SYNTHESIS OF 2,3,8,9-TETRAMETHOXY-11-PHENYL-5,6-DIHYDRODIBENZ[2,3;7,8]INDOLIZINE

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2,3,8,9-Tetramethoxy-11-phenyldibenz[2,3;7,8]indolizine was obtained in high yield from (6,7-dimethoxyisoquinolin-1-yl)-(3,4-dimethylphenyl)phenylcarbinol by cyclization in the presence of formic acid. The behavior of (6,7-dimethoxyisoquinolin-1-yl)-(3,4-dimethoxyphenyl)methylcarbinol and (6,7-dimethoxyisoquinolin-1-yl-(3,4-dimethoxyphenyl)carbinol was studied under these same conditions. 2,3,7,8-Tetramethoxy-11-phenyl-5,6-dihydrodibenz[2,3;7,8]indolizine was obtained by hydrogenation on rhenium heptasulfide.

The alkaloid crystaustoline, exhibiting curare-like activity [1], has a dibenzo[2,3;7,8]tetrahydroindolizine structure. The present article is devoted to development of a method for synthesis of structural analogs of this alkaloid on the basis of heterocyclization of derivatives of the alkaloid papaverine (I).

First of all we studied the possibility of dehydrocyclization of papaverine I itself on a K-16 oxide-type commercial catalyst in the range 350-600°C. At relatively low temperatures for such cyclizations [2-4], 350-400°C, we observed significant resinification and mainly recovery of unreacted papaverine. At higher temperatures, 500-600°C, from a complex mixture of pyrolysis products it was possible to recover in insignificant yield (~1%) unsubstituted dibenz[2,3;7,8]indolizine (II), the PMR and mass-spectral data and melting point of which were the same as those published in [2, 4]. Thus, synthesis of tetramethoxy-substituted dibenzindolizine by high-temperature heterogeneous catalysis does not seem possible because of the low thermal stability of polymethoxy-substituted derivatives of isoquinoline and dibenzindolizine.

Because of what has been stated above, we developed a different method for synthesis of cryptaustoline analogs based on acid-catalyzed cyclization of tertiary α-pyridylaryl-substituted carbinols. Previously, such heterocyclization in the presence of formic acid was successfully used to obtain aryl-substituted indolizines [5], with the yield of the cyclization products amounting to 20-30% and increasing to 50-60% with the presence of CH_3O groups in aryl substituents of carbinols.

For appropriate synthesis of substituted isoquinolylarylcarbinols IV-VI, necessary for a study of the possibility of their acid heterocyclization, a new method was used for oxidation of papaverine I to known ketone III. The methylene group in compound I was oxidized to the carbonyl group by reaction with gaseous oxygen in dimethyl sulfoxide in the presence of catalytic amounts of alkali at 30-50°C. It should be noted that this oxidation method, effective for fluorene [6] and azafluorenes [7], has thus far not been used for oxidation of arylhetarylmethanes. It was established that in this reaction there is an induction period from 1 to 2 h (depending on the amount of the substrate being oxidized), then the color of the solution begins to change, and after discontinuation of stirring it is possible to observe the appearance of an intense dark-blue color, which indicates the formation of a carbanion. Subsequently, with the formation of ketone III, it began to precipitate.

Arylhetarylcarbinols IV-VI were synthesized by two methods. Secondary alcohol IV was obtained in moderate yield by the reaction of sodium tetrahydroborate with ketone III. The PMR spectrum of compound IV contained all the peaks characteristic of papaverine and two additional singlet peaks at 6.13 (narrow, 1H, H—C—O—) and 6.35 ppm (wide, 1H, OH). Aromatic protons gave peaks of analogous multiplet nature and with the same chemical shifts as for papaverine, except for the 8-H proton, which experienced the effect of the OH group and resonated in a stronger (by 0.25 ppm) field.

Carbinols V and VI were synthesized by reaction of ketone III with phenylmagnesium bromide or methylmagnesium iodide. The PMR spectrum of alcohol VI contained four singlet peaks of CH_3O groups. The hydroxyl proton gave a very wide peak in the region of 5.9 ppm. In a weak field we distinguished two doublet peaks of 3-H and 4-H protons with a spin—spin

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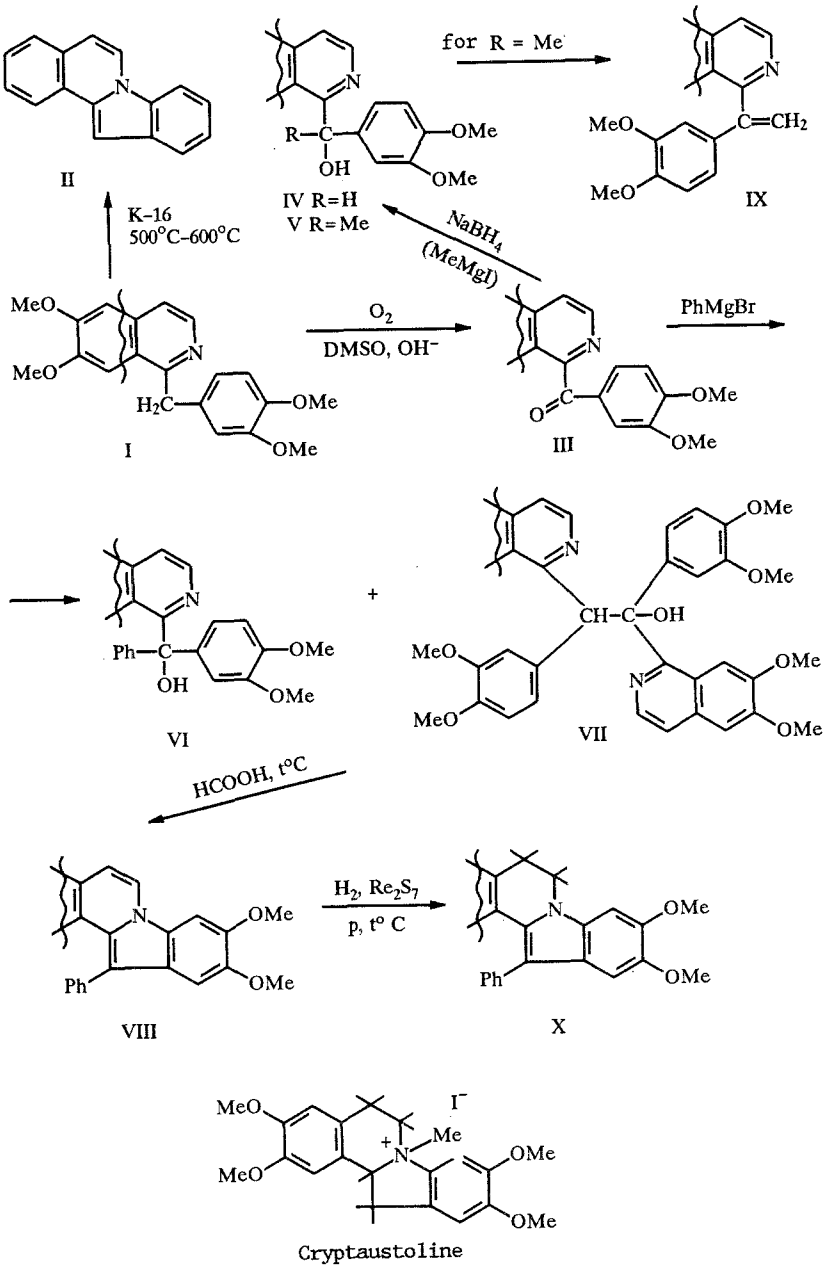
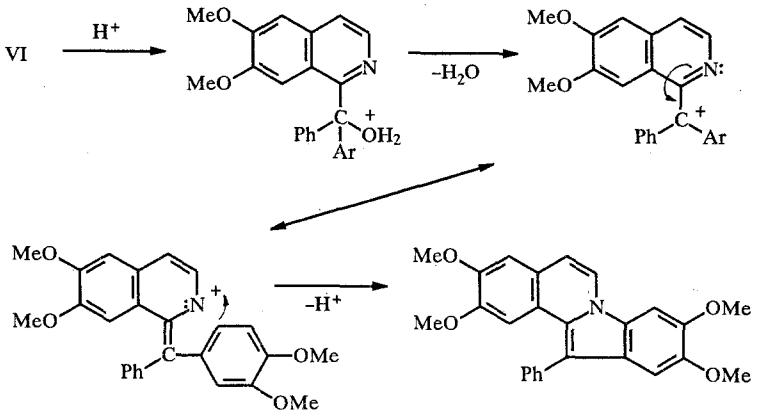


coupling constant of 5.8 Hz and one singlet peak of two proton units 5-H and 8-H. Also distinguishable was a doublet of a 5′-H proton with a large spin—spin coupling constant of 8.4 Hz. From the reaction mixture we recovered not only alcohol VI, but also tetraaryl-substituted ethanol VII (11% yield), the structure of which was confirmed by the PMR spectrum.

Cyclization of alcohols IV-VI was carried out in boiling formic acid. In the case of triarylcarbinol VI, cyclization occurred quantitatively in 2 h. Tetramethoxy-substituted dibenzindolizine VIII was recovered in 90% yield. The high yield in this key synthesis step was probably due to the fact that methoxy groups in the dimethoxyphenyl substituent increased the electron sensitivity of the ring, which favored nucleophilic attack at the nitrogen atom of isoquinoline (see scheme on following page).

During cyclization, only one of three possible polycycles formed, although C—N cyclization is formally possible at the 2′ and 6′ positions of both the dimethoxyphenyl substituent and the unsubstituted phenyl radical. The presence of both unsubstituted phenyl and the dimethoxyphenyl radical in the starting molecule enables direct comparison of their reactivity in this cyclization. The results indicate that the cyclization tendency of the dimethoxyphenyl radical is much greater than that of the phenyl radical. The high regiospecificity is probably due to the fact that of the two aryl radicals the unsubstituted phenyl one is less nucleophilic [5]. In the dimethoxyphenyl substituent itself, of the two positions 2′ and 6′, only the 6′ carbon atom reacted with nitrogen, which is probably due to large steric hindrances created by the CH_3O group for the 2′ position.



The PMR spectrum of dibenzindolizine VIII contained four singlet peaks of protons of four CH_3O groups. During transition from compound VI to condensed polycycle VIII, the chemical shifts and spin—spin coupling constants of the doublet peaks of the two pyridine protons α-H and β-H changed. Thus, in the case of carbinols IV-VI, the α-protons gave doublet peaks at 8.4-8.5 ppm with a spin—spin coupling constant of 5.8 Hz, and the β-protons gave peaks in the region of 7.5-7.7 ppm. For dibenzindolizine VIII, analogous protons resonated in a stronger (by 0.5 and 1 ppm) field at 7.95 and 6.6 ppm with a larger spin—spin coupling constant, 7.4 Hz (ΔJ = 1.6 Hz). These data are a criterion for distinguishing condensed dibenzindolizine systems from starting substituted isoquinolines.

Heating of diarylmethylcarbinol V under analogous conditions (up to 10 h) did not give a cyclization product. Here dehydration and formation of disubstituted ethylene IX occurred. The PMR spectrum of compound IX contained two doublet peaks of pyridine protons with chemical shifts and spin—spin coupling constants (6 Hz) characteristic of them. The vinyl geminal protons resonated in the form of two doublets with a spin—spin coupling constant of 1 Hz at 5.6 and 6.0 ppm. The IR spectrum of ethylidene IX contained absorption bands characteristic of the $>C=CH_2$ group.

Cyclization of secondary carbinol IV to dibenzindolizine also did not occur, and starting alcohol IV was recovered virtually quantitatively from the reaction mixture. In this case, the formation of a carbocation capable of cyclization probably did not occur [5, 8].

To obtain a partially reduced cryptaustoline analog, the synthesized dibenzindolizine VIII was hydrogenated over rhenium heptasulfide (140 atm, 200°C, 4 h). As a result of chromatographic separation of the complex reaction mixture, 5,6-dihydro-2,3,8,9-tetramethoxy-11-phenyldibenzindolizine (X) was obtained in 6% yield. In the PMR spectrum of this compound, the two doublet peaks of protons of the pyridine part were absent, and two triplet peaks (2H each) appeared in a strong field at 3.13 and 4.18 ppm, belonging to four methylene protons in the 5 and 6 positions. There were also three singlet (4H in all) aromatic protons and four peaks of methyl groups. These data, together with the mass-spectral data, indicate that under the studied conditions neither the pyrrole ring nor the ether bonds in compound IX underwent hydrogenation.

EXPERIMENTAL

The PMR spectra were recorded in $CDCl_3$ with a Bruker WP-80 instrument, and the internal standard was TMS. The IR spectra were recorded in KBr tablets with a UR-20 spectrometer The molecular weights were determined with an MX-1303 mass spectrometer with an ionizing-electron energy of 70 eV. The course of the reactions and the purity of the synthesized compounds were monitored by thin-layer chromatography on Silufol plates, and the eluent was ether or ether—alcohol (1:1). Chromatographic separation and purification of the substances were carried out on columns with silica gel (2 × 30 cm).

The data of elemental analysis for C, H, and N corresponded to the calculated values.

Pyrolysis of Papaverine. Through a flow-type quartz reactor filled with 20 ml of K-16 catalyst was passed in 2 h 3.4 g (0.01 mole) of papaverine I in 100 ml of benzene at 600°C. The catalyzate was filtered, the solvent was driven off, and the residue was chromatographed on a column with silica gel. The eluent was hexane—ether (1:1). We obtained 20 mg (1%) of dibenz[2,3;7,8]indolizine II, identical in PMR spectrum, mass spectrum, and melting point to the described compound [4].

1-(3,4-Dimethoxybenzoyl)-6,7-dimethoxyisoquinoline (III, $C_{20}H_{19}NO_3$). Though a solution of 5.0 g (14.7 mmoles) of papaverine in 50 ml of DMSO, oxygen was passed with stirring for 6 h (~50 ml/min) at 40°C. At hourly intervals three

drops of a 50% KOH solution were added to the solution. After completion of the reaction, 150 ml of water was added to the mixture, the resulting precipitate was separated, washed several times on the filter with water, and dried, and 4.5 g (86%) of ketone III, colorless crystals, was obtained with mp 204-205°C [9], R_f 0.26 (ether), and M^+ 353.

(6,7-Dimethoxyisoquinolin-1-yl)-(3,4-dimethoxyphenyl)phenylcarbinol (VI, $C_{26}H_{25}NO_5$) and 1,2-Bis(3,4-dimethoxyphenyl)-1,2-bis(6,7-dimethoxyisoquinolin-1-yl)ethanol (VII, $C_{40}H_{40}N_2O_9$). To a solution of phenylmagnesium bromide prepared from 3.9 g of bromobenzene and 0.68 g of magnesium in 100 ml of ether and cooled to 0°C was gradually added (in 10 min) 1.0 g (2.83 mmoles) of ketone III. The whole was stirred for 1 h at 0°C and 1 h at 20°C. Then 100 ml of a saturated aqueous NH_4Cl solution was added, the organic layer was separated, and the aqueous layer was extracted with benzene (6 × 30 ml). The extract was washed with water (2 × 50 ml) and dried with Na_2SO_4, the solvent was driven off, and the residue was separated on a column with silica gel. We obtained 0.57 g (47%) of carbinol VI. The R_f was 0.4 (ether). Carbinol VI, with mp 55-56°C, was crystallized from hexane. PMR spectrum: 3.40; 3.69; 3.78; 3.95 (12H, 4 singlets, 4 × OCH_3); 5.90 (1H, broadened singlet, OH); 6.72 (2H, singlet, 5- and 8-H); 7.00 (1H, doublet, J = 8.4 Hz, 5-H); 7.20-7.40 (7H, multiplet, Ph, 2′- and 6′-H); 7.55; 8.40 ppm (2H, 2 doublets, J = 5.8 Hz, 4- and 3-H). Mass spectrum, m/z (I, %): 431 (M^+, 100); 414 (21) M—OH; 413 (57) M—H_2O; 400 (20) M—OCH_3; 354 (18) M—Ph; 294 (50).

Then 0.11 g (11%) of dimer VII, colorless crystals with mp 120-123°C and R_f 0.2 (ether), was recovered from the column. PMR spectrum: 3.75; 3.80; 3.82; 3.93; 3.95; 3.98; 4.04 (24H, 7 singlets, 8 × OCH_3); 6.12 (1H, singlet, CH—C—OH); 6.77; 6.85 (2H, 2 doublets, J = 8.2 Hz, $C_6H_3(OCH_3)_2$, 5′- and 5″-H); 6.80; 7.70 (2H, 2 doublets, J = 2.0 Hz, $C_6H_3(OCH_3)_2$, 2′- and 2″-H); 6.90 and 7.41 (2H, double doublet and double double doublet, J = 8.20 Hz and 2.00 Hz and J = 8.20, 2.00, and 1.00 Hz, 6″- and 6′-H); 7.06; 7.10; 7.12; 7.53 (4H, 4 singlets, 2 × 5-H and 2 × 8-H); 7.50, 7.63, and 8.39, 8.44 ppm (4H, 4 doublets, J = 5.6 Hz, 2 × 4-H and 2 × 3-H). IR spectrum (cm^{-1}): 3350, 3180 (OH); 2970, 2850, 1646, 1612.

(7,8-Dimethoxyisoquinolin-1-yl)-(3,4-dimethoxyphenyl)carbinol (IV, $C_{20}H_{21}NO_5$). To a suspension of 3.53 g (10 mmoles) of ketone III in 50 ml of ethanol was added 0.76 g (20 mmoles) of $NaBH_4$, and the whole was stirred for 2 h at 40°C. The mixture was diluted with water (100 ml), and the precipitate was separated and crystallized from hexane. We obtained 1.9 g (53%) of alcohol IV, colorless crystals with sublimation temperature 153°C [10]. PMR spectrum: 3.77; 3.83; 4.00 (12H, 3 singlets, 4 × OCH_3); 6.13 (1H, singlet, C<u>H</u>—OH), 6.33 (1H, broadened singlet, O<u>H</u>); 6.82 (3H, multiplet, 2′-, 5′-, and 6′-H); 7.08; 7.13 (2H, 2 singlets, 8- and 5-H); 7.50; 8.40 ppm (2H, 2 doublets, J = 6.0 Hz, 4- and 3-H). IR spectrum (cm^{-1}): 3460, 3170, 3065 shoulder, 3016 shoulder, 2970, 2930 shoulder, 2845, 1630, 1615.

(7,8-Dimethoxyisoquinolin-1-yl)-(3,4-dimethoxyphenyl)methylcarbinol (V, $C_{21}H_{23}NO_5$). We obtained 0.28 g (54%) similarly to compound VI from CH_3MgBr (1.7 g, 28 mmoles of CH_3I, and 0.68 g of Mg) and 0.5 g (1.42 mmoles) of ketone III, colorless crystals, with mp 63-65°C* (from hexane) and R_f 0.49 (ether—alcohol, 10:1). PMR spectrum: 2.05 (3H, singlet, CH_3); 3.60; 3.70; 3.83 and 3.97 (12H, 4 singlets, 4 × OCH_3); 6.85 (2H, 2 doublets, J = 8.4 Hz, J = 2.0 Hz, 5′- and 2-H); 7.03 (2H, broadened singlet, 5- and 8-H); 7.1 (1H, double doublet, J = 8.7 and 2.0 Hz, 6-H); 7.65 and 8.35 ppm (2H, 2 doublets, J = 6 Hz, 4- and 3-H). IR spectrum (cm^{-1}): 3300, 3180, 2970, 2860. Mass spectrum, m/z (I, %): 369 (M^+, 58), 354 (33), 338 (7), 189 (100), 188 (51), 181 (30), 175.5 (11), 165 (25).

2,3,8,9-Tetramethoxy-11-phenyldibenz[2,3;7,8]indolizine (VIII, $C_{26}H_{23}NO_4$). A solution of 0.2 g (0.45 mmoles) of carbinol VI in 5 ml of HCOOH was boiled for 2 h. The mixture was cooled, poured into 50 ml of water, and alkalized with a soda solution to pH 10, and the precipitate was separated, washed with water, and dried. We obtained 0.18 g (95%) of indolizine VIII, with mp 200-202°C and R_f 0.78 (ether—alcohol, 10:1). PMR spectrum: 3.50; 3.90; 3.94; 4.03 (12H, 4 singlets, 4 × OCH_3); 6.60; 7.95 (2H, 2 doublets, J = 7.4 Hz, 5-H and 6-H); 6.93; 7.00 (2H, 2 singlets, 7-H and 10-H); 7.25 (2H, singlet, 1-H and 4-H); 7.43-7.75 ppm (5H, multiplet, Ph). IR spectrum (cm^{-1}): 3160, 2970, 2840, 1660, 1630, 1550, 1530. Mass spectrum, m/z (I, %): 413 (M^+, 100), 398 (41), 382 (9), 351 (6).

1-(6,7-Dimethoxyisoquinolin-1-yl)-1-(3,4-dimethoxyphenyl)ethylene (IX, $C_{21}H_{21}NO_4$). We obtained 0.45 g (90%) similarly to the synthesis of VIII from 0.5 g (13.6 mmoles) of carbinol V, a beige-colored powder with mp 128-130°C (published data [9], mp 130°C) and R_f 0.37 (ether—alcohol, 10:1). PMR spectrum, ppm: 3.75; 3.77; 3.85; 4.04 (12H, 4 singlets, 4 × OCH_3); 5.5; 6.0 (2H, 2 doublets, J = 1 Hz, C=CH_2); 6.77 (2H, doublet, J = 1 Hz, 5-H and 6-H); 6.95; 7.08; 7.25 (3H, 3 singlets, 2-H, 5-H, 6-H); 7.50 and 8.47 (2H, 2 doublets, J = 6.0 Hz, 3-H and 4-H). IR spectrum, cm^{-1}: 3068, 2965, 1660, 1644, 1629, 1614, 890.

2,3,9,10-Tetramethoxy-12-phenyl-5,6-dihydrodibenz[b,g]indolizine (X, $C_{26}H_{25}NO_4$). Into a steel autoclave was placed an ampul with a solution of 0.5 g (12.1 mmoles) of compound IX in 30 ml of benzene and 50 mg of a Re_2S_7 catalyst. Hydrogenation

*Published data [10]: mp 90-92°C as the crystal hydrate $C_{21}H_{23}NO_5 \cdot \frac{1}{2}H_2O$.

was carried out at hydrogen pressure 140 atm and 200°C for 4 h with stirring. After the reaction, the catalyst was removed from the mixture by filtration, the solution was evaporated, and the residue was chromatographed on a column and eluted with hexane, benzene, and then ether. We obtained 30 mg (6%) of indolizine X, a dark-beige powder with mp 136-138°C. PMR spectrum, ppm: 3.12 (2H, triplet, J = 6.4 Hz, 5-H); 3.35; 3.90; 3.92 and 3.99 (12 H, 4 singlets, 4 × OCH_3); 4.15 (2H, triplet, J = 6.4 Hz, 6-H); 6.85 and 6.95 (2H, 2 singlets, 10-H and 7-H); 7.36 (2H, singlet, 1-H and 4-H); 7.20-7.66 (5H, multiplet, Ph).

REFERENCES

1. J. Ewing, G. K. Hughes, E. Ritchie, and W. C. Taylor, Aust. J. Chem., **6**, 78 (1953).
2. J. Braun and J. Nelles, Ber. Deut. Chem. Ges, **70**, 1767 (1937).
3. A. T. Soldatenkov, M. V. Bagdadi, P. K. Radzhan, O. S. Brinda, S. A. Édogiaverie, A. A. Fomichev, and N. S. Prostakov, Zh. Org. Khim., **18**, 1326 (1983).
4. A. T. Soldatenkov, M. V. Bagdadi, A. A. Fomichev, and N. S. Prostakov, Zh. Org. Khim., **18**, 902 (1982).
5. H. H. Wasserman and W. R. Waterfied, Chem. Ind., No. 8, 1220 (1961).
6. G. E. Niznik, US Patent No. 3,875,237; Ref. Zh., Khim., Abstract No. 3N150P (1976).
7. N. S. Prostakov, A. T. Soldatenkov, and V. O. Fedorov, Khim. Geterotsikl. Soedin., No. 8, 101 (1969).
8. H. A. Smith and C. W. Holley, J. Am. Chem. Soc., **80**, 3714 (1958).
9. E. Späth and N. Polgar, Ber. Deut. Chem. Ges., **59**, 2787 (1926).
10. C. Vaccher, P. Berthelot, M. Devergnies, and M. Debaert, J. Heterocycl. Chem., **26**, 811 (1989).