propionamide (see col. 2). The retention time (63 min.) of this material was found to be the same as that of pure N,N-diethyl-β-(1-indolyl)propionamide and, with the exception of minor OH (2.90 μ), NH (3.02), and C═O (5.78) absorptions, the infrared spectra of these two materials were very similar.

Fraction F slowly solidified and an analytical sample was obtained as colorless microcrystals, m.p. 114–116°, after several crystallizations from isopropyl ether followed by toluene. A mixture melting point with authentic N,N-diethyl-β-(3-indolyl)-propionamide (see col. 2) was undepressed, and the infrared spectra of the two were found to be identical in detail.

Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 73.73; H, 8.25; N, 11.47. Found: C, 73.67; H, 8.40; N, 11.29.

Integration of the g.l.c. peak areas of all fractions and mid-fractions provided the following approximate yields of the reaction products: 7% N,N-diethylpropionamide; 7% indole; 15% 3-ethylindole; 5% 1,2,3,4-tetrahydrocarbazole; 9% N,N-diethyl-β-(1-indolyl)propionamide; and 8% N,N-diethyl-β-(3-indolyl)-propionamide.

The Reaction of Indole with Methacrylic Acid in the Presence of Triethylamine. Isolation of 1-Methyl-1,2,3,4-tetrahydrocarbazole.—*In the manner described for the reaction of indole with* acrylic acid and triethylamine, 234 g. (2.0 moles) of indole, 172 g. (2.0 moles) of methacylic acid, and 303 g. (3.0 moles) of triethylamine reacted to give 292 g. of distilled products, b.p. to 250° (0.75 mm.), and 79 g. of nonvolatile residue. Further fractionationation produced 138 g. of a mixture containing indole (34%) and 3-ethylindole (66%), b.p. to 104° (0.75 mm.), and 20 g. (5%) of 1-methyl-1,2,3,4-tetrahydrocarbazole, b.p. 128–131° (0.5 mm.), $n^{30}\mathrm{D}$ 1.6007. The sample slowly solidified but defied recrystallization (lit.[15] m.p. 65°), $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (ε), 278 (shoulder), 283 (7050), 292 (5850). Signals in the nuclear magnetic resonance spectrum were observed at 1.1 p.p.m. (doublet, methyl group), 1.75 p.p.m. (multiplet, 2,3-methylene groups), and 2.66 p.p.m. (multiplet, methine and 4-methylene group) in a ratio of 3:4:3. Resonance due to the 5,6,7,8, and N protons occurred at 7.0–7.5 p.p.m.

Anal. Calcd. for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.42; H, 8.49; N, 7.43.

Dehydrogenation of 1-Methyl-1,2,3,4-tetrahydrocarbazole.—A 1.02-g. sample of the tetrahydrocarbazole from the reaction of indole, methyacrylic acid, and triethylamine and 0.10 g. of 5% palladium on carbon were mixed and heated to 300° until the evolution of hydrogen ceased. The cooled mixture was slurried with hot ethanol and filtered to remove the catalyst. Evaporation of the filtrate and crystallization of the residue from hexane afforded 0.72 g. of colorless plates, m.p. 117–118°. Further crystallization from the same solvent raised the m.p. to 120–121° (lit.[8] m.p. 120.5°).

N,N-Diethyl-β-(1-indolyl)propionamide.—Following the procedure of Shaw and Wooley,[16] 20 g. (0.1 mole) of 1-indolepropionic acid[3] and 23 g. (0.1 mole) of phosphorus pentachloride were mixed in 200 ml. of dry ether. After 30 min. at 0° and 30 min. at 25°, the mixture was poured over 100 g. of diethylamine and ice. The ether was evaporated in a stream of nitrogen to leave 22 g. (90%) of light brown solids, m.p. 40–44°. Several crystallizations from hexane (Dry Ice–acetone cooling) provided an analytical sample as colorless microcrystals, m.p. 42–44°.

Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 73.73; H, 8.25; N, 11.47. Found: C, 74.00; H, 8.32; N, 11.51.

N,N-Diethyl-β-(3-indolyl)propionamide.—This amide was prepared[17] in 95% yield by the procedure described for the synthesis of the 1-isomer. Several crystallizations from ethyl acetate gave a sample, m.p. 115–117°, identical in all respects to the material isolated from the reaction of indole, acrylic acid, and triethylamine.

Ethyl 1-Indolepropionate.—A solution of 115 g. (0.61 mole) of 1-indolepropionic acid,[3] 20 g. of *p*-toluenesulfonic acid monohydrate, and 1500 ml. of ethanol was refluxed for 17 hr. The ester (115 g., 88%) was isolated in the usual manner as a colorless liquid, b.p. 132–134° (0.75 mm.), $n^{30}\mathrm{D}$ 1.5565.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 72.06; H, 7.20; N, 6.74.

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[17] By J. A. Durden of this laboratory.