The mass spectrum showed a parent peak at 461 mass units and fragmentation typical of ethanol and 4H-flavene. The nmr spectrum was like that of **6** except for absorption by the ethoxy protons.

The preparation of **3a**, **3b**, and **3c** by the reaction of flavylium perchlorate (**1**) and 4H-flavene (**2**) is illustrated by the preparation of **3c**. A solution of 3 g of **1**, 2 g of **2**, 1.5 g of sodium acetate, and 75 ml of ethanol was stirred for 2 hr. Some white solid began to precipitate in a short time. The reaction mixture was diluted with 15 ml of water, and the solid was collected and recrystallized from ethanol to give 2.4 g of **3c**, mp 169–170°.

4H-Flavene (2).—To a stirred solution of 5 g of flavylium perchlorate in 100 ml of acetonitrile was added 1 g of sodium borohydride in portions. The colorless solution was diluted with some water to destroy the excess sodium borohydride and then evaporated to dryness on a rotary evaporator. The residue was extracted with ether, the extract was dried (magnesium sulfate), and the ether was removed. The residue was recrystallized from methanol to yield 2.6 g of product, mp 54–55°. The melting point and infrared spectrum of the product were identical with those of a sample prepared previously.[3]

Anal. Calcd for $C_{15}H_{12}O$: C, 86.6; H, 5.8. Found: C, 86.5; H, 5.7.

The nmr spectrum (in deuteriochloroform) showed a doublet centered at τ 6.45 (two protons), a triplet centered at 4.32 (one proton), and a multiplet centered at 2.4 (nine protons).

Essentially, the same results were obtained when flavylium perchlorate was treated with sodium borohydride in *t*-butyl alcohol, although the yield of **2** was slightly less.

2-Phenylnaphtho[2,1-*b*]-4H-pyran (5a).—A mixture of 3 g of 2-phenylnaphtho[1,2-*b*]pyrylium perchlorate (**4a**), 100 ml of ethanol, and 0.5 g of sodium borohydride was stirred for 1 hr and diluted with 200 ml of water, and the solid was collected and recrystallized from toluene to give 1.5 g of **5a**, mp 186–187°.

Anal. Calcd for $C_{19}H_{14}O$: C, 88.4; H, 5.4. Found: C, 88.5; H, 5.3.

The nmr spectrum (in deuteriochloroform) showed two methylene protons (doublet) at τ 6.22; one vinyl proton (triplet) at 4.4; and 11 aromatic protons over the range 2.1–2.9.

2-(4-Ethoxyphenyl)naphtho[2,1-*b*]-4H-pyran (5b).—This compound was prepared by the procedure described for the preparation of **5a** and the product (1.4 g) melted at 174°.

Anal. Calcd for $C_{21}H_{18}O_2$: C, 83.4; H, 6.0. Found: C, 83.6; H, 6.3.

2-Ethoxy-3-ethyl-2H-flavene (7).—To a suspension of 3 g of 3-ethylflavylium perchlorate (**6**) in 70 ml of ethanol was added 0.7 g of sodium borohydride. The solid quickly dissolved to give a pale yellow solution. The solution was stirred for 15 min and then diluted with 100 ml of water. The oil that separated was extracted with methylene chloride, the extract was dried (magnesium sulfate), and the solvent was removed. The residue was distilled to give 1.8 g of **15**, bp 134° (0.3 mm).

Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.4; H, 7.1. Found: C, 81.5; H, 7.1.

The nmr spectra (in deuteriochloroform) had the following absorption: CH_3–, τ 8.79 (t), J = 7 cps, and 9.08 (t), J = 7 cps; $MeCH_2$–, τ 8.04 (split q); $MeCH_2O$–, τ 6.45 (q), J = 7 cps; vinyl H, τ 3.5 (s); nine aromatic protons.

A solution of 2 g of 3-ethylflavylium perchlorate (**6**), 20 ml of ethanol, and 5 ml of 40% sodium hydroxide solution was allowed to stand overnight and diluted with 100 ml of water; the oil that separated was extracted with ether. The extract was dried (magnesium sulfate), the solvent was removed, and the residue was distilled to give 2.1 g of product which had an infrared absorption spectrum which was identical with that of the sample of **7** prepared by the sodium borohydride procedure.

Registry No.—2, 494-13-3; **3a**, 14319-49-4; **3b**, 14161-90-1; **3c**, 14161-91-2; **5a**, 14271-36-4; **5b**, 14161-92-3; **7**, 14161-93-4; sodium borohydride, 1303-74-8.

Acknowledgment.—We wish to thank Mr. D. P. Maier, for the determination and interpretation of the mass spectra, and Dr. T. H. Regan and Mr. R. L. Young, for the determination and interpretation of the nmr spectra.

1,2,5,6-Tetrahydro-12H-pyrrolo[1′,2′:1,2]azepino[3,4-*b*]indoles and 5H,7H,14H-8,9-Dihydroisoindolo[2′,1′:1,2]azepino[3,4-*b*]indoles[1]

S. WAWZONEK AND M. M. MAYNARD

Department of Chemistry, University of Iowa, Iowa City, Iowa 52240

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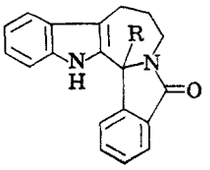
The reaction products from 3-(3-aminopropyl)indole and γ-keto acids and phthalaldehydic acid varied with the structure of the acid used. *o*-Benzoylbenzoic acid gave 5-oxo-5H,7H,14H-8,9-dihydro-14b-phenylisoindolo[2′,1′:1,2]azepino[3,4-b]indole (Ia). *o*-Acetylbenzoic acid gave 2-[3-(3-indolyl)propyl]-3-methylenephthalimidine (II) which was cyclized to the tetrahydroazepine (Ib) with acid. Phthalaldehydic acid gave amorphous products. The tetrahydroazepine (Ic) was synthesized from the phthalimide derivative of 3-(3-aminopropyl)indole. The γ-lactones of 4-hydroxy-4-phenyl-3-butenoic acid and 4-hydroxy-3-pentenoic acid were used to synthesize the 1,2,5,6-tetrahydro-12H-pyrrolo[1′,2′:1,2]azepino[3,4-*b*]indole derivatives (VIII). Lithium aluminium hydride reduction of the various lactams gave the corresponding amines in all cases except Ic.

The successful synthesis of pyrrolo-β-carbolines[2] and the indolo-β-carbolines[3] from tryptamine and γ-keto acids and phthalaldehydic acids suggested a study of the condensation of 3-(3-aminopropyl)indole with phthalaldehydic acid and γ-keto acids as a method for the preparation of substituted azepines. The reaction products obtained differed with the structure of the acid used.

o-Benzoylbenzoic acid was the only acid which gave lactam Ia directly under the condition used previously.[2] Proof for the structure of Ia was a negative Ehrlich test and the infrared spectrum.

The condensation of *o*-acetylbenzoic acid with 3-(3-aminopropyl)indole did not give the expected lactam



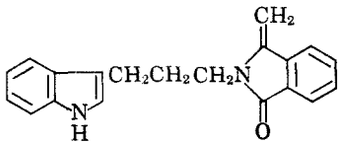
Ia, R = C_6H_5
b, R = CH_3
c, R = H

(1) Abstracted in part from the Ph.D. Thesis of M. M. Maynard, State University of Iowa, June 1966.

(2) S. Wawzonek and J. D. Nordstrom, *J. Med. Chem.*, **8**, 265 (1965).

(3) S. Wawzonek and G. E. Nelson, *J. Org. Chem.*, **27**, 1377 (1962).

Ib but produced instead 2-[3-(3-indolyl)propyl]-3-methylenephthalimidine (II). Proof for the structure

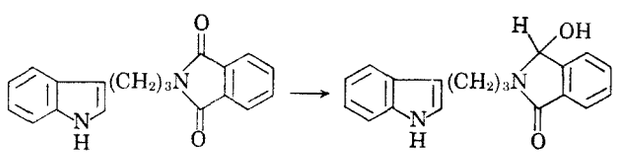


II

was the nmr and infrared spectra and a positive Ehrlich test. Similar substituted phthalimidine derivatives have been obtained from the condensation of *o*-acetylbenzoic acid[4] and phthalideneacetic acid[5] with various amines.

The phthalimidine II when treated with either hydrochloric, acetic, or formic acids gave the desired lactam Ib. This compound which could be obtained directly by the condensation of phthalideneacetic acid with 3-(3-aminopropyl)indole in acetic acid, gave a negative Ehrlich test.

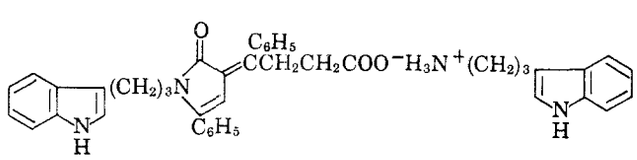
The direct condensation of phthalaldehydic acid with 3-(3-aminopropyl)indole gave two neutral products which did not show any of the expected properties of lactam Ic. These compounds were not further investigated. The desired lactam (Ic) was prepared from the phthalimide derivatives of 3-(3-aminopropyl)indole. The imide III when reduced with magnesium in methanol gave 3-hydroxy-2-[3-(3-indolyl)-propyl]phthalimidine (IV) which was cyclized to 5-



III IV

oxo-5H,7H,14H-8,9-dihydroisoindolo[2′,1′:1,2]azepino-[3,4-*b*]indole (Ic) with hydrochloric acid in methanol.

The reaction of 3-(3-aminopropyl)indole and β-benzoylpropionic acid gave a yellow solid which is best represented by structure V. Evidence for this struc-

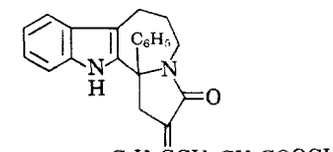


V

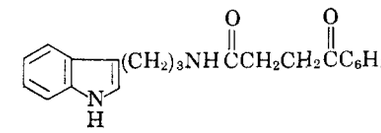
ture was a positive Ehrlich test, a neutralization equivalent of 639, and a carbonyl absorption at 1667 cm^{-1}. A similar type of compound has been reported to be formed by heating β-benzoylpropionic acid with ammonium acetate at 160°.[6]

Treatment of this salt with hydrochloric acid in methanol gave ester VI. The product was insoluble in ethanolic alkali and gave a negative Ehrlich test. The nmr and infrared spectra were in agreement with this formulation.

The desired 1,2,5,6-tetrahydro-3-oxo-12H-12b-phenylpyrrolo[1′,2′:1,2]azepino[3,4-*b*]indole (VIIIa) was obtained by a two-step synthesis from 4-hydroxy-4-phenyl-3-butenoic acid γ-lactone and 3-(3-aminopropyl)indole. Condensation of these two compounds gave 3-benzoyl-2-[3-(3-indolyl)propyl]propionamide



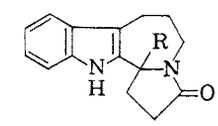
VI



VII

(VII), which upon treatment with hydrochloric acid in methanol gave the lactam (VIIIa).

1,2,5,6-Tetrahydro-3-oxo-12H-12b-methylpyrrolo-[1′,2′:1,2]azepino[3,4-*b*]indole (VIIIb) was obtained directly by treating a solution of 3-(3-aminopropyl)-indole and 4-hydroxy-3-pentenoic acid γ-lactone in ethanol with gaseous hydrogen chloride. This type



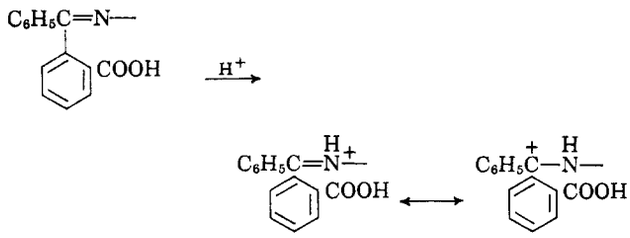
VIIIa, R = C_6H_5
b, R = CH_3

of acid-catalyzed condensation occurs also between 5-methoxytryptamine and 4-hydroxy-4-phenyl-3-butenoic acid γ-lactone and gives the known 1,2,3,5,6,11b-hexahydro-8-methoxy-3-oxo-11b-phenyl-11 H-pyrrolo-[2,1-*a*]-β-carboline.[2]

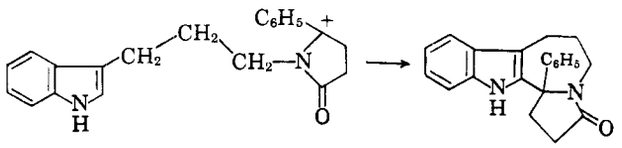
In these condensation reactions cyclization could also occur on the indole nitrogen and form the isomeric δ-lactams. Evidence against this structure was the lack of basicity for the condensation products and the ultraviolet and infrared spectra. The former show λ_{max} at 244, 274, and 301 mμ for indoles with acyl groups on the indole nitrogen.[7] The infrared spectra for the lactam carbonyl in the products appears between 1665 and 1672 cm^{-1}; similar abnormally low-frequency carbonyl bands have been observed in the related β-carboline series.[2] Structures with a δ-lactam ring would be expected to show absorption above 1700 cm^{-1} in a similar manner to the E ring of the alkaloid *dl*-eburnamoine.[8]

The behavior of the various keto acids in the condensation with 3-(3-aminopropyl)indole suggests that an initial condensation occurs with the carbonyl group to Schiff's bases. This base can cyclize to lactams by forming enamine structures in the case of *o*-acetylbenzoic acid and β-benzoylpropionic acid. The product from *o*-benzoylbenzoic acid is not capable of such a change and remains as the Schiff's base which is basic enough to be protonated by the parent acid to a species which is capable of cyclization. The enamines II and V require stronger acids in order to accomplish the same cyclization. Complications are introduced

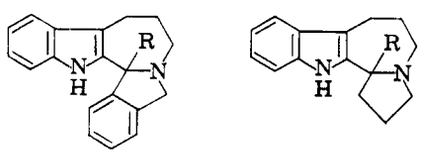
(4) J. Honzl, *Collection Czech. Chem. Commun.*, **21**, 725 (1956).
(5) C. E. Dent, *J. Chem. Soc.*, 1 (1938).
(6) H. Fiesselmann and W. Ehmann, *Chem. Ber.*, **91**, 1713 (1958).
(7) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," International Series of Monographs on Organic Chemistry, Vol. 7, The Macmillan Co., New York, N. Y., 1964, pp 298–299.
(8) M. F. Bartlett and W. I. Taylor, *J. Am. Chem. Soc.*, **82**, 5941 (1960).



with β-benzoylpropionic acid in that the enamine can condense with excess of the γ-keto acid and form compound V. This complication can be avoided by preforming the amide VII. Cyclization would then proceed through the protonated enamine in the absence of excess β-benzoylpropionic acid.



The lactams with the exception of Ic were reduced with lithium aluminum hydride to the corresponding tertiary amines IX and X.



IXa, R = C_6H_5
b, R = CH_3

Xa, R = C_6H_5
b, R = CH_3

The ultraviolet spectra of these amines were similar to the corresponding lactams; the infrared spectra did not show carbonyl bands.

Lactam Ic could not be reduced with lithium aluminum hydride in ether, tetrahydrofuran, dioxane, or N-ethylmorpholine. Similar difficulties have been encountered in the reduction of related β-carbolines.[3]

Experimental Section[9]

5-Oxo-5H,7H,14H-8,9-dihydro-14b-phenylisoindolo[2′,1′:1,2]azepino[3,4-*b*]indole (Ia).—A solution of 3-(3-aminopropyl)indole (5.47 g), prepared by the procedure given for the methoxy compound,[10] and *o*-benzoylbenzoic acid (7.12 g) in 500 ml of dry xylene was refluxed with stirring for 24 hr. The solution was cooled and the water was removed by a Dean–Stark trap and the lactam which precipitated was filtered. The xylene from the filtrate was reduced in volume and additional product was obtained. Recrystallization of the combined fractions from absolute ethanol gave white rods (3.04 g) melting at 313–314°. This lactam gave a negative Ehrlich test.

Anal. Calcd for $C_{25}H_{20}N_2O$: C, 82.39; H, 5.53; N, 7.69. Found: C, 82.69; H, 5.56; N, 7.95.

The lactam has infrared absorptions (Nujol mull) at 3355 (NH), 1672 (C=O), 763, 741, and 700 cm^{-1} (aromatic); ultraviolet absorption, $\lambda_{max}^{95\%\text{ethanol}}$ mμ (log ε), 222 (4.62), 285 (3.96), 293 (3.91); λ_{min} mμ (log ε), 253 (3.68).

2-[3-(3-Indolyl)propyl]-3-methylenephthalimidine (II).—A mixture of 3-(3-aminopropyl)indole (5.59 g) and *o*-acetylbenzoic acid (5.27 g) in 250 ml of xylene was heated with stirring for 48 hr and the water was removed by a Dean–Stark trap. The mixture was cooled and the solvent was removed. The yellow-brown residue was dissolved in 250 ml of chloroform and washed with 2 *N* hydrochloric acid, a saturated solution of sodium bicarbonate, and water. The chloroform solution was dried and the solvent was removed. Recrystallization from chlorobenzene gave a yellow product melting at 130–131°; yield 8.8 g.

Anal. Calcd for $C_{20}H_{18}N_2O$: C, 79.47; H, 5.96; N, 9.27; mol wt, 302. Found: C, 79.12; H, 6.32; N, 9.47; mol wt (osmometer in chloroform), 307.

The lactam has infrared absorptions (Nujol mull) at 3390 (NH) and 1694 cm^{-1} (C=O); nmr bands ($CDCl_3$) at 2.08 (multiplet, $-CH_2-$), 2.86 and 3.87 (triplet, $-CH_2-$), 4.75 (doublet, $-CH_2$), 5.14 (doublet, $=CH_2$), 7.0–7.7 ppm (multiplet, aromatic); ultraviolet absorptions, $\lambda_{max}^{95\%\text{ethanol}}$ mμ (log ε), 255 (4.24), 224 (4.85); λ_{min} mμ (log ε), 238 (4.10). The compound gave a positive Ehrlich test.

5-Oxo-5H,7H,14H-8,9-dihydro-14b-methylisoindolo[2′,1′:1,2]azepino[3,4-*b*]indole (Ib). Method I.—A mixture of 2-[3-(3-indolyl)propyl]-3-methylenephthalimide (0.1 g), 25 ml of absolute ethanol, and two drops of concentrated hydrochloric acid was stirred at reflux for 24 hr. The reaction mixture after cooling and removing the ethanol gave a solid which was triturated with absolute ethanol and filtered. Recrystallization from acetic acid gave yellow crystals (0.08 g) melting at 321–322° dec.

Anal. Calcd for $C_{20}H_{18}N_2O$: C, 79.47; H, 5.96; N, 9.27; mol wt, 302. Found: C, 79.18; H, 6.04; N, 9.17; mol wt (Rast), 293.

The lactam has infrared absorptions (Nujol mull) at 3223 (NH) and 1665 cm^{-1} (C=O); ultraviolet absorptions, $\lambda_{max}^{95\%\text{ethanol}}$ mμ (log ε), 225 (4.63), 2.83 (4.02), 292 (3.96); λ_{min} mμ (log ε), 260 (3.93). The lactam gave a negative color test with Ehrlich reagent.

Method II.—A solution of 3-(3-aminopropyl)indole (4.55 g) and phthalideneacetic acid (4.82 g) in 45 ml of glacial acetic acid was refluxed for 2 hr. The mixture upon cooling gave 5.37 g of lactam Ia. The infrared spectrum and the melting point were identical with the compound prepared by method I.

2-[3-(3-Indolyl)propyl]phthalimide (III).—A mixture of 3-(3-aminopropyl)indole (1.70 g) and phthalic anhydride (1.70 g) in a 50-ml round bottom flask was carefully heated with a microburner until the material formed a red melt. Recrystallization of the resulting imide from absolute ethanol gave 2.38 g of yellow needles melting at 131–132° (lit.[11] mp 132°).

The imide has infrared absorptions (Nujol mull) at 3443 (NH), 1695 and 1762 (C=O), 719 and 745 cm^{-1} (aromatic); ultraviolet absorptions, $\lambda_{max}^{95\%\text{ethanol}}$ mμ (log ε), 200 (4.85), 282 (3.82), 290 (3.80); λ_{min} mμ (log ε), 252 (3.52); nmr bands ($CDCl_3$) at 2.15 (quartet, $-CH_2-$), 2.81 and 3.78 (triplet, $-CH_2-$), 7.20–7.75 ppm (multiplet, aromatic).

3-Hydroxy-2-[3-(3-indolyl)propyl]phthalimidine (IV).—A solution of 2-[3-(3-indolyl)propyl]phthalimidine (10 g) in 250 ml of methanol and 40 ml of a saturated ammonium chloride solution was heated to 60° and magnesium turnings (4.0 g) were added to the mixture. The solution was stirred until the yellow color had disappeared. The resulting mixture was filtered hot and the solvent was removed. Warm water (200 ml) was added to the residue and the mixture was filtered. The product was washed with 200 ml of water and air dried. The white crystals melted at 167–168°; yield, 9.77 g.

Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.13; H, 5.95; N, 9.22.

The lactam has infrared absorptions (Nujol mull) at 1653 (C=O), 806, 769, 748, and 694 cm^{-1} (aromatic); nmr bands (pyridine) at 2.48, 3.04, 4.07 ppm (multiplet, $-CH_2-$); ultraviolet absorptions, $\lambda_{max}^{95\%\text{ethanol}}$ mμ (log ε), 222 (4.64), 283 (3.84), 292 (3.72); λ_{min} mμ (log ε), 244 (3.68). The compound gave a positive Ehrlich test.

5-Oxo-5H,7H,14H-8,9-dihydroisindolo[2′,1′:1,2]azepino[3,4-*b*]indole (Ic).—A mixture of 3-hydroxy-2-[3-(3-indolyl)propyl]-phthalimidine (5.0 g), methanol (250 ml), and 2 *N* hydrochloric acid (1 ml) was stirred and refluxed for 24 hr. The mixture was cooled in an ice bath and the precipitate was collected by filtration. Reducing the volume of the filtrate by half gave a second crop of crystals. The total amount of lactam melting at 200–205° was 4.00 g.

Anal. Calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72; mol wt, 288. Found: C, 78.99; H, 5.76; N, 9.73; mol wt, 307.

The lactam has infrared absorptions (Nujol mull) at 3230

(9) All melting points are corrected and were determined on a Nalge block. Molecular weights were determined in a vapor pressure osmometer in all examples except one.

(10) A. Allais, G. Mueller, and L. Velluz, French Patent 1,238,738 (1960).

(11) R. W. Jackson and R. H. Manske, *J. Am. Chem. Soc.*, **52**, 5029 (1930).

(NH), 1670 (C=O), 700, 725, 785, and 800 cm^{-1} (aromatic); ultraviolet absorptions, $\lambda_{max}^{95\%ethanol}$ mμ (log ε), 223 (4.68), 278 (4.07), 292 (3.96); λ_{min} mμ (log ε), 258 (3.96).

3-Benzoyl-2-[3-(3-indolyl)propyl]propionamide (VII).—A mixture of 3-(3-aminopropyl)indole (1.33 g), absolute methanol (30 ml), and of 4-hydroxy-4-phenyl-3-butenoic acid γ-lactone (0.975 g) was refluxed with stirring for 1.5 hr. Anhydrous potassium carbonate was added to the solution and the mixture was refluxed for an additional 18 hr. The mixture upon cooling and removing the solvent gave a brown residue which was dissolved in chloroform and washed with water. The chloroform layer was dried and the solvent was removed under reduced pressure. Recrystallization of the residue from benzene gave 1.03 g of white crystals melting at 133–134°.

Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.34; H, 6.69; N, 8.13.

The amide had infrared absorptions (Nujol mull) at 3333 (NH), 1680 (C=O, ketone), 1638 (C=O, amide), 676, 733, 761, and 825 cm^{-1} (aromatic); ultraviolet absorptions, $\lambda_{max}^{95\%ethanol}$ mμ (log ε), 223 (4.58), 283 (3.81), 291 (3.74); λ_{min} mμ (log ε), 261 (3.60). The Ehrlich test was positive.

1,2,5,6-Tetrahydro-3-oxo-12H-12b-phenylpyrrolo[1′,2′:1,2]azepino[3,4-b]indole (VIIIa).—A solution of N-[3-(3-indolyl)propyl]benzoylpropionamide (0.5 g), in 30 ml of methanol and 1.0 ml of concentrated hydrochloric acid was stirred and heated at 45° for 48 hr. The solution was cooled and the resulting lactam melted at 288–289°; yields 0.373 g.

Anal. Calcd for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37; N, 8.86. Found: C, 79.47; H, 6.70; N, 8.79.

The lactam has infrared absorptions (Nujol mull) at 3290 (NH), 1657 (C=O), 702, 750, and 806 cm^{-1} (aromatic); ultraviolet absorptions, $\lambda_{max}^{95\%ethanol}$ mμ (log ε), 223 (4.60), 282 (3.91), 292 (3.82); λ_{min} mμ (log ε), 250 (3.68).

1,2,5,6-Tetrahydro-3-oxo-12H-12b-methylpyrrolo[1′,2′:1,2]azepino[3,4-b]indole (VIIIb).—A solution of 3-(3-aminopropyl)-indole (10 g) and 4-hydroxy-3-pentenoic acid γ-lactone (5.63 g) in 150 ml of absolute ethanol was stirred at room temperature for 2 hr, and then saturated with dry hydrogen chloride. The stirring was continued for an additional 18 hr. The solvent was removed and the residue was dissolved in chloroform. The chloroform solution was filtered and washed with 200 ml of 2 *N* hydrochloric acid, 150 ml of cold 5% potassium hydroxide solution, and finally with water. The organic layer was dried and the solvent was removed under reduced pressure. The resulting yellow oil was dissolved in 20–30 ml of acetone and gave the lactam upon standing. Recrystallization of the lactam from acetone gave 4.71 g of white crystals melting at 192–193°.

Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.59; H, 7.09; N, 11.02; mol wt, 254. Found: C, 75.43; H, 7.32; N, 10.93; mol wt, 277.

The lactam has infrared absorptions (Nujol mull) at 3300 (NH), 1660 (C=O), 698, 707, 733, and 802 cm^{-1} (aromatic); ultraviolet absorptions, $\lambda_{max}^{95\%ethanol}$ mμ (log ε), 225 (4.61), 284 (3.93), 292 (3.85); λ_{min} mμ (log ε), 246 (3.15). This lactam gave a negative Ehrlich test.

1,2,3,5,6,11b-Hexahydro-8-methoxy-3-oxo-11b-phenyl-11H-pyrrolo[2,1-a]-β-carboline.—A solution of 5-methoxytryptamine, (0.5 g) and 4-hydroxy-4-phenyl-3-butenoic acid γ-lactone (0.4 g) in 50 ml of absolute ethanol was stirred at room temperature for 2 hr. Dry hydrogen chloride was bubbled through the solution for 10 min and the solution was stirred an additional 18 hr. The solvent was removed and the residue was dissolved in chloroform. The chloroform solution was extracted with 2 *N* hydrochloric acid, aqueous sodium hydroxide, and water. Removal of the solvent gave a solid which, when recrystallized from benzene–ethanol, gave 0.179 g of white crystals melting at 256–257°. The melting point and the infrared spectrum were identical with an authentic sample.[2]

Reaction of 3-(3-Aminopropyl)indole and β-Benzoylpropionic Acid.—A mixture of 3-(3-aminopropyl)indole (7.3 g), β-benzoylpropionic acid (7.5 g), and 500 ml of toluene was refluxed for 24 hr and the water was removed with a Dean–Stark trap. The mixture was cooled and the resulting yellow solid was filtered. Recrystallization of the material from ethanol gave 5.29 g of solid melting at 148–151°. The solid gave a positive Ehrlich test and was not purified further.

Anal. Calcd for $C_{42}H_{42}N_4O_3$: C, 77.54; H, 6.46; N, 8.62. Found: C, 76.51; H, 6.51; N, 8.49.

The yellow solid (1.0 g) was dissolved in 40 ml of methanol containing 1.0 ml of concentrated hydrochloric acid and the solution was stirred at 45° for 24 hr. The solution upon cooling gave a solid. Recrystallization of the product from a methanol–ethanol (10:1) mixture gave 0.5 g of white needles melting at 227–228°. The compound correctly analyzed for 2-(1-phenyl-3-carbomethoxypropylidene)-3-oxo-1,2,5,6-tetrahydro-12H-12b-phenyl-pyrrolo[1′,2′:1,2]azepino[3,4-b]indole (VI).

Anal. Calcd for $C_{32}H_{30}N_2O_3$: C, 78.34; H, 6.16; N, 5.71. Found: C, 78.37; H, 6.39; N, 5.86.

The nmr spectrum showed a singlet at 3.47 ppm for the methoxy protons, and the infrared spectrum showed bands at 3280 (NH), 1740 ($COOCH_3$), 1650 (CON), and 773, 745 and 704 cm^{-1} (aromatic).

5H,7H,14H-8,9-Dihydro-14b-methylisoindole[2′,1′:1,2]azepino[3,4-b]indole (IXb).—5-Oxo-5H,7H,14H-8,9-dihydro-14b-methylisoindolo[2′,1′:1,2]azepino[3,4-b]indole (3.0 g) was extracted from a Soxhlet extractor with a refluxing solution of tetrahydrofuran (250 ml) containing lithium aluminum hydride (3.6 g) for 24 hr, and then cooled to room temperature. The excess hydride was decomposed by the careful addition of 4.0 ml of water in 10 ml of tetrahydrofuran and 10 ml of a 15% potassium hydroxide solution. The lithium salts were filtered and washed with hot tetrahydrofuran. The filtrates were collected and the solvent was removed under reduced pressure. The residue was dissolved in 30 ml of ether and chromatographed on a column containing 80 g of alumina. Eight ether-eluted fractions (40 ml) were collected and the solvent was removed under a stream of nitrogen. Recrystallization of the residue from hexane gave 1.04 g of white crystals melting at 75–80°.

Anal. Calcd for $C_{20}H_{20}N_2$: C, 83.29; H, 6.99; N, 9.72, mol wt, 288. Found: C, 80.62; H, 7.20; N, 9.30; mol wt, 294.

The amine has infrared absorptions (Nujol mull) at 3363 (NH), 690 and 743 cm^{-1} (aromatic); ultraviolet absorptions, λ_{max}^{MeOH} mμ (log ε), 225 (4.53), 272 (3.86), 283 (3.90), 292 (3.85); λ_{min} mμ (log ε), 252 (3.57).

5H,7H,14H-8,9-Dihydro-14b-phenylisoindolo[2′,1′:1,2]azepino[3,4-b]indole (IXa).—A solution of 5-oxo-5H,7H,14H-8,9-dihydro-14b-phenylisoindolo[2′,1′:1,2]azepino[3,4-b]indole (6.41 g) dissolved in 100 ml of dry dioxane was slowly added to a refluxing solution of lithium aluminum hydride (6.5 g) in 500 ml of dioxane. The mixture was stirred for 12 hr, allowed to cool to room temperature, and then decomposed by the addition of 6.5 ml of water in 15 ml of dioxane and 21 ml of a 15% potassium hydroxide solution. The resulting mixture was filtered hot and the aluminum salts were washed with 100 ml of hot dioxane. The filtrate and the washings were combined and the solvent was removed under reduced pressure. Recrystallization of the residue from hexane gave 4.24 g of white crystals melting at 188–189°.

Anal. Calcd for $C_{25}H_{22}N_2$: C, 85.68; H, 6.33; N, 8.00; mol wt, 350. Found: C, 85.45; H, 6.50; N, 8.16; mol wt, 340.

The amine has infrared absorptions (Nujol mull) at 3450 (NH), 1603, 743, and 697 cm^{-1} (aromatic); nmr spectrum ($CDCl_3$) at 3.30 and 4.20 (multiplet, $-CH_2-$) and 7.20 ppm (multiplet, aromatic); ultraviolet absorptions, $\lambda_{max}^{95\%ethanol}$ mμ (log ε), 222 (4.62), 285 (3.96), 293 (3.91); λ_{min} mμ (log ε), 253 (3.68).

1,2,5,6-Tetrahydro-12H-12b-methylpyrrolo[1′,2′:1,2]azepino(3,4-b)indole (IXb).—A solution of 1,2,5,6-tetrahydro-3-oxo-12H-12b-methylpyrrolo[1′,2′:1,2]azepino[3,4-b]indole (5.0 g) in 100 ml of tetrahydrofuran was added dropwise to a refluxing slurry of lithium aluminum hydride (6.5 g) in 400 ml of tetrahydrofuran. The resulting mixture was stirred and refluxed for an additional 48 hr. The solution was cooled to room temperature and the slurry was treated with 6.5 ml of water in 10 ml of tetrahydrofuran and 19 ml of a 15% potassium hydroxide solution. The contents were filtered and the aluminum salts were washed with 50–100 ml of solvents. The filtrate and washings were combined and the solvent was removed. The residue was dissolved in 50 ml of ether and upon cooling gave 4.2 g of white crystals, mp 98–100°.

Anal. Calcd for $C_{16}H_{20}N_2 \cdot 0.5H_2O$: C, 77.06; H, 8.45; N, 11.24. Found: C, 76.99; H, 8.99; N, 10.66.

The amine has infrared absorptions (Nujol mull) at 3333–3030 (NH and OH) and 735 cm^{-1} (aromatic); ultraviolet absorptions $\lambda_{max}^{95\%ethanol}$ mμ (log ε), 225 (4.50), 276 (3.82), 282 (3.84), 291 (3.81); λ_{min} mμ (log ε), 248 (3.36).

The citrate was formed in ether–isopropyl alcohol mixture and softens at 70°, begins to foam at 120°, decarboxylates at 147–197°, and decomposes at 200°.

Anal. Calcd for $C_{22}H_{28}N_2O_7$: C, 61.10; H, 6.53; N, 6.48. Found: C, 61.04; H, 6.79; N, 6.65.

1,2,5,6-Tetrahydro-12H-12b-phenylpyrrolo[1′,2′:1,2]azepino-[3,4-*b*]indole (Xb).—A solution of 3.67 g of 1,2,5,6-tetrahydro-3-oxo-12H-12b-phenylpyrrolo[1′,2′:1,2]azepino[3,4-*b*]indole in 100 ml of tetrahydrofuran was added dropwise to a slurry of 4.00 g of lithium aluminum hydride in 250 ml of tetrahydrofuran and treated as above. Recrystallization of the residue from absolute ethanol gave 3.13 g of white crystals melting at 105–106°.

Anal. Calcd for $C_{21}H_{22}N_2 \cdot 0.5H_2O$: C, 81.04; H, 7.45; N, 9.00. Found: C, 81.43; H, 7.31; N, 8.38.

The amine has infrared absorptions (Nujol mull) at 3500 (NH and OH) and 760, 741, and 701 cm^{-1} (aromatic); ultraviolet absorptions, λ_{max}^{MeOH} mμ (log ϵ), 226 (4.51), 283 (3.84), 292 (3.81); λ_{min} mμ (log ϵ), 255 (3.55).

The picrate was prepared in absolute ethanol and when recrystallized from ethanol gave yellow prisms melting at 205–208° dec.

Anal. Calcd for $C_{27}H_{25}N_5O_7$: C, 61.01; H, 4.74; N, 13.18. Found: C, 61.24; H, 4.92; N, 12.92.

Registry No.—Ia, 14161-47-8; Ib, 14161-48-9; Ic, 14161-49-0; II, 14271-21-7; III, 14161-50-3; IV, 14161-51-4; V, 14161-52-5; VI, 14161-53-6; VII, 14161-54-7; VIIIa, 14161-55-8; VIIIb, 14161-56-9; IXa, 14161-57-0; IXb, 14161-58-1; Xa, 14271-22-8; Xa-picrate, 14161-59-2; Xb, 14161-60-5; Xb-citrate, 14319-48-3.

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Indolothiapyrylium Compounds. III. Pseudoazulenic Thiapyrano[4,3-*b*]indoles[1,2]

THOMAS E. YOUNG, CYRUS J. OHNMACHT,[3] AND COLEMAN R. HAMEL

William H. Chandler Chemistry Laboratory, Lehigh University, Bethlehem, Pennsylvania

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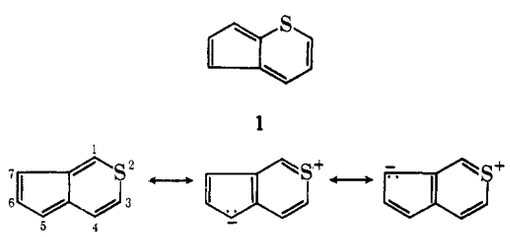
Dehydrogenation of 1,3,4,5-tetrahydrothiapyrano[4,3-*b*]indoles (**8a–h**) with chloranil or dicyanodichloroquinone gave 2–37% yields of the corresponding yellow-orange thiapyrano[4,3-*b*]indoles (**9a–h**), which exemplify a new heteroaromatic ring system iso-π-electronic with benz[*a*]azulene. The nmr spectra of these pseudoazulenes (**9**) show two strongly deshielded protons characteristic of H-1 (δ = 8.63–8.95 ppm) and H-4 (δ = 8.10–8.27 ppm) of the thiapyran ring. HMO calculations on the parent compound (**9a**) clearly show a displacement of electrons from sulfur toward nitrogen, indicating pronounced thiapyrylium character of the sulfur-containing ring.

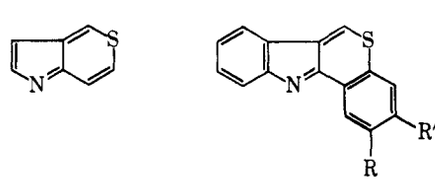
Although Mayer's[4] expectation of aromaticity of cyclopenta[*b*]thiapyran (**1**) was not fully realized,[5] the isomeric cyclopenta[*c*]thiapyran (**2**) has been shown to be a reasonably stable, π-excessive pseudoazulene,[6,7]



1

2 **3** **4**

in which dipolar canonical forms such as **3** and **4** contribute significantly to the ground-state structure.[6] Since Hückel molecular orbital (HMO) calculations[5] on **2** corroborate the high, and nearly equal, electron densities (*ca.* 1.17) at positions 5 and 7, it seemed to us likely that replacement of the methine carbon at either of these positions by a more electronegative heteroelement, such as nitrogen, would increase the contributions of the dipolar forms in which each ring tends toward the aromatic sextet condition, and enhance the stability of the resulting π-system. While the parent pyrrolo[3,2-*c*]thiapyran (**5**), formally considered as a 5-aza derivative of cyclopenta[*c*]thiapyran (**2**), is not yet known, we have already reported the synthesis of 1,2,3,4-tetrahydronaphth[2,3-*b*]indolo[2,3-*d*]thiapyran (**6**, R plus R′ equals tetramethylene), the first of this new class of pseudoazulenes.[2] The unsubstituted tetranuclear system (**6**, R and R′ are H), several derivatives (**6**, R′ = H; R = Cl, Me, MeO), and two higher benzologs have subsequently been described by Buu-Hoi and co-workers.[8] We now wish to report the synthesis of thiapyrano[4,3-*b*]indole (**9a**) and several substituted derivatives (**9b–h**) along with spectral evidence relevant to π delocalization in this new heteroaromatic system.



5 **6**

With the exception of the nitro compound (**8h**), the precursor 1,3,4,5-tetrahydrothiapyrano[4,3-*b*]indoles (**8a–g**) were all obtained directly in yields of 10–63% by condensation of tetrahydro-1,4-thiapyrone (**7**)[9] with the appropriately substituted phenylhydrazine in

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