1. $CF_3CF{=}CF_2 + AlCl_3 \longrightarrow AlCl_3F^- + \overset{+}{C}F_2{-}CF{=}CF_2$

2. $\overset{+}{C}F_2{-}CF{=}CF_2 + AlCl_3F^- \longrightarrow CF_2Cl{-}CF{=}CF_2 + AlCl_2F$

3. $CF_2ClCF{=}CF_2 \xrightarrow{AlCl_3} CF_3CF{=}CFCl$

4. $CF_3CF{=}CFCl + AlCl_2F \longrightarrow \overset{+}{C}F_2{-}CF{=}CFCl + AlCl_2F_2^-$

5. $\overset{+}{C}F_2{-}CF{=}CFCl + AlCl_2F_2^- \longrightarrow CF_2Cl{-}CF{=}CFCl + AlClF_2$

6. $CF_2Cl{-}CF{=}CFCl \xrightarrow{AlCl_3} CF_3CF{=}CCl_2$

7. $CF_3CF{=}CCl_2 + AlCl_3 \longrightarrow AlCl_3F^- + \overset{+}{C}F_2{-}CF{=}CCl_2$

8. $\overset{+}{C}F_2{-}CF{=}CCl_2 + AlCl_3F^- \longrightarrow CF_2ClCF{=}CCl_2 + AlCl_2F$

Steps 3 and 6 involve intramolecular rearrangement. Step 8 continues stepwise until $CCl_3CF{=}CCl_2$ is ultimately formed. This latter compound, $CCl_3CF{=}CCl_2$, which resists quite strongly the action of $AlCl_3$ to convert it to $CCl_3{-}CCl{=}CCl_2$, may be partially explained on the basis of the peculiar geometry of the molecule which prevents the complexing of $AlCl_3$ with $CCl_3CF{=}CCl_2$.

BOULDER, COLO.

[CONTRIBUTION FROM THE LABORATORY FOR THE STUDY OF HEREDITARY AND METABOLIC DISORDERS, AND THE DEPARTMENTS OF BIOLOGICAL CHEMISTRY AND MEDICINE, UNIVERSITY OF UTAH]

Preparation and Properties of β-3-Indolyl Compounds Related to Tryptophan Metabolism[1]

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3-Indolylpyruvic acid was prepared from DL-tryptophan *via* the *N*-chloroacetyl derivative and 2-methyl-4-(3′-indolal)-5-oxazolone, and also from 3-formylindole *via* 2-methyl-4-(1′-acetyl-3′-indolal)-5-oxazolone. The pyruvic acid was converted to β-(3-indolyl)lactic and β-(3-indolyl)-α-oximinopropionic acids. β-(3-Indolyl)acrylic and β-(3-indolal)malonic acids were synthesized from 3-formylindole and malonic acid. 3-Indolylglyoxylic acid, amide, and methyl ester were prepared from indole and oxalyl chloride *via* 3-indolylglyoxylyl chloride. 3-Indolylglycolic acid was obtained as a stable sodium salt by reduction of the glyoxylic acid and the instability of the free glycolic acid was confirmed. 3-Indolylcarboxylic acid was prepared from 3-cyanoindole which was obtained from 3-indolylglyoxylic acid or from 3-formylindole *via* the aldoxime. 3-Indolylacetamide was synthesized from 3-indolylacetic acid *via* the acid chloride. The factors which influence the yield, stability, and purity of these compounds are considered in relation to inadequacies in earlier literature.

Only a minor portion of the tryptophan ingested by man follows the known metabolic paths, which lead to nicotinic acid or to serotonin, and the fate of the remainder is uncertain.[4] Varying small amounts of many indole compounds are present in human urine; an abnormal excretion of some of these compounds has been reported in cases of phenylketonuria,[5] malignant carcinoid tumor,[6,7] and Hartnup disease.[8] The preparation of several 3-indolyl compounds, which were required in a study of urinary indole acids and their possible significance in relation to other metabolic paths,[9] is reported in the present paper. New syntheses of indolepyruvic acid, sodium indoleglycolate, and indoleacetamide are presented, together with effective procedures for indoleacrylic, indolecarboxylic, indoleglyoxylic, and indolelactic acids. The conditions which influence the yield, stability, and purity of the compounds are considered. These factors have not been treated sufficiently in many of the earlier publications, and procedures frequently have not been described or are inadequate.

β-(3-Indolyl)pyruvic acid (I) was prepared in 43% overall yield from DL-tryptophan *via* its *N*-chloroacetyl derivative (II) and 2-methyl 4-(3′-indolal)5-oxazolone (III). Cooley and Wood[10] used this approach to make *N*-acetyldehydrotryptophan, but did not isolate I and III. I also was obtained in low yield *via* 2-methyl-4-(1′-acetyl-3′-indolal)-5-oxazolone by condensing 3-formylindole with acetylglycine. Bentley *et al.*[11] recently described the

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(4) For recent reviews on the metabolism of tryptophan, see A. H. Meister, *Biochemistry of the Amino Acids*, Academic Press Inc., New York, 1957, pp. 333, 407, and C. E. Dalgliesh, *Advances in Protein Chemistry*, **10**, 79 (1955).

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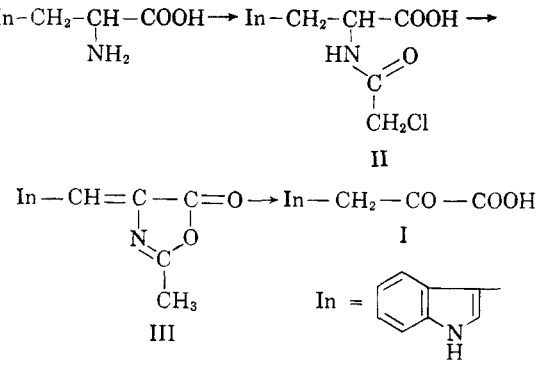

preparation of I (46% yield crude) from β-(3-indolal)hydantoin and reported that earlier syntheses, which involved the condensation of 3-formylindole with hippuric acid,[12] or with rhodanine,[13] are unsatisfactory.

The preparation of II by treating DL-tryptophan in alkaline solution with chloroacetyl chloride is well known.[14] The reported yield, however, has not exceeded 50-60%,[15] possibly because of side reactions.[16] In the present work, pure II was obtained readily in 88% yield by careful control of *p*H during acylation.

The Bergmann rearrangement[17] of II with pyridine and acetic anhydride provided crude oxazolone III in 92% and purified III in 56% yield. III reacts slowly with water or alcohols in the cold, but more rapidly on heating. Crystalline III has shown no change in properties during storage at 5° for several years.

The pyruvic acid I was prepared in 53% yield from crude oxazolone III and in 67% yield from purified III by alkaline hydrolysis. The yield and purity were impaired unless I was isolated rapidly from the aqueous hydrolyzate at a low temperature with exclusion of air. These precautions were adopted following the observation that the stability of I varies markedly with *p*H and solvent. A lower decomposition point of I and color development indicate slow deterioration in aqueous suspension, which is accelerated by mineral acids, and which also occurs to a lesser extent in alcoholic solution. The oxidative character of the breakdown is apparent from a recent report that I decomposes extensively in water on paper chromatograms,[11] where a fast reaction would be expected with a thin film exposed to air. I decomposes more rapidly at *p*H 8. Attempts to make the monosodium salt in water or absolute alcohol, analogous to the stable sodium phenylpyruvate,[18] yielded colored products of uncertain character, and the formation of 3-indoleacetic acid and 3- ormylindole was observed when a sodium bicarbonate solution of I was exposed to air. Stowe[19] has mentioned recently that a rapid conversion of enolic free acid to the keto form at *p*H 8 is followed by "other unknown changes." The decomposition of I in hot alkali during synthesis is relatively slow because of exclusion of air, and possibly because of further ionization to a more stable doubly charged anion.

Solutions of I in non-reactive dry organic solvents are relatively stable; however, short crystallization periods (3–4 hr.) and avoidance of prolonged heating are advisable. I forms stable solvates with dioxane or acetic acid; the acetic acid solvate is useful in isolation and purification because of its poor solubility. The pure solvates and free I in crystalline form have shown no change in properties during storage at 5° for three years, or at room temperature for several weeks; impure preparations slowly deteriorated at room temperature.

I was converted to its oxime (IV) by a modification of the method of Holland and Nayler.[20] The high yield (88%) and stability make IV of potential interest as a means of recovering small amounts of I from biological preparations.

β-(3-Indolyl)lactic acid (V) was prepared from the pyruvic acid I in 38% yield by reduction with sodium amalgam, and in 74% yield by hydrogenation over palladium oxide. An earlier report on sodium amalgam reduction gave no procedure or yield.[21] The poor yield from this method may be attributed to instability and partial loss of sodium indolepyruvate which is present at the start of the reaction. Side reactions also occurred during catalytic hydrogenation. The reduction of I to V in 85% yield by hydrogenation over Raney nickel was indicated without details in an earlier report.[22] The preparation of V in two steps from gramine and diethyl acetoxymalonate (52% overall yield) was reported recently from this laboratory.[23] A circuitous reduction of methyl indolepyruvate with sodium borohydride also has been described.[11] The earliest synthesis of V involved basic racemization of the D-antipode[21] which was obtained by

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fermentation of L-tryptophan with *Oidium lactis*.[24] V is stable in crystalline form, or in organic solutions. Decomposition occurs when aqueous solutions are concentrated,[24] however, and is accelerated by mineral acids.

β-(3-Indolyl)acrylic acid (VI) was obtained in 50% yield by condensation of 3-formylindole with malonic acid. Paper chromatography was used to follow the reaction. About 77% of the 3-formylindole was converted to a crude product containing 85% VI and 15% of the intermediate indolalmalonic acid (VII), which were separated readily by extraction and fractional crystallization. In contrast, most of the VI was destroyed and the remainder was grossly contaminated with decomposition products when the procedure of Baugess and Berg[22] was followed: *i.e.* repeated precipitation of VI by acidification of an alkaline solution and final recrystallization from water. Others also have criticized the original procedure because of low variable yields.[25,26] A synthesis of VI from 1-acetyl-3-formylindole and malonic acid (48% yield) was reported recently.[26] Solutions of VI in nonreactive organic solvents are stable. Crystalline VI has shown no change in properties during storage at 5° for three years.

3-Indolylglyoxylic acid (VIII) was prepared in 87% yield by condensation of oxalyl chloride with indole and hydrolysis of the resulting indoleglyoxylyl chloride (IX). The methyl ester and amide also were obtained in high yields from IX. Giua[27] erroneously designated an impure product of this reaction as 2-indolylglyoxylic acid; its correct nature was indicated by Kharasch *et al.*[28] and confirmed recently by Speeter and Anthony,[29] but sparse data were given. Other less efficient syntheses have involved the action of indolylmagnesium halides or indolylsodium on alkoxalyl chlorides or diethyl oxalate.[30-34] VIII is generally more stable than its homolog I. It decomposes slightly in hot aqueous alcohol solutions, however, and complete decomposition is observed when a hot alkaline solution is acidified.

Sodium 3-indolylglycolate (Na-X) was prepared from the glyoxylic acid VIII in 68% yield by reduction with sodium amalgam, and in 85% yield by hydrogenation over palladium oxide. Na-X also has been obtained, but without isolation, by condensation of indole with sodium glyoxylate,[35] and by reduction and saponification of esters of VIII.[11,33] Na-X is stable and readily purified; in contrast, the free acid X decomposes easily. Baker[33] observed a rapid breakdown when an aqueous solution of Na-X was acidified and concluded that X might be sensitive to atmospheric oxidation. Solutions of X in ether or methanol can be handled in air for short periods without serious loss, however, but X decomposes quickly as soon as it is precipitated from solution, even in absence of air and water. It is possible that aggregation to the solid state promotes an autocatalytic dehydration of X, with reactivity of the resulting 3-carboxymethyleneindolenine (XI) or intermediate carbonium ion leading to further changes. A similar mechanism was proposed recently to explain the behavior of 3-hydroxymethylindole.[36] In view of the instability of X, doubts may be held concerning a recently reported isolation of X from cabbage,[37] and earlier claims of synthesis by treatment of 3-dichloroacetylindole with alkali, or by oxidation of 3-chloroacetylindole.[38]

Several procedures were tested for converting the glyoxylic acid VIII to its oxime (XII) which was desired as a possible precursor for 3-indolylglycine.

(24) F. Ehrlich and K. A. Jacobsen, *Ber.*, **44**, 888 (1911).
(25) F. C. Happold and L. Hoyle, *Biochem. J.*, **29**, 1918 (1935).
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(27) M. Giua, *Gazz. chim. ital.*, **54**, 593 (1924).
(28) M. S. Kharasch, S. S. Kane, and H. C. Brown, *J. Am. Chem. Soc.*, **62**, 2243 (1940).
(29) M. E. Speeter and W. C. Anthony, *J. Am. Chem. Soc.*, **76**, 6208 (1954).
(30) R. Majima and T. Shigematsu, *Ber.*, **57**, 1449 (1924).
(31) R. Majima, T. Shigamatsu, and T. Rokkaku, *Ber.*, **57**, 1453 (1924).
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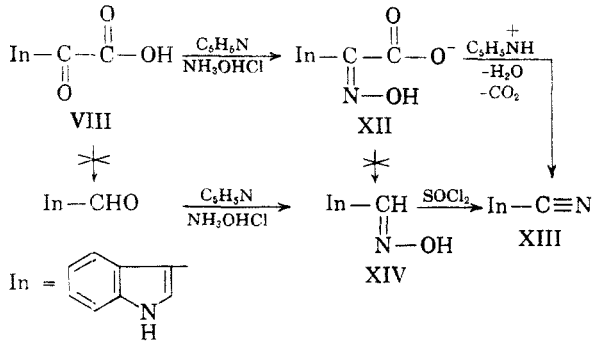
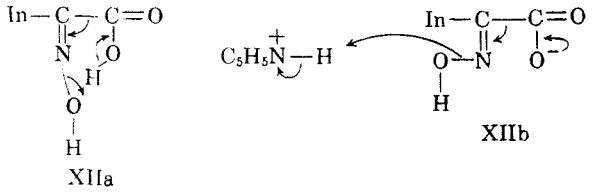
(36) E. Leete and L. Marion, *Can. J. Chem.*, **31**, 775 (1953).
(37) A. Fischer, *Planta*, **43**, 288 (1954); also see D. Racusen, *Arch. Biochem. Biophys.*, **58**, 508 (1955).
(38) G. Sanna, *Gazz. chim. ital.*, **59**, 838 (1929) [*Chem. Abstr.*, **24**, 2127 (1930)]; *Rend. seminario facolta sci. univ. Cagliari*, **4**, 28 (1934) [*Chem. Abstr.*, **30**, 6363 (1936)].

VIII was recovered unchanged after treatment with hydroxylamine hydrochloride in sodium bicarbonate solution at room temperature, conditions under which the homologous pyruvic acid I is transformed readily to its oxime IV. The lesser reactivity of VIII may be attributed to conjugation of the carbonyl and ring imino groups. When VIII was treated with hydroxylamine hydrochloride in boiling alcoholic pyridine, however, 3-cyanoindole (XIII) was obtained in 82% yield instead of oxime XII. An initial conversion to oxime XII probably occurs, followed by a simultaneous



dehydration and decarboxylation, which could be autocatalytic (XIIa) or catalyzed by pyridinium cation (XIIb). Simple decarboxylations of VIII or XII, which would lead to the aldoxime XIV as an



intermediate, are excluded as possible mechanisms because 3-formylindole is converted quantitatively to aldoxime XIV, and not to nitrile XIII, under conditions used for the glyoxylic acid VIII. The formation of XIII from VIII in hot potassium acetate solution was indicated without details in an earlier report.[31] XIII also has been prepared by dehydration of oxime XIV with acetic anhydride (*via* the 1-acetyl nitrile),[39] or with thionyl chloride,[40] by dehydration of 3-indolecarboxamide with phosphorus oxychloride,[40] and by the action of cyanogen chloride on indolylmagnesium iodide.[31]

The nitrile XIII is weakly acidic, and its solubility in water or aqueous alcohol increases upon addition of alkali. This property, which reflects electron withdrawal by the 3-cyano from the ring imino group, is useful in purification. XIII is stable in crystalline form or in organic solutions.

3-Indolylcarboxylic acid (XV) was prepared in 91% yield by alkaline hydrolysis of nitrile XIII. Majima *et al.*[31] mentioned without details the use of this reaction to characterize XIII. Other methods for the synthesis of XV which were tested included oxidation of 3-formylindole with alkaline permanganate,[41] reaction of indolyl magnesium iodide with carbon dioxide,[40,42] and oxidation of glyoxylic acid VIII with alkaline hydrogen peroxide. The yields from these reactions were inferior, however, and the products decomposed 12–20° lower than the product from hydrolysis of nitrile XIII, because of the presence of minor impurities which were revealed by paper chromatography.[9] The reaction of indolyl magnesium iodide with ethyl chloroformate has been used to make 3-carbethoxyindole (54–78% yield),[42,43] but hydrolysis of this ester to XV has not been reported. XV is stable in crystalline form and in alkaline solution. A partial decomposition of free XV in hot water however, has been mentioned in earlier reports.[44,45]

3-Indolylacetamide (XVI) was synthesized in 71% yield from indoleacetic acid *via* indoleacetyl chloride. The yield of acid chloride was increased from 66%[46] to 83% by use of low temperature and exclusion of moisture. The acid chloride was converted smoothly to amide XVI by the action of dry ammonia; an unsuccessful attempt to use this route was reported earlier.[47] XVI has been obtained previously in low yield by dry distillation of ammonium indoleacetate,[47] or as a byproduct in the hydrolysis of indoleacetonitrile to indoleacetic acid.[48–50]

EXPERIMENTAL

*N-Chloroacetyl-*DL*-tryptophan* (II). A solution of 102.1 g. (0.50 mole) of DL-tryptophan in 600 ml. of 0.83*N* sodium hydroxide was stirred vigorously at 5–10° while 59.3 g. (0.525 mole) of chloroacetyl chloride was added dropwise during 1 hr. The *p*H was held at 10.0–11.0 (Beckman *p*H meter) by concurrent addition of 115 ml. of 5*N* sodium hydroxide in small portions. The solution was stirred for 10 min. more, 500 ml. of ethyl acetate was added, and the mixture was acidified to *p*H 1.7 with 6*N* sulfuric acid.[51] The aqueous phase was separated and extracted with 3 more 100-ml. portions of ethyl acetate. The combined ethyl acetate extracts were washed with water, dried over anhydrous sodium sulfate, treated with charcoal, and concen-

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(40) F. P. Doyle, W. Ferrier, D. O. Holland, M. D. Mehta, and J. H. C. Nayler, *J. Chem. Soc.*, 2853 (1956).
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(46) E. Shaw and D. W. Woolley, *J. Biol. Chem.*, **203**, 979 (1953).
(47) J. W. Baker and F. C. Happold, *Biochem. J.*, **34**, 657 (1940).
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(50) F. Poppelsdorf and S. J. Holt, *J. Chem. Soc.*, 4094 (1954).
(51) When the solution was acidified in absence of ethyl acetate, impure II precipitated as a gum which crystallized slowly.

trated at a reduced pressure to 350 ml. The solution was seeded with a rubbed aliquot during the final stage of concentration and stored at 5° for 2–3 days with occasional shaking[52]; 98.5 g. (70% yield) of cream-colored crystals was collected, m.p. 154–155° (dec.) (in bath at 150°, 1° per minute).[53] A second crop of 25.8 g. (18% yield), m.p. 152–154° (dec.), was obtained from the filtrate. A sample was recrystallized from ethyl acetate with charcoal treatment,[54] m.p. 156–157° (dec.) (lit.[10] m.p. 154–155°).

Anal.[55] Calcd. for $C_{13}H_{13}ClN_2O_3$: C, 55.62; H, 4.67; Cl, 12.63; N, 9.98. Found: C, 55.89; H, 4.60; Cl, 12.35; N, 9.69.

2-Methyl-4-(3'-indolal)-5-oxazolone (III). A mixture of 112.3 g. (0.40 mole) of II, 300 ml. (3.20 moles) of acetic anhydride, and 100 ml. (1.24 mole) of anhydrous pyridine (distilled over barium oxide) was allowed to stand for 20 min. with occasional stirring. II dissolved rapidly and the temperature rose to 50°. The wine-red solution was stirred vigorously with a mixture of 1 kg. of crushed ice and 1 kg. of ice water for 30 min. The resulting mustard-yellow precipitate of III was collected on a filter, washed successively with cold water, cold 95% ethanol, and dried *in vacuo* over concentrated sulfuric acid and potassium hydroxide; 82.9 g. (92% yield), m.p. 175–182° (in bath at 160°). This material is suitable for preparation of indolepyruvic acid. A 32.0 g. portion was recrystallized from 2400 ml. of boiling benzene with charcoal treatment; brown floccules amounting to 8–10% of crude III thus were removed. III was recovered after 2 days at 5° and dried *in vacuo*[56]; 19.4 g. (56% yield), m.p. 195–197° (in bath at 190°). A second crop of 4.6 g. (13% yield), m.p. 181–190°, was obtained from the filtrate. A sample of the first crop was recrystallized 3 times from benzene (once with charcoal treatment) to give brilliant yellow needles, m.p. 200–201°.

Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.39. Found: C, 68.88; H, 4.46; N, 12.30.

In the optimal procedure, 3 moles of pyridine and 8 moles of acetic anhydride per mole of II react for 20 min. No effect was observed with larger proportions of pyridine or acetic anhydride. The yield of crude III decreased to 85% with 2 moles and to 60% with 1.5 moles of pyridine. The proportion of acetic anhydride was less critical; 5 moles still gave an 82% crude yield. With a 10 min. reaction period, the crude yield decreased to 83%. With reaction periods up to 24 hr., the crude yield was fairly constant; the m.p. of crude III decreased gradually, however, and its solubility in benzene increased; the recovery of purified III from benzene and its m.p. also declined progressively. Formation of an increasing proportion of the more soluble 1'-acetyl oxazolone (next section) may have been partly responsible for these changes.

2-Methyl-4-(1'-acetyl-3'-indolal)-5-oxazolone. A mixture of 5.86 g. (0.05 mole) of acetylglycine, 7.26 g. (0.05 mole) of 3-formylindole,[57] 4.10 g. (0.05 mole) of anhydrous sodium acetate, and 20 ml. (0.2 mole) of acetic anhydride was heated at 100° for 7 hr. The solution was cooled to room temperature and stirred rapidly with 50 ml. of cold water and 50 g. of ice for 30 min. The resulting brown gummy precipitate was collected on a filter, washed with cold water and several portions of cold ethanol, and dried *in vacuo* over phosphorus pentoxide and potassium hydroxide; 9.15 g., m.p. 112–175°. This material was recrystallized from benzene with charcoal treatment; 3.00 g. (23% yield), m.p. 196–199°. After 2 more recrystallizations from benzene, 1.97 g. of bright yellow needles was obtained, m.p. 204–205° (in bath at 190°); mixed with oxazolone III (m.p. 200–201°), m.p. 164–189°.

Anal. Calcd. for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.24; H, 4.53; N, 10.00.

This oxazolone was converted to indolepyruvic acid in the same manner as oxazolone III (next section).

β-(3-Indolyl)pyruvic acid (I). A suspension of 22.62 g. (0.10 mole) of oxazolone III, m.p. 195–197°, in 300 ml. of 10*N* sodium hydroxide was refluxed for 4 hr. under a stream of nitrogen. The sodium salt of *N*-acetyldehydrotryptophan precipitated at first, but redissolved quickly. The orange solution was cooled to 5°; 1200 g. of crushed ice and 500 ml. of peroxide-free ether then were added. The mixture was stirred vigorously and acidified to *p*H 1.7 *as rapidly as possible* with 6*N* sulfuric acid at a temperature not exceeding 10°. The aqueous phase, which contained sodium sulfate crystals, was separated and extracted with 3 more 500-ml. portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate, treated with charcoal, and concentrated at a reduced pressure under nitrogen until crystallization started (about 100 ml.); 500 ml. of benzene then was added and the solution was concentrated to dryness at <40°. Addition of benzene markedly curtailed darkening of the residue in the final stage of concentration. The residue was dissolved in 90 ml. of hot acetone and 90 ml. of glacial acetic acid was added. Following refrigeration, brownish-yellow crystals of I-acetic acid solvate were recovered; 16.20 g., dec. 217° (in bath at 215°, 3° per minute).[58] A further 2.52 g., dec. 216°, was recovered from the mother liquor. The combined crude crops were recrystallized from acetone-acetic acid (1:1) with charcoal treatment to give light yellow clustered blades;[59] 15.76 g., dec. 219°, and 1.86 g., dec. 218° (67% total yield). The yield decreased to 61% when the hydrolysis time was increased to 6 hr. When crude oxazolone III, m.p. 175–182°, was hydrolyzed for 4 hr., the yield was 53%.

Anal. Calcd. for $C_{11}H_9NO_3.C_2H_4O_2$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.15; H, 4.66; N, 5.21.

The solvate was recrystallized from acetone-benzene (1:3) to give free I (94% recovery, 2 crops) as pale yellow hexagonal plates, dec. 219°.[60] Free I also may be obtained by drying the solvate over potassium hydroxide *in vacuo*.[12]

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.05; H, 4.47; N, 6.89. Found: C, 64.85; H, 4.20; N, 6.67.

The dioxane solvate was obtained as a colorless powder, dec. 219°, when I was recrystallized from dioxane-benzene (1:5). Dioxane was removed from the solvate by drying at 100° and 0.1 mm. for 24 hr., or by recrystallization from acetone-benzene (1:3).

Anal. Calcd. for $2C_{11}H_9NO_3.C_4H_8O_2$: $C_4H_8O_2$, 17.8. Found: $C_4H_8O_2$, 18.1.

Stability of β-(3-indolyl)pyruvic acid (I) *in sodium bicarbonate solution.* A solution of 2.03 g. (0.01 mole) of I in 140 ml. of 1*N* sodium bicarbonate solution was allowed to stand

(52) More rapid crystallization could be promoted by adding cyclohexane, but the m.p. of II was then lower.

(53) Melting points are corrected and were taken in open capillary tubes.

(54) When II was recrystallized from boiling water,[14] an odor of indole was apparent, II acquired a violet color which was not removed by recrystallization from other solvents, and its m.p. was not improved. Crystalline II is slightly photosensitive.

(55) Analyses were performed by the Weiler and Strauss Microanalytical Laboratory, Oxford, England.

(56) Several days were required for removal of benzene at 10 mm. and 25°; the air-dried weight, 25.9 g., corresponded to one mole of benzene of crystallization.

(57) G. F. Smith, *J. Chem. Soc.*, 3842 (1954).

(58) Values reported in the literature range from 193° to 214°. Despite a recent contrary statement,[11] the decomposition point is readily reproducible and is a reliable criterion of purity under controlled heating conditions. The acetic acid and dioxane solvates decompose at the same temperature as free I, after initial decrepitation.

(59) Four more recrystallizations alternately from acetone-benzene and acetone-acetic acid yielded a colorless solvate, dec. 219°.

(60) Free I retained a pale yellow color even when a colorless solvate was recrystallized from acetone alone; the recovery in one crop was 20% or less unless benzene was added. A colorless free acid has been reported to result from repeated crystallization from acetone.[11]

at room temperature for 24 hr. with occasional shaking. The initially colorless solution darkened rapidly. The solution was extracted with four 150-ml. portions of ether; the combined ether extracts were dried over anhydrous sodium sulfate and concentrated at a reduced pressure to 0.05 g. of light brown solid in which only 3-formylindole was detected by paper chromatography.[61] The aqueous phase, after addition of 300 ml. of ether, was acidified with 6*N* sulfuric acid to *p*H 1.8 with stirring at 5°. The aqueous phase was separated and extracted with 2 more 150-ml. portions of ether. The combined *p*H 1.8 ether extracts were dried over anhydrous sodium sulfate and concentrated to dryness at a reduced pressure under nitrogen. The residue was crystallized from acetone-acetic acid (1:1) to give 1.27 g. (48% recovery) of I-acetic acid solvate in 4 crops, dec. 216–218°. The final mother liquor was concentrated to 0.90 g. of dark brown oily residue which was estimated by paper chromatography[61] to contain about 0.10 g. of I, 0.40 g. of indoleacetic acid, 0.02 g. of 3-formylindole, and other unidentified products.

β-(3-Indolyl)-α-oximinopropionic acid (IV). The procedure described in the preceding section was used with 3.47 g. (0.05 mole) of hydroxylamine hydrochloride added to the sodium bicarbonate solution before I. The neutral ether extracts were discarded. The residue from the *p*H 1.8 ether extracts was crystallized from anhydrous ether-petroleum ether (b.p. 30–60°) (1:3) to give 1.92 g. (88% yield) of IV as faintly yellow clustered blades, dec. 156° (in bath at 150°, 3° per min.). IV was recrystallized (88% recovery) from ethyl acetate-benzene (1:4) with charcoal treatment, dec. 158° (lit. dec. >175°,[22] 155°[20]).

β-(3-Indolyl)lactic acid (V). *A. Sodium amalgam reduction.* To a solution of 4.37 g. (0.021 mole) of I in 45 ml. of 1*N* sodium hydroxide was added 100 g. (0.13 g.-at.) of freshly-pulverized 3% sodium amalgam[62] in 10 equal portions at 5-min. intervals with high speed stirring. The mixture was stirred for 1 hr. more. The aqueous layer was separated, decolorized with charcoal, and extracted with ether to eliminate neutral impurities. The aqueous phase was treated with 100 ml. of ether and acidified with 6*N* hydrochloric acid to *p*H 1.6 with stirring at 5°. The aqueous phase was separated and extracted with 3 more 100-ml. portions of ether. The combined *p*H 1.6 ether extracts were dried over anhydrous sodium sulfate, treated with charcoal, and concentrated at a reduced pressure to dryness. The residue was dissolved in 240 ml. of hot 1,2-dichloroethane and the solution was treated with charcoal to remove tar. The filtrate was concentrated at a reduced pressure to 100 ml.; a small amount of purplish gum was separated by decantation. Following refrigeration, 2.06 g. of mauve-tinted powder was recovered, m.p. 140–144°. The crude V was recrystallized from 1,2-dichloroethane with charcoal treatment to give 1.66 g. (38% yield) of cream-colored powder, m.p. 144–145° (slow dec.) (lit.[11] m.p. 146–147°). Further material obtained from the mother liquors melted at a lower temperature over a wide range.

B. Catalytic Hydrogenation. To a solution of 10.53 g. (0.04 mole) of I-acetic acid solvate in 200 ml. of 95% ethanol was added 2.0 g. of palladium oxide. The mixture was hydrogenated at 50 lbs. pressure for 6 hr.; the uptake of hydrogen was not appreciable after 4 hr.[63] The catalyst was removed by filtration and the yellow filtrate, which darkened upon exposure to air, was concentrated to dryness at a reduced pressure. The residue was dissolved in 100 ml. of boiling ethyl acetate. The solution was filtered to remove 0.4 g. of brown amorphous powder, dec. 85–87°, and was treated with charcoal; the filtrate was concentrated to dryness. The residue was crystallized from ethyl acetate; 4.58 g. of V, m.p. 144–145° (dec.). The filtrate[64] was concentrated to dryness and the residue was crystallized from acetone-acetic acid (1:1); 0.52 g. of I-acetic acid solvate, dec. 217°. The filtrate was concentrated to dryness; the residue was concentrated to dryness again with benzene and with ethyl acetate, and then crystallized from ethyl acetate; 1.17 g. of V, m.p. 144–145° (dec.). The total yield of V was 74%, with allowance made for recovered I. The combined crops of V were recrystallized from ethyl acetate with charcoal treatment to give colorless crystals; 3.80 g., m.p. 146–147° (no dec.), and 0.98 g., m.p. 144–145° (dec.), (lit.[11] m.p. 146–147°).

β-(3-Indolyl)acrylic acid (VI). A solution of 14.52 g. (0.10 mole) of 3-formylindole[57] and 31.22 g. (0.30 mole) of malonic acid in a mixture of 160 ml. of pyridine (distilled over barium oxide) and 2.0 ml. of piperidine was maintained at 40° for 45 hr. The solution was concentrated at a reduced pressure and at <45° to an orange oil (68 g.). The oil was diluted with 250 ml. of water and the *p*H was adjusted to 11.0 with 2*N* sodium hydroxide. The solution was extracted with four 200-ml. portions of ethyl acetate to remove bases and neutral impurities. The aqueous phase was treated with charcoal, and the filtrate was acidified to *p*H 1.8 by dropwise addition of 6*N* hydrochloric acid with stirring at 5°. The resulting yellow precipitate was washed well with cold water and dried *in vacuo* over phosphorus pentoxide and potassium hydroxide; 14.68 g., dec. 173° (in bath at 170°, 3° per minute). The crude VI, which contained about 15% of 3-indolalmalonic acid (VII),[65] was extracted successively with 2500 and then 500 ml. of boiling anhydrous ether; 1.59 g. of VII, VI content 3%, remained undissolved as a greenish-yellow powder, dec. 178°. The combined ether extracts were concentrated at a reduced pressure to dryness. The residue was dissolved in 700 ml. of boiling ethyl acetate; the solution was treated with charcoal and the filtrate was concentrated at a reduced pressure to 175 ml. Following refrigeration, 9.33 g. (50% yield) of VI was obtained, VII content 0.1%, dec. 184° (in bath at 170°, 3° per minute), dec. 193° (in bath at 190°, 3° per minute). A sample recrystallized from ethyl acetate-cyclohexane (1:2) with charcoal treatment gave pale yellow clustered blades, VII content <0.02%, dec. 195° (in bath at 190°, 3° per minute) (lit.[26] dec. 192–3°).

Anal. Calcd. for $C_{11}H_9NO_2$: C, 70.59; H, 4.85; N, 7.48. Found: C, 70.62; H, 4.87; N, 7.45.

The crude VII (1.59 g.) from the ether extraction was recrystallized twice from hot methanol with charcoal treatment; in each case, the filtrate was concentrated at a reduced pressure until crystallization commenced. VII (0.66 g.) was obtained as intense yellow needles, VI content <0.02%, dec. 209° (in bath at 205°, 3° per minute) (lit.[26] dec. 208–209°).

(61) The decomposition and paper chromatography of I under various conditions will be described in a future publication.

(62) L. F. Fieser, *Experiments in Organic Chemistry*, 2nd ed., D. C. Heath and Co., New York, 1941, p. 418.

(63) Introduction of more catalyst at this point might have been helpful, since reduction was incomplete in 6 hours. Hydrogenation was slower in dioxane-95% ethanol (1:1), and did not occur at a measurable rate in dioxane, ethyl acetate, ethyl acetate-ethanol (4:1), or absolute ethanol.

(64) No further crystallization of V was induced by partial concentration. The filtrate, which was analyzed by paper chromatography, contained about 1.8 g. of V, 0.3 g. of indoleacetic acid, and 0.6 g. of I in 2.7 g. of total solutes.

(65) An appropriate series of aliquots of a tetrahydrofuran solution was chromatographed for 2 hr. on Whatman No. 1 paper with benzene-propionic acid-water (100:70:5) as the solvent together with authentic compounds (0.5–2.5 γ in 0.5 γ increments). The sheets were dried in air and sprayed with Ehrlich's *p*-dimethylaminobenzaldehyde reagent.[9] The composition of a crop was determined by visual comparison of the spots produced: 0.1 γ of VI or VII was readily detectable. The R_f's and the initial and final colors were as follows: VI, 0.73, light green → turquoise; VII, 0.14, yellow → turquoise.

Anal. Calcd. for $C_{12}H_9NO_4$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.46; H, 4.08; N, 5.96.

A suspension of 250 mg. of pure VI in 50 ml. of water was boiled gently while water (350 ml.) was added portionwise until the crystals just disappeared. The total heating time was 10 min. A white turbid mixture resulted and true solution was not observed. Following refrigeration, 147 mg. of pink powder was recovered, m.p. 93–134° (dec.); the VI content of this material was only 15%.

3-Indolylglyoxylyl chloride (IX). To a stirred solution of 29.3 g. (0.25 mole) of indole in 500 ml. of anhydrous ether at 0–5°, 25.0 ml. (0.29 mole) of oxalyl chloride was added dropwise during 30 min.; stirring and cooling were continued for 1 hr. more. The resulting yellow crystals of IX were collected on a filter, washed with anhydrous ether, and dried *in vacuo* over potassium hydroxide; 48.1 g. (92% yield), dec. 134° (in bath at 130°, 3° per minute). A sample was recrystallized from benzene, dec. 135° (lit.[28] dec. 135–136°); this material darkened to a copper color during storage at 5° for 3 years, dec. 131°.

3-Indolylglyoxylic acid (VIII). A suspension of IX in ether, prepared in the manner described above, was stirred at 0–5° and 1*N* potassium hydroxide (about 1000 ml.) was added slowly until the *p*H of the aqueous phase was 12. The fluorescent ether layer was separated and the aqueous phase was extracted with 3 more portions of ether to remove neutral impurities. The aqueous phase was treated with charcoal and 700 ml. of ethyl acetate was added to the filtrate; the mixture was stirred at 0–5° and acidified to *p*H 1.6 with 6*N* hydrochloric acid.[66] The ethyl acetate phase was separated and the aqueous phase was extracted twice more with ethyl acetate. The ethyl acetate extracts were dried over anhydrous sodium sulfate, treated with charcoal, and concentrated to dryness at a reduced pressure. The residue was dissolved in 250 ml. of boiling 95% ethanol and 1250 ml. of hot water was added. Following refrigeration, yellow crystals of VIII were recovered (a reddish-brown film suggested slight decomposition); 41.3 g. (87% yield from indole), dec. 218° (in bath at 215°, 3° per minute) (lit.[32] dec. 216°). Recrystallization from acetone-benzene (1:4) with charcoal treatment gave brilliant yellow dendrites (90–95% recovery), dec. 218°.

VIII (1.89 g., 0.01 mole) was subjected to the procedure described above for conversion of indolepyruvic acid (I) to its oxime (IV); 1.58 g. (84%) of VIII was recovered unchanged, dec. 217°, and no glyoxylic oxime (XII) was obtained.

Methyl 3-indolylglyoxylate. A mixture of 23.75 g. (0.114 mole) of crude IX, 10 ml. of pyridine and 1600 ml. of methanol was boiled gently until IX had dissolved. Following refrigeration, 21.70 g. (94% yield) of ester was obtained in two crops, m.p. 228–230° (no sintering), (lit.[33] m.p. 224°, with sintering at 210°). The crude ester was recrystallized from methanol with charcoal treatment and was recovered (88%) as pale yellow needles, m.p. 230–231°.

3-Indolylglyoxylamide. Crude IX (3.47 g., 0.0167 mole) was added slowly with stirring to 170 ml. of 1*N* ammonium hydroxide. After stirring for 30 min. more at 5°, the amide was recovered as a light brown powder; 2.89 g. (92% yield), m.p. 253–256° (dec.) (in bath at 250°, 3° per minute). Recrystallization from acetone-cyclohexane (1:1) with charcoal treatment, then absolute ethanol, gave 1.98 g. of colorless needles, m.p. 257–258° (dec.) [lit.[33] "slightly impure," m.p. 252° (dec.)].

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.9. Found: C, 63.66; H, 4.39; N, 14.7.

Sodium 3-indolylglycolate (Na-X). A. Catalytic hydrogenation. A suspension of 9.46 g. (0.05 mole) of crude VIII in 50 ml. of water was titrated to *p*H 7.5–8.0 with 2*N* carbonate-free sodium hydroxide; a small amount of insoluble material was removed by charcoal treatment. The filtrate and washings were treated with 1.0 g. of palladium oxide and hydrogenated at 50 lbs. pressure for 10 hr.; uptake of hydrogen was complete in 8 hr. The catalyst was removed by filtration and the filtrate was concentrated to dryness at a reduced pressure. The residue was concentrated to dryness again with absolute ethanol to remove water. The residue was simmered with 100 ml. of absolute ethanol, filtered, washed well with hot ethanol, then ether, and dried *in vacuo*. Na-X was obtained as a white powder; 9.32 g., dec. 306° (bath temperature 300°, 3° per minute). A solution of crude Na-X in 450 ml. of boiling methanol was treated with charcoal; an equal volume of ether was added to the filtrate. Following refrigeration, 8.91 g. (85% yield) was recovered in 2 crops. The salt was recrystallized again from methanol-ether, dec. 306°.

Anal. Calcd. for $C_{10}H_8NO_3Na$: C, 56.33; H, 3.78; N, 6.57; Na, 10.79. Found: C, 55.68; H, 4.10; N, 6.50; Na, 10.73.

The purity of Na-X was established by paper chromatography.[67] An unidentified by-product, which constituted about 10% of the residue from hydrogenation, 3% of the crude salt, and <1% after the first recrystallization, was not detectable after the second recrystallization. Similar proportions of this by-product were obtained when a hydrogenation was conducted over 4.0 g. of 5% palladium on charcoal (20 hr.); in this case, however, the yield of crude Na-X decreased to 70%, and 10% of the starting material was converted to indoleacetic acid.

B. Sodium amalgam reduction. A solution of 3.78 g. (0.02 mole) of crude VIII in 40 ml. of 0.5*N* sodium hydroxide was reduced with 61.3 g. (0.08 g.-at.) of 3% sodium amalgam[62] in the manner described above for preparation of indolelactic acid. The mixture was stirred for 90 min. more. The aqueous layer was separated, extracted with ether to remove neutral impurities, and treated with charcoal. The filtrate was mixed with 100 ml. of ether and acidified with 6*N* hydrochloric acid to *p*H 1.6 with stirring at 5°. The aqueous phase was separated and extracted with 3 more 100-ml. portions of ether. The combined *p*H 1.6 ether extracts were dried over anhydrous sodium sulfate, and treated with charcoal. The ether filtrate was colorless, but formed a reddish-violet residue if allowed to evaporate. The ether filtrate was mixed with 50 ml. of water, and 2*N* sodium hydroxide was added with stirring until the *p*H of the aqueous phase was 7.5–8.0. The aqueous phase was separated and treated in the manner described for the hydrogenation filtrate in the preceding section to give 2.88 g. (68% yield) of crude Na-X, dec. 306°. Chromatographically pure Na-X was obtained by a single recrystallization from methanol-ether (1:1).

C. Decomposition of 3-indolylglycolic acid (X).[68] A solution of 1.06 g. (0.005 mole) of Na-X in 50 ml. of methanol was shaken for 5 min. with 20 ml. of Dowex 50-X16 resin (hydrogen cycle, 2.6 m. eq./ml.) which had been washed well with water, boiling ethanol, and boiling methanol. The resin was removed by filtration, and the colorless filtrate was concentrated to dryness at a reduced pressure. The reddish-purple residue was shaken with 100 ml. of anhydrous ether to give an almost colorless solution; part of the residue remained undissolved. The mixture was treated with charcoal and filtered; 100 ml. of petroleum ether (b.p. 30–60°) was added to the filtrate to give an initially colorless flocculent precipitate which darkened rapidly. The mixture was

(66) In one run, the aqueous phase was acidified while hot; rapid decomposition ensued and no indoleglyoxylic acid was recovered.

(67) See (65): samples dissolved in methanol were chromatographed for 15 hours with isopropyl alcohol-aqueous ammonia-water (8:1:1) as the solvent. Colors developed by spraying with Ehrlich's reagent[9] and R_f values were Na-X, rose, 0.39; indoleacetic acid, blue-purple, 0.47; by-product, yellow, 0.43; VIII, no color with spray, dark blue under ultraviolet light, 0.48.

(68) A nitrogen atmosphere was used in this procedure until solid X had been isolated.

allowed to stand for 10 min.; 0.38 g. of rose-colored powder was recovered, dec. 203° (in bath at 200°, 3° per minute). Carbon dioxide was evolved when a sample was dissolved in 1*N* sodium bicarbonate; the bicarbonate solution was examined by paper chromatography.[67] The powder contained <10% indoleglycolic acid and at least four unidentified decomposition products.

3-Cyanoindole (XIII). *A. From* VIII. A mixture of 18.92 g. (0.10 mole) of crude VIII, 13.90 g. (0.20 mole) of hydroxylamine hydrochloride, 80 ml. (1.0 mole) of pyridine (distilled over barium oxide) and 80 ml. of absolute ethanol was refluxed for 4 hr. The solvents were removed at a reduced pressure; the residue was concentrated to dryness with three successive portions of absolute ethanol and then shaken with 100 ml. of water for several minutes until crystallization was complete. Following refrigeration, 11.64 g. (82% yield) of yellow-brown powder was obtained, m.p. 179–181°. Crude XIII was recrystallized from 50% aqueous ethanol with charcoal treatment and was recovered (91%) as light yellow clustered blades, m.p. 181–182°, unchanged by further recrystallization from benzene-methanol (12:1) (lit.[31] m.p. 178–180.5°).

Anal. Calcd. for $C_9H_6N_2$: C, 76.04; H, 4.25; N, 19.7. Found: C, 75.80; H, 4.28; N, 20.0.

B. From 3-formylindole. 3-Formylindole[67] (14.52 g., 0.10 mole) was subjected to the procedure described in the preceding section, with refluxing for 2 instead of 4 hr. Crude 3-indolylaldoxime (XIV) was obtained as peach-colored crystals; 15.87 g. (99% yield), m.p. 193–195° (dec.) (in bath at 190°, 3° per minute). A sample was recrystallized twice from ethanol-water (1:3) with charcoal treatment, and then from ethyl acetate, m.p. 201–202° (dec.) (lit.[69] m.p. 197–198°). Crude XIV was dehydrated with thionyl chloride[40] to give dark brown flakes of XIII (83% yield), m.p. 179–181°, unchanged by recrystallization from 50% aqueous ethanol. A sample (2.60 g.) of XIII suspended in 50 ml. of 50% aqueous ethanol at room temperature was dissolved by adding 30 ml. of 0.5*N* sodium hydroxide in 50% aqueous ethanol. The solution was decolorized by treatment with charcoal and the filtrate was adjusted to *p*H 6.5 with 6*N* hydrochloric acid. Following refrigeration, 2.20 g. (85% recovery) of colorless dendritic blades was obtained m.p. 182°, not depressed by admixture with XIII prepared from VIII.

3-Indolylcarboxylic acid (XV). A suspension of 7.11 g. (0.05 mole) of crude XIII in 75 ml. of 10*N* sodium hydroxide was refluxed under a stream of nitrogen for 7 hr. Crystals of indole (0.30 g., m.p. 50–51°) collected in the condenser; evolution of ammonia diminished in the last hour. The orange hydrolyzate was cooled to 5°, diluted with 300 g. of crushed ice, and acidified to *p*H 7.5 with 12*N* hydrochloric acid with stirring and continued cooling. The solution was extracted with 3 portions of ethyl acetate to remove neutral impurities; the aqueous phase then was filtered to eliminate gelatinous silica. The filtrate was stirred at 5° and acidified to *p*H 2.0 with 2*N* hydrochloric acid. The resulting XV was collected after refrigeration; 7.31 g. (91% yield), dec. 247° (in bath at 240°, 3° per minute), dec. 240° (in bath at 220°, 3° per minute) (lit.[40] dec. 220–224°); colorless needles after recrystallization from acetone-benzene (1:4) with charcoal treatment, dec. 247°.

Anal. Calcd. for $C_9H_7NO_2$: C, 67.06; H, 4.38; N, 8.69. Found: C, 67.01; H, 4.38; N, 8.77.

3-Indolylacetamide (XVI). To a stirred solution of 4.38 g. (0.025 mole) of indoleacetic acid in 100 ml. of anhydrous ether at −10°, 5.73 g. (0.0275 mole) of phosphorus pentachloride was added in small portions during 20 min.; stirring was continued for 10 min. more. The solution was concentrated to 40 ml. at a reduced pressure, treated with 400 ml. of cold petroleum ether (b.p. 30–60°) and filtered quickly to remove a small amount of dark red amorphous precipitate. Pale pink plates were collected after 4 hours at 5°; 1.55 g., m.p. 67–68° (dec.) (lit.[46] m.p. 68°). The filtrate was concentrated to 100 ml. at a reduced pressure to give 2.46 g. of cream-colored plates, m.p. 65–66° (dec.). Each crop was dried briefly *in vacuo* over phosphorus pentoxide and potassium hydroxide to remove phosphorus oxychloride; the total yield of indoleacetyl chloride was 83%.

A brisk current of dry ammonia was passed through a solution of the 2 crops of acid chloride in 100 ml. of anhydrous tetrahydrofuran (distilled over lithium aluminum hydride) at 5° for 30 min.[70] The mixture was filtered after 30 min. more to remove ammonium chloride. The filtrate was concentrated to dryness at a reduced pressure. The residue was crystallized from ethyl acetate-cyclohexane (1:1) with charcoal treatment; 3.10 g. (86% yield from the acid chloride, 71% from indoleacetic acid) m.p. 153–154°. Colorless blunt needles of XVI were obtained by recrystallization from ethyl acetate, m.p. 154° (lit.[48] m.p. 153°).

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(69) N. Putochin, *Ber.*, 59, 1987 (1926).

(70) Up to this point, equipment was thoroughly dried, and exposure to atmospheric moisture was kept to a minimum.