[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

Gliotoxin. VII. Synthesis of Pyrazinoindolones and Pyridindolones[1]

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Earlier studies have established the presence in the gliotoxin molecule of an indole nucleus which appears to be condensed into a pyrazinoindole system, since the latter is found in two of the crystalline degradation products.[3] However, the structure of the most significant degradation product, desthiogliotoxin, has not yet been established and the available evidence does not exclude the presence in gliotoxin of a pyridindole system, or a bicyclic system which is converted to a pyrazinoindole by the reagents used for degradation. The present paper deals with an investigation of the ring closure of derivatives of 2-indolecarboxamide for the purpose of securing reference compounds desired for structural studies of desthiogliotoxin and for further exploration of the use of absorption spectra for distinguishing between pyrazinoindolones and pyridindolones.

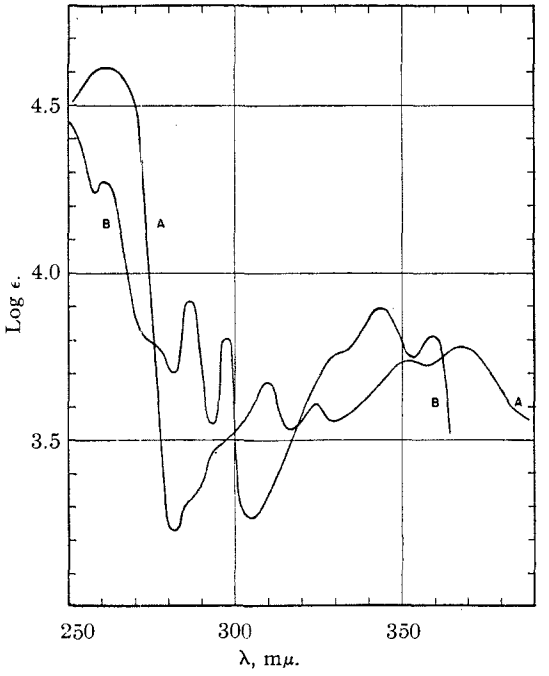
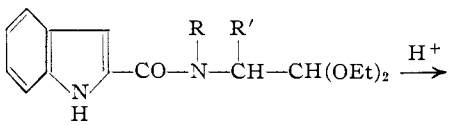


Fig. 1.—Ultraviolet absorption curves of reference compounds: A, 2,10-dimethylpyrazino[1.2-a]indole-1(2)-one; B, 2,9-dimethylpyrid[3.4-b]indole-1(2)-one; in ethanol solutions.

The reaction of 2-indolecarbonyl chloride with α-aminoacetals furnishes acylaminoacetals (I) which undergo cyclization by hydrogen chloride to form either pyrazino[1.2-a]indolones (II) or 2,9-pyrid[3.4-b]indolones (III), or mixtures of the two.[4,5] For reference three pairs of model com-



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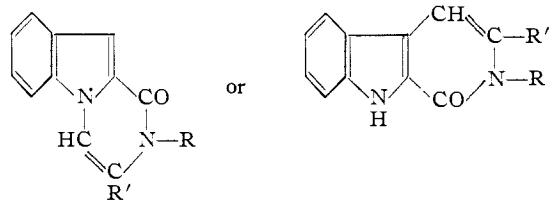


II Pyrazinoindolone type III Pyridindolone type

pounds of known structure were secured by blocking the 1- or 3-position of the indole system with a methyl group, so that only one type of ring closure could occur. Comparisons of the ultraviolet absorption spectra of these pairs of isomers disclosed differences sufficient to permit the use of spectroscopic data as a means of distinguishing between the structural types (*cf.* Fig. 1).[6]

The acylaminoacetal (I, R=R′=H) prepared from 2-indolecarbonyl chloride and aminoacetal, when treated with ethanolic hydrogen chloride or with ethereal sulfuric acid, furnished a crystalline cyclization product in yields of 90–95%. After repeated crystallizations the compound melted at 250–251° and the absorption spectrum showed it to be pyrazino[1.2-a]indole-1(2)-one, confirming the structure assigned by Kermack, Perkin and Robinson[4] on the basis of color reactions and other properties. Comparison of the ultraviolet absorption spectrum of the crude reaction product with that of the pure pyrazinoindolone revealed the presence of about 20% of the isomeric pyridindolone in the crude material. After several preliminary experiments it was found that the pyridindolone could be extracted selectively from a chloroform-ethanol solution by 6 *N* sulfuric acid and eventually the hitherto unknown 2,9-pyrid[3.4-b]indole-1(2)-one was isolated in a pure state. The spectra of the isomers are shown in Fig. 2.

The reaction of 2-indolecarbonyl chloride with methylaminoacetal and with α-methylaminopropionacetal, followed by cyclization of the acylaminoacetals in the usual way, furnished ex-

(1) Previous paper, THIS JOURNAL, **67**, 1736 (1945).

(2) The Wm. S. Merrell Company Fellow in Chemistry.

(3) Johnson, Hasbrouck, Dutcher and Bruce, THIS JOURNAL, **67**, 423 (1945).

(4) Kermack, Perkin and Robinson, *J. Chem. Soc.*, **119**, 1602 (1921); **121**, 1872 (1922).

(5) Blaikie and Perkin, *ibid.*, **125**, 320 (1924).

(6) We are indebted to Dr. M. G. VanCampen of the Research Laboratory of the William S. Merrell Company for absorption data on several of the compounds reported in this paper.

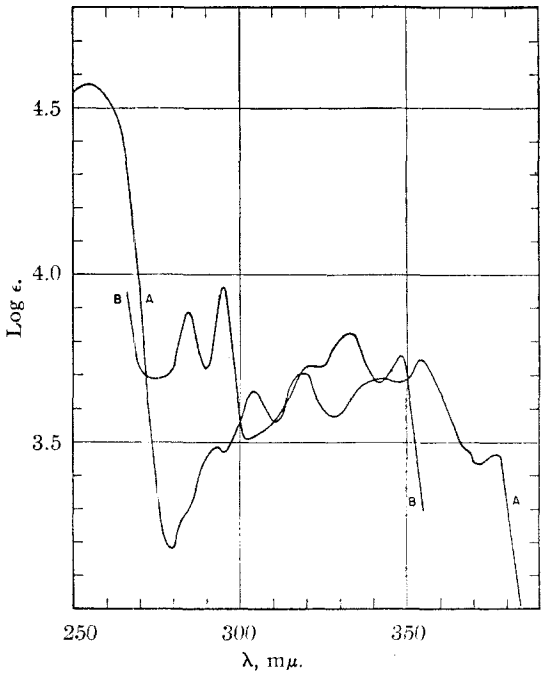


Fig. 2.—Ultraviolet absorption curves: A, pyrazino[1.2-a]indole-1(2)-one; B, pyrid[3,4-b]indole-1(2)-one; in ethanol solutions.

clusively the corresponding pyridindolones (III, R = CH_3, R′ = H, and R = R′ = CH_3, respectively). These observations and those of previous investigators show that the presence of an alkyl group on the nitrogen atom of the aminoacetal strongly disfavors formation of the pyrazinoindolone isomer. Experiments to be described later indicate clearly that a similar generalization is not valid for the ring closure of 2-indolecarbonyl derivatives of α-amino esters.

Owing to unfavorable orientation of the cyclization reaction when alkylaminoacetals are used, an indirect method was developed to secure N-alkylated pyrazinoindolones. It has been found that pyrazinoindolones having a hydrogen in the 2-position (and analogous pyridindolones, as well) can be alkylated on the nitrogen atom by conventional methods. Although O-alkylation could occur in these systems, it has not been observed in any of the cases examined. Thus, treatment of 10-methylpyrazinoindole-1(2)-one with dimethyl sulfate in an alkaline medium gave a crystalline methyl derivative identical with authentic 2,10-dimethylpyrazinoindole-1(2)-one prepared from 3-methylindole-2-carbonyl chloride and methylaminoacetal. In a similar way, 9-methylpyridindole-1(2)-one was methylated to give 2,9-dimethylpyridindole-1(2)-one, which was identical with an authentic specimen prepared from 1-methylindole-2-carbonyl chloride and methylaminoacetal.

The N-alkylation of pyrazinoindole-1(2)-ones appears to be a general reaction. On treatment with chloroacetic acid in alkaline medium, pyrazinoindole-1(2)-one gave the corresponding carboxymethyl derivative, 1(2)-oxopyrazino[1.2-a]indole-2-acetic acid (II, R = CH_2CO_2H, R′ = H), and the sodium derivative of 10-methylpyrazinoindole-1(2)-one on treatment with 2-diethylaminoethyl bromide, furnished 2-(2′-diethylaminoethyl)-10-methylpyrazino[1.2-a]indole-1(2)-one, isolated as the hydrochloride.[7]

A particularly significant reference compound is 2,3-dimethylpyrazino[1.2-a]indole-1(2)-one, which contains the entire carbon–nitrogen skeleton that is present in our preferred formulations of gliotoxin and desthiogliotoxin. The first step in the synthesis of this compound was the reaction of aminopropionacetal with 2-indolecarbonyl chloride, which furnished the crystalline acylaminoacetal (I, R = H, R′ = CH_3) in good yields. Cyclization of this compound gave a product melting over a wide range, and the absorption spectrum of the crude product indicated that it was a mixture of about 65% of 3-methylpyrazinoindole-1(2)-one and 35% of the isomeric 3-methylpyridindole-1(2)-one (II and III, respectively; R = H, R′ = CH_3). The pure individuals were obtained by preliminary partitions between chloroform and 6 *N* sulfuric acid, followed by recrystallizations from ethanol, and were identified by their absorption spectra. The sodium derivative of the pyrazindolone isomer was alkylated by methyl iodide to obtain 2,3-dimethylpyrazinoindole-1(2)-one, which crystallizes in pale yellow needles, m.p.

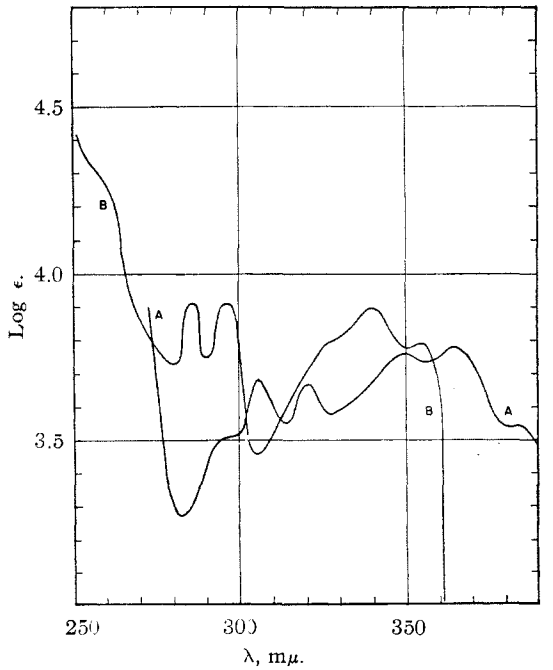


Fig. 3.—Ultraviolet absorption curves: A, 2,3-dimethylpyrazino[1.2-a]indole-1(2)-one; B, 2,3-dimethylpyrid[3.4-b]indole-1(2)-one; in ethanol solutions.

(7) We are indebted to Dr. L. I. Diuguid for the preparation of this compound.

206–207.5°. The isomeric 2,3-dimethylpyridindolone forms colorless needles melting above 290°. Experiments are in progress to correlate the structure of desthiogliotoxin with one of these compounds. The spectra of the isomers are shown in Fig. 3.

We wish to thank The Wm. S. Merrell Company for a generous research grant in support of this work.

Experimental

Aminoacetals.—The diethyl acetal of aminoacetaldehyde was prepared according to the procedure of Allen and Clark,[8] except that chloroacetal was used in place of bromoacetal. The yields were 40–50% of the theoretical, and the redistilled product boiled at 160.5–161.5° (732 mm.), $n^{25}D$ 1.4182.

The diethyl acetal of methylaminoacetaldehyde was prepared in similar fashion by heating 285 g. (9 moles) of anhydrous methylamine, 300 cc. of absolute ethanol, and 152.5 g. (1 mole) of chloroacetal in a bomb at 140° for fourteen hours. Diethyl methylaminoacetal was formed in 40% yield; b. p. 164–165° (735 mm.), $n^{22}D$ 1.4140.

The diethyl acetal of α-bromopropionaldehyde was prepared in 70% yield by treating a cooled and stirred mixture of 67 g. (0.5 mole) of diethyl propionacetal and 28 g. of calcium carbonate with 80 g. (0.5 mole) of bromine, at such a rate that the temperature did not exceed 10°; the product boiled at 78–79° (20 mm.), $n^{20}D$ 1.441.[9] On heating 47 g. (0.22 mole) of α-bromopropionacetal, 375 cc. of absolute ethanol and 85 g. (5 moles) of ammonia in a bomb at 130° for twelve hours, α-aminopropionacetal[9] was obtained in 55% yield; b. p. 81–82° (43 mm.), $n^{20}D$ 1.418.

The diethyl acetal of α-methylaminopropionaldehyde[9] was prepared in 40% yields by a similar procedure, from 47 g. of α-bromopropionacetal, 50 cc. of absolute ethanol and 47 g. of anhydrous methylamine; b. p. 73–74° (26 mm.), $n^{20}D$ 1.415.

2-Indolecarboxylic Acids.—Ethyl 2-indolecarboxylate was prepared by the convenient method of Cornforth and Robinson[10] from *o*-nitrotoluene and ethyl oxalate, and the purified ester was hydrolyzed with aqueous-methanolic potassium hydroxide solution. The over-all yield of 2-indolecarboxylic acid, m. p. 202–204°, was 35% of the theoretical, based on *o*-nitrotoluene.

Ethyl 3-methylindole-2-carboxylate was prepared by a modification of the method used for ethyl 2-indolecarboxylate, involving methylation of the intermediate ethyl *o*-nitrophenylpyruvate. A cooled solution of sodium ethoxide, prepared from 13.8 g. (0.6 gram-atom) of sodium and 200 cc. of absolute ethanol, was treated with 82.2 g. (0.6 mole) of *o*-nitrotoluene and 87.6 g. (0.6 mole) of ethyl oxalate. After heating for fifteen minutes on a steam-bath the reaction mixture was cooled, 57 g. (0.4 mole) of methyl iodide was added, and the solution refluxed for twenty-four hours. A second portion of methyl iodide was then added (28.4 g., 0.2 mole) and the solution refluxed for three days. The nitroarylpyruvic ester was reduced by sodium hydrosulfite (80 g.) in the usual way and gave ethyl 3-methylindole-2-carboxylate, m. p. 134.5–136°, in 20% yield (based on *o*-nitrotoluene). Hydrolysis of the ester by aqueous-methanolic potassium hydroxide solution gave 3-methylindole-2-carboxylic acid, m. p. 164–165°, in 90–95% yields (18% over-all yield from *o*-nitrotoluene). This method was more convenient than the extended series of reactions used in our earlier work.[3]

1-Methylindolecarboxylic acid was prepared from the α-methyl-α-phenylhydrazone of pyruvic acid, as described in a previous paper.[3]

Pyrazino[1.2-a]indole-1(2)-one.—A cooled and stirred solution of the acid chloride[1] prepared from 3 g. (18 millimoles) of 2-indolecarboxylic acid, in 30 cc. of anhydrous ether, was treated dropwise with a solution of 5 g. (37 millimoles) of diethyl aminoacetal in 5 cc. of ether over a period of ten minutes. After stirring for twenty minutes longer the white crystalline precipitate was collected with suction. This material, consisting of a mixture of the acylaminoacetal and aminoacetal hydrochloride, was washed with two 10-cc. portions of ether, with dilute aqueous ammonia, and finally with water. The residual crude acylaminoacetal after drying melted at 130–135° (weight 3.5 g., 60% yield); from the ethereal filtrates about 1 g. of less pure material was recovered. Recrystallization of the main crop from ethanol gave colorless crystals of 2-indolecarboxamidoacetal, m. p. 134–135°.

Three grams of the acylaminoacetal was dissolved in a cold solution of 55 g. of concentrated sulfuric acid in 150 cc. of anhydrous ether. The yellow sulfate of the pyrazinoindolone separated slowly and after twenty-four hours was collected on a filter. The product was treated with dilute aqueous ammonia to liberate the free base, which was washed thoroughly with water and dried. The crude, yellow product melted at 215–230° and weighed 1.9 g. (95% yield). Recrystallization from 90 cc. of ethanol gave 1 g. of pale yellow crystals, m. p. 247–250°; further recrystallization, with addition of decolorizing charcoal, gave almost colorless needles, m. p. 250–251° (previously reported, m. p. 247°).[4]

Pyrid[3.4-b]indole-1(2)-one.—The ultraviolet absorption spectrum of the crude reaction product (m. p. 215–230°), obtained as described in the preceding preparation, showed maxima and minima in the regions characteristic of both the pyrazinoindolones and pyridindolones. In a preliminary trial it was found that an eight plate countercurrent distribution[11] between ether and 3 *N* potassium hydroxide gave no separation of the isomers but a good separation was obtained by a seven-plate countercurrent distribution between ether and 3 *N* hydrochloric acid. Owing to the very limited solubility of the compounds in ether other combinations were examined. Excellent separation was secured by an eight plate distribution between chloroform and 6 *N* sulfuric acid, and this method showed that the crude product consisted of about 80% of pyrazinoindole-1(2)-one and 20% of pyridindole-1(2)-one. The distribution coefficient of the former between the upper and lower layers of this system is approximately 0.038, while that of the pyridindolone is 2.3. The difference is sufficient to permit a separation that is nearly complete with only one or two partitions between chloroform and sulfuric acid. In operating with quantities of 1–2 g., it was convenient to add ethanol to the system as described below.

A sample of 0.8 g. of the crude reaction product was shaken with 150 cc. each of the upper and lower phases obtained by equilibration of 8 parts (by volume) of 6 *N* sulfuric acid, 8 parts of U. S. P. chloroform, and 3 parts of 95% ethanol. After all of the substance had dissolved the lower layer was drawn off and reserved for isolation of the pyrazinoindolone. The upper aqueous layer was made slightly basic by careful addition of strong aqueous ammonia and shaken with 150 cc. of chloroform. The chloroform layer after separation, drying, and evaporation under reduced pressure, gave 0.08 g. of the slightly impure pyridindolone as light yellow crystals. This material was crystallized once from ethanol–water, with addition of decolorizing carbon, and finally from ethanol. The pure pyridindole-1(2)-one formed almost colorless crystals, m. p. 251.5–252.5° (cor.) on a micro m. p. block. The ultraviolet absorption of this material is shown in Fig. 2.

Anal. Calcd. for $C_{11}H_8N_2O$: N, 15.22. Found: N, 14.83, 14.94.

Pyridindole-1(2)-one on heating above 150° sublimes to form fine needles which rae metastable above 210°. The transition apparently occurs through the vapor phase

(8) Allen and Clark, "Organic Syntheses," **24**, 3 (1944).

(9) Burtles, Pyman and Roylance, *J. Chem. Soc.*, **127**, 585 (1925).

(10) Cornforth and Robinson, *ibid.*, 681 (1942).

(11) Craig, *J. Biol. Chem.*, **150**, 33 (1943); **155**, 519 (1944); **161**, 321 (1945).

as no solid–solid interface was observed between the two phases. The high-melting form melts at 260–261.5° (corr.), but the undercooled melt does not resolidify to the higher-melting form at temperatures below its melting point. When a sample of pyridindolone was heated rapidly it melted either at 251–253° (low-melting form) or over a range of about 10°, owing to incomplete transition to the higher-melting form. The existence of similar transitions was observed with several pyridindolones and pyrazinoindolones, and rendered capillary melting points of doubtful value as criteria of purity.

2-Methylpyrazino[1.2-a]indole-1(2)-one.—(a) Sodium methoxide procedure: One gram (5.4 millimoles) of recrystallized pyrazino[1.2-a]-indole-1(2)-one was dissolved in sodium methoxide solution prepared from 0.13 g. of sodium and 16 cc. of methanol. To the cooled solution 0.6 cc. (6.3 millimoles) of dimethyl sulfate was added and the solution was refluxed for twelve hours. Two more 0.3-cc. portions of dimethyl sulfate were added and the solution refluxed for eight hours after each addition. After distilling off the methanol the residue was heated on a steam-bath for three hours with 75 cc. of 10% aqueous sodium hydroxide. The insoluble material was then subjected to a second treatment with alkali in the same manner. The white, alkali-insoluble product was collected on a filter and washed with water. The crude product weighed 0.55 g. (50% yield); m. p. 140–145°. Two recrystallizations from methanol gave colorless needles, m. p. 147–148° (cor.).

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.69; H, 5.09; N, 14.13. Found: C, 72.30; H, 4.95; N, 14.08.

(b) Sodium Hydride Procedure: One gram of pyrazinoindolone (5.4 millimoles) was converted to the sodium derivative by refluxing with 1.8 g. (7.5 millimoles) of commercial sodium hydride in 50 cc. of dry benzene. Most of the benzene was distilled off, 8 g. of methyl iodide was added, and the mixture was refluxed for three hours; a second 8-g. portion of methyl iodide was added and the mixture was refluxed for three days. Benzene (50 cc.) was added and the unreacted methyl iodide was distilled off. The hot benzene suspension was filtered and the solid residue was extracted with two 25-cc. portions of hot benzene. The remaining solid, consisting of sodium iodide and sodium hydride, was treated cautiously with water; subsequent titration showed the presence of one equivalent of iodide ion. The combined benzene solutions were evaporated on a steam-bath and gave 0.85 g. of a pale yellow product. The crude material was shaken with 40 cc. of 10% aqueous sodium hydroxide on a steam-bath for ten minutes and the alkaline solution was discarded; the washing with hot alkali was repeated four times. Finally, the alkali-insoluble product was collected on a filter and washed thoroughly with water; after drying the weight was 0.85 g., m. p. 141–143° (85% yield). Crystallization from methanol gave 0.52 g. of pale yellow crystals, m. p. 145–146° (uncor.). The absorption spectrum of this compound is almost identical with that of pyrazinoindole-1(2)-one.

2-Methylpyrid[3.4-b]indole-1(2)-one.—A solution of 3.7 g. (25 millimoles) of methylaminoacetal in 10 cc. of dry chloroform was added with stirring to a solution of 2-indolecarbonyl chloride prepared from 2 g. (12.4 millimoles) of the acid. After stirring for twenty minutes the chloroform was removed under reduced pressure. The residual oil was stirred with 10 cc. of dilute aqueous ammonia and 200 cc. of ice–water. After standing overnight the crude 2-indolecarbonyl derivative of the aminoacetal solidified to form slightly brownish crystals (3 g., 87% yield). The crystals melted with evolution of gas at about 85° and formed a new solid which melted at approximately 230°.

A slurry of 1 g. of the crude acylaminoacetal in 10 cc. of dry ether was added in portions to a cold, stirred solution of 10 cc. of sulfuric acid in 50 cc. of dry ether. By the same procedure used for pyrazinoindole-1(2)-one there was obtained 0.4 g. (75% yield) of pale yellow crystals, m. p. 250–254°. Recrystallizations from benzene and from ethanol gave colorless crystals of 2-methylpyridindole-1(2)-one, m. p. 264–265°. The product obtained by this method was identical with a sample prepared by the method of Kermack, Perkin and Robinson,[4] using alcoholic hydrogen chloride for cyclization of the acylaminoacetal.

As the ultraviolet absorption spectrum of the crude cyclization product (m. p. 250–254°) was substantially identical with that of the purified material and very similar to the spectra of the authentic pyridindolones, we conclude that practically none of the pyrazinoindolone isomer was formed.

3-Methylpyrazino[1.2-a]indole-1(2)-one.—An ethereal solution of 5.6 g. of α-aminopropionacetal was added dropwise, with stirring, to a cooled ethereal solution of 2-indolecarbonyl chloride prepared from 3 g. of 2-indolecarboxylic acid. After stirring for ten minutes the ether was evaporated under reduced pressure. The residual liquid was treated with 3 cc. of dilute aqueous ammonia and allowed to stand overnight. The crude 2-indolecarbonyl derivative of the aminoacetal was washed thoroughly and dried; the yield was 5.1 g. (94%). Recrystallization from ethanol gave almost colorless crystals, m. p. 111.5–112.5° (uncor.).

Five grams of the unpurified acylaminoacetal was cyclized by dissolving in a cold solution of 80 g. of sulfuric acid in 250 cc. of dry ether, following the procedure described for pyrazinoindolone. The crude, yellow product weighed 3 g. (86% yield); m. p. 236–242°. Separation of the isomeric products was effected in the following way: One gram of material was shaken with 250 cc. chloroform, 50 cc. ethanol and 250 cc. of ice-cold 6 *N* sulfuric acid; the lower layer was subjected to four successive extractions with 250-cc. portions of cold 6 *N* sulfuric acid mixed with 50 cc. of ethanol. The chloroform layer was washed with sodium bicarbonate solution, treated with water and subjected to steam distillation to remove the solvent. After cooling the aqueous mixture, the non-volatile organic product was taken up in ether. Evaporation of the solvent left 0.6 g. of the crude pyrazinoindolone. Recrystallization from ethanol gave 0.4 g. of pure 3-methylpyrazino[1.2-a]indole-1(2)-one; pale yellow needles, m. p. 253–254°.

Anal. Calcd. for $C_{12}H_{10}N_2O$: N, 14.14. Found: N, 13.91, 14.11.

3-Methylpyrid[3.4-b]indole-1(2)-one.—The sulfuric acid extracts from the preceding preparation were neutralized immediately with aqueous ammonia and the precipitate was collected on a filter and washed. The dried product weighed 0.3 g. and melted at 259–261°. Recrystallization from ethanol gave colorless crystals (0.15 g.) of the pure pyridindolone, m. p. 267–268.5°. The ultraviolet absorption of this compound showed the maxima and minima characteristic of the pyridindolones.

Anal. Calcd. for $C_{12}H_{10}N_2O$: N, 14.14. Found: N, 13.86, 13.83.

9-Methylpyrid[3.4-b]indole-1(2)-one.—This compound was prepared in 65% yield from aminoacetal and 3-methylindole-2-carbonyl chloride by the method of Kermack, Perkin and Robinson.[4] Recrystallizations from benzene (100 cc./g.) and from ethanol (30 cc./g.) gave colorless crystals, m. p. 242–242.5°.

10-Methylpyrazino[1.2-a]indole-1(2)-one.—A solution of 4.6 g. (34.2 millimoles) of aminoacetal in 5 cc. of dry ether was added dropwise, with stirring and cooling, to an ethereal solution of 3-methyl-2-indolecarbonyl chloride prepared from 3 g. of the acid. After stirring for twenty minutes the precipitated solid was collected and washed with two 10-cc. portions of dry ether. The residual solid was washed with water to remove aminoacetal hydrochloride and there remained 2.2 g. of the 3-methyl-2-indolecarbonyl derivative of aminoacetal; white crystals, m. p. 116–118°.

The ethereal filtrate and the crystalline acylaminoacetal were treated separately with a cold solution of 15 cc. of concentrated sulfuric acid in 75 cc. of dry ether and allowed to stand for twenty-four hours. The precipitated hydrosulfates from the two reaction mixtures were

combined, and triturated with dilute aqueous ammonia. After washing thoroughly with water, and drying, the crude, brownish product weighed 2.4 g. (70% yield); m. p. 205–206°. Recrystallization from methanol, with addition of decolorizing carbon, gave long yellow needles, m. p. 210–211°. Further crystallizations from benzene raised the m. p. to 212–213° (previously reported, 210°).[4]

2,3-Dimethylpyrazino[1.2-a]indole-1(2)-one.—A suspension of 1.05 g. of 3-methylpyrazino[1.2-a]indole-1(2)-one in 75 cc. of dry benzene was added to a slurry of 1.6 g. of commercial sodium hydride in 20 cc. of benzene and the mixture was refluxed for eight hours. The benzene was distilled off and 30 cc. of methyl iodide was added. After refluxing for two days, 100 cc. of dry benzene was added; the mixture was heated to boiling and filtered hot. The residue was extracted with two 25-cc. portions of boiling benzene. The combined benzene solutions on evaporation gave 0.35 g. of pale yellow, crystalline material, m. p. 195–198°. The bulk of the product remained in the benzene-insoluble portion, admixed with sodium iodide and sodium hydride. This mixture was added cautiously in small portions to 250 cc. of water and the resulting suspension was boiled for fifteen minutes. The insoluble, pale yellow product was collected and washed with water; weight 0.64 g., m. p. 205–207°. The two portions of crude product amounted to 1.0 g. (90% yield). Recrystallization from ethanol (45 cc.) furnished 0.6 g. (55% yield) of pure 2,3-dimethylpyrazinoindolone; pale yellow crystals, m. p. 206–207.5°.

Anal. Calcd. for $C_{13}H_{12}N_2O$: N, 13.22. Found: N, 13.22, 13.30.

2,3-Dimethylpyrid[3.4-b]indole-1(2)-one.—A solution of 6.6 g. (37.2 millimoles) of α-methylaminopropionacetal in 10 cc. of dry ether was added with stirring to a cold ethereal solution of 2-indolecarbonyl chloride prepared from 3 g. (18.6 millimoles) of the acid. After stirring for fifteen minutes the precipitate of methylaminopropionacetal hydrochloride was collected and washed with two 10-cc. portions of dry ether. Evaporation of the ethereal filtrate and washings under reduced pressure gave a red, oily liquid, which solidified after stirring with 10 cc. of dilute aqueous ammonia and 200 cc. of ice-water. The crude 2-indolecarbonyl derivative of α-methylaminopropionacetal, after washing with cold ethanol, was obtained as almost colorless crystals (3.5 g., 80% yield). The substance melts at about 73° with evolution of gas and is transformed into a new solid that melts above 240°. This acylaminoacetal undergoes cyclization with great ease, even at low temperatures in the absence of mineral acids. Ring closure was effected in three ways: (a) One gram of the acylaminoacetal was heated in an evaporating dish on a steam-bath, with occasional stirring, until evolution of gas had ceased (one-half hour). The crude product was almost colorless and weighed 0.4 g.; m. p. 275–285° (capillary tube). (b) A slurry of 1 g. of the acylaminoacetal in 10 cc. of dry ether was added to a cold solution of 10 cc. of sulfuric acid in 50 cc. of dry ether and the solution was allowed to stand at 20°. The yellow precipitate of the hydrosulfate was collected and treated with dilute aqueous ammonia. The free base was washed with water and dried. There was obtained 0.4 g. of almost colorless crystals; m. p. 286–288° (capillary tube). (c) One gram of the acylaminoacetal was mixed with 10 cc. of ethanol and 0.3 cc. of concentrated aqueous hydrochloric acid, and the mixture allowed to stand at 20° for two days with occasional shaking. The precipitated solid was collected, triturated with dilute ammonia and washed with water. The white product weighed 0.45 g. and melted at 283–288° (capillary tube).

The cyclization product is sparingly soluble in ethanol, benzene, ether and benzine. Crystallization for 80% aqueous acetic acid (25 cc./g.), followed by recrystallization from ethanol and from benzene, gave small, colorless needles; m. p. 291–293° (capillary tube), 303–304° (Dennis–Shelton melting point bar).

Anal. Calcd. for $C_{13}H_{12}N_2O$: C, 73.55; H, 5.70; N, 13.22. Found: C, 73.56; H, 5.70; N, 13.26.

The ultraviolet absorption spectra of the crude products obtained by the three different methods of cyclization were quite similar to each other and practically identical with the spectrum of the purified material. Evidently little or none of the pyrazinoindolone isomer is formed.

2,9-Dimethylpyrid[3.4-b]indole-1(2)-one.—A sample of 0.5 g. of 9-methylpyridindolone was alkylated by means of dimethyl sulfate, using the sodium methoxide procedure described for the methylation of pyrazinoindole-1(2)-one. After repeated washings with hot 10% aqueous alkali and with water, the crude product weighed 0.27 g. (50% yield); m. p. 156–158°. Recrystallization from ethanol gave colorless needles, m. p. 158.5–159°, which showed no depression when mixed with an authentic sample of the dimethylpyridindolone prepared from methylaminoacetal and 1-methylindole-2-carbonyl chloride.[3]

2,10-Dimethylpyrazino[1.2-a]indole-1(2)-one.—(a) A solution of 5 g. of methylaminoacetal was added to an ethereal solution of 3-methyl-2-indolecarbonyl chloride from 3 g. of the acid, and the mixture stirred for twenty minutes. The precipitate was collected and washed with two 10-cc. portions of dry ether. The residual solid apparently consisted only of methylaminoacetal hydrochloride, since it was completely soluble in water. The ethereal filtrate and washings were evaporated under reduced pressure and the residual oil was treated with 20 cc. of ethanol and 0.5 cc. of concentrated hydrochloric acid. The ethanolic solution was heated to boiling for a few minutes and set aside to cool for several hours. After separating the first crop of crystals, the filtrate was heated to boiling, diluted with hot water to incipient turbidity, and allowed to cool to deposit a second crop. The combined crops weighed 2.1 g. (58% yield) and melted at 158–162°. Crystallization from ethanol, with decolorizing charcoal, followed by recrystallization from benzene, gave almost colorless needles, m. p. 161.5–162° (previously reported, m. p. 159°).

(b) A sample of 0.5 g. of 10-methylpyrazino[1.2-a]-indole-1(2)-one was methylated by the sodium methoxide procedure described above. The crude, alkali-insoluble, methylation product (50% yield) on recrystallization from methanol formed colorless needles, m. p. 160–161°. There was no depression of the melting point when this sample was admixed with the compound obtained from methylaminoacetal and 3-methyl-2-indolecarbonyl chloride.

2,3,9-Trimethylpyrid[3.4-b]indole-1(2)-one.—A cooled ethereal solution of the acid chloride prepared from 2 g. (11.4 millimoles) of 1-methylindole-2-carboxylic acid was treated dropwise, with stirring, with a solution of 3.7 g. (22.4 millimoles) of α-methylaminopropionacetal in 5 cc. of anhydrous ether. After stirring for one-half hour, the precipitate of α-methylaminopropionacetal hydrochloride was filtered off and the filtrate was evaporated under reduced pressure. The residual liquid (crude 1-methylindole-2-carbonyl derivative of the aminoacetal) was treated with 20 cc. of ethanol and 1 cc. of concentrated hydrochloric acid, heated to gentle boiling, and allowed to cool to 20°. The solution was then saturated with hydrogen chloride and allowed to stand. The precipitate of the pyridindolone hydrochloride was collected and triturated with dilute aqueous ammonia; the free base was filtered and washed thoroughly with water. After crystallization from ethanol the crude product formed cream colored needles, m. p. 141–143° (weight, 1.4 g.; 62% yield). Two crystallizations from methanol gave colorless needles, m. p. 143–144°.

Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.29; H, 6.24; N, 12.37. Found: C, 74.01; H, 6.18; N, 12.40.

2,3,10-Trimethylpyrazino[1.2-a]indole-1(2)-one.—From 3.7 g. (22.8 millimoles) of α-methylaminopropionacetal and 3-methylindole-2-carbonyl chloride (11.4 millimoles), following the general procedure used for 2,3,9-trimethylpyridindole-1(2)-one, there was obtained 1.6 g. (62% yield) of the crude pyrazinoindolone, m. p. 200–202°. Recrystallization from ethanol, with addition of decolorizing carbon, gave the pure compound; long, yellow needles, m. p. 201–202.5°.

TABLE I

ULTRAVIOLET ABSORPTION DATA FOR PYRAZINO[1.2-a]INDOLE-1(2)-ONES[a]

Substituents	Max.	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.
None	254	280	305	310	320	327	340	346	355	370	378
	4.57	3.30	3.68	3.61	3.73	3.65	3.75	3.71	3.78	3.54	3.58
2-Methyl		280	305	312	319	327	340	347	355	370	375
		3.12	3.65	3.53	3.67	3.61	3.72	3.69	3.75	3.50	3.52
3-Methyl		281	304	312	320	328	347	355	364	380	382
		3.26	3.66	3.54	3.67	3.57	3.73	3.70	3.75	3.53	3.54
10-Methyl[b]	258	280	308	315	320	330	350	358	367	378	388
	4.60	3.18	3.62	3.47	3.60	3.51	3.69	3.67	3.73	3.52	3.54
2,3-Dimethyl		282	306	315	320	328	350	357	366	382	385
		3.27	3.68	3.55	3.67	3.58	3.76	3.73	3.78	3.53	3.55
2,10-Dimethyl[b]	260	282	310	317	325	329	352	358	370		
	4.62	3.23	3.68	3.53	3.61	3.56	3.74	3.73	3.78		
2,3,10-Trimethyl[b]	260	285	310	319	324	331	364	370	379		
	4.66	3.34	3.69	3.51	3.60	3.48	3.76	3.75	3.79		
2-Carboxymethyl		282	305	312	319	325	341	348	357	372	377
		3.15	3.67	3.52	3.68	3.62	3.76	3.73	3.80	3.54	3.56

[a] For each entry the upper figure is the wave length in millimicrons and the lower figure is log ϵ. [b] Model pyrazinoindolone from 3-methylindole-2-carboxylic acid.

TABLE II

ULTRAVIOLET ABSORPTION DATA FOR PYRID[3.4-b]INDOLE-1(2)-ONES[a]

Substituents	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.
None	274	285	290	295	303	333	342	348
	3.69	3.88	3.72	3.97	3.51	3.83	3.68	3.76
2-Methyl	279	285	290	296	303	333	341	348
	3.73	3.92	3.69	3.94	3.50	3.86	3.71	3.77
3-Methyl	278	286	292	297	305	339	348	355
	3.65	3.85	3.66	3.93	3.38	3.85	3.72	3.77
9-Methyl[b]	282	287	293	298	305	344	353	360
	3.69	3.92	3.56	3.88	3.25	3.88	3.71	3.81
2,3-Dimethyl	280	286	290	296	305	340	350	354
	3.73	3.92	3.75	3.91	3.46	3.90	3.78	3.79
2,9-Dimethyl[b]	282	287	294	298	305	344	353	359
	3.70	3.92	3.55	3.81	3.27	3.90	3.75	3.81
2,3,9-Trimethyl[b]	282	286	294	299	310	350	355	356
	3.75	3.79	3.60	3.78	3.28	3.92	3.88	3.93

[a] For each entry the upper figure is the wave length in millimicrons and the lower figure is log ϵ. [b] Model pyridindolone from 1-methylindole-2-carboxylic acid.

Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.29; H, 6.24; N, 12.37. Found: C, 74.01; H, 6.24; N, 12.47.

1(2)-Oxopyrazino[1.2-a]indole-2-acetic Acid.—One gram (5.4 millimoles) of pyrazinoindole-1(2)-one was refluxed for ten minutes with a solution of two equivalents of sodium methoxide in 25 cc. of methanol. The solution was cooled, 0.51 g. (5.5 millimoles) of chloroacetic acid added, and the mixture refluxed for three hours. The precipitate was collected and dissolved in 50 cc. of 10% sodium carbonate solution; the solution was filtered and the filtrate made acid to congo red with strong hydrochloric acid. The sparingly soluble acid was collected and washed thoroughly with water; weight, 0.45 g. (35% yield), m. p. 263–266° (dec.). Two crystallizations from methanol gave colorless needles, m. p. 275–277° (dec.).

Anal. Calcd. for $C_{13}H_{10}N_2O_3$: C, 64.45; H, 4.16; N, 11.57; neut. equiv., 242. Found: C, 64.59; H, 4.08; N, 11.45; neut. equiv., 240.

In a subsequent preparation pyrazinoindole-1(2)-one was heated with commercial sodium hydride in benzene, and the suspension of the sodium derivative was treated with a large excess of methyl chloroacetate and refluxed with stirring for twenty-four hours. Benzene and most of the methyl chloroacetate were removed by distillation, and the residue was treated cautiously with 20 cc. of water. Four grams of potassium hydroxide and 25 cc. of ethanol were added and the mixture was refluxed for five hours on a steam-bath to saponify the ester. The ethanol was distilled off, water was added, and the mixture extracted with ether to remove alkali-insoluble material. Acidification with strong hydrochloric acid gave the crude 1-oxopyrazinoindole-2-acetic acid in yields of 70–80%. Recrystallizations from ethanol gave almost colorless needles, m. p. 275–277° (dec.), identical with the compound prepared from the sodium derivative and chloroacetic acid.

2-(2′-Diethylaminoethyl)-10-methylpyrazino[1.2-a]-indole-1(2)-one.[7]—Five grams of 10-methylpyrazinoindole-1(2)-one was added, with stirring, to a suspension of 1 g. of sodium amide in 300 cc. of dry benzene. The mixture was heated in an oil-bath at 110° for one hour, when a greenish-yellow flocculent precipitate of the sodium derivative had formed. A solution of 23 g. of freshly prepared 2-diethylaminoethyl bromide in 20 cc. of benzene

was added dropwise, with stirring, over a period of thirty minutes. After stirring for an hour, the mixture was refluxed for twenty-four hours.

To the cold reaction mixture was added 100 cc. of 10% sodium hydroxide solution and the mixture was steam distilled to remove the solvent and facilitate solution of any unalkylated starting material. The insoluble organic product was taken up in benzene, and the filtered solution was distilled to remove the solvent. The excess of diethylaminoethyl bromide was removed by distillation under reduced pressure (b. p. 60° (4 mm.)) and the residual liquid dissolved in 150 cc. of dry benzene. Under anhydrous conditions, dry hydrogen chloride was passed over the solution for several hours. The benzene was removed by decantation and the sticky hydrochloride of the base was dissolved in hot butanol. An equal volume of dry acetone and several volumes of dry ether were added, and the solution was chilled thoroughly. The purified hydrochloride was collected by centrifuging, and subjected to several reprecipitations in a similar way. Eventually there was obtained 1 g. of fine white crystals of the hydrochloride of the base; m. p. 173–174°.

Anal. Calcd. for $C_{18}H_{23}N_3O\cdot HCl$: N, 12.59. Found: N, 12.39, 12.31.

Several grams of slightly less pure material were recovered from the filtrates. The free base was converted to the sulfate, phosphate and *p*-toluenesulfonate, but these salts were hygroscopic and difficult to purify.

Ultraviolet Absorption Spectra.—The ultraviolet absorption spectra were obtained with a Beckmann spectrophotometer and ethanol was used as solvent. Curves are shown in detail for three pairs of isomers (Figs. 1–3). Tabulations of the characteristic maxima and minima for the pyrazinoindolones and pyridindolones are given in Tables I and II.

Summary

A number of pyrazino[1.2-a]indole-1(2)-ones and pyrid[3.4-b]indole-1(2)-ones have been prepared by ring closure of the 2-indolecarbonyl derivatives of α-aminoacetals. It has been found that these two different structural types can be distinguished from one another by means of their ultraviolet absorption spectra.

Pyrazinoindole-1(2)-ones and pyridindole-1(2)-ones having a hydrogen in the 2-position undergo N-alkylation at that position by the conventional methods of alkylation. This procedure permits the preparation of 2-alkylpyrazinoindole-1(2)-ones that are not accessible by direct cyclization.

2,3-Dimethylpyrazinoindole-1(2)-one and the isomeric 2,3-dimethylpyridindole-1(2)-one, which are important reference structures for gliotoxin degradation products, have been synthesized.

ITHACA, N. Y. RECEIVED MAY 7, 1947

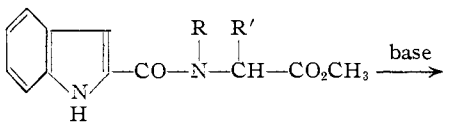
[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

Pyrazinoindole-1,4-diones. Ring Closure of 2-Indolecarbonyl Derivatives of α-Aminoesters

BY JOHN R. JOHNSON, JOHN H. ANDREEN[1] AND ANN D. HOLLEY[1]

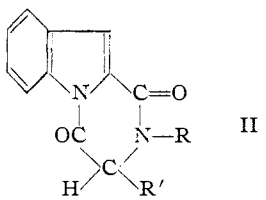
One of the important degradation products of the antibiotic substance gliotoxin is a crystalline compound of the formula $C_{13}H_{12}N_2O_2$, which is obtained readily by reduction of gliotoxin with hydriodic acid and red phosphorus.[2] A synthesis of this degradation product was effected by reaction of 2-indolecarbonyl chloride with the methyl or ethyl ester of *dl*-N-methylalanine to form the 2-indolecarbonyl derivative of the aminoester (I), which underwent ring closure spontaneously in the reaction mixture.[2,3] Evidence from ultraviolet absorption studies indicated that the cyclization product is 2,3-dimethylpyrazino[1.2-a]indole-1,4(2,3)dione (II, R = R′ = CH_3) rather than the isomeric pyridindole-1,4-(2,3)-dione (III, R = R′ = CH_3).

In the earlier report[2] the spontaneous cyclization of the 2-indolecarbonyl derivative of the aminoester was attributed to the presence of free hydrogen chloride formed in the first step of the reaction, as it is known that this reagent effects ring closure of analogous derivatives of α-amino-



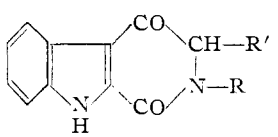
I

2-Indolecarboxamido ester



II

Pyrazinoindole-1,4(2,3)-dione
(observed ring closure)



III

Pyridindole-1,4(2,3)-dione
(alternative ring closure)

(1) The Wm. S. Merrell Company Fellow in Chemistry.

(2) Dutcher, Johnson and Bruce, THIS JOURNAL, **66**, 617 (1944).

(3) Johnson, Hasbrouck, Dutcher and Bruce, *ibid.*, **67**, 423 (1945).