

poured onto cracked ice, 30 ml. of water was added, and the mixture was extracted twice with 50-ml. portions of ether. The combined extract was washed successively with water, 10% potassium carbonate (20 ml.), and water. After drying over sodium sulfate and evaporation of the ether the residue was dissolved in 8 ml. of ethanol and treated with 2,4-dinitrophenylhydrazine. Recrystallization of the precipitate from glacial acetic acid gave orange needles, m.p. 239–240° (recorded¹⁰ m.p. 238–239°). A mixed melting point with an authentic specimen of benzophenone 2,4-dinitrophenylhydrazone showed no depression. The infrared spectra of the two samples (chloroform solution) were totally superimposable.

Biological results. In tests with house flies, the ethanes

(10) E. H. Huntress and S. P. Mulliken, *Identification of Pure Organic Compounds*, Order I, John Wiley and Sons, Inc., New York, 1941, p. 363.

carrying *p*-chloro- and *p*-bromo-substituents were the most active insecticides of the entire series of compounds; the corresponding ethanols were somewhat less active. None of the acetates and ethenes displayed significant insecticidal activity.

On the other hand, the *p*-chloro- and *p*-bromo-substituted ethanes, ethanols, and acetates proved to be excellent synergists for DDT in tests with DDT-resistant house flies. The synergistic activity of these compounds surpassed that of 1,1-bis(*p*-chlorophenyl)ethanol (DMC), one of the most effective DDT synergists.¹¹ The ethenes were less effective. A detailed report of this study will be published elsewhere.

NATICK, MASS.

(11) R. L. Metcalf, *Organic Insecticides, Their Chemistry and Mode of Action*, Interscience Publishers, Inc., New York, 1955, p. 368.

[CONTRIBUTION FROM THE CENTRAL RESEARCH DEPARTMENT, RESEARCH AND ENGINEERING DIVISION, MONSANTO CHEMICAL COMPANY]

Cupric Acetate Catalyzed Monocyanoethylation of Aromatic Amines

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Cupric acetate monohydrate has been shown to be a highly effective new catalyst for the monocyanoethylation of a variety of aromatic amines. Unlike other cyanoethylation catalysts, its action is not appreciably inhibited by the presence of *ortho*- or *N*-substituents on the amines to be cyanoethylated. Also, its use leads to improved yields and shorter reaction times than obtained with conventional catalysts.

Cyanoethylation of 17 aromatic amines with cupric acetate catalyst is reported, and some observations are made on the relative influence of steric and electronic effects of the substituent groups upon the mechanism of the reaction, the reaction conditions required, and yields and nature of the products obtained.

The reaction of acrylonitrile with compounds containing active hydrogen atoms has been widely investigated.^{1,2} While primary and secondary aliphatic amines react readily with acrylonitrile in the absence of catalysts to give high yields of 3-aminopropionitriles, some heterocyclic amines (carbazole, indole, pyrrole) react only in the presence of basic catalysts.¹ Aniline, however, does not react with acrylonitrile in the absence of catalysts,³ and early investigators reported that aniline does not undergo cyanoethylation even in the presence of basic catalysts.^{3,4} The cyanoethylation of a variety of aromatic amines is reported, however, to proceed readily with acid catalysts, particularly acetic acid.^{4,5,6} It has also been shown that copper salts, particularly cuprous chloride, have a beneficial

effect when employed in conjunction with acetic acid.^{6,7,8} Also reported is cyanoethylation of aromatic amines in the presence of acetic anhydride,⁹ aniline salts,¹⁰ and by the exchange reaction of an aromatic amine hydrochloride with 3-diethylaminopropionitrile.¹¹

This last reaction has been considered to occur *via* an S_N2 reaction involving attack of the arylamino nitrogen upon the β-carbon of the cyanoethyl group rather than an S_N1 elimination-addition reaction.^{11c}

Pietra¹² has recently disclosed that good yields

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(8) (a) British Patent 404,744, to I. G. Farbenindustrie, (1933). (b) British Patent 457,621, to I. G. Farbenindustrie, (1936).

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(1) H. A. Bruson, *Org. Reactions*, **V**, 79 (1949).

(2) American Cyanamid Company, *The Chemistry of Acrylonitrile*, Beacon Press, Inc., New York, 1951.

(3) F. C. Whitmore, H. S. Mosher, R. R. Adams, R. B. Taylor, E. C. Chapin, C. Weisel, and W. Yanko, *J. Am. Chem. Soc.*, **66**, 725 (1944).

(4) R. C. Cookson and F. G. Mann, *J. Chem. Soc.*, 67 (1949).

(5) R. C. Elderfield, *et al.*, *J. Am. Chem. Soc.*, **68**, 1259 (1946).

(6) (a) J. T. Brauholtz and F. G. Mann, *J. Chem. Soc.*, 3046 (1952). (b) J. T. Brauholtz and F. G. Mann, *J. Chem. Soc.*, 1817 (1953). (c) J. T. Brauholtz and F. G. Mann, *J. Chem. Soc.*, 651 (1954).

of arylaminopropionitriles can be obtained by the base(choline)-catalyzed reaction of acrylonitrile and certain substituted aromatic amines. This is the first report of a base-catalyzed cyanoethylation of an aromatic amine, and is particularly interesting in light of the amines employed, the majority of which are substituted with electronegative groups (NO_2 , Cl) and have not been reported to undergo acid-catalyzed cyanoethylations.

During preparation of a series of arylaminopropionitriles in these laboratories, most of the previously mentioned acidic catalysts were ineffective in producing consistently good yields of monocyanoethylated aromatic amines. Two major problems were observed. First, the acetic acid catalyst was not sufficiently active to produce acceptable yields of cyanoethylated derivatives from sterically hindered (*ortho*-substituted) or deactivated (negatively-substituted) aromatic amines even when employed in large excess and at high temperatures for long periods of time.^{6a} This difficulty is shared by the Cymerman-Craig exchange reaction between an aniline hydrochloride and diethylaminopropionitrile.^{11d} Second, while the addition of cuprous chloride to acetic acid considerably enhanced its catalytic activity, it frequently produced undesired mixtures of mono- and dicyanoethylated derivatives, even when the acrylonitrile was not employed in excess. Thus, the need for a catalyst capable of giving consistently good yields of monocyanoethylated product from all types of substituted aromatic amines remained.

It was observed in these laboratories that addition of sodium acetate to the acetic acid-cuprous chloride mixture caused an improvement in yield over that obtained by either acetic acid or the acetic acid-cuprous chloride catalyst. This was particularly apparent in the case of the less reactive aromatic amines and may be illustrated by two experiments with *o*-chloroaniline in a bomb at 150° for 12 hr.: With acetic acid (7.1%) plus cuprous chloride (0.4%) catalyst, a 14% yield of 3-(*o*-chloroanilino)propionitrile resulted, while with a catalyst containing acetic acid (7.1%), cuprous chloride (0.4%), and sodium acetate (2.0%) the yield of propionitrile was 39%.

It was also found that replacement of the acetic acid/cuprous chloride/sodium acetate system by cupric acetate monohydrate provided still further improvements, and that this salt was, in fact, a highly effective catalyst of general utility for monocyanoethylation of a wide variety of aromatic amines. The cupric acetate employed throughout this work was in the form of the monohydrate, a readily available commercial product. It was demonstrated, however, that anhydrous cupric acetate was identical with the monohydrate in catalytic activity. As the utility of copper salts in the cyanoethylation of aromatic amines had previously been mentioned,^{1,6,7,8} it was of interest to determine whether other copper salts would serve as cyano-

ethylation catalysts in the absence of acetic acid.¹³ The catalytic activity of several salts in the cyanoethylation of aniline (at 100° for 1.5 hr.) was compared, using 0.025 mole of catalyst per mole of aniline. Cupric acetate monohydrate gave a 73% yield of 3-anilinopropionitrile, cuprous chloride gave 52%, while cupric sulfate, copper powder, cupric oxalate, cupric borate, and acetic acid alone were completely ineffective at this concentration. Sodium acetate, effective in improving yields when added to acetic acid-cuprous chloride mixtures, had no catalytic activity when used alone, nor did polyphosphoric acid or stannic chloride. It is thus apparent that cupric acetate possesses a high order of catalytic activity, shared only by cuprous chloride among the copper salts tested, and then to a lesser degree. A combination of 0.025 mole each of cuprous chloride and acetic acid gave a slightly improved (61%) yield of the monopropionitrile.

Summarized in Table I are the results obtained from cyanoethylation of 17 anilines of various structures with from 2 to 5% (by weight of the amine) of cupric acetate as catalyst.

Several major advantages are obtained from the use of cupric acetate as a cyanoethylation catalyst for aromatic amines. Foremost is the observed activity of the catalyst with both sterically hindered and certain negatively-substituted anilines. Thus *ortho* substituents on the aromatic nucleus do not reduce the activity of this catalyst as they do with other methods of carrying out the cyanoethylation of aromatic amines. This is shown by the results obtained with three isomeric chloroanilines and *ortho* and *meta*-toluidine (Table I). Steric interference by a bulky substituent attached to the amino nitrogen appears to be of only minor importance since *N-n*-butylaniline gave a 68% yield of the cyanoethylated derivative with cupric acetate catalyst. Ready cyanoethylation of the chloroanilines, *p*-bromoaniline and *m*-nitroaniline in good yields with cupric acetate demonstrates the ability of the catalyst to promote cyanoethylation of even some negatively-substituted anilines, although the *ortho* and *para*-nitroanilines failed to react to any appreciable extent.

A further advantage of this new catalyst is its ability to promote monocyanoethylation as the primary and in most instances, exclusive reaction. It was shown, however, that under vigorous conditions (excess acrylonitrile, 10% cupric acetate and 12 hr. at reflux) dicyanoethylation of aniline did occur to the extent of 32%. Thus, while cupric acetate is not a selective catalyst for monocyanoethylation, under ordinary reaction conditions employing equimolar quantities of acrylonitrile and

(13) The reported value of copper salts in promoting cyanoethylation of aromatic amines has, with the possible exception of cuprous chloride, always been in conjunction with acetic acid.^{1,6,7,8} Their mode of action was originally ascribed to functioning as polymerization inhibitors,^{1,8} a claim not supported by our work.

TABLE I
 CYANOETHYLATION OF AROMATIC AMINES WITH CUPRIC ACETATE CATALYST

Amine	Catalyst, %	Time, hr.	Yield, ^a %	B.P., °C./mm.	n_D^{25}	M.P., ^b °C.
Aniline	2.0	1.0	73	114-116/0.3	1.5632	52-53 ^c
<i>o</i> -Chloroaniline	3.9	3.0	62	139-141/0.3 ^d	1.5734	—
<i>m</i> -Chloroaniline	5.0	2.0	65	146-149/0.3	1.5785	48-49 ^e
<i>p</i> -Chloroaniline	5.0	1.25	78	168-169/1.0	—	73.5-75 ^f
<i>p</i> -Bromoaniline	5.0	1.0	96	—	—	96.5-97.5 ^g
<i>o</i> -Toluidine	4.9	1.5	62	139-140/1.0 ^h	1.5590	—
<i>m</i> -Toluidine	4.7	0.33	71	143-146/0.5	—	49.5-50.5 ⁱ
Amylaniline ^j	3.1	3.0	66	172-180/0.8	1.5332	—
Dodecylaniline ^k	3.4	3.0	64	197-202/0.3	1.5167	—
<i>o</i> -Nitroaniline	7.2	12.0	—	—	—	—
<i>m</i> -Nitroaniline	5.0	12.0	81	—	—	95-96 ^l
<i>p</i> -Nitroaniline	5.0	6.0	—	—	—	—
	10.0	12.0	<10	—	—	121-123 ^m
<i>N</i> - <i>n</i> -Butylaniline	3.4	5.0	68	145-148/0.7 ⁿ	1.5360	—
α -Naphthylamine	3.5	5.5	89	180-210/0.5	—	69-70 ^o
Benzidine	5.0	4.0	93 ^p	—	—	—
4,4'-Methylenedianiline	5.0	3.0	96	—	—	115-117 ^q
<i>o</i> -Phenylenediamine	4.6	14.0	63	—	—	115-118 ^r
<i>m</i> -Phenylenediamine	5.0	0.67	95 ^s	—	—	—

^a Runs at 100° or reflux. Yield of monocyanoethyl derivative based on distilled liquids or crude, nondistillable products.

^b Uncorrected. ^c Reported m.p. 51.5°. ^d Calcd. for C₉H₉ClN₂: C, 59.9; H, 5.0; N, 15.5. Found: C, 60.1; H, 4.9; N, 15.5. ^e Reported m.p. 48°. ^f Reported m.p. 74.5-75.5°. ^g Calcd. for C₉H₉BrN₂: C, 48.0; H, 4.0; N, 12.5. Found: C, 48.1; H, 4.2; N, 12.3. ^h Reported b.p. 120-121°/0.7 mm., n_D^{25} 1.5530. ⁱ Reported m.p. 47.5-48.5°. ^j Commercial alkylaniline, average C₈. ^k Commercial alkylaniline, average C₁₂. ^l Reported m.p. 97.5°^{6c}, also reported m.p. 135.5°. ^m Crude. Reported m.p. 128-130°. ⁿ Calcd. for C₁₃H₁₃N₂: C, 77.2; H, 9.0; N, 13.9. Found: C, 77.4; H, 9.0; N, 13.5. ^o Reported m.p. 70-71°. ^p Crude. Reported m.p. 245-245.5°. ^q Calcd. for C₁₉H₂₀N₄: C, 75.0; H, 6.6; N, 18.4. Found: C, 74.6; H, 6.8; N, 18.4. ^r Reported m.p. 118.5-119°. ^s Crude product. Calcd. for C₁₂H₁₄N₄: C, 67.3; H, 6.6; N, 26.1. Found: C, 66.7; H, 6.5; N, 25.2.

the amine, dicyanoethyl derivatives are not formed. This contrasts with the action of cuprous chloride which appears to favor dicyanoethylation in the majority of cases.^{6b,7}

Finally, cupric acetate promotes rapid reactions, frequently observed to be exothermic, and in most cases produces higher yields of the monocyanoethylated products than have been previously reported. Formation of by-product acetanilide, sometimes reported to occur with acetic acid or acetic acid-cuprous chloride catalysts,^{6a,6b} has not been observed.

In addition to the cupric acetate catalyzed cyanoethylations of aromatic amines in Table I, a number of additional cyanoethylations using catalytic amounts of acetic acid as catalyst have been carried out and are summarized in Table II. In these cases, good yields were usually obtained by refluxing the reactants for from 12 to 24 hr. Included in this table are three isomeric hydroxyanilines whose reaction with acrylonitrile has not previously been reported. That cyanoethylation of the amino group occurs in preference to the hydroxy group in the presence of acidic catalysts was shown by spectroscopic examination of the propionitriles obtained. All showed marked cyano absorption at 2220-2260 cm.⁻¹ and phenolic hydroxyl at 1240-1280 cm.⁻¹ Confirming the phenolic hydroxyl, the ultraviolet spectrum of the product from cyanoethylation of *o*-hydroxyaniline (0.01% in ethanol) showed a characteristic maximum at

292 m μ . Addition of sodium hydroxide to the solution caused a shift in this maximum to 305 m μ , as expected if phenolic hydroxyl were present.

From our work and a review of the literature on the cyanoethylation of aromatic amines, certain conclusions may be drawn. Cyanoethylation of activated anilines (*e.g.* with electron-donating substituents) is readily accomplished with acid catalysts such as acetic acid. Sterically hindered anilines (those with *ortho* or *N*-substituents) react less readily and require catalysis with cuprous chloride-acetic acid mixtures, or, preferably, cupric acetate. Negatively substituted anilines, on the other hand, may require either acidic or basic catalysts, depending upon the location of the substituent groups. *meta*-Nitroaniline cyanoethylates readily with cupric acetate or other acidic catalysts,^{6b,6c} whereas *ortho* and *para*-nitroanilines react with acrylonitrile to a limited extent or not at all in the presence of acids. By the choline-catalyzed method of Pietra, this order of reactivity is reversed,¹⁴ suggesting that the basic strength of the aniline is the major factor determining whether acidic or basic

(14) A discrepancy in melting points for 3-(*m*-nitroanilino)propionitrile exists: Braunkholtz and Mann report the melting point of the acid-catalyzed addition product as 97.5°,^{6c} while Pietra reports 135.5° for the product from the base-catalyzed reaction.¹² Use of cupric acetate gave a product, m.p. 95-96° (Table I), whose infrared spectrum showed CN absorption at 2240 cm.⁻¹ and an NH band at 3260 cm.⁻¹

TABLE II
 CYANOETHYLATION OF AROMATIC AMINES WITH ACETIC ACID CATALYST^a

Amine	Catalyst, %	Time, hr.	Yield, ^b %	B.P., °C./mm.	n_D^{25}	M.P., ^c °C.
<i>p</i> -Toluidine ^d	7.0	12	56	148–155/1.0	—	103.5–105 ^e
<i>o</i> -Ethylaniline	8.2	12	53	125–132/0.3 ^f	1.5529	—
<i>N</i> -Methylaniline	12.5	22	84	170–171/19 ^g	1.5590	—
<i>N</i> -Ethylaniline	9.1	19	52	172–176/19 ^h	1.5511	—
<i>o</i> -Anisidine	8.1	18	33	140–141/1.0 ⁱ	1.5599	—
<i>p</i> -Anisidine	20.3	15	84 ^j	154–155/0.8 ^k	—	59–61 ^l
<i>o</i> -Phenetidine	7.3	22	45	141–143/0.7 ^m	1.5476	—
<i>p</i> -Phenetidine	8.5	22	90	165–166/0.7	—	73–75 ⁿ
<i>o</i> -Hydroxyaniline	12.0	24	78	—	—	110–111 ^o
<i>m</i> -Hydroxyaniline	9.2	24	69 ^p	—	1.573	—
<i>p</i> -Hydroxyaniline	12.2	24	22	—	—	86–88 ^q
<i>o</i> -Aminobiphenyl	10.0	12	56	180–185/1.0	1.6021	85–86.5 ^r

^a Reactions run at reflux unless specified otherwise. ^b Yields of monocyanoethyl derivative based on distilled products. ^c Uncorrected. ^d 0.7% CuCl and 2.1% sodium acetate used as additional catalysts at 150°. 36% dipropionitrile, m.p. 61–62°, also obtained. Reported m.p. 62°. ^e Reported m.p. 103–104°. ^f Run at 150°. Calcd. for C₁₁H₁₄N₂: C, 75.8; H, 8.1; N, 16.1. Found: C, 75.4; H, 8.0; N, 15.7. ^g Reported b.p. 175–177°/20 mm. ^h Reported b.p. 126–127°/0.5 mm. ⁱ Reported b.p. 165–167°/0.6 mm., n_D^{25} 1.5600. ^j Also obtained 14% of dipropionitrile, b.p. 210–212°/0.7 mm., m.p. 100–101°. Reported m.p. 100–101°. ^k Reported b.p. 247°/0.7 mm. ^l This boiling point reported by Elderfield for the mono-propionitrile is considerably higher than that found for the authentic dipropionitrile (see *j* above). ^m Reported m.p. 62–64°. ⁿ Calcd. for C₁₁H₁₄N₂O: C, 69.4; H, 7.4; N, 14.7. Found: C, 69.8; H, 7.5; N, 14.4. ^o Reported m.p. 75–76°. ^p Calcd. for C₉H₁₀N₂O: C, 66.7; H, 6.2; N, 17.3. Found: C, 66.8; H, 6.3; N, 16.5. ^q Crude, noncrystalline product. ^r Calcd. for C₉H₁₀N₂O: C, 66.7; H, 6.2; N, 17.3. Found: C, 66.7; H, 6.7; N, 16.9. Low yield was due to high losses in crystallization. ^s Run at 150°. Reported m.p. 86°. ^{6b}

catalysis is required. Basic catalysts undoubtedly function by removal of a proton from the aniline and subsequent attack of the anion upon the β -carbon atom of acrylonitrile. Acid catalysts, on the other hand, probably operate through the cyano group or the acrylonitrile and promote the development of an electron deficiency upon the β -carbon atom.

While the actual role the copper catalysts play in the cyanoethylation of aromatic amines has not been experimentally established, it is undoubtedly associated with the well-known activity of cupric and cuprous ions in complex formation, since both the amino group of the aniline and the cyano group of acrylonitrile are capable of forming complexes with these ions. The relative efficiency of the acetate compared with other salts of copper is probably due mainly to its greater solubility in the reaction mixture. Use of other known complexing agents as catalysts for cyanoethylation reactions is being investigated, as is use of cupric acetate in other reactions known to be catalyzed by copper salts.

EXPERIMENTAL

The catalyst employed in Table I was commercially available cupric acetate monohydrate, used without further treatment. The acrylonitrile was a commercially available grade containing 35 p.p.m. hydroquinone monomethyl ether as inhibitor, and was ordinarily employed in from equimolar quantities with the amine to a 2 to 1 excess with relatively little influence upon the yields observed. In most runs, 0.5 to 2% of hydroquinone was added as additional inhibitor. The cyanoethylated products were isolated by direct vacuum distillation of the reaction mixtures, and subsequent recrystallization of solid products from 95% ethanol or eth-

anol-water mixtures. In all cases virtually quantitative recovery of the unreacted aromatic amine as lower boiling fraction was obtained. No evidence of acetanilide formation was observed. With anilines melting above 75°, dioxane was used as solvent and the products were isolated by pouring the reaction mixtures into water and recrystallizing the resulting solids. The reactions were usually carried out at the reflux temperature of the mixture or at 100–110°, whichever was lower. The addition of the catalyst initially or at the reflux temperature was observed to have no influence upon yields obtained. The cyanoethylation of aniline with cupric acetate monohydrate catalyst is exemplary of the general procedure employed.

3-Anilinopropionitrile. A 500-ml. three-necked flask equipped with a stirrer, reflux condenser, and thermometer was charged with 186 g. (2.0 moles) of aniline, 106 g. (2.0 moles) of acrylonitrile and 3.72 g. (2.0% by weight of aniline) of cupric acetate monohydrate. The contents were then heated to 95° when rapid refluxing of the acrylonitrile began. Heating was discontinued, and the exothermic reaction carried the temperature to 105° in 30 min. before refluxing ceased and the temperature began to drop. The mixture was then heated at 100° for an additional 30 min. Unchanged acrylonitrile and aniline were stripped off under reduced pressure and the 3-anilinopropionitrile distilled as a slightly yellow liquid, solidifying in the receiver. The distillate, 214 g. (73%), b.p. 114–116°/0.3 mm., gave large, colorless prisms, m.p. 52–53° from 95% ethanol. Reported m.p. 51.5°.

Cyanoethylations with acetic acid catalyst were carried out at reflux or occasionally in a stainless steel bomb at 150° as noted in Table II. An excess of 1.5 or 2 moles of acrylonitrile per mole of amine was usually employed, with recovery of the excess upon distillation. An example of this method is the cyanoethylation of *o*-phenetidine.

3-(o-Phenetidino)propionitrile. A mixture of 412 g. (3.0 moles) of *o*-phenetidine, 265 g. (5.0 moles) of acrylonitrile and 30 ml. of glacial acetic acid was refluxed for 22 hr. The unreacted acrylonitrile was removed under reduced pressure and the residue vacuum-distilled, collecting 220 g. of unchanged *o*-phenetidine, b.p. 84–90°/1.5 mm., and 256 g.

(45%) of colorless 3-(*o*-phenetidino)propionitrile, b.p. 141–143°/0.7 mm., n_D^{25} 1.5476. The analytical values are reported in Table II.

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Convenient Synthesis for β -(3-Indolyl)-DL-Lactic Acids¹

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A convenient synthesis of β -(3-indolyl)-, β -[3-(5-methoxyindolyl)]-, and β -[3-(5-benzyloxyindolyl)]-DL-lactic acids is described.

Many of the procedures used to synthesize α -hydroxy acids cannot be used with compounds containing an indole group because of the chemical reactivity of this nucleus toward acidic and oxidizing conditions. Thus, the usual methods which involve halogenation of β -substituted- α -carboxypropionic acids followed by decarboxylation and hydrolysis of the α -halo acids in the manner used for the preparation of β -phenyllactic acid,² or known conversions of α -amino acids to the α -hydroxy acids *via* the diazonium salt by treatment with nitrous acid,³ nitrosyl bromide,⁴ or silver nitrite⁵ do not seem applicable as convenient preparative routes to indolelactic acids. Syntheses from the appropriately substituted aldehydes *via* the cyanohydrin as an intermediate⁶ are precluded because of the difficulty of preparation and the instability of some indole-substituted acetaldehydes.⁷

β -(3-Indolyl)lactic acid, itself, appears to be the only indolelactic acid which has been prepared. This compound was first made by the biological conversion of L-tryptophan to β -(3-indolyl)-D-lactic acid by the mold *Oidium lactis*;⁸ the racemic compound has been prepared from this product by racemization with alkali.^{9,10} The completely syn-

thetic approaches to indolelactic acid all have involved the use of indolepyruvic acid as an intermediate; it is readily converted to indolelactic acid by reduction with sodium amalgam.⁹ The chemical instability of indolepyruvic acid itself^{11,12} indicated that the use of substituted indolepyruvic acids as intermediates would be impractical unless they could be prepared readily and in good yield from available precursors. Consequently, a more direct route to indolelactic acid and substituted indolelactic acids was sought.

Tryptophan and some of its derivatives have been prepared conveniently by the condensation of gramine and substituted gramines with various aminomalonate derivatives using alkaline catalysis.^{13,14} By analogy with this reaction, the condensation of gramine (I) with diethyl acetoxy-malonate (II) was investigated and was found to proceed smoothly. Hydrolysis of the product (III) yielded β -(3-indolyl)- α -carboxy- α -hydroxypropionic acid (IV), which was decarboxylated to give indolelactic acid (V), in a yield of 52%, based on I.

With a similar sequence of reactions, 5-methoxyindolelactic acid (VI) was prepared from 5-methoxygramine (VII), and 5-benzyloxyindolelactic acid (VIII) from 5-benzyloxygramine (IX). 5-Hydroxyindolelactic acid (X), which is of interest as a possible metabolite of 5-hydroxytryptophan, was prepared by catalytic hydrogenation of VIII. It was not possible to obtain X crystalline, but paper chromatography showed the compound to be homogeneous and to have the expected properties.

The generality of this procedure for the preparation of other substituted lactic acids was

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