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Synthesis of Pyrroloisoquinolines from Papaverine

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Abstract—Papaverine and its derivatives react with *p*-chlorophenacyl bromide to give the corresponding quaternary salts, which are converted into pyrrolo[2,1-*a*]isoquinolines by the action of bases.

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Papaverine is an isoquinoline alkaloid possessing valuable pharmacological properties; in particular, it is used as spasmolytic agent [1]. Search for new papaverine derivatives exhibiting analgetic, spasmolytic, and anticholinergic activity are now in progress [1]. The following transformations of papaverine have been reported: bromination [2], nitration [3], oxidation at the methylene group [4], demethoxylation [5], hydrogenation [6], oxidation to the corresponding *N*-oxide [7], and quaternization at the izoquinoline nitrogen atom [2, 8]. The latter way of chemical modification gave rise to polycyclic systems of the pyrroloizoquinoline series [8]. However, only one example was described in [8], namely the reaction of papaverine with 4-methoxyphenacyl bromide. Our attempts to reproduce the procedure reported in [8] gave unsatisfactory results. By reaction of papaverine with 4-methoxyphenacyl bromide in the presence of sodium hydrogen carbonate in anhydrous alcohol we obtained a mixture containing ~30% of 1-(3,4-dimethoxyphenyl)-8,9-dimethoxy-2-(4-methoxyphenyl)pyrrolo-[2,1-*a*]isoquinoline and 70% of initial papaverine.

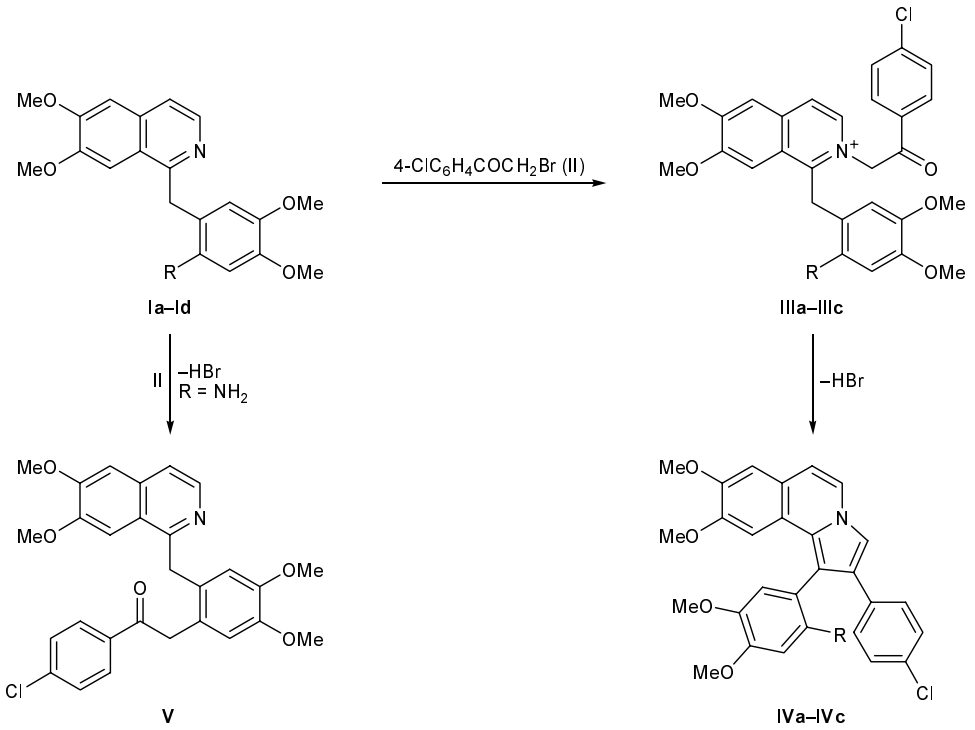
We carried out the transformation in two steps. In the first step, papaverine (**Ia**) and bromopapaverine **Ib** were brought into reaction with 4-chlorophenacyl bromide (**II**) in acetone. We thus obtained quaternary salts **IIIa** and **IIIb** in 50–96% yield. Treatment of the latter with aqueous sodium hydrogen carbonate afforded 70–80% of substituted indolizines **IVa** and **IVb** (Scheme 1). An analogous reaction with aminopapaverine (**Id**) [3] gave 4-chlorophenacylamino derivative **V** whose structure was confirmed by the ^{1}H NMR data. The ^{1}H NMR spectrum of **V** contained signals typical of the papaverine [2] and 4-chlorophenacyl fragments and a signal at δ 6.27 ppm from the NH proton; no signals characteristic of papaverine quaternary salts were present [2].

Nitropapaverine **Ie** [3] and acetylaminopapaverine **If** [3] failed to react with 4-chlorophenacyl bromide under the above conditions (boiling acetone, 24 h), and only the initial reactant were identified in the reaction mixtures. A probable reason is steric hindrances. Therefore, we synthesized pyrrolylpapaverine **Ic** by reaction of aminopapaverine **Id** with 2,5-dimethoxytetrahydrofuran, and compound **Ic** was brought into reaction with bromoketone **II**; despite the presence of a bulky substituent in the veratryl fragment of molecule **Ic**, we isolated 76% of quaternary salt **IIIc**, and its intramolecular cyclization afforded 66% of 2-(4-chlorophenyl)-1-[4,5-dimethoxy-2-(1*H*-pyrrol-1-yl)-phenyl]-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline (**IVc**). This result indicates that steric hindrances in the veratryl fragment do not affect the transformation under study. We thus presumed that the reaction of phenacyl bromide **II** with nitropapaverine **Ie** and acetylaminopapaverine **If** is hampered by formation of intramolecular hydrogen bond between the hydrogen atom transferred from the methylene bridge to the isoquinoline nitrogen atom and oxygen atom of the nitro or *N*-acetyl group or by electronic interaction between these nitrogen and oxygen atoms.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker AM-500 spectrometer (500 MHz) from 1% solutions in DMSO-d_6 using HMDS as internal reference. The melting points were determined on an HMK Kofler

Scheme 1.



R = H (**a**), Br (**b**), 1*H*-pyrrol-1-yl (**c**), NH_2 (**d**).

melting point apparatus. Thin-layer chromatography was performed on Silufol UV-254 plates using benzene–anhydrous ethanol (9:1; **IVa**–**IVc**, **V**) or 96% ethanol (**IIIa**–**IIIc**) as eluent.

1-(2-Bromo-4,5-dimethoxybenzyl)-6,7-dimethoxyisoquinoline (**Ib**) [2], 2-(6,7-dimethoxyisoquinolin-1-ylmethyl)-4,5-dimethoxyaniline (**Id**) [3], 1-(4,5-dimethoxy-2-nitrobenzyl)-6,7-dimethoxyisoquinoline (**Ie**) [3], and *N*-[2-(6,7-dimethoxyisoquinolin-1-ylmethyl)-4,5-dimethoxyphenyl]acetamide (**If**) [3] were synthesized by known procedures; their melting points coincided with those reported in the literature.

1-[4,5-Dimethoxy-2-(1*H*-pyrrol-1-yl)benzyl]-6,7-dimethoxyisoquinoline (Ic). 2,5-Dimethoxytetrahydrofuran, 10 mmol, was added to a solution of 10 mmol of aminopapaverine **Ie** in 20 ml of acetic acid. The mixture was heated for 1 h under reflux and cooled, the solvent was distilled off under reduced pressure, and the residue was ground first with 50 ml of water and then with diethyl ether and recrystallized from methanol. Yield 86% (chromatographically pure substance), light brown needles, mp 111–112°C. ^{1}H NMR spectrum, δ, ppm: 3.62 s (3H, OCH_3), 3.79 s (6H, OCH_3), 3.92 s (3H, OCH_3), 4.27 s (2H, CH_2), 6.15 s (2H, 3-H, 4-H, pyrrole), 6.70 s (1H, H_{arom}), 6.82 s (1H, H_{arom}), 6.87 s (2H, 2-H, 5-H, pyrrole), 6.93 s (1H, H_{arom}), 7.16 s (1H, H_{arom}), 7.43 d (1H, H_{arom}, J = 6 Hz), 8.21 d (1H, H_{arom}, J = 6 Hz). Found, %: C 71.32; H 6.04; N 6.99. $C_{24}H_{24}N_2O_4$. Calculated, %: C 71.27; H 5.98; N 6.93.

Reaction of 4-chlorophenacyl bromide with substituted papaverines Ia–Ic (*general procedure*). Compound **Ia**–**Ic**, 10 mmol, was added to a solution of 10 mmol of 4-chlorophenacyl bromide in 100 ml of anhydrous acetone, and the mixture was heated for 24 h under reflux. The mixture was cooled, and the precipitate of quaternary salt **IIIa**–**IIIc** was filtered off and recrystallized from appropriate solvent.

2-[2-(4-Chlorophenyl)-2-oxoethyl]-1-(3,4-dimethoxybenzyl)-6,7-dimethoxyisoquinolinium bromide (IIIa). Yield 96%, mp 184–185°C (from ethanol). ^{1}H NMR spectrum, δ, ppm: 3.51 s (3H, OCH_3), 3.63 s (3H, OCH_3), 3.99 s (3H, OCH_3), 4.12 s (3H, OCH_3), 5.09 s (2H, CH_2), 6.44 d (1H, H_{arom}, J = 8 Hz), 6.56 d (1H, H_{arom}, J = 8 Hz), 6.78 s (2H, CH_2CO), 6.85 s (1H, H_{arom}), 7.55 d (2H, C_6H_4Cl, J = 8 Hz), 7.83 s (1H, H_{arom}), 7.88 s (1H, H_{arom}), 8.02 d (2H, C_6H_4Cl, J = 8 Hz), 8.30 d (1H, H_{arom}, J = 7 Hz), 8.52 d (1H, H_{arom}, J = 7 Hz). Found, %: C 58.33; H 4.85; N 2.52. $C_{28}H_{27}BrClNO_5$. Calculated, %: C 58.70; H 4.75; N 2.44.

1-(2-Bromo-4,5-dimethoxybenzyl)-2-[2-(4-chlorophenyl)-2-oxoethyl]-6,7-dimethoxyisoquinolinium bromide (IIIb). Yield 50%, mp 189–191°C (from acetonitrile). ^{1}H NMR spectrum, δ, ppm: 3.55 s (3H, OCH_3), 3.71 s (3H, OCH_3), 3.94 s (3H, OCH_3), 4.12 s (3H, OCH_3), 4.99 s (2H, CH_2), 6.52 s (1H, H_{arom}), 6.81 s (2H, CH_2CO), 6.87 s (1H, H_{arom}), 7.56 d (2H, C_6H_4Cl, J = 8 Hz), 7.63 s (1H, H_{arom}), 7.88 s (1H, H_{arom}), 8.05 d (2H, C_6H_4Cl, J = 8 Hz), 8.39 d (1H, H_{arom}, J = 7 Hz), 8.68 d (1H, H_{arom}, J = 7 Hz). Found, %: C 51.63; H 4.12; N 2.04. $C_{28}H_{26}Br_2ClNO_5$. Calculated, %: C 51.60; H 4.02; N 2.15.

2-[2-(4-Chlorophenyl)-2-oxoethyl]-1-[4,5-dimethoxy-2-(1*H*-pyrrol-1-yl)benzyl]-6,7-dimethoxyisoquinolinium bromide (IIIc). Yield 76%, mp 205–206°C (from ethanol). ^{1}H NMR spectrum, δ, ppm: 3.57 s (3H, OCH_3), 3.71 s (3H, OCH_3), 3.93 s (3H, OCH_3), 4.10 s (3H, OCH_3), 4.92 s (2H, CH_2), 5.50 s (2H, CH_2CO), 6.53 s (2H, 3-H, 4-H, pyrrole), 6.57 s (1H, H_{arom}), 6.59 s (2H, 2-H, 5-H, pyrrole), 6.89 s (1H, H_{arom}), 7.55 s (1H, H_{arom}), 7.61 d (2H, C_6H_4Cl, J = 8 Hz), 7.67 s (1H, H_{arom}), 7.99 d (2H, C_6H_4Cl, J = 8 Hz), 8.18 d (1H, H_{arom}, J = 6 Hz), 8.37 d (1H, H_{arom}, J = 6 Hz). Found, %: C 60.25; H 4.79; N 4.51. $C_{32}H_{30}BrClN_2O_5$. Calculated, %: C 60.25; H 4.74; N 4.39.

1-Aryl-2-(4-chlorophenyl)-8,9-dimethoxypyrrolo[2,1-*a*]isoquinolines IVa–IVc (*general procedure*). Quaternary salt **IIIa**–**IIIc**, 10 mmol, was dispersed in 100 ml of water, 15 mmol of sodium hydrogen carbonate was added, and the mixture was heated at the boiling point for 4 h under vigorous stirring. The mixture was cooled, and the precipitate was filtered off and recrystallized from acetonitrile.

2-(4-Chlorophenyl)-1-(3,4-dimethoxyphenyl)-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline (IVa). Yield 50%, mp 191–192°C. ^{1}H NMR spectrum, δ, ppm: 3.37 s (3H, OCH_3), 3.72 s (3H, OCH_3), 3.84 s (3H, OCH_3), 3.85 s (3H, OCH_3), 6.68 d (1H, H_{arom}, J = 7 Hz), 6.82 s (1H, H_{arom}), 6.89 d (2H, C_6H_4Cl, J = 8 Hz), 6.95 d (1H, H_{arom}, J = 7 Hz), 6.97 s (1H, H_{arom}), 7.16 s (1H, H_{arom}), 7.17 d (2H, C_6H_4Cl, J = 8 Hz), 7.21 s (1H, H_{arom}, J = 8 Hz), 7.57 s (1H, pyrrole), 7.83 d (1H, H_{arom}, J = 8 Hz). Found, %: C 71.04; H 5.00; N 2.80. $C_{28}H_{24}ClNO_4$. Calculated, %: C 70.96; H 5.10; N 2.96.

1-(2-Bromo-4,5-dimethoxyphenyl)-2-(4-chlorophenyl)-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline (IVb). Yield 52%, mp 121–122°C. ^{1}H NMR spectrum, δ, ppm: 3.40 s (3H, OCH_3), 3.68 s (3H, OCH_3), 3.85 s (3H, OCH_3), 3.89 s (3H, OCH_3), 6.64 s (1H, H_{arom}), 6.75 d (1H, H_{arom}, J = 7 Hz), 6.87 s (1H, H_{arom}), 7.02 s (1H, H_{arom}), 7.20 d (2H, C_6H_4Cl, J = 9 Hz), 7.24 d (2H, C_6H_4Cl, J = 9 Hz), 7.25 s (1H, H_{arom}), 7.20 s (1H, H_{arom}), 7.66 s (1H, pyrrole), 7.90 d (1H, H_{arom}, J = 7 Hz). Found, %: C 60.92; H 4.22; N 2.60. $C_{28}H_{23}BrClNO_4$. Calculated, %: C 60.83; H 4.19; N 2.53.

2-(4-Chlorophenyl)-1-[4,5-dimethoxy-2-(1*H*-pyrrol-1-yl)phenyl]-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline (IVc). Yield 66%, mp 257–258°C. ^{1}H NMR spectrum, δ, ppm: 3.40 s (3H, OCH_3), 3.75 s (3H, OCH_3), 3.83 s (3H, OCH_3), 3.90 s (3H, OCH_3), 5.70 s (2H, 3-H, 4-H, pyrrole), 6.27 s (2H, 2-H, 5-H, pyrrole), 6.72 d (1H, H_{arom}, J = 14 Hz), 6.82 s (1H, H_{arom}), 6.98 d (2H, C_6H_4Cl, J = 8 Hz), 7.05 s (1H, H_{arom}), 7.13 d (2H, C_6H_4Cl, J = 8 Hz), 7.15 s (1H, H_{arom}), 7.20 s (1H, H_{arom}), 7.60 s (1H, 3-H), 7.85 d (1H, H_{arom}, J = 14 Hz). Found, %: C 71.39; H 5.12; N 5.22. $C_{32}H_{27}ClN_2O_4$. Calculated, %: C 71.30; H 5.05; N 5.20.

Reaction of aminopapaverine Id with 4-chlorophenacyl bromide. Compound **Id**, 10 mmol, was added to a solution of 10 mmol of 4-chlorophenacyl bromide in 100 ml of anhydrous acetone, and the mixture was stirred for 24 h. The precipitate was filtered off and recrystallized twice from acetonitrile. Yield of compound **V** 35%, mp 194–195°C. ^{1}H NMR spectrum, δ, ppm: 3.64 s (3H, OCH_3), 3.74 s (3H, OCH_3), 3.93 s (3H, OCH_3), 3.94 s (3H, OCH_3), 4.40 s (2H, CH_2), 4.62 s (2H, CH_2CO), 6.27 s (1H, NH), 6.92 s (1H, H_{arom}), 7.15 s (1H, H_{arom}), 7.52 d (1H, H_{arom}, J = 7 Hz), 7.61 s (2H, C_6H_4Cl, J = 8 Hz), 7.61 s (1H, H_{arom}), 8.11 d (2H, C_6H_4Cl, J = 8 Hz), 8.17 d (1H, H_{arom}, J = 7 Hz). Found, %: C 66.49; H 5.37; N 5.63. $C_{28}H_{27}ClN_2O_5$. Calculated, %: C 66.33; H 5.37; N 5.53.

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