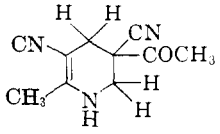
again heated to 70°. After cooling and scratching, a yellow precipitate was formed, which was filtered off after dilution with water (200 ml.). The solid was washed with ether; yield 1.8 g. (52%), m.p. 188.5–190° following five recrystallizations from methanol. The substance when pure was *colorless*, had ultraviolet maxima at 2588 Å. (ϵ_{max} 14900) in acetonitrile, 2613 Å. (ϵ_{max} 15600) in methanol, and infrared absorption which indicated a double bond, a cyano group and a *saturated carbonyl* group. Finally, the analysis fit the empirical formula $C_{10}H_{11}N_3O$. Calcd.: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.58, 63.43; H, 6.19, 5.85; N, 21.67, 22.18. The compound was assigned the structure VIII.



VIII

2,6-Dimethyl-3,5-dicarbethoxy-1,4-dihydropyridine (I) was prepared by the method of Hantzsch[18] and 2,4,6-trimethyl-3,5-dicarbethoxy-1,4-dihydropyridine by a similar method.[19]

Spectra.—All spectra were measured with a Cary recording spectrophotometer, model 11 or 14, using 10-cm., 5-cm., 2-cm., 1-cm., 0.2-cm., 0.1-cm., and 0.01-cm. quartz cells. The maxima were rerun three to five times at lowest speed. All solvents were of Spectrograde quality or were correspondingly purified.

Acknowledgment.—The authors would like to thank Mr. Joseph A. Skorcz for his work on the diesters.

(18) A. Singer and S. M. McElvain, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 215.
(19) W. Traber and P. Karrer, *Helv. Chim. Acta*, **41**, 2066 (1958).

[CONTRIBUTION FROM THE LABORATORY OF THE ALDRICH CHEMICAL CO., MILWAUKEE 10, WIS.]

Indoles. II.[1a,1b] The Acid-catalyzed Rearrangement of N-2-Alkenylanilines

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The acid-catalyzed rearrangement of N-2-alkenylanilines provides a convenient and simple method for the preparation of many indoles and indolines.

In studying the reactions of N-alkenylanilines, the observation was made[1b] that N-crotylaniline reacts with polyphosphoric acid to yield 2,3-dimethylindoline and 2,3-dimethylindole. Further work has shown that this proton-catalyzed Claisen-type rearrangement of N-crotylaniline is but one instance of a general reaction not limited either to polyphosphoric acid or to N-crotylaniline.

In the simplest case, N-allylaniline reacts with hydrochloric acid at 180° to yield 2-methylindoline and 2-methylindole, and as N-allylaniline can be made almost quantitatively by heating aniline with allyl chloride,[2] 2-methylindoline and 2-methylindole become easily accessible. Under the conditions used, N-allylaniline is in stoichiometric excess over hydrochloric acid, and the ratio of amine salt to free amine is approximately 2:1. The rearrangement of N-crotylaniline to yield 2,3-dimethylindoline and 2,3-dimethylindole proceeds so smoothly that refluxing of a mixture of excess aniline with crotyl chloride or bromide suffices. The rearrangement is quite exothermic, and an inert solvent such as 2-methylnaphthalene is helpful in controlling the reaction.

At least two competing reactions tend to reduce the yields of the simple indolines and indoles. Firstly, N-alkenylanilines are thermally unstable; thus while N-allylaniline can be distilled at atmospheric pressure, N-crotylaniline cannot, and in the reactions of N-allylaniline, N-crotylaniline and N-allyl-N-methylaniline with hydrochloric acid, some aniline is formed. Secondly, the disproportionation which yields aniline also liberates allyl moieties which alkylate the indoles further. Thus, in the simplest case, 2-methylindole is accompanied by 2-methyl-3-propylindole[3]; presumably the intermediate 2-methyl-3-allylindole is hydrogenated by the considerable quantities of hydrogen evolved. The identity of the 2-methyl-3-propylindole was proved by comparison with a sample prepared by the lithium aluminum hydride reduction of 2-methyl-3-propionylindole.

2-Methylindoline is converted slowly to 2-methylindole by the action of hydrochloric acid at 240°, and larger amounts of indoline and smaller of indole are isolated when the reaction mixture is not allowed to reflux after the initial exothermic reaction has subsided. Actually, even when the indoles rather than the indolines are wanted, it is easier to isolate the indolines, which are colorless, stable liquids, distilling without decomposition at atmospheric pressure, and then to dehydrogenate them. The simplest, quantitative mode of dehydrogenation is to heat the indoline with palladium-on-charcoal at 200° for 15–20 minutes.

The indolines can be characterized by solid derivatives such as arylsulfonamides and the high melting, easily purified diketolilolidines, formed in the reaction of indolines with diethyl malonate.[4] The easiest characterization of indolines is, however, their dehydrogenation to the crystalline indoles.

The rearrangement also can be applied to many ring-substituted anilines. Thus N-allyl-*o*-toluidine and N-allyl-*p*-toluidine yield 2,7- and 2,5-dimethylindole and 2,7- and 2,5-dimethylindoline, respectively, and the reaction of *o*-toluidine with crotyl chloride yields 2,3,7-trimethylindoline and 2,3,7-trimethylindole. The rearrangement is not confined to N-alkenylanilines monosubstituted on nitrogen; N-allyl-N-methylaniline rearranges easily

(1) (a) Presented in part at the 137th National Meeting of the American Chemical Society, Cleveland, Ohio, April, 1960. (b) For Paper I, see J. E. Hyre and A. R. Bader, *J. Am. Chem. Soc.*, **80**, 437 (1958).
(2) C. D. Hurd and W. W. Jenkins, *J. Org. Chem.*, **22**, 1418 (1957).
(3) A. E. Arbuzov, I. A. Zaltzev and A. I. Razumov, *Ber.*, **68B**, 1792 (1935); B. Oddo and C. Alberti, *Gazz. chim. ital.*, **63**, 236 (1933).
(4) E. Bamberger and H. Sternitzki, *Ber.*, **26**, 1300 (1895).

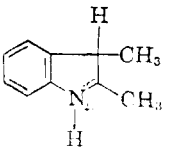
though less vigorously than N-allylaniline, and this preparation of 1,2-dimethylindole is much easier than either the alkylation of 2-methylindole with methyl iodide and sodium hydride or the Fischer indole synthesis.[5]

N-Allyl-*p*-fluoroaniline yields 5-fluoro-2-methylindoline and 5-fluoro-2-methylindole, and N-allyl-*p*-chloroaniline rearranges more vigorously to yield 5-chloro-2-methylindole[6] but no indoline. In each case the indole can be prepared from the aniline and allyl chloride without isolation of the intermediate N-allylaniline.

This general preparation of indoles is limited to those made from anilines sufficiently soluble to allow the preparation of the N-allylanilines and not cleaved by the strongly acidic conditions of the rearrangement. The N-allylanisidines and *p*-benzyloxyaniline, for instance, decompose under the reaction conditions and we have been unable to isolate methoxy- or benzyloxyindoles in the attempted rearrangement.

When first investigating[1b] the reaction of N-crotylaniline with polyphosphoric acid, we observed that the 2,3-dimethylindoline obtained in the rearrangement differed in spectra and solid derivatives from the 2,3-dimethylindoline obtained by the metal and acid reduction of the indole.[7] We then suggested the latter might be the *trans* isomer, and the dehydrogenation following this rearrangement might be stereospecific in such a manner that only the *trans*-indoline was dehydrogenated to the indole. A more careful investigation of the products of the metal and acid reduction of 2,3-dimethylindole and of this rearrangement has shown this not to be the case. The high pressure hydrogenation[8] of 2,3-dimethylindole is essentially stereospecific to yield the *trans*-2,3-dimethylindoline,[9] of lower density and lower refractive index[10] than the mixture of *ca.* 60% *cis*- and 40% *trans*-2,3-dimethylindoline obtained in the tin and hydrochloric acid reduction[7] of the indole. The lack of stereospecificity of the metal–acid reduction probably is due to the addition of hydrogen in separate steps perhaps involving the cation I as intermediate. The 2,3-dimethylindoline obtained in the rearrangement of N-crotylaniline contains, besides small amounts of other bases, *trans*- and *cis*-2,3-dimethylindolines in the ratio of 3 to 1.

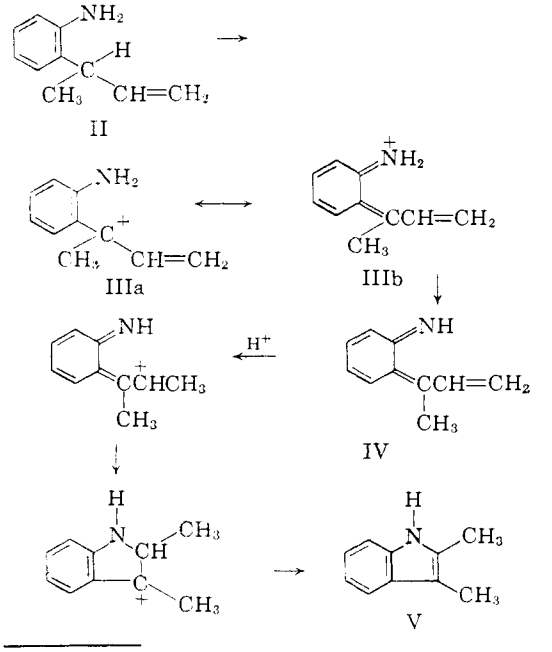
Discussion of the mechanism of this reaction must include consideration of the interesting work of Hurd and Jenkins.[2] These workers found that N-allylaniline refluxed with zinc chloride in xylene gave a fair yield of *o*-allylaniline. The reaction of N-allylaniline with zinc chloride at 200–250° without solvent yielded aniline, some *p*-propylaniline, and gaseous hydrogen. The analogous reaction of N-cinnamylaniline yielded 2-phenylquinoline and *o*-cinnamylaniline. No indolines or indoles were found in any of these reactions.



I

As *o*-allylaniline[2] yields 2-methylindoline when treated with hydrochloric acid at 190–200°, it seems likely that in the formation of 2-methylindoline discussed in this paper, *o*-allylaniline is an intermediate. However, to explain the formation of 2,3-dimethylindoline and 2,3-dimethylindole from N-crotylaniline, it is necessary to assume that the intermediate is *o*-(1-methylallyl)-aniline (II), rather than *o*-crotylaniline which would lead to 2-ethylindoline and 2-ethylindole or 2-methylquinoline derivatives. The rearrangement of N-crotylaniline takes place, therefore, by a Claisen-type mechanism with inversion,[11] whereas the rearrangement of N-cinnamylaniline under the conditions of Hurd and Jenkins proceeds without inversion.

An interesting feature of the reaction presented here is the dehydrogenation that produces indoles. Whereas 2-methylindoline heated with hydrochloric acid at 240° is dehydrogenated slowly to 2-methylindole, the 2,3-dimethylindolines are unaffected by such treatment. Therefore, presumably the dehydrogenation involved in the formation of indoles takes place before cyclization. Since N-crotylaniline, for instance, on direct loss of hydrogen, would give a Schiff base that would not lead



II IIIa IIIb IV V

(5) L. Marion and C. W. Oldfield, *Can. J. Research*, **25B**, 1 (1947).

(6) (a) E. B. Towne and H. M. Hill, U. S. Patent 2,607,779 (August 19, 1952); *C. A.*, **47**, 5452 (1953); (b) British Patent 773,440 (July 3, 1954); *C. A.*, **51**, 12147 (1957).

(7) A. Steche, *Ann.*, **242**, 371 (1887).

(8) H. Adkins and R. E. Burks, Jr., *J. Am. Chem. Soc.*, **70**, 4174 (1948).

(9) The usual rule that catalytic hydrogenation proceeds *cis* is not applicable in this case, as the vigorous hydrogenation employed reaches a true equilibrium involving appreciable dehydrogenation of the indoline. Thus the indoline actually obtained is the more stable *trans* isomer.

(10) K. v. Auwers, *Ann.*, **420**, 84 (1920).

(11) Contrary to Hurd and Jenkins,[2] we think that the Claisen rearrangement does not necessarily involve electron transfer from the hetero-atom to the benzene ring, but will be facilitated in amine salts compared to free amines because of delocalization of the positive charge in the transition state.[1b]

to an indole, it may be that the intermediate oxidized is *o*-(1-methylallyl)-aniline (II). Loss of hydride ion to some acid would give the cation III, which could proceed to the imine IV, and thence by normal, acid-catalyzed cyclization to 2,3-dimethylindole (V).

Experimental

2-Methylindole and 2-Methylindoline. (a) Without Solvent.—N-Allylaniline (350 g.) and concentrated hydrochloric acid (150 cc.) were heated with water removal. At *ca.* 180° the reaction became vigorously exothermic, considerable gas, largely hydrogen, was evolved, and the temperature spontaneously rose to 255°. When the reaction had subsided, the mixture was refluxed at 220° for 15 minutes, cooled, and separated into hydrochloric acid-soluble and -insoluble fractions. The acid-insoluble fraction (180 g.) on fractional distillation yielded 40 g. of a fraction A, b.p. 115–125° (1.5 mm.), which crystallized completely in the receiver, and 45 g. of a fraction B, b.p. 135–145° (1.5 mm.). Fraction A crystallized from ligroin in white platelets, m.p. 56–58° which did not depress the m.p. of authentic 2-methylindole.

Fraction B, 2-methyl-3-propylindole was redistilled, b.p. 131–132° (1.1 mm.), λ_{max}^{EtOH} 225.5 mμ (log ε 4.49), shoulder 276 mμ (log ε 3.81), 281 mμ (log ε 3.83), shoulder 289.5 mμ (log ε 3.77), and characterized by a picrate, red-brown needles from methanol, m.p. 145–147°.

Anal. Calcd. for $C_{12}H_{15}N$ (fraction B): C, 83.24; H, 8.67; N, 8.09. Found: C, 83.09; H, 8.44; N, 8.53. Calcd. for $C_{18}H_{18}N_4O_7$ (picrate): C, 53.73; H, 4.50; N, 13.93. Found: C, 53.84; H, 4.33; N, 14.24.

The acid-soluble fraction (149 g.) on distillation yielded 48 g. of a fraction, b.p. 180–210°, largely aniline, and 82 g. of a fraction, b.p. 220–240°, largely 2-methylindoline. Redistillation of this fraction yielded 70 g. of 2-methylindoline, b.p. 226–230°, characterized by its dehydrogenation to 2-methylindole as described below, and by its reaction with diethyl malonate[4] to yield α′-methyldiketolilolidine, m.p. 298°.

Repeating the reaction as above, but refluxing the mixture for 8 hours instead of 15 minutes, gave more acid-insoluble product (234 g.) yielding 87 g. of a crystalline fraction, b.p. 115–125° (1.5 mm.), largely 2-methylindole, and 73 g. of a liquid fraction, b.p. 125° (0.8 mm.)–132° (0.3 mm.), largely 2-methyl-3-propylindole, characterized as above. The acid-soluble fraction (100 g.) again yielded aniline (50 g.) and a fraction (28 g.), b.p. 200–235°, from which no crystalline 2-methylindole could be obtained on dehydrogenation.

(b) **With Solvent.**—The same quantities of N-allylaniline and hydrochloric acid were heated in 500 g. of 2-methylnaphthalene. At 180° vigorous evolution of gas started, but the reaction was much more easily controlled than without solvent. Reflux was continued for 8 hours, during which time the reflux temperature rose from 220 to 232°. From the acid-soluble fraction (192 g.) there was obtained 55 g. of aniline and 101 g. of 2-methylindoline, characterized as above. From the acid-insoluble fraction (624 g.) there was obtained besides the solvent, 30 g. of 2-methylindole and 60 g. of 2-methyl-3-propylindole,

Other acids, for instance methanesulfonic acid, also react with N-allylanilines to yield the indoles and indolines, but seem to offer no practical advantages.

2-Methyl-3-propylindole.[3]—2-Methyl-3-propionylindole,[12] prepared from 2-methylindole, propionic anhydride and anhydrous sodium acetate analogous to the preparation of 3-acetyl-2-methylindole,[13] melts at 190–192° and strongly depresses the m.p. of 3-acetyl-2-methylindole. Reduction of 2-methyl-3-propionylindole (20 g.) suspended in ether with lithium aluminum hydride (10 g.) yielded an oil (14.5 g.), b.p. 131–135° (1 mm.), characterized by a picrate, m.p. 145–147°, which does not depress the m.p. of the picrate described above. The infrared and ultraviolet spectra of this oil and the 2-methyl-3-propylindole from the reaction of N-allylaniline with acid are identical.

2,3-Dimethylindole and 2,3-Dimethylindoline. (a) From Aniline and Crotyl Bromide.—To 559 g. (6 moles) of aniline, there was added gradually with stirring 402 g. (3 moles) of crotyl bromide. The mixture then was refluxed for 8 hours, the reaction temperature gradually rising to 186°. The mixture was cooled, and separated into a fraction soluble in dilute aqueous hydrochloric acid, and one insoluble. The acid-insoluble fraction (90 g.) on distillation yielded a crystalline fraction (66 g.), b.p. 120–130° (0.5 mm.), m.p. 70–80°, which after one crystallization from ligroin melts at 100–102° and does not depress the m.p. of authentic 2,3-dimethylindole.[14]

The acid-soluble fraction was made alkaline, extracted with toluene, the solvent removed and the residue (460 g.) distilled to yield 211 g. of a fraction boiling from 170 to 210°, mainly aniline, and a fraction (140 g.), b.p. 230–250°, a colorless liquid, $n^{25}D$ 1.554, mainly 2,3-dimethylindoline as indicated by its dehydrogenation to 2,3-dimethylindole as described below. The 2,3-dimethylindoline also was characterized by a benzenesulfonamide, m.p. 101–103°, identical with the benzenesulfonamides made from the indoline obtained in the reaction[1b] of N-crotylaniline with polyphosphoric acid, and the indoline obtained in the high-pressure hydrogenation of 2,3-dimethylindole. Vapor phase chromatographic examination (Apiezon L supported on Celite 545, 100–120 mesh, 130°, flow rate 35 ml./min.) of the 2,3-dimethylindoline fraction showed the presence of two major components, presumed to be the stereoisomeric 2,3-dimethylindolines (see below), and three unidentified compounds[15] present in lesser amounts. Other indolines formed similarly were also shown to contain minor impurities.

The reaction of crotyl chloride with aniline proceeds similarly.

(b) **From Crotylaniline and Hydrochloric Acid.**—A mixture of N-crotylaniline[1b] (750 g., b.p. 95–100° (2.5 mm.))[16] and concentrated hydrochloric acid (300 cc.) was heated with water removal to 180° when an exothermic reaction raised the temperature to 220°. The mixture was refluxed at 220–230° for 4 hours, cooled and separated through its solubility in hydrochloric acid into an acid-insoluble fraction A (320 g.) and a soluble fraction B (340 g.). Fraction A on distillation yielded 160 g. of a fraction, b.p. 125–150° (1.5 mm.), which crystallized and which after one crystallization from ligroin melts at 95–98°, mixed m.p. with 2,3-dimethylindole not depressed. Fraction B yielded 170 g. of aniline and 95 g. of a fraction, b.p. 230–240°, which on redistillation boiled at 235–237° and was shown to be 2,3-dimethylindoline by its dehydrogenation to 2,3-dimethylindole.

2,3,7-Trimethylindole and 2,3,7-Trimethylindoline.—The reaction of *o*-toluidine and crotyl chloride yielded 2,3,7-trimethylindoline (presumably a mixture of *cis* and *trans* isomers), b.p. 238–242°, and 2,3,7-trimethylindole, crystallized from ligroin, m.p. 76–77°, characterized by a picrate, m.p. 155–157°.

Anal. Calcd. for $C_{11}H_{15}N$ (2,3,7-trimethylindoline): C, 81.95; H, 9.37; N, 8.68. Found: C, 81.91; H, 9.14; N, 8.51. Calcd. for $C_{11}H_{13}N$ (2,3,7-trimethylindole): C, 82.98; H, 8.23; N, 8.79. Found: C, 82.69; H, 8.06; N, 8.67. Calcd. for $C_{17}H_{16}N_4O_7$ (2,3,7-trimethylindole picrate): N, 14.43. Found: N, 14.40.

Dehydrogenation of the Indolines. (a) With Palladium-on-Charcoal.—When 10 g. of 2-methylindoline and 1 g. of 10% palladium-on-charcoal were heated at 200° for 30 minutes, vigorous evolution of gas occurred, and the mixture solidified completely on cooling, quantitatively yielding 2-methylindole. Similarly, each of the 2,3-dimethylindolines (the mixture of isomers prepared by tin and acid reduction[7] of 2,3-dimethylindole, the *trans* isomer prepared by high-pressure hydrogenation of the indole, and the mixture of isomers from the acid-soluble reaction product of aniline and crotyl bromide) gave 2,3-dimethylindole in high yield.

(b) **With Acid.**—A mixture of 50 g. of 2-methylindoline and 25 cc. of concentrated hydrochloric acid was heated with water removal to 240°, and refluxed for 2 hours. Separation

(12) B. Oddo, *Gazz. chim. ital.*, **43II**, 208 (1913).

(13) E. Fischer, *Ann.*, **242**, 379 (1887).

(14) Examination of the mother liquors from the crystallization of 2,3-dimethylindole failed to show the presence of 2-ethylindole. Any 2-ethylindole formed may have been alkylated further, perhaps to 2-ethyl-3-butylindole analogous to the formation of 2-methyl-3-propylindole from N-allylaniline.

(15) Perhaps 2-ethylindoline and 2-methyl-1,2,3,4-tetrahydroquinoline formed *via* *o*-crotylaniline are among these.

(16) While N-allylaniline can be distilled at atmospheric pressure, N-crotylaniline decomposes considerably.

through acid solubility yielded 14 g. of an acid-insoluble fraction, largely 2-methylindole, and 35 g. of an acid-soluble fraction, unreacted 2-methylindoline, characterized through its quantitative conversion by palladium-on-charcoal to 2-methylindole.

Similar treatment of the mixture of 2,3-dimethylindolines made by tin and acid reduction of the indole and of the mixture of 2,3-dimethylindolines made from N-crotylaniline and hydrochloric acid, with hydrochloric acid at 250° for 10 hours, yielded no 2,3-dimethylindole, the indolines being recovered unchanged.

N-Allyl-*o*-toluidine.—The reaction of *o*-toluidine (2 moles) with allyl chloride (1 mole) yielded N-allyl-*o*-toluidine, b.p. 236–238° (760 mm.).

Anal. Calcd. for $C_{10}H_{13}N$: N, 9.52. Found: N, 9.71.

2,7-Dimethylindoline and 2,7-Dimethylindole.—The reaction of 510 g. of N-allyl-*o*-toluidine and 275 ml. of concentrated hydrochloric acid became exothermic with gas evolution at 230°, and the mixture was refluxed at 250° for 15 minutes. The cooled mixture was separated into aqueous hydrochloric acid-soluble and insoluble fractions. The acid-soluble fraction (300 g.) yielded besides *o*-toluidine, 140 g. of 2,7-dimethylindoline, b.p. 240–245°, $n^{22}D$ 1.563. Dehydrogenation with 10% palladium-on-charcoal yielded 2,7-dimethylindole, b.p. 112–116° (1 mm.) which crystallized on standing, m.p. 33–35°.

The acid-insoluble fraction (100 g.) yielded 30 g. of 2,7-dimethylindole, (identical with the above) which was characterized by a picrate, m.p. 154–156° crystallized from ethanol.

Anal. Calcd. for $C_{10}H_{13}N$ (2,7-dimethylindoline): C, 81.62; H, 8.85; N, 9.53. Found: C, 81.18; H, 9.18; N, 9.24. Calcd. for $C_{10}H_{11}N$ (2,7-dimethylindole): C, 82.69; H, 7.63; N, 9.64. Found: C, 82.14; H, 7.84; N, 9.59. Calcd. for $C_{16}H_{14}N_4O_7$ (2,7-dimethylindole picrate): C, 51.93; H, 3.77; N, 14.97. Found: C, 51.45; H, 4.16; N, 14.94.

2,5-Dimethylindoline and 2,5-Dimethylindole.—The reaction of N-allyl-*p*-toluidine and hydrochloric acid carried out analogously is strongly exothermic, and there were isolated 2,5-dimethylindole, m.p. 112–113°; 2,5-dimethyl-3-propylindole, a yellow oil, b.p. 155–160° (1.3 mm.), characterized by a picrate, m.p. 126°; and 2,5-dimethylindoline,[17] b.p. 239–240° at 760 mm., a colorless oil, characterized by its dehydrogenation to 2,5-dimethylindole.

Anal. Calcd. for $C_{10}H_{13}N$ (2,5-dimethylindoline): C, 81.58; H, 8.90; N, 9.52. Found: C, 81.46; H, 9.21; N, 9.58. Calcd. for $C_{13}H_{17}N$ (2,5-dimethyl-3-propylindole): C, 83.37; H, 9.15; N, 7.48. Found: C, 83.16; H, 9.19; N, 7.41. Calcd. for $C_{19}H_{20}N_4O_7$ (2,5-dimethyl-3-propylindole picrate): C, 54.80; H, 4.84; N, 13.46. Found: C, 54.46; H, 4.80; N, 13.72.

1,2-Dimethylindoline and 1,2-Dimethylindole.—The reaction of N-allyl-N-methylaniline, b.p. 213–214°, with hydrochloric acid is much less vigorous than the analogous reaction of N-allylaniline. Four hundred grams of the aniline and 200 cc. of concentrated hydrochloric acid were heated with water removal to 217° and refluxed for 4 hours. The cooled mixture was diluted with ligroin, and the crystalline solid (60 g.), aniline hydrochloride, m.p. 192–195°, filtered off. The filtrate was extracted with dilute hydrochloric acid. Distillation of the acid-insoluble fraction (53 g.) yielded 21 g. of a crystalline fraction, b.p. 90° at 0.2 mm. to 105° at 0.4 mm., m.p. 57–59° after one crystallization from aqueous methanol. This indole depresses the m.p. of 2-methylindole, and does not depress the m.p. of 1,2-dimethylindole made by the alkylation of 2-methylindole with methyl iodide and sodium hydride in dimethylformamide.

The acid-soluble product yielded 102 g. of a fraction, b.p. 225–235°, a colorless oil, which on redistillation gave 90 g. of 1,2-dimethylindoline,[18] b.p. 227–228°, characterized by its dehydrogenation to the crystalline 1,2-dimethylindole.

Anal. Calcd. for $C_{10}H_{13}N$: C, 81.58; H, 8.90; N, 9.52. Found: C, 81.20; H, 8.89; N, 9.91.

5-Chloro-2-methylindole.—A mixture of *p*-chloroaniline (1280 g.) and allyl chloride (840 g.) was refluxed for 3 hours, while 800 g. of 50% aqueous sodium hydroxide was added slowly. The mixture was cooled, concentrated hydrochloric acid (700 cc.) was added, and the mixture heated with water removal to 230° when vigorous exothermic reaction with evolution of hydrogen commenced. When the reaction had subsided, the mixture was cooled, and partitioned between aqueous hydrochloric acid and toluene. The acid-soluble fraction yielded only *p*-chloroaniline; no chloroindoline could be isolated. The acid-insoluble fraction was distilled to yield a fraction, b.p. 130–140° (0.1 mm.) (350 g.), which crystallized in the receiver. Recrystallization from petroleum ether yielded 260 g. of 5-chloro-2-methylindole, m.p. 114–116°.

Anal. Calcd. for C_9H_8ClN: C, 65.27; H, 4.87; N, 8.46. Found: C, 65.04; H, 5.03; N, 8.47.

The next fraction (100 g.), b.p. 154–160° (0.2 mm.) 5-chloro-2-methyl-3-propylindole, λ_{max}^{EtOH} 232 mμ (log ε 4.51), shoulder 284 mμ (log ε 3.79), 290 mμ (log ε 3.82), shoulder 298 mμ (log ε 3.76), did not crystallize, and was characterized by a picrate, m.p. 135–136°.

Anal. Calcd. for $C_{12}H_{14}ClN$ (5-chloro-2-methyl-3-propylindole): C, 69.37; H, 6.79; N, 6.74. Found: C, 69.72; H, 7.28; N, 6.92. Calcd. for $C_{18}H_{17}ClN_4O_7$ (5-chloro-2-methyl-3-propylindole picrate): C, 49.50; H, 3.92; N, 12.82. Found: C, 49.63; H, 3.72; N, 12.92.

5-Chloro-2-methylindole also can be obtained from N-allyl-*p*-chloroaniline, b.p. 267–270° (760 mm.), but the isolation of this intermediate offers no practical advantages.

Anal. Calcd. for $C_9H_{10}ClN$: C, 64.48; H, 6.01. Found: C, 64.57; H, 6.12.

5-Fluoro-2-methylindole and 5-Fluoro-2-methylindoline.—The analogous one-step reaction of *p*-fluoroaniline with allyl chloride is less vigorous than the reaction of *p*-chloroaniline, and from the reaction mixture about equal amounts of 5-fluoro-2-methylindole, b.p. 112–120° (0.1 mm.), m.p. 99–101° after crystallization from heptane, and 5-fluoro-2-methylindoline, b.p. 225–227° (760 mm.), were obtained. A vapor phase chromatogram showed the latter to be 97% pure, but to contain eleven minor impurities.

Anal. Calcd. for C_9H_8NF (5-fluoro-2-methylindole): C, 72.47; H, 5.41. Found: C, 72.15; H, 5.36. Calcd. for $C_9H_{10}NF$ (5-fluoro-2-methylindoline): C, 71.50; H, 6.67; N, 9.27. Found: C, 71.40; H, 7.03; N, 9.50.

Both indole and indoline can be obtained also from N-allyl-*p*-fluoroaniline, b.p. 228–233°, but here also isolation of the intermediate offers no practical advantages.

Anal. Calcd. for $C_9H_{10}NF$: N, 9.27. Found: N, 8.91.

Dehydrogenation of 5-fluoro-2-methylindoline with palladium-on-charcoal quantitatively yielded 5-fluoro-2-methylindole.

2-Methylindoline from *o*-Allylaniline.—The reaction of *o*-allylaniline (200 g. prepared by the method of Hurd and Jenkins[2] and characterized by its benzenesulfonanilide, m.p. 83–84°, and its benzanilide, m.p. 122°) with hydrochloric acid (100 cc. of concentrated acid) at 190–200° for 2 hours yielded almost no acid-insoluble product, and from the acid-soluble fraction (170 g.), there was obtained 80 g. of a fraction, b.p. 226–234°, largely 2-methylindoline, as shown by its dehydrogenation to crystalline 2-methylindole in 90% yield.

The 2,3-Dimethylindolines.—The reduction[8,19] of 2,3-dimethylindole (86 g.) in dioxane at 170° in the presence of 17 g. of copper chromite and a maximum hot pressure of 18400 p.s.i. yielded 13 g. of unchanged 2,3-dimethylindole and 63 g. of an acid-soluble, colorless oil, b.p. 235°, *trans*-2,3-dimethylindoline, which a vapor phase chromatogram showed to be homogeneous. Its benzenesulfonamide, m.p. 101–103°, is identical with the benzenesulfonamide described above. The assignment of the *trans* configuration to this isomer is based on a comparison[10] of its refractive index and density with those of the mixtures of isomers described below. The 2,3-dimethylindoline from this hydrogenation has $n^{25}D$ 1.551 and d^{25} 0.987; the molecular refraction is then 47.5 cc., calculated by group refractivities for 2,3-dimethylindoline, 47.5.

(17) M. Treppenhauer, German Patent 623,693 (Dec. 31, 1935); *C. A.*, **30**, 4874 (1936); French Patent 792,064 (Dec. 21, 1935), *C. A.* **30**, 4181 (1936).

(18) D. A. Cockerill, Sir R. Robinson and J. E. Saxton, *J. Chem. Soc.*, 4369 (1955).

(19) We sincerely thank Dr. William H. Jones for his help with this hydrogenation.

The reduction[7] of 2,3-dimethylindole with tin and hydrochloric acid yielded a colorless, acid-soluble oil, b.p. 234–236°, $n^{25}D$ 1.556, d^{25} 0.994, which a vapor phase chromatogram showed to contain *ca.* 60% *cis*- and *ca.* 40% *trans*-2,3-dimethylindoline. The benzenesulfonamide[15] of the *cis* isomer isolated from this mixture melts at 70–71°.

The acid-soluble product of the reaction of aniline with crotyl bromide was fractionated. As shown by vapor phase chromatogram, the fraction b.p. 230–240°, $n^{25}D$ 1.554, d^{25} 0.990, contained besides three other compounds, *ca.* 55% *trans*-2,3-dimethylindoline and *ca.* 19% *cis*-2,3-dimethylindoline.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, URBANA, ILL.]

Synthesis of Substituted Pyrrolidines and Pyrrolizidines

BY ROGER ADAMS, SEIJI MIYANO AND M. D. NAIR

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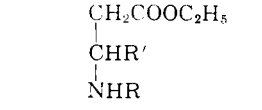
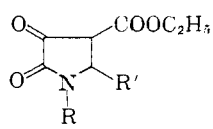
Condensation of N-substituted β-aminopropionitriles with diethyl oxalate yields N-substituted 4-cyano-2,3-dioxopyrrolidines. Application of this reaction to the synthesis of pyrrolizidine and octahydropyrrocoline ring systems is described. The relationship of synthetic *dl*-1-hydroxymethyl-2-hydroxypyrrolizidine to the Senecio bases macronecine, hastanecine or turneforcidine is discussed.

The synthesis of 2,3-dioxopyrrolidines (I) and derivatives by means of the condensation of esters of oxalic acid with β-aminopropionic esters was first reported by Southwick and co-workers.[1,2] This reaction now has been applied to the synthesis of pyrrolizidine derivatives, some of which represent the basic moieties of certain Senecio alkaloids.

Condensation of ethyl aspartate (II) and ethyl β-aminoglutaconate (III) with dimethyl oxalate yielded the expected 4,5-dicarbethoxy-2,3-dioxopyrrolidine (IV) and 4-carbethoxy-5-carbethoxymethylene-2,3-dioxopyrrolidine (V), respectively. Diazomethane converted these dioxo compounds into their enol ethers IVa and Va.



II, R = H, R′ = $COOC_2H_5$

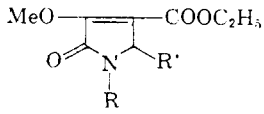


I, R = H, R′ = H

III, R = H, R′ = $CHCOOC_2H_5$

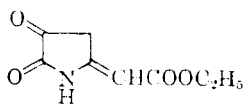
IV, R = H, R′ = $COOC_2H_5$

V, R = H, R′ = $CHCOOC_2H_5$

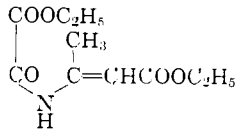


IVa, R = H, R′ = $COOC_2H_5$

Va, R = H, R′ = $CHCOOC_2H_5$



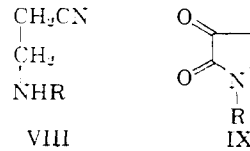
VI



VII

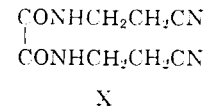
On the other hand, condensation of diethyl oxalate with ethyl β-aminocrotonate in the presence of potassium ethoxide did not yield the cyclization product VI but instead a compound of molecular formula $C_{10}H_{15}NO_5$, presumably ethyl β-oxalylaminocrotonate (VII). This structure is supported by its infrared spectrum which shows the presence of a secondary non-cyclic amide band[3] at 1507 cm.$^{-1}$.

A reaction of similar character is the condensation of β-aminopropionitriles (VIII) with diethyl oxalate to give 2,3-dioxo-4-cyanopyrrolidines (IX). N-Methyl-, N-ethyl-, N-β-cyanoethyl-, N-benzyl- and N-cyclohexyl-β-aminopropionitriles (VIII) condensed smoothly with diethyl oxalate in the presence of sodium alkoxides to give the corresponding N-substituted 4-cyano-2,3-dioxopyrrolidines (IX). Reaction of N - β - cyanoethyl - 4 - cyano - 2,3 - dioxopyrrolidine with diazomethane yielded the enol ether. As these β-aminopropionitriles are conveniently prepared by cyanoethylation of amines, the oxalate condensation provides a very convenient route to substituted pyrrolidines. The parent compound, β-aminopropionitrile, reacted otherwise, however, and gave with diethyl oxalate only β-cyanoethyloxamide (X), characterized by analysis and infrared spectrum.



VIII

IX



X

R = CH_3, C_2H_5, CH_2CH_2CN, $CH_2C_6H_5$, C_6H_{11}

The extension of this reaction to the synthesis of pyrrolizidine derivatives involved the condensation of ethyl 2-pyrrolidylacetate (XI) with diethyl oxalate in the presence of sodium ethoxide. A single product, 1 - carbethoxy - 2,3 - dioxo - pyrrolizidine (XII), resulted in good yield. Diazomethane converted this product to its enol ether, 1-carbethoxy-2-methoxy-3-oxopyrrolizid-1,3-ene.

The required ethyl pyrrolidylacetate (XI) could be prepared conveniently by reduction of ethyl pyrrolylacetate with 5% rhodium-on-alumina[4,5] catalyst at ordinary pressure, a method superior to

(1) P. L. Southwick and L. L. Selvard, *J. Am. Chem. Soc.*, **71**, 2532 (1949).

(2) P. L. Southwick and R. I. Crouch, *ibid.*, **75**, 3414 (1953).

(3) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1959, p. 205.

(4) C. G. Overberger, L. C. Palmer, B. S. Marks and N. R. Byrd, *J. Am. Chem. Soc.*, **77**, 4100 (1955).

(5) R. Adams, S. Miyano and D. Fleš, *ibid.*, **82**, 1466 (1960).