INTRODUCTION OF SUBSTITUENTS INTO THE BENZENE NUCLEUS OF INDOLE

X. Synthesis of Indolino- and Indolopyrazines*

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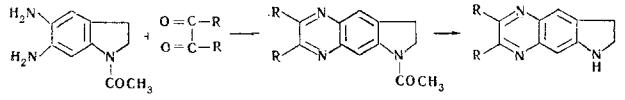
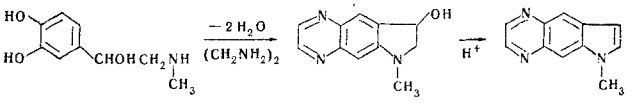
A method for the synthesis of indolinopyrazines has been proposed. The possibility has been shown of dehydrogenating the indolinopyrazines to the corresponding indole derivatives.

In a preceding paper [1], we proposed a synthesis of o-dinitro- and o-diaminoindolines, and using these we were able to approach a difficultly accessible class of heterocyclic compounds—indolino- and indolopyrazines.

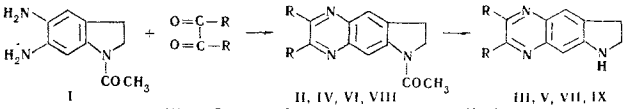


It may be expected that substances the molecule of which contains an indoline or indole ring condensed with a pyrazine nucleus will exhibit qualitatively new physiological properties. It is known that phenazine derivatives comprise a large group of neuroleptics which are widely used in medicine [2]. Quinoxaline structures are present in the composition of several antibiotics [3] and vitamin B_2, and pyrazinamide is active against the causal agent of tuberculosis [4].

In 1949, the formation of a stable fluorescent compound by the reaction of epinephrine with ethylenediamine in the presence of oxygen was shown [5]. Optically active 3-hydroxy-1-methyl-2,3-dihydropyrrolo-4,5-quinoxaline possesses an intense green fluorescence in solution. Subsequently, a method for determining epinephrine was based on this reaction. The 3-hydroxy derivative obtained readily splits off water on boiling in an acid medium with the formation of 1-methylpyrrolo-4,5-quinoxaline.



We have performed the synthesis of similar substances. The initial compound was 1-acetyl-5,6-diaminoindoline (I), and the carbonyl components used were glyoxal (in the form of the sodium bisulfite derivative), biacetyl, benzil, and phenanthraquinone.

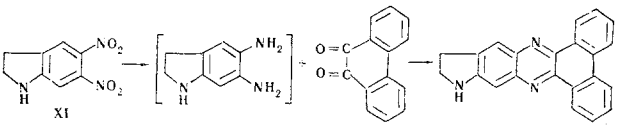


I II, III R = H; IV, V R = CH_3; VI, VII R = C_6H_5; VIII, IX 2 R = $C_{12}H_8$

The reaction was carried out in methanol at room temperature or with brief heating. The indolinopyrazines obtained (with yields of 60 to 80%) were purified by repreated recrystallization. It is an intersting fact that chromatography on a column of alumina did not free them from a stable colored impurity.

The acetyl group was removed by 40% caustic soda; hydrolysis led to considerable resinification. The rate of hydrolysis falls rapidly according to the substituent in the pyrazine ring in the sequence C_6H_5 > H > CH_3 > > $C_{12}H_8$. Thus, for example, in the case of 1-acetylphenanthro[9,10-b]indolino[5,6-e]pyrazine (VIII), the reaction does not go to completion even on boiling for 92 hr. In the other cases, the reaction takes place quantitatively, while with the unsubstituted compound and the 6,7-dimethyl derivative, the reaction is carried out at a temperature not exceeding 80° C.

Nonacetylated indolinopyrazines were obtained by condensing 5,6-diaminoindoline with benzil and phenanthraquinone.



XI

Nevertheless, it is best to carry out the reaction without the isolation of the diamine.

The indolino[5,6]pyrazines that we obtained are high-melting crystalline substances with various shades of yellow. Their solubility in organic solvents depends greatly on the substituents introduced into the pyrazine ring. Thus, for example, VIII dissolves only in dimethylformamide. In aqueous solutions of acid, they all give a bright red coloration which is apparently connected with salt formation.

A general characteristic of all the compounds described in their well-marked fluorescence, like that of other pyrazine derivatives. Solutions of 1-acetylindolino-[5,6]pyrazines fluoresce violet, while the fluorescence of the nonacetylated derivatives depends on the polarity of the solvent, this effect increasing on passing to simpler derivatives: for example, for the unsubstituted indolino[5,6]pyrazine the color of the fluorescence changes from bright yellow in aqueous solution to green in ethanol and blue in benzene. The same phenomenon is observed with 6,7-diphenylindolo[5,6]pyrazine. Its fluorescence changes from orange in ethanol to green in benzene and blue-green in carbon tetrachloride.

In general it may be stated that the color of the fluorescence depends little on the substitutents in the pyrazine nucleus but changes markedly with a transformation of the pyrrole part of the molecule.

*For part IX, see [1].

EXPERIMENTAL

1-Acetyl-5, 6-diaminoindoline (I) and 5, 6-dinitroindoline (XI) were obtained by the procedure described previously [1].

1-Acetylindolino[5, 6]pyrazine (II). A solution of 3 g of the sodium bisulfite compound of glyoxal in 40 ml of water was added to a solution of 1.9 g of I in 60 ml of methanol. The mixture was heated under reflux for half an hour, and then the excess of ethanol was distilled off in vacuum. The precipitate that deposited was filtered off to give 1.7 g (80%) of a dark yellow substance with mp 178–180° C. After recrystallization from benzene in the presence of activated carbon, it formed white silky crystals with mp 181–181.5° C. UV spectrum, λ_{max}, nm (log ε): 260–262 (4.47), 357–362 (4.08) (in methanol). Found, %: C 67.67, 67.74; H 5.49, 5.41. Calculated for ($C_{12}H_{11}OH_3$), %: C 67.59; H 5.20.

Indolino[5, 6]pyrazine (III). A suspension of 0.42 g of **II** in 10 ml of 40% caustic soda was stirred for 40 hr and was then filtered from the alkali and dissolved in benzene, and this solution was filtered. The benzene solution was evaporated in vacuum to give a quantitative yield of yellowish needles. After recrystallization from benzene, mp 164–164.5° C. UV spectrum, λ_{max}, nm (log ε): 265 (4.37), 410 (3.92) (in methanol). Found, %: C 70.32, 70.29; H 5.27, 5.35. Calculated for ($C_{10}H_9N_3$), %: C 70.15; H 5.30.

1-Acetyl-6, 7-dimethylindolino[5, 6]pyrazine (IV). To a solution of 1.9 g of I in 60 ml of methanol was added 1.2 ml of freshly distilled biacetyl. The mixture was heated for 30 min in a flask with a reflux condenser, and then the excess of methanol was distilled off in vacuum and 1.6 g (66%) of dark-colored substance was filtered off. After recrystallization from benzene in the presence of activated carbon, it formed lemon-yellow needles with mp 227–227.5° C. UV spectrum, λ_{max}, nm (log ε): 260 (4.39), 357 (4.05) (in methanol). Found, %: C 69.62, 69.52; H 6.48, 6.48. Calculated for ($C_{14}H_{15}ON_3$), %: C 69.59; H 6.27.

6, 7-Dimethylindolino[5, 6]pyrazine (V). A suspension of 0.5 g of **IV** in 20 ml of 40% caustic soda was heated at 70–80° C in the water bath with stirring for 60 hr. After the usual treatment, 0.4 g (quantitative yield) of yellow needles with mp 217–218° C (from aqueous methanol) was obtained. UV spectrum, λ_{max}, nm (log ε): 220 (4.64), 262 (4.46), 396–397 (3.99) (in methanol). Found, %: C 72.34, 72.74; H 6.66, 6.49. Calculated for ($C_{12}H_{13}N_3$), %: C 72.33; H 6.57.

1-Acetyl-6, 7-diphenylindolino[5, 6]pyrazine (VI). A solution of 2.2 g of benzil in 20 ml of methanol was added to a solution of 1.9 g of I in 60 ml of methanol. The precipitate that formed immediately was filtered off to give 3.0 g (82%) of dark gray silky crystals. After recrystallization from ethanol with the addition of activated carbon, the substance formed colorless needles with mp 226–227° C. UV spectrum, λ_{max}, nm (log ε): 270 (4.52), 380 (4.28), (in dimethylformamide). Found, %: C 79.24, 79.49; H 5.50, 5.58. Calculated for ($C_{24}H_{19}ON_3$), %: C 78.88; H 5.24.

6, 7-Diphenylindolino[5, 6]pyrazine (VII). a) A suspension of 0.73 g of **VI** in 20 ml of 40% caustic soda was boiled with stirring for 6 hr, after which it was filtered off from the alkali. The residue was dissolved in methanol, the solution was filtered, and the filtrate was evaporated in vacuum to give 0.6 g (quantitative yield) of bright yellow needles with mp 260–260.5° C (from methanol). UV spectrum, λ_{max}, nm (log ε): 255 (4.42), 295 (4.36), 425 (4.17) (in methanol). Found, %: C 81.59, 81.64; H 5.59, 5.60. Calculated for ($C_{22}H_{17}N_3$), %: C 81.70; H 5.29.

b) A solution of 2.1 g of **XI** in 40 ml of methanol was treated with 4 ml of hydrazine hydrate and a small amount of Raney nickel. After the end of the reaction, the solution was filtered and a solution of 2.2 g of benzil in 10 ml of methanol was added. A precipitate deposited immediately, and this was filtered off to give 2.6 g (81%) of **VII**, mp 259–260° C (from dimethylformamide).

1-Acetylphenanthro[9, 10-b]indolino[5, 6-e]pyrazine (VIII). A solution of 2.2 g of phenanthraquinone in 20 ml of acetic acid was added to a hot solution of 1.9 g of I in 60 ml of methanol. The precipitate that deposited immediately was filtered off after the reaction mixture had been cooled, giving 2.6 g (72%) of a greenish-yellow powder. After recrystallization from dimethylformamide in the presence of activated carbon it formed bright yellow needles with mp 331° C. UV spectrum, λ_{max}, nm (log ε): 400 (4.12), 425 (4.23) (in dimethylformamide). Found, %: C 79.51, 79.50; H 4.79, 4.80. Calculated for ($C_{24}H_{17}ON_3$), %: C 79.32; H 4.72.

Phenanthro[9, 10-b]indolino[5, 6-e]pyrazine (IX). A solution of 1.05 g of **XI** in 20 ml of methanol was treated with 2 ml of hydrazine hydrate and a small amount of Raney nickel. After the end of the reaction, the mixture was filtered and the filtrate was treated with a solution of 1.1 g of phenanthraquinone in 35 ml of 70% acetic acid. The precipitate that deposited was filtered off to give 1.2 g (75%) of a dark residue. After recrystallization from nitromethane in the presence of activated carbon, it formed greenish yellow crystals with mp 288–289° C. UV spectrum, λ_{max}, nm (log ε): 270 (4.57), 320 (4.59), 412 (3.98), 465 (4.21) (in dimethylformamide). Found, %: C 82.09. 82.31; H 4.41, 4.52. Calculated for ($C_{22}H_{15}N_3$), %: C 82.21; H 4.70.

6, 7-Diphenylindolo[5, 6]pyrazine (X). A solution of 1 g of **VII** in 40 ml of xylene was treated with 0.76 g of chloranil, and the mixture was boiled for 10 hr. After the end of the reaction, the solvent was driven off and the residue was treated with 10% caustic soda. The precipitate was filtered off and extracted with ether in a Soxhlet apparatus. The extract was evaporated in vacuum to give 0.6 g (62%) of a yellow substance, mp 231–231.5° C (from carbon tetrachloride). UV spectrum, λ_{max}, nm (log ε): 245 (4.39), 295 (4.64), 376 (4.22) (in methanol). Found, %: C 82.25, 82.26; H 4.64, 4.73. Calculated for ($C_{22}H_{15}N_3$), %: C 82.21; H 4.70.

The course of the reactions was followed and the purity of the compounds obtained was checked by thin-layer ascending chromatography in a nonfixed layer of alumina of Brockmann activity II. The UV spectra were taken on an SF-4A instrument.

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