[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, HARVARD MEDICAL SCHOOL]

# The Cyclization of β-(4-Carboxy-3-indole)-propionic Acids

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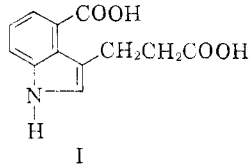
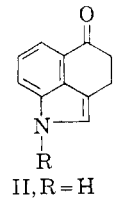
The course of the transformation of β-(4-carboxy-3-indole)-propionic acids to tricyclic benz[cd]indole derivatives is discussed. The isolation of intermediate cyclic anhydrides is described. An account of the preparation of a number of new precursors of the dicarboxylic acids is presented.

Some years ago we reported the synthesis of 5-keto-1,3,4,5-tetrahydrobenz[cd]indole (II) from β-(4-carboxy-3-indole)-propionic acid (I) with acetic anhydride in the presence of potassium cyanide.[1] At that time the procedure appeared to be an unusually specific one inasmuch as earlier ventures, under many modifications, to effect ring closure of the dicarboxylic acid, or of its esters, had been wholly without issue.

Treatment of the N-acetyl dimethyl ester of I with basic reagents under Dieckmann conditions, or pyrolysis of alkaline earth salts of I, for example, had led only to recovery of unchanged bicyclic indole. In fact, the approach to tricyclic structures through intermediates of the type of I was about to be suspended when it was found that prolonged reflux of an acetic anhydride solution of the propionic acid derivative, followed by alkaline hydrolysis, gave rise to the well crystalline, lemon-yellow ketone II in 80% yield.[2]



I



II, R = H
III, R = $COCH_3$

Subsequent experimentation soon demonstrated, however, that this successful performance could not invariably be repeated. Indeed, in no repetition did the yield of the desired product duplicate that of the very first attempt and eventually, with new supplies of I, the transformation could no longer be accomplished at all. It was recognized that these erratic results probably were related to an inconstant quality of the successive samples of the dicarboxylic acid which had been used. The compound habitually had been precipitated with mineral acid from a concentrated alkaline hydrolytic medium, circumstances under which it separates in a voluminous, hydrated form, doubtless occluding ions difficult to remove by washing alone. Moreover, because of the losses attendant on purification, the material had not been recrystallized, an expedient then considered justified by the fact that the melting point of the crude product differed very little from that of the analytical specimen.

In any case, it appeared likely that those lots of I which had given II might have contained trace amounts of a substance which had acted in catalytic fashion. As a test of this notion, a series of experiments was carried out, in the presence of selected inorganic salts, with samples of I which had failed to give II with acetic anhydride alone. In the most satisfactory of these trials, addition of small quantities of potassium cyanide was found to lead to the production of II in excellent yield.

This purely empirical observation was accepted and a set of conditions was defined which, in practice, served fairly well for a time in routine preparative work, although inexplicable failures still were not uncommon. In the impetus to proceed with later stages of a multi-step synthetic scheme, the cyclization reaction itself was not subjected to further scrutiny. Admittedly, the actual course of the transformation and the function of the catalyst were not entirely understood. More recently, we have been interested in summarizing our experience and in contributing an interpretation of the process, stimulated in part by the appearance in the literature of reports[3] of the application of our as yet unexpounded conditions in endeavors to induce ring closures which had not succeeded with conventional methods.

In a re-examination of the transformation, we confirmed first, beyond doubt, that a catalyst is indeed obligatory. A procedure was devised for purification of the dicarboxylic acid which ensured its homogeneity and freedom from metal ions. When this material was allowed to react for several days with acetic anhydride at 140°, the solution remained nearly colorless, as opposed to the coal-black hue of the customary reaction mixture with crude dicarboxylic acid or with dicarboxylic acid in the presence of potassium cyanide. Alkaline treatment, subsequent to vacuum distillation of the reagent, demonstrated the absence of neutral product and permitted virtually complete recovery of the starting compound.

However, an alternative work-up by diminished pressure evaporation of the acetic anhydride, followed by sublimation at 0.05 mm., gave a crystalline product which was shown to be the N-acetyl anhydride IV.[4] The substance furnished an infrared spectrum with prominent bands at 5.56 and 5.73 μ, attributed to a cyclic anhydride constitution[5]

(1) F. C. Uhle, THIS JOURNAL, **71**, 761 (1949).

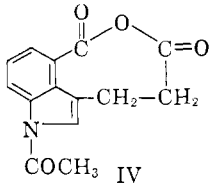
(2) Friedel–Crafts cyclization of the acid chloride of β-(3-indole)-propionic acid with stannic chloride had proceeded with entry only into the 2-position of the indole nucleus to give the isomeric 1,2-dihydrocyclopent(b)indole-3(4)-one in relatively low conversion.

(3) *Cf., e.g.*, W. J. Horton, H. W. Johnson and J. L. Zollinger, THIS JOURNAL, **76**, 4587 (1954); H. Rapoport and J. Z. Pasky, *ibid.*, **78**, 3788 (1956).

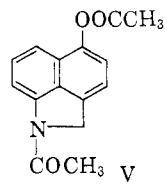
(4) The reaction mixture crystallized even before sublimation, giving, from ethyl acetate, a material which began to melt at *ca.* 100°, followed by solidification and subsequent remelting at a higher temperature, suggesting the initial presence of linear anhydrides.

(5) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," second edition, John Wiley and Sons, Inc., New York, N. Y., 1958, p. 127.

and afforded the N-acetyl derivative of I when gently treated with water.[6]




IV




V

This new eight-membered ring anhydride was found to be remarkably stable to pyrolysis. No evidence of decarboxylation was apparent at temperatures as high as 300°. Reflux of a xylene solution in the presence of powdered glass was ineffectual in provoking any change.[7] With anhydrous pyridine in a sealed tube at 150°, on the other hand, decomposition set in, and the ketone II was isolated in 50% yield, suggesting the involvement of basic catalysis.

Indeed, since potassium cyanide is known[8] to react with acetic anhydride to give α-acetoxy-α-methyl-malononitril ("diacetyl cyanide") and potassium acetate, it appeared that in the standardized procedure the salt had functioned essentially as a base and that the cyanide radical, as such, had played no indispensable role in the cyclization process. In fact, when a boiling acetic anhydride solution of IV was treated with 0.25 equivalent of potassium acetate, or of sodium acetate, the ketone II was produced in yields of the order of 80%. Exposure of IV to 0.25 equivalent of *p*-toluenesulfonic acid in hot acetic anhydride, followed by subjection to dilute alkali, led only to substantially quantitative return of I. Comparable results were obtained when the dicarboxylic acid I was substituted for the anhydride IV as the starting compound in these several experiments.

An acetic anhydride solution of I containing 0.25 equivalent of triethylamine, after 15 hours at 140°, gave rise to 25% of II, accompanied by regain of unused dicarboxylic acid. Moreover, a modest yield (32%) of the ketone II was secured simply by fusion in a sublimation tube of an intimate mixture of IV and 0.30 equivalent of anhydrous sodium acetate.

In the presence of one equivalent of potassium acetate in refluxing acetic anhydride with IV, or with I, on the other hand, the reaction mixture rapidly darkened[9] and the diacetylaminonaphthol derivative V, representing rearrangement of the double bonds of II, was the lone product isolated.[10]

At the time of the early cyclization work, the problem of the 5-keto-1,3,4,5-tetrahydrobenz(cd)-indole–5-hydroxy-1,2-dihydrobenz(cd)indole,[11] or indole–naphthalene (indoline), interrelationship which was destined to assume a central position in studies of benz(cd) indole chemistry had not as yet been explored extensively. While we had succeeded in preparing the N-acetyl derivative III from II with acetic anhydride alone,[12] investigators in another laboratory later demonstrated a rather singular influence of alkali acetates on the acylation.[13] According to these authors, sodium acetate in acetic anhydride favored the preparation of III, although with lithium acetate the product was a molecular complex of II and III, while potassium acetate brought about complete conversion to V. It is difficult to judge whether or not these findings are to be ascribed at least in some measure to metal ion properties other than relative basic strength.[14]

In any event, experience with the anhydride IV, and with the rigidly purified dicarboxylic acid I, together with recognition of the propensity to double bond migration within the tetrahydrobenz(cd)indole nucleus under certain circumstances, prompted insight into the ostensibly mercurial nature of the ring closure reaction. It is now clear that, while a base is required to initiate collapse of the anhydride to the cyclic ketone, sufficiently active catalysts in unduly high concentrations lead further to transformation to the naphthalene tautomer, probably through initial formation of the enol acetate.[15]

The outcome of any individual experiment thus is sensitively dependent on a number of variables, including the intrinsic power and concentration of the catalyst as well as the temperature and duration of exposure. With potassium acetate, for example, the range over which the equivalence of the salt may vary is severely restricted.

Presumably in the early successful productions of II, a promoting agent must fortuitously have been present in an amount within the limits permitting condensation without extensive rearrangement. Inasmuch as work-up of most runs had involved an alkaline hydrolysis step,[16] failure of cyclization

(6) Anhydrous hydrogen chloride in benzene solution gave the half acid chloride of the N-acetyl derivative of I which, as attested by its infrared spectrum, appears to be 1-acetyl-β-(4-chlorocarbonyl)-3-indole)-propionic acid.

(7) *Cf.* the postulated generalization of M. S. Newman and E. G. Calfisch, Jr., THIS JOURNAL, **80**, 862 (1958), that "solid surfaces catalyze reactions in solution in which a gas is formed."

(8) S. Kleeman, *Ber.*, **18**, 256 (1885); K. Brunner, *Monatsh.*, **15**, 747 (1894); C. S. Marvel, N. O. Brace, F. O. Miller and A. R. Johnson, THIS JOURNAL, **71**, 34 (1949).

(9) Observation of pronounced discoloration of the reaction mixture in the presence of bases was, in general, in itself a reliable indication that naphthol acetate formation had occurred.

(10) As much as 2.5 equivalents of sodium acetate, however, still allowed isolation of II in 65% yield.

(11) C. A. Grob and J. Voltz, *Helv. Chim. Acta*, **33**, 1796 (1950).

(12) F. C. Uhle, THIS JOURNAL, **73**, 2402 (1951).

(13) C. A. Grob and P. Payot, *Helv. Chim. Acta*, **36**, 839 (1953). We have been unable to substantiate the claim of these workers that III, once formed, proved stable to potassium acetate in acetic anhydride solution. In our hands, III is unquestionably transformed to V under these conditions.

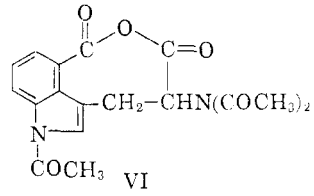
(14) Review of the imposing body of often seemingly discordant findings with series of the various alkali and alkaline earth acetates in acetic anhydride solution which has accumulated as a consequence of over 80 years study of the Perkin reaction is an exercise sufficiently sobering to caution restraint in attempting to give a meaningful explanation of results of this type; *cf.* J. R. Johnson in "Organic Reactions," edited by R. Adams, John Wiley and Sons, Inc., New York, N. Y., Vol. 1, 1942, p. 210.

(15) While the facts reported in this communication do not, of course, incontrovertibly prove the intermediacy of the anhydride IV in the reactions employing the dicarboxylic acid I, all evidence at hand is consistent with this view.

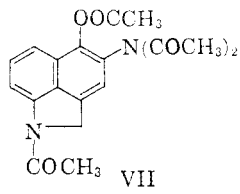
(16) In one series, vacuum distillation of the reagent was followed by Soxhlet extraction of the remaining magma with low boiling petroleum ether to provide the N-acetyl derivative III directly. This procedure serves well in the event that reaction has proceeded without appreciable tautomerization. However, mixtures of III and V are exceedingly difficult, if not impossible, to separate by fractional crystallization. On a column of aluminum oxide, V invariably undergoes ester hydrolysis, followed by partial oxidation, giving rise to a complex mixture of products.

as witnessed by minimal obtention of II could have been "actual," due to the absence of ring closure altogether, or only "apparent," with the indoline derivative, connoting an alteration of the primary product, secluded in the basic medium as a phenolic salt.[17]

From the outset, attempts to secure tricyclic amino ketones by ring closure of $\alpha$-acetylamino derivatives of I with acetic anhydride in the presence of potassium cyanide had given naphthalene (indoline) tautomers as the sole crystalline products.[18] In the knowledge of the newer results with IV, we were interested in preparing and in studying the behavior of the corresponding $\alpha$-acetylamino anhydride. Curiously enough, this substance could not be realized with acetic anhydride alone under the conditions which gave IV. However, in the presence of 0.25 equivalent of potassium acetate after a reaction period of 2 hours at 140°, the substituted anhydride VI was readily acquired in 60% yield.



VI



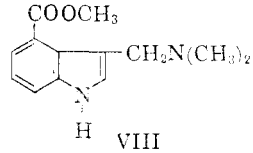
VII

In formal analogy with base-catalyzed reactions of esters characterized by the presence of only a single $\alpha$-hydrogen atom,[19] the diacetylamino anhydride VI proved considerably more resistant than IV to internal condensation. Pyridine, triethylamine, two equivalents of lithium acetate in acetic anhydride, four equivalents of sodium acetate in acetic anhydride, all at 140°, left the substance unattacked. In the presence of four equivalents of potassium acetate, however, an acetic anhydride solution rapidly darkened, presaging indoline formation and, indeed, the tetraacetylaminonaphthol VII was the single product isolated. It appears that with the diacetylamino anhydride VI, conditions required for condensation so closely approximate those effective in evoking double bond migration as to exclude the possibility of preparing 1,3,4,5-tetrahydrobenz(cd)indole amino ketones by this route.[20]

Apparently the earliest examples of the preparation of cyclic ketones by treatment of dicarboxylic acids with acetic anhydride are to be credited to Lapworth and Chapman[21] and to Perkin and Thorpe[22] at the turn of the century. It remained for Blanc,[23] in 1907, to put forward the generalization that substituted adipic and pimelic acids give, respectively, five- and six-membered ring ketones while succinic and glutaric acids, when heated with acetic anhydride, afford only cyclic anhydrides. Subsequently, this so-called "Blanc rule" was much invoked in establishment of ring size during the early days of structural studies of polycyclic systems, notably of the sterols and of the bile acids.

While many illustrations of the exploitation of the transformation as a synthetic device have been recorded,[24] the mechanism of the change appears to have received little attention. In most applications, the dibasic acid merely has been allowed to react with refluxing acetic anhydride, followed by distillation of those products sufficiently volatile. Although a tedious canvass of the literature for relevant previous experience bearing on the point is obviously subject to errors of omission, we are not aware of an exact precedent for our findings. The case under consideration, of course, represents an example of especial complexity with the hazard of supervention of the double bond rearrangement peculiar to the benz(cd)indole system.

We take this occasion to set down the experimental details for the synthesis of a new series of precursors of the $\beta$-(4-carboxy-3-indole)-propionic acids employed in these studies. 4-Carbomethoxygramine (VIII) was prepared from 4-carbomethoxyindole with formaldehyde and dimethylamine and was utilized as a Mannich alkylating agent with appropriate active methylene compounds. Condensation with the sodium derivatives of dimethyl malonate, dimethyl acetaminomalonate and dimethyl acetylmethylaminomalonate[25] afforded the substituted malonic esters in excellent yields.



VIII

As in the fully studied case of methyl $\alpha$-acetylmethylamino - $\alpha$ - carbomethoxy - $\beta$ - (4 - cyano-3-indole)-propionate,[18b] hydrolysis of the acetylamino esters in concentrated fixed alkaline solution presented difficulties, presumably again associated with side chain cleavage. A related instance has recently been reported from another laboratory.[26]

Nevertheless, the requisite dicarboxylic acids were successfully obtained by stepwise hydrolysis.

(17) Acidification of the highly pigmented alkaline phase in most cases gave only a dark intractable resin. Since the free phenolic compound is understandably rather labile and since the dicarboxylic acid I precipitates only slowly and incompletely from such a solution, an accurate accounting of the composition of the basic extract was rarely feasible. It is now recognized that treatment of the entire desiccated fraction with methanol in the presence of sulfuric acid, followed by isolation of the well crystalline dimethyl ester of I, offers the method of choice for estimation of percentage conversion.

(18) (a) F. C. Uhle and S. H. Robinson, THIS JOURNAL, **77**, 3544 (1955); (b) F. C. Uhle and L. S. Harris, *ibid.*, **79**, 102 (1957).

(19) *Cf.* C. R. Hauser and B. E. Hudson, Jr., in "Organic Reactions," Edited by R. Adams, John Wiley and Sons, Inc., New York, N. Y., Vol. 1, 1942, p. 266.

(20) Treatment of 4-acetamino-5-keto-1,3,4,5-tetrahydrobenz(cd)-indole (A. Stoll, J. Rutschmann and Th. Petrzilka, *Helv. Chim. Acta*, **33**, 2257 (1950)) with 2.5 equivalents of potassium acetate in refluxing acetic anhydride gave 80% of VII.

(21) A. Lapworth and E. M. Chapman, *J. Chem. Soc.*, 464 (1900).

(22) W. H. Perkin, Jr., and J. F. Thorpe, *ibid.*, 128 (1904); W. H. Perkin, Jr., *ibid.*, 416 (1904); 1640 (1906).

(23) H. G. Blanc, *Compt. rend.*, **144**, 1356 (1907); *Bull. soc. chim.*, **3**, 778 (1908).

(24) *Cf.*, *inter alia*, W. Borsche and E. Lange, *Ann.*, **434**, 231 (1923); W. Hückel, *ibid.*, **444**, 14 (1925); W. Hückel and H. Friederich, *ibid.*, **451**, 153 (1927); J. C. Bardhan, *J. Chem. Soc.*, 1848 (1936); A. Windaus, W. Hückel and G. Revery, *Ber.*, **56**, 91 (1923); M. Levitz, D. Perlman and M. T. Bogert, *J. Org. Chem.*, **6**, 105 (1941); W. E. Bachmann and N. C. Deno, THIS JOURNAL, **71**, 3540 (1949).

(25) F. C. Uhle and L. S. Harris, *ibid.*, **78**, 381 (1956).

(26) H. R. Snyder and D. S. Matteson, *ibid.*, **79**, 2217 (1957), have observed that attempted alkaline hydrolysis of diethyl (3-indolylethylidene)-acetamidomalonate gave acetylglycine.

In a modified sequence, condensation of 4-carbomethoxygramine with dibenzylacetaminomalonate, followed by hydrogenolysis with palladium, alkaline hydrolysis and decarboxylation with pyridine, gave α-acetamino-β-(4-carboxy-3-indole)-propionic acid in good over-all conversion. Certain newly observed properties of this compound have been mentioned in the Experimental section.

Finally, we record the preparation of several related substances which were desired for particular purposes. Among these derivatives were ethyl α - carbomethoxy - α - bromo - β - (4 - cyano-3-indole)-propionate, diethyl α,α-di-(4-cyanoskatyl)malonate, (4-cyano-3-indolyl)-acetonitrile and methyl (4-carbomethoxy-3-indole)-acetate.

## Experimental

The melting points were observed on a calibrated micro hot-stage. The microanalyses were performed by Dr. S. M. Nagy and associates of the Massachusetts Institute of Technology, Cambridge, Mass. The infrared spectra, in potassium bromide or in chloroform solution, were recorded with Perkin–Elmer spectrophotometers, models 21 and 137. The bands indicated are those of significance in interpretation.

**β-(4-Carboxy-3-indole)-propionic Acid (I).**—A solution of 1.8 g. of crude acid, obtained by alkaline hydrolysis of ethyl α-carboethoxy-β-(4-cyano-3-indole)-propionate[1] followed by precipitation with hydrochloric acid (light red powder, m.p. 170–180°), in 50 ml. of methanol containing 1.5 ml. of concentrated sulfuric acid was maintained at reflux temperature for 15 hours. The color of the solution resembled that of potassium permanganate. The methanol was distilled under reduced pressure. The residue was extracted with ether. The organic phase was washed with dilute aqueous potassium bicarbonate and with water. The residue from the dried ($MgSO_4$) ether solution was recrystallized 5 times from methanol to give 1.5 g. of methyl β-(4-carbomethoxy-3-indole)-propionate, m.p. 93–95°.[27]

A solution of this colorless material in 50 ml. of 10% aqueous methanolic (1:3) potassium hydroxide was maintained at reflux temperature for 4 hours. The methanol was distilled under reduced pressure. The residual aqueous phase was acidified with 6 *N* hydrochloric acid to give a clear solution from which, after a few minutes, clusters of fine needles began to separate. After 15 hours at 0°, the colorless precipitate was collected by filtration, washed with water and dried; yield 1.3 g., m.p. 175–180°. The product was recrystallized 5 times from a mixture of acetic acid and water according to the following proportions: 1.0 g. of the dicarboxylic acid was treated with 3.0 ml. of glacial acetic acid, followed by the addition of 10 ml. of water. The repeatedly recrystallized compound melted at 179–181°.[27]

**Reaction of β-(4-Carboxy-3-indole)-propionic Acid with Acetic Anhydride in the Presence of 0.25 Equivalent of Sodium Acetate. A.**—A solution of 115 mg. (0.0005 mole) of β-(4-carboxy-3-indole)-propionic acid (I) (m.p. 179–181°) and 10 mg. (0.00012 mole) of fused sodium acetate in 5 ml. of acetic anhydride was maintained at reflux temperature, in the absence of light, for 15 hours. The acetic anhydride was distilled under reduced pressure. The residue was dissolved in 5 ml. of 5% aqueous methanolic (1:1) potassium hydroxide. After 1 hour at reflux temperature the methanol was distilled under reduced pressure. The residue was extracted with a mixture of ether and chloroform (3:1). The extract was washed with 2 *N* aqueous hydrochloric acid and with water and was dried over anhydrous sodium sulfate. The residue (69 mg.) from vacuum distillation of the solvents was recrystallized from a mixture of acetone and petroleum ether (b.p. 30–60°) to give 58 mg. (68%), m.p. 160–164°; infrared spectrum identical with that given by 5-keto-1,3,4,5-tetrahydrobenz(cd)indole(II): 6.07μ (carbonyl associated with NH).

**B.**—A solution of 115 mg. (0.0005 mole) of β-(4-carboxy-3-indole)-propionic acid (I) (m.p. 179–181°) and 10 mg. (0.00012 mole) of fused sodium acetate in 5 ml. of acetic anhydride was maintained at reflux temperature for 15 hours. The acetic anhydride was distilled under reduced pressure. The residue was extracted with refluxing benzene. The benzene solution was clarified by filtration and concentrated under reduced pressure. The remainder was recrystallized from a mixture of acetone and petroleum ether (b.p. 30–60°) to give 63 mg., m.p. 135–140°. A second recrystallization from the same solvents afforded 41 mg. (39%),[28] m.p. 142–147°; infrared spectrum identical with that given by 1-acetyl-5-keto-1,3,4,5-tetrahydrobenz(cd)-indole(III): 5.92μ (carbonyl), 5.97μ (>$NCOCH_3$).

**Reaction of β-(4-Carboxy-3-indole)-propionic Acid (I) with Acetic Anhydride in the Presence of 0.25 Equivalent of Potassium Acetate.**—A solution of 143 mg. (0.0006 mole) of β-(4-carboxy-3-indole)-propionic acid and 15 mg. (0.00015 mole) of potassium acetate in 5 ml. of acetic anhydride was maintained at reflux temperature for 16 hours. The acetic anhydride was distilled under reduced pressure. The residue was extracted with refluxing benzene. The solution was clarified by filtration and concentrated under diminished pressure. The remainder (125 mg.) was recrystallized from a mixture of dichloromethane and ether to give 104 mg., m.p. 120–142°. Recrystallization from a mixture of dichloromethane and ether gave 90 mg. (71%) of III, m.p. 147–152°; infrared spectrum identical with that of 1-acetyl-5-keto-1,3,4,5-tetrahydrobenz(cd)indole (III): 5.92μ (carbonyl), 5.97μ (>$NCOCH_3$).

**Reaction of β-(4-Carboxy-3-indole)-propionic Acid (I) with Acetic Anhydride in the Presence of 1 Equivalent of Potassium Acetate.**—A solution of 200 mg. (0.00086 mole) of β-(4-carboxy-3-indole)-propionic acid and 120 mg. (0.0012 mole) of potassium acetate in 10 ml. of acetic anhydride was maintained at reflux temperature for 15 hours. The solution was divided into two equal parts which were processed according to (a) and (b), respectively.

(a) The acetic anhydride was distilled under reduced pressure. The residue was extracted with refluxing benzene. The benzene solution was clarified by filtration and concentrated *in vacuo*. The remainder was recrystallized from a mixture of dichloromethane and ether to give 70 mg. (64%) of V, m.p. 164–170°; infrared spectrum identical with that given by 1-acetyl-5-acetoxy-1,2-dihydrobenz(cd) indole (V): 5.70μ (phenolic ester), 5.98μ (>$NCOCH_3$).

(b) The acetic anhydride was distilled under reduced pressure. The residue was dissolved in 10 ml. of 5% aqueous methanolic (1:1) potassium hydroxide. After 45 minutes at reflux temperature the methanol was distilled under reduced pressure. The residue was extracted with a mixture of ether and chloroform (3:1). The extract was washed with 2 *N* aqueous hydrochloric acid and with water and was dried over anhydrous sodium sulfate. The remainder (11 mg.) from vacuum evaporation of the solvents gave, from a mixture of acetone and petroleum ether (b.p. 30–60°) 4 mg. (5%) of II, m.p. 160–163°; infrared spectrum identical with that of 5-keto-1,3,4,5-tetrahydro-benz(cd)indole (II): 6.07μ (carbonyl associated with NH).

**Reaction of β-(4-Carboxy-3-indole)-propionic Acid (I) in the Presence of 0.25 Equivalent of Triethylamine.**—A solution of 117 mg. (0.0005 mole) of I and 12.5 mg. (0.000125 mole) of triethylamine in 6 ml. of acetic anhydride was kept at reflux temperature for 15 hours. The acetic anhydride was distilled under reduced pressure. The residue was extracted with several successive portions of hot benzene. The benzene was evaporated *in vacuo* to give 140 mg. of oil which failed to crystallize. This material was dissolved in 10 ml. of a 5% aqueous methanolic (1:1) potassium hydroxide solution. After 1 hour at reflux temperature the methanol was distilled under diminished pressure. The aqueous alkaline phase was extracted with a mixture of chloroform and ether (1:3). The organic solution was washed with water and was dried over anhydrous sodium sulfate. Vacuum distillation of the solvents gave 22 mg. (25%) of a yellow crystalline residue of II, m.p. 150–160°. Recrystallization from a mixture of acetone and ether brought the melting point to 160–162°.

The alkaline aqueous phase was acidified with 3 *N* hydrochloric acid and evaporated to dryness under reduced pressure. The residue was treated with 10 ml. of absolute methanol containing 0.5 ml. of concentrated sulfuric acid. After 5 hours at reflux temperature the methanol was distilled under reduced pressure. The residue was diluted with 5 ml.

(27) This melting point supersedes that given in the first publication.[1]

(28) The lower yield in procedure B reflects the greater difficulty of isolation of the N-acetyl derivative in a high degree of purity.

of water and extracted with ether. The organic phase was washed with water and was dried over anhydrous sodium sulfate. The residue (68 mg.) from vacuum evaporation of the ether gave, from a mixture of ether and petroleum ether (b.p. 30–60°), 30 mg. (23%) of the dimethyl ester of I, m.p. 90–94°.

**Treatment of β-(4-Carboxy-3-indole)-propionic Acid (I) with Acetic Anhydride in the Presence of 0.25 Equivalent of *p*-Toluenesulfonic Acid.**—A solution of 115 mg. (0.0005 mole) of I and 25 mg. (0.000125 mole) of *p*-toluenesulfonic acid hydrate in 5 ml. of acetic anhydride was kept at reflux temperature for 1 hour. The acetic anhydride was distilled under reduced pressure. The residue was dissolved in 5 ml. of a 5% aqueous methanolic (1:1) potassium hydroxide solution. After 15 minutes at reflux temperature the methanol was distilled *in vacuo*. The aqueous alkaline phase was extracted with ether. Distillation of the ether revealed no neutral material. The water solution was acidified with 6 *N* hydrochloric acid and evaporated to dryness under diminished pressure. A solution of the residue in 20 ml. of absolute methanol containing 1 ml. of concentrated sulfuric acid was maintained at reflux temperature for 4 hours. The methanol was removed by vacuum distillation. The residue was extracted with ether. The organic phase was washed with 0.03 *N* aqueous potassium hydroxide and with water. The ether solution was dried over anhydrous sodium sulfate. Vacuum distillation of the solvent gave 125 mg. (96%) of a solid residue of the dimethyl ester of I.

**1-Acetyl-β-(4-carboxy-3-indole)-propionic Acid Anhydride (IV).**—A solution of 233 mg. (0.001 mole) of β-(4-carboxy-3-indole)-propionic acid (I) in 100 ml. of acetic anhydride was maintained at reflux temperature, in the absence of light, for 75 hours. The solution remained nearly colorless. The acetic anhydride was distilled under reduced pressure. The residual traces of acetic anhydride were removed in a vacuum desiccator over potassium hydroxide. The product, which had entirely solidified, weighed 280 mg. The crude substance melted *ca.* 110°, followed by solidification and remelting at a higher temperature, presumably indicating the presence of linear anhydrides. The total solid was sublimed at 0.1 mm. at a bath temperature of 150–190°. The white sublimate was recrystallized from a mixture of ethyl acetate and ether; yield 185 mg. (72%), m.p. 185–195°; infrared spectrum: 5.56 and 5.73μ (anhydride), 5.82μ (>NCOCH$_3$).

*Anal.* Calcd. for $C_{14}H_{11}NO_4$ (257.24): C, 65.36; H, 4.31; N, 5.45. Found: C, 65.27; H, 4.57; N, 5.84.

**1-Acetyl-β-(4-carboxy-3-indole)-propionic Acid.**—A solution of 1-acetyl-β-(4-carboxy-3-indole)-propionic acid anhydride in a mixture of 4 ml. of pyridine and 1 ml. of water was maintained at reflux temperature for 2.5 hours. The solvents were distilled under reduced pressure. The residue was recrystallized from ethyl acetate; m.p. 249–252°; infrared spectrum: 5.82μ (>NCOCH$_3$), 5.87μ (aliphatic carboxyl), 5.98μ (aromatic carboxyl).

*Anal.* Calcd. for $C_{14}H_{13}NO_5$ (275.27): C, 61.09; H, 4.76; N, 5.09. Found: C, 60.87; H, 4.83; N, 5.37.

**Treatment of 1-Acetyl-β-(4-carboxy-3-indole)-propionic Acid Anhydride (IV) with Anhydrous Hydrogen Chloride in Benzene.**—A solution of 51 mg. (0.0002 mole) of IV in 2 ml. of anhydrous benzene was saturated with dry hydrogen chloride and sealed in a Pyrex tube. After a few minutes at ordinary temperature, fine needles began to separate. After 5 hours at ordinary temperature, the crystals were collected by filtration and washed with anhydrous benzene to yield 51 mg. (86%) of 1-acetyl-β-(4-chlorocarbonyl-3-indole)-propionic acid, m.p. 127–130°. The analytical sample was recrystallized from ether; m.p. 132–136°; infrared spectrum 5.62μ (aromatic acid chloride), 5.87μ (aliphatic carboxyl), 5.82 μ (>NCOCH$_3$).

*Anal.* Calcd. for $C_{14}H_{12}NO_4Cl$ (293.56): C, 57.23; H, 4.12; N, 4.77. Found: C, 58.00; H, 4.37; N, 4.35.

**Reaction of 1-Acetyl-β-(4-carboxy-3-indole)-propionic Acid Anhydride (IV) with Sodium Acetate.**—A mixture of 97 mg. (0.00038 mole) of 1-acetyl-β-(4-carboxy-3-indole)-propionic acid anhydride and 10 mg. (0.00012 mole) of fused sodium acetate was maintained at 200° for 30 minutes under reduced pressure in a sublimation apparatus. Evolution of a gas was observed. The colorless sublimate was recrystallized from a mixture of acetone and ether to give 38 mg., m.p. 118–135°. The infrared spectrum of the crystalline material indicated it to be a mixture of unchanged anhydride IV and 1-acetyl-5-keto-1,3,4,5-tetrahydrobenz(cd)indole (III). The substance was dissolved in 5 ml. of 10% aqueous methanolic (1:1) potassium hydroxide. After 15 minutes at reflux temperature the methanol was distilled under reduced pressure. The residue was extracted with a mixture of ether and chloroform (3:1), washed with 2 *N* aqueous hydrochloric acid and with water and dried over anhydrous sodium sulfate. The remainder from vacuum distillation of the solvents was recrystallized from a mixture of acetone and ether to give 20 mg. (32%) of II, m.p. 155–160°; infrared spectrum identical with that of 5-keto-1,3,4,5-tetrahydrobenz(cd) indole (II).

**Reaction of 1-Acetyl-β-(4-carboxy-3-indole)-propionic Acid Anhydride (IV) with Anhydrous Pyridine.**—A mixture of 159 mg. (0.00062 mole) of 1-acetyl-β-(4-carboxy-3-indole)-propionic acid anhydride (IV) and 0.3 ml. of anhydrous pyridine was sealed in a Pyrex tube and kept at 150° for 2.5 hours. The pyridine was distilled under reduced pressure. The residue was dissolved in 10 ml. of 5% aqueous methanolic (1:1) potassium hydroxide. After 1 hour at reflux temperature the methanol was distilled *in vacuo*. The remainder was extracted with a mixture of ether and chloroform (3:1). The extract was washed with 2 *N* aqueous hydrochloric acid and with water and was dried over anhydrous sodium sulfate. The yellow residue (65 mg.) was dissolved in benzene and passed through a column of aluminum oxide (Woelm non-alkaline). The material which eluted with a mixture of benzene and chloroform (1:3) was recrystallized from a mixture of acetone and ether to give 53 mg. (50%) of II, m.p. 160–162°; infrared spectrum identical with that given by 5-keto-1,3,4,5-tetrahydrobenz(cd)indole (II).

**Reaction of 1-Acetyl-β-(4-carboxy-3-indole)-propionic Acid Anhydride (IV) with Acetic Anhydride in the Presence of 2.5 Equivalents of Sodium Acetate.**—A solution of 103 mg. (0.0004 mole) of 1-acetyl-β-(4-carboxy-3-indole)-propionic acid anhydride (IV) and 82 mg. (0.001 mole) of fused sodium acetate in 9 ml. of acetic anhydride was maintained at reflux temperature, in the absence of light, for 2.5 hours. The acetic anhydride was distilled under reduced pressure. The residue was dried in a vacuum desiccator over potassium hydroxide. The material was recrystallized from absolute ethanol to give 54 mg. (64%) of III, m.p. 139–147°; recrystallization from absolute ethanol brought the m.p. to 145–147°; infrared spectrum identical with that given by 1-acetyl-5-keto-1,3,4,5-tetrahydrobenz(cd)indole (III).

**1-Acetyl-5-keto-1,3,4,5-tetrahydrobenz(cd)indole (III).**—A solution of 100 mg. of 5-keto-1,3,4,5-tetrahydrobenz-(cd)indole (II) in 6 ml. of acetic anhydride was maintained at reflux temperature in the absence of light for 20 hours. The acetic anhydride was distilled under reduced pressure. The residue was dried in a vacuum desiccator over potassium hydroxide. Recrystallization from benzene gave 88 mg. (70%) of long needles, m.p. 140–142°. The analytical sample was recrystallized from absolute ethanol; m.p. 148–149°; infrared spectrum: 5.92μ (carbonyl), 5.97μ (>NCO-CH$_3$).

*Anal.* Calcd. for $C_{13}H_{11}NO_2$ (213.23): C, 73.22; H, 5.20; N, 6.57; $CH_3CO$, 20.18. Found: C, 72.95; H, 5.24; N, 6.37; $CH_3CO$, 20.44.

Inasmuch as, during the early work, the impression had been gained that light favored formation of the naphthalene tautomer, acylations routinely were carried out in covered flasks. However, repetition of the above experiment under illumination with a 200 watt bulb at 10 cm. resulted in the isolation of the N-acetyl derivative III in 56% yield.

**Reaction of 1-Acetyl-5-keto-1,3,4,5-tetrahydrobenz(cd) indole (III) with Acetic Anhydride in the Presence of 2.5 Equivalents of Potassium Acetate.**—A solution of 90 mg. (0.0004 mole) of 1-acetyl-5-keto-1,3,4,5-tetrahydrobenz(cd) indole (III) (m.p. 147–149°) and 100 mg. (0.001 mole) of fused potassium acetate in 2.2 ml. of acetic anhydride was maintained at reflux temperature, in the absence of light, for 5 hours. The acetic anhydride was distilled under reduced pressure. The residue was treated with 30 ml. of ethyl acetate and extracted 3 times with water. The residue from the dried ($MgSO_4$) ethyl acetate solution was recrystallized from absolute ethanol to give 57 mg. (56%), m.p. 165–168°; infrared spectrum identical with that given by 1-acetyl-5-acetoxy-1,2-dihydrobenz(cd)indole (V).[13]

**1-Acetyl-α-(diacetyl)-amino-β-(4-carboxy-3-indole)-propionic Acid Anhydride (VI).**—A solution of 356 mg. (0.00115 mole) of α-acetamino-β-(4-carboxy-3-indole)-propionic acid hydrate[15a] (m.p. 143–146°/212–216°) and 25 mg. (0.00025

mole) of potassium acetate in 5 ml. of acetic anhydride was maintained at reflux temperature for 2 hours. The acetic anhydride was distilled under reduced pressure. Three successive portions of toluene were distilled from the residue *in vacuo* to ensure removal of the last traces of acetic anhydride. The remainder was extracted with refluxing benzene. The benzene solution was clarified by filtration and concentrated under diminished pressure. The residue (430 mg.) was recrystallized from a mixture of dichloromethane and ether to give 251 mg. (61%), m.p. 162–170°. The analytical sample was obtained as colorless prisms after 4 recrystallizations from a mixture of dichloromethane and ether; m.p. 165–180°; infrared spectrum: 5.50 μ, 5.70 μ (anhydride), 5.88 μ (indole >NCOCH$_3$), 6.00 μ (–N(COCH$_3$)$_2$).

*Anal.* Calcd. for $C_{18}H_{16}N_2O_6$ (356.32): C, 60.57; H, 4.53; N, 7.86. Found: C, 60.83; H, 4.84; N, 7.84.

**Reaction of 1-Acetyl-α-(diacetyl)-amino-β-(4-carboxy-3-indole)-propionic Acid Anhydride (VI) with Basic Reagents.** (a) **Pyridine.**—A mixture of 100 mg. of VI and 0.3 ml. of anhydrous pyridine was sealed in a Pyrex tube and kept at 150° for 2 hours; result: no bicarbonate-insoluble material.

(b) **Triethylamine.**—A solution of 100 mg. of VI and 0.3 ml. of triethylamine (which had been distilled from solid potassium hydroxide) was sealed in a Pyrex tube and kept at 150° for 2 hours; result: no bicarbonate-insoluble material.

(c) **Lithium Acetate (2 Equivalents) in Acetic Anhydride.**—A solution of 14 mg. (0.0006 mole) of lithium hydroxide in 2 ml. of acetic acid was concentrated to dryness under diminished pressure. To the residue was added a solution of 104 mg. (0.0003 mole) of VI in 5 ml. of acetic anhydride. The solution was kept at reflux temperature for 4 hours; result: recovery of 80 mg. (80%) of VI.

(d) **Sodium Acetate (1 Equivalent) in Acetic Anhydride.**—A solution of 104 mg. (0.0003 mole) of VI in 5 ml. of acetic anhydride was treated with 25 mg. (0.0003 mole) of anhydrous sodium acetate and kept at 140° for 4 hours; result: recovery of 85 mg. (82%) of VI.

(e) **Sodium Acetate (4 Equivalents) in Acetic Anhydride.**—Conditions and result identical with that of experiment (d).

(f) **Potassium Acetate (4 Equivalents) in Acetic Anhydride.**—A solution of 140 mg. (0.00039 mole) of VI and 150 mg. (0.0015 mole) of potassium acetate in 5 ml. of acetic anhydride was maintained at reflux temperature for 4 hours. The acetic anhydride was distilled under reduced pressure. Three successive portions of toluene were distilled *in vacuo* from the residue to ensure removal of the final traces of acetic anhydride. The remainder was extracted with refluxing benzene. The benzene solution was clarified by filtration and concentrated under diminished pressure. The residue (100 mg.) was recrystallized from ethyl acetate to give 50 mg. of VII, m.p. 175–190°. Three additional recrystallizations from ethyl acetate gave material of m.p. 181–186°; infrared spectrum identical with that of 1-acetyl-4-diacetamino-5-acetoxy-1,2-dihydrobenz(cd)indole: 5.60 μ (phenolic ester), 5.77 μ (–N(COCH$_3$)$_2$), 5.90 and 5.97 μ (>NCOCH$_3$).[29]

**Reaction of 4-Acetamino-5-keto-1,3,4,5-tetrahydrobenz(cd) indole with Acetic Anhydride in the Presence of Potassium Acetate.**—A solution of 50 mg. (0.0002 mole) of 4-acetamino-5-keto-1,3,4,5-tetrahydrobenz(cd)indole (m.p. 186–192°)[20] and 50 mg. (0.0005 mole) of potassium acetate in 110 ml. of acetic anhydride was maintained at reflux temperature, in the absence of light, for 2 hours. The acetic anhydride was distilled under reduced pressure. Four successive portions of toluene were vacuum distilled from the residue to ensure removal of the final traces of acetic anhydride. The remainder was extracted with refluxing benzene. The benzene solution was clarified by filtration and concentrated under diminished pressure. The residue was recrystallized from methanol to give 40 mg. (80%), m.p. 180–186°; infrared spectrum identical with that given by 1-acetyl-4-diacetamino-5-acetoxy-1,2-dihydrobenz(cd)-indole.[18a]

**4-Carbomethoxyindole.**—To a solution of 1.9 ml. of concentrated sulfuric acid in 120 ml. of methanol was added 3.3 g. (0.02 mole) of 4-indolecarboxylic acid.[1] After the mixture had been maintained at reflux temperature for 20 hours, 200 ml. of chloroform was added. The solution was extracted with water and with dilute aqueous sodium bicarbonate. The residue from the dried ($MgSO_4$) chloroform solution was recrystallized from a mixture of methanol and water; yield 3.55 g. (91%), m.p. 69.5–70.5°.[27]

*Anal.* Calcd. for $C_{10}H_9NO_2$(175.18): C, 68.56; H, 5.18; N, 8.00. Found: C, 68.84; H, 5.70; N, 7.70.

The picrate was prepared in methanol and was recrystallized from the same solvent: m.p. 141–143°.

*Anal.* Calcd. for $C_{16}H_{12}N_4O_9$ (404.29): C, 47.53; H, 2.99; N, 13.86. Found: C, 47.23; H, 3.16; N, 13.56.

**4-Carbomethoxygramine (VIII).**—To a solution of 230 mg. (0.00013 mole) of 4-carbomethoxyindole in 2 ml. of acetic acid was added 0.48 ml. of a 4.1 *N* aqueous dimethylamine solution, followed by 0.16 ml. of 37% aqueous formaldehyde. After two hours at ordinary temperature, the mixture was taken to dryness by concentration under diminished pressure with 10 successive quantities of 10 ml. of benzene. To the residue was added 3 ml. of 5.5% methanolic hydrogen chloride. The solution was concentrated to dryness under reduced pressure with the aid of 3 successive 10-ml. quantities of a 1:1 mixture of methanol and benzene. The crystalline salt was recrystallized from a mixture of methanol and acetone; yield 346 mg. (98%); m.p. 200–203°.

*Anal.* Calcd. for $C_{13}H_{17}N_2O_2Cl$ (268.75): C, 58.10; H, 6.38; N, 10.43. Found: C, 58.42; H, 6.48; N, 10.66.

The hydrochloride was transformed to the free Mannich-base by either of the following procedures.

**A.**—To a solution of 223 mg. (0.00083 mole) of 4-carbomethoxygramine hydrochloride in 2.5 ml. of methanol was added 100 mg. of silver oxide. After the mixture had been stirred for 30 minutes, the silver salts were removed by filtration and washed with methanol. The filtrate was concentrated under diminished pressure. The residue was recrystallized from a mixture of anhydrous ether and petroleum ether (b.p. 30–60°); yield 136 mg. (70%), m.p. 103–110°.

**B.**—To a solution of 366 mg. (0.00136 mole) of 4-carbomethoxygramine hydrochloride in 3 ml. of water (0°) was added 1 ml. of a 0.362 *N* aqueous potassium hydroxide solution. The base separated as an oil which soon crystallized. After 15 hours at 0°, the product was collected by filtration and washed with 2 ml. of water; yield 269 mg. (85%), m.p. 100–107°.

*Anal.* Calcd. for $C_{13}H_{16}N_2O_2$ (232.28): C, 67.22; H, 6.94; N, 12.06. Found: C, 66.92; H, 7.09; N, 12.11.

The picrate was prepared in methanol and was recrystallized from the same solvent; m.p. 176–178°.

*Anal.* Calcd. for $C_{19}H_{19}N_5O_9$ (461.38): C, 49.46; H, 4.15; N, 15.18. Found: C, 49.62; H, 4.42; N, 15.17.

**4-Carboxygramine.**—To a solution of 996 mg. (0.0062 mole) of 4-indolecarboxylic acid[1] in 1.8 ml. of 4.1 *N* aqueous dimethylamine was added 0.6 ml. of 37% aqueous formaldehyde. After 48 hours at ordinary temperature 10 ml. of ethanol was added. The crystalline deposit which had separated after 15 hours at 0° was collected by filtration, washed with water and dried. Recrystallization from a mixture of methanol and acetone gave 1.10 g. (75%), m.p. 202–206°.

*Anal.* Calcd. for $C_{12}H_{14}N_2O_2 \cdot H_2O$ (236.27): C, 61.00; H, 6.82; N, 11.86. Found: C, 60.27; H, 6.88; N, 11.65.

**Methyl α-Carbomethoxy-β-(4-carbomethoxy-3-indole)-propionate.**—To a solution of 250 mg. (0.011 mole) of sodium in 10 ml. of absolute methanol was added 0.7 ml. (0.006 mole) of dimethyl malonate followed by 348 mg. (0.0015 mole) of 4-carbomethoxygramine (VIII) and 1.8 ml. (0.02 mole) of dimethyl sulfate. After 30 minutes at ordinary temperature 40 ml. of water and 4 ml. of 1 *N* hydrochloric acid were added. After 15 hours at 0°, the precipitate was collected by filtration, washed with water and dried; yield 45 mg. (94%), m.p. 123–129°. The analytical sample was recrystallized from methanol; m.p. 126–129°.

*Anal.* Calcd. for $C_{16}H_{17}NO_6$ (319.31): C, 60.18; H, 5.37; N, 4.39. Found: C, 60.36; H, 5.67; N, 4.43.

**Ethyl α-Carboethoxy-β-(4-carbomethoxy-3-indole)-propionate.**—To a solution of 18.4 mg. of sodium (0.0008 mole) in 4 ml. of absolute ethanol was added 0.092 ml. (0.0008 mole) of dimethyl malonate and 140 mg. (0.0008 mole) of 4-carbomethoxygramine (VIII), followed by 0.2 ml. (0.002 mole) of dimethyl sulfate.[30] After 15 minutes at ordinary temperature, 20 ml. of water was added. The oil was ex-

(29) *Cf.* the infrared spectrum of 1-acetoxy-2-diacetaminobenzene (m.p. 78–79°) (E. Diepolder, *Ber.*, **44**, 3500 (1911)): 5.62 μ (phenolic ester), 5.80 μ (–N(COCH$_3$)$_2$).

(30) Apparently complete transesterification of the aliphatic carboxyl groups occurred under these conditions.

tracted with 50 ml. of ether. The organic phase was washed with water. The residue from vacuum distillation of the ether was recrystallized from a mixture of methanol and water; yield 146 mg. (76%), m.p. 91–93°.

*Anal.* Calcd. for $C_{18}H_{21}NO_6$ (347.36); C, 62.24; H, 6.09; N, 4.03. Found: C, 62.14; H, 6.08; N, 4.40.

**α-Carboxy-β-(4-carboxy-3-indole)-propionic Acid.**—A solution of 103 mg. (0.0004 mole) of methyl α-carbomethoxy-β-(4-carbomethoxy-3-indole)-propionate and 280 mg. (0.005 mole) of potassium hydroxide in a mixture of 2 ml. of water and 10 ml. of methanol was allowed to remain at ordinary temperature for 7 days. The methanol was distilled under reduced pressure. The solution was acidified with 8 ml. of 6 *N* hydrochloric acid and the volume was reduced under diminished pressure. After 15 hours at 0°, the precipitate was collected by filtration, washed with water and dried; yield 92 mg. (81%), m.p. 190–196° with decarboxylation; analytical sample (prisms after two recrystallizations from water), m.p. 198–200° with decarboxylation.

*Anal.* Calcd. for $C_{13}H_{11}NO_6$ (277.24): C, 56.32; H, 4.00; N, 5.05. Found: C, 55.88; H, 4.20; N, 5.03.

**β-(4-Carboxy-3-indole)-propionic Acid from Methyl α-Carbomethoxy-β-(4-carbomethoxy-3-indole)-propionate.**—A solution of 319 mg. (0.001 mole) of methyl α-carbomethoxy-β-(4-carbo-methoxy-3-indole)-propionate, 683 mg. (0.012 mole) of potassium hydroxide, 5 ml. of water and 25 ml. of methanol was allowed to remain at ordinary temperature for 7 days. The methanol was distilled under diminished pressure. The aqueous solution was acidified with 2 ml. of 6 *N* hydrochloric acid. The precipitate was collected by filtration, washed with water and dissolved in 6 ml. of pyridine. After 2 hours at reflux temperature, the pyridine was distilled under reduced pressure. The residue was crystallized from a mixture of 0.5 ml. of acetic acid and 3 ml. of water. After 3 weeks at 0°, the precipitate was collected by filtration, washed with water and dried; yield 150 mg. (65%), m.p. 165–180°. A second recrystallization from a mixture of acetic acid and water gave 110 mg., m.p. 170–180°.

**Ethyl α-Carboethoxy-α-acetamino-β-(4-carbomethoxy-3-indole)-propionate.**—To a solution of 20 mg. (0.0006 mole) of sodium in 5 ml. of absolute ethanol was added 135 mg. (0.0006 mole) of diethyl acetaminomalonate and 121 mg. (0.0005 mole) of 4-carbomethoxygramine (VIII), followed by 0.15 ml. (0.0015 mole) of dimethyl sulfate. After 30 minutes at ordinary temperature the precipitate was collected by filtration, washed with water, dried and recrystallized from ethanol; yield 170 mg. (81%), m.p. 207–209°.

*Anal.* Calcd. for $C_{20}H_{24}N_2O_7$ (404.41): C, 59.40; H, 5.98; N, 6.93. Found: C, 59.19; H, 6.28; N, 6.87.

**Dibenzyl α-Acetamino-α-(4-carbomethoxyskatyl)-malonate.**—To a solution of 340 mg. (0.00146 mole) of 4-carbomethoxygramine (VIII) in 10 ml. of toluene was added 510 mg. (0.0015 mole) of dibenzylacetaminomalonate[26] and 10 mg. of sodium methoxide. The mixture was maintained at 85° with passage of dry nitrogen for 8 hours. During the final hour the solution was permitted to concentrate to 3 ml. The mixture was diluted to 25 ml. with benzene and was clarified by filtration. The filtrate was concentrated to 10 ml. and allowed to crystallize; yield 607 mg. (78%), m.p. 167–171°.

*Anal.* Calcd. for $C_{30}H_{28}N_2O_7$ (528.54): C, 68.17; H, 5.34; N, 5.30. Found: C, 68.04; H, 5.55; N, 5.40.

**α-Acetylamino-β-(4-carboxy-3-indole)-propionic Acid from α-Acetamino α-(4-Carbomethoxyskatyl)-dibenzylmalonate.**—A solution of 605 mg. (0.00146 mole) of the dibenzyl ester in 15 ml. of methanol was shaken with hydrogen in the presence of 120 mg. of 10% palladium-on-carbon. After 54.3 ml. of hydrogen had been absorbed during 1.5 hours (theory 51 ml.) the catalyst was removed by filtration. The methanol was distilled under reduced pressure. The residue was recrystallized from a mixture of 0.5 ml. of methanol and 4 ml. of water to yield 300 mg. (75%) of α-(4-carbomethoxyskatyl)-α-acetaminomalonic acid, m.p. 150–164° with decarboxylation. A solution of this material in a mixture of 2 ml. of pyridine and 3 ml. of water was maintained at reflux temperature for 4 hours. The solvents were distilled under reduced pressure. A solution of the residue in 3 ml. of 1 *N* aqueous potassium hydroxide was maintained at reflux temperature for 1 hour. The solution was acidified with 6 *N* hydrochloric acid. After 45 hours at 0°, the crystalline deposit was collected by filtration, washed with water and dried; yield 230 mg. (87%), m.p. 145–150°.

An attempt to recrystallize this substance from a mixture of acetic acid and water resulted in the isolation of a compound identical with the anhydrous form previously obtained by vacuum evaporation of a solution of the hydrate in absolute ethanol and benzene[18a]; m.p. 223–225°. At the melting point, the molten mass evolved a gas, rapidly became colored deep red and deposited large golden gem-like crystals. When the temperature of the melt derived from the hydrate (m.p. 145–150°) was slowly elevated above 150°, resolidification occurred with final melting again at 223–225°. While the infrared spectrum (KBr) of the hydrate displayed the expected bands (5.85 μ (aliphatic carboxyl), 5.92 μ (aromatic carboxyl), 6.15 μ, 6.41 μ (-NHCOCH$_3$)), the KBr spectrum of the anhydrous form unaccountably exhibited a band in the carbonyl region: 5.66 μ (?), 5.85 μ (aliphatic carboxyl), 5.96 μ (aromatic carboxyl), 6.19 and 6.40 μ (-NHCOCH$_3$). However, the spectra of the two substances measured in ethanol solution with a $CaF_2$ cell were virtually identical; hydrate: 5.84, 5.93, 6.03 μ; anhydrous: 5.85, 5.92, 6.01μ.

**Methyl α-Acetylamino-β-(4-carbomethoxy-3-indole)-propionate.**—To a solution of 154 mg. (0.0005 mole) of α-acetylamino-β-(4-carboxy-3-indole)-propionic acid hydrate in 2 ml. of methanol was added an ethereal solution of diazomethane prepared from 1.0 g. of *N*-methyl-*N*-nitroso-*N'*-nitroguanidine and 3 ml. of 40% aqueous potassium hydroxide. After 2 hours at ordinary temperature the solvents were removed *in vacuo* to give an oil which was recrystallized from a mixture of 5.0 ml. of methanol and 8 ml. of water; yield 130 mg. (82%), m.p. 156–168°; the analytical sample was recrystallized from benzene, m.p. 161–172°.

*Anal.* Calcd. for $C_{16}H_{18}N_2O_5$ (318.32): C, 60.37; H, 5.70; N, 8.80. Found: C, 60.43; H, 5.87; N, 8.51.

**Methyl α-Carbomethoxy-α-acetylmethylamino-β-(4-carbomethoxy-3-indole)-propionate.**—To a solution of 161 mg. (0.00092 mole) of 4-carbomethoxygramine in 8 ml. of absolute methanol was added 282 mg. (0.00125 mole) of dimethyl acetylmethylaminomalonate sodium[25] and 0.20 ml. (0.002 mole) of dimethyl sulfate. After 20 hours at ordinary temperature the methanol was distilled under reduced pressure. The residue was partitioned between dichloromethane and water. The remainder (375 mg.) from vacuum distillation of the dried ($MgSO_4$) dichloromethane solution was recrystallized from methanol; yield 100 mg. (37%), m.p. 168–170°.

*Anal.* Calcd. for $C_{19}H_{22}N_2O_7$ (394.39): C, 57.86; H, 5.62; N, 7.11. Found: C, 58.29; H, 5.85; N, 7.04.

**Ethyl α-Carboethoxy-α-bromo-β-(4-cyano-3-indole)-propionate.**—To a solution of 945 mg. (0.003 mole) of ethyl α-carboethoxy-β-(4-cyano-3-indole)-propionate in 100 ml. of carbon tetrachloride which was stirred by means of a magnetic device and irradiated with a 150 watt bulb was added, during 15 minutes, a solution of 480 mg. (0.003 mole) of bromine in 30 ml. of carbon tetrachloride. After 5 hours at ordinary temperature the mixture was concentrated on the steam-bath. The crystalline deposit which had separated after 15 hours at 0° was collected by filtration; yield 860 mg. (73%), m.p. 131–135°. The analytical sample was recrystallized four times from carbon tetrachloride; m.p. 138–139°.

*Anal.* Calcd. for $C_{17}H_{17}N_2O_4Br$ (393.24): C, 51.92; H, 4.36; N, 7.13. Found: C, 52.06; H, 4.54; N, 7.34.

This substance failed to react with N-methyl-N-benzylamine under any of the following conditions: (a) 100 mg. (0.00025 mole) of bromo ester, 600 mg. (0.001 mole) of methylbenzylamine, 0.5 ml. of ethanol, 3 hours at reflux temperature; (b) 100 mg. (0.00025 mole) of bromo ester, 60 mg. (0.0005 mole) of methylbenzylamine, 1 ml. of xylene, reflux temperature 4 hours; (c) solution of bromo ester in large excess of methylbenzylamine at ordinary temperature for a prolonged period.[31]

**1,2-Dihydrocyclopent(b)indole-3(4)-one.**—A mixture of 378 mg. (0.002 mole) of β-(3-indole)-propionic acid, 416 mg. (0.002 mole) of phosphorus pentachloride and 5 ml. of benzene was allowed to remain at ordinary temperature for 3 hours. The dark purple solution was concentrated under reduced pressure. Four successive quantities of benzene

(31) The preparation of the bromo ester and the study of its behavior with methylbenzylamine were carried out by Mr. Michael A. Simon.

were vacuum distilled from the residue. The remaining material was dissolved in 3 ml. of benzene and treated with 520 mg. (0.002 mole) of stannic chloride. After 1 hour at ordinary temperature, the mixture was diluted with ether and extracted successively with 2 *N* aqueous hydrochloric acid, 2 *N* aqueous potassium hydroxide and water. The remainder from the dried ($MgSO_4$) ether solution was recrystallized from a mixture of ethanol and water; yield 34 mg. (10%); infrared spectrum: 6.10 $\mu$ (carbonyl associated with NH); m.p. 250–252°.[32]

*Anal.* Calcd. for $C_{11}H_9NO$ (171.19): C, 77.17; H, 5.30. Found: C, 77.04; H, 5.66.

**Diethyl $\alpha,\alpha$-di-(4-cyanoskatyl)-malonate** was isolated from the mother liquors remaining after the crystallization of ethyl $\alpha$-carboethoxy-$\beta$-(4-cyano-3-indole)-propionate[1] and was purified by recrystallization from acetone; m.p. 235–237°.

*Anal.* Calcd. for $C_{27}H_{24}N_2O_4$ (440.48): C, 69.22; H, 516; N, 11.96. Found: C, 69.10; H, 5.50; N, 11..97.

**Methyl (4-Carbomethoxy-3-indole)-acetate.**—To a solution of 200 mg. (0.001 mole) of 4-cyanogramine and 326 mg. (0.005 mole) of potassium cyanide in 25 ml. of methanol was added, in 4 portions at 15-minute intervals, 2.0 ml. (0.02 mole) of dimethyl sulfate. After 3 hours at ordinary temperature the solution was concentrated to a volume of 3 ml. Addition of water, followed by removal of a small quantity of resinous material, gave, at 0°, 135 mg. (74%) of (4-cyano-3-indolyl)-acetonitrile, m.p. 155–165°. Two recrystallizations from methanol left 100 mg. (55%), m.p. 163–165°.

A mixture of 258 mg. of the dinitrile prepared in this fashion and 2.7 ml. of 20% aqueous potassium hydroxide was maintained at reflux temperature for 24 hours. The cooled solution was clarified by filtration and acidified with 0.8 ml. of 12 *N* hydrochloric acid. The precipitate was collected by filtration, washed with water and dried; yield 305 mg. (98%), m.p. 247–249°.

The dicarboxylic acid was methylated in ether solution with diazomethane prepared from N-methyl-N-nitroso-N'-nitroguanidine. The product was recrystallized from a mixture of ether and petroleum ether (30–60°) to give 272 mg. (79%), m.p. 96–98°. The analytical sample was recrystallized from methanol; m.p. 100–101°.

*Anal.* Calcd. for $C_{18}H_{18}NO_4$ (247.26): C, 63.15; H, 5.30; N, 5.67. Found: C, 63.61; H, 5.70; N, 5.64.

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[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY AND PHARMACEUTICAL CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

# Studies of Hydrogen Bonding. III. Intramolecular Hydrogen Bonding in 3-Piperidinols

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The infrared spectra of *dl*-3-piperidinol and three substituted 3-piperidinols have been studied in the 3100–3800 cm.$^{-1}$ region. All of these compounds appear to form intramolecular hydrogen bonds of moderate strength from hydroxyl to nitrogen.

Intramolecular hydrogen bonds can form between diaxial *cis*-1,3-substituents on cyclohexane rings. Some examples are *cis*-1,3-cyclohexanediol[2] and various 3-substituted cyclohexanols in the steroid series.[3] Intramolecular hydrogen bonds might also form between *cis*-1,4-substituents on a cyclohexane ring, if the ring were to adopt the boat form. No examples are known of such transannular hydrogen bonds in cyclohexane compounds. However, Lyle has shown that intramolecular hydrogen bonding between hydroxyl and nitrogen takes place in 1-methyl-4-phenyl-2,2,6,6-tetramethyl-4-piperidinol, which must therefore exist in the boat form.[4] Other examples of 1,4-hydrogen bonding are known in highly substituted 4-piperidinols in the tropine series.[5]

This paper reports extension of these studies of intramolecular hydrogen bonding to *dl*-3-piperidinol and some substituted 3-piperidinols, using high-resolution infrared spectroscopy in the OH stretching region to detect hydrogen bond formation. Two additional substituted 4-piperidinols also have been studied.

## Experimental

**Materials.**—Reagent grade *dl*-3-piperidinol and 1-methyl-4-piperidinol were used as obtained from the Aldrich Chemical Co. The *dl*-1-methyl-3-piperidinol was a commercial sample obtained from Dr. J. Cannon. It was purified by repeated fractional distillation under vacuum. The preparation of *dl*-1-methyl-3-benzoyl-3-piperidinol and *dl*-1-methyl-4-benzoyl-4-piperidinol is described in a previous publication.[6] *dl*-1-Methyl-3-phenyl-3-piperidinol was prepared from a sample of 1-methylpiperidone hydrochloride hydrate kindly supplied by Dr. R. Lyle. To 785 mg. (5.0 millimoles) of anhydrous bromobenzene dissolved in 50 ml. of anhydrous ether was added 122 mg. (5 millimoles) of ether-washed, dried magnesium turnings. After refluxing for 3 hours 35–40 ml. of the ether was removed and replaced with 60 ml. of anhydrous benzene. To this refluxing mixture was added 250 mg. (1.5 millimoles) of 1-methyl-3-piperidone hydrochloride monohydrate. The solvent was removed after refluxing for 3 hours. The dry solid was treated with 15 ml. of 5% hydrochloric acid. The solution was made basic and extracted with purified petroleum ether, b.p. 35°. The petroleum ether extracts were dried over sodium sulfate, treated with carbon, and filtered through sintered glass to give, after removal of the solvent, a colorless oil, 140 mg. (0.73 millimole, 49% yield), which was microdistilled in a sublimation apparatus at reduced pressure.

The methiodide salt was prepared and recrystallized from ethanol–ether, m.p. 238–239° dec. (lit.[7] m.p. 239.5–240.5°).

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