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SHORT COMMUNICATIONS

Unusual Reactivity of α-Aminopapaverine

D. V. Krivorotov[a], M. V. Vorob'ev[a], V. A. Polukeev[b], M. L. Petrov[a], E. N. Glibin[†a], and A. V. Didenko[a]

[a] *St. Petersburg State Institute of Technology, Moskovskii pr. 26, St. Petersburg, 190013 Russia*
e-mail: den@orgchem.spb.ru

[b] *"Vekton" Ltd., St. Petersburg, Russia*

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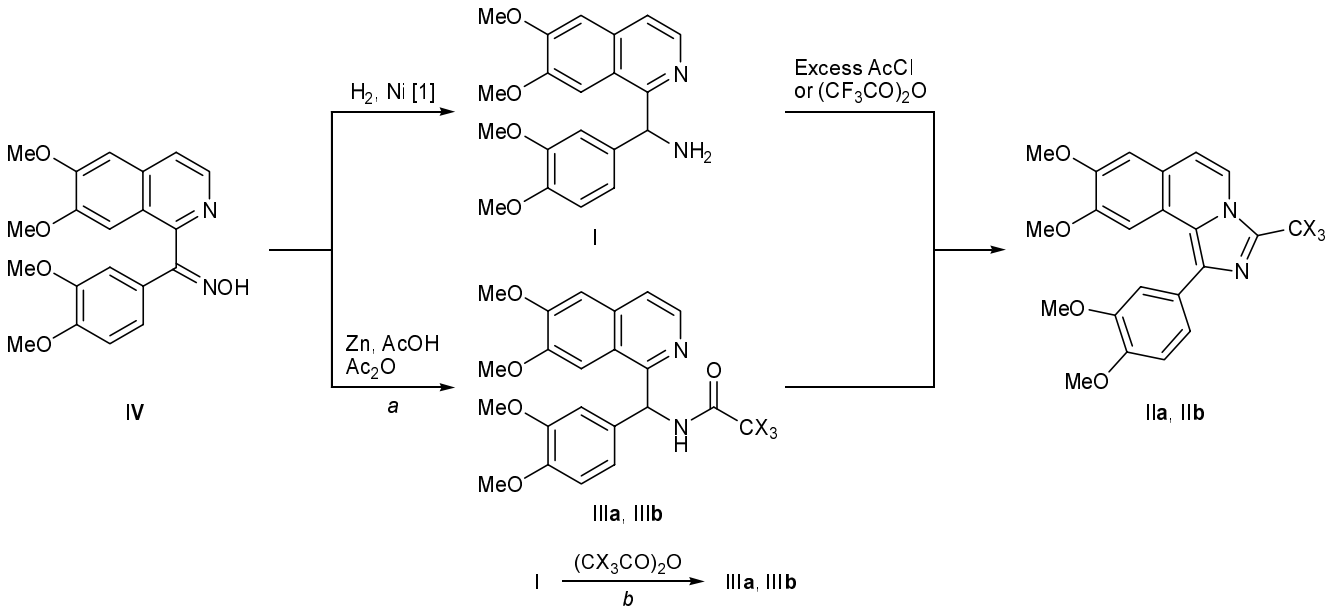
The chemistry of α-aminopapaverine [**I**, (6,7-dimethoxyisoquinolin-1-yl)-3,4-dimethoxyphenylmethanamine] has been studied very poorly, though Lespagnol et al. [1] reported on the synthesis of amides by treatment of α-aminopapaverine (**I**) with carboxylic acid halides [1]. α-Acetamides and α-trifluoroacetamides derived from papaverine were not described previously.

We have found that the reactions of α-aminopapaverine (**I**) with excess acetyl chloride or trifluoroacetic anhydride lead to the formation of 3-methyl- and 3-trifluoromethylimidazoisoquinolines **IIa** and **IIb**, respectively, rather than *N*-acetyl- and N-trifluoroacetyl-α-aminopapaverines **IIIa** and **IIIb**. We succeeded in obtaining amide **IIIa** by reductive acylation of oxime **IV** in the system acetic acid–acetic anhydride–zinc (method *a*), as well as by acylation of α-aminopapaverine (**I**) with an equimolar amount of acetic anhydride (method *b*). Likewise, using trifluoroacetic anhydride we synthesized the corresponding trifluoroacetamide **IIIb**.

It should be noted that the transformation of *N*-acetyl-α-aminopapaverine **IIIa** into 3-methylimidazoisoquinoline **IIa** occurs unexpectedly readily. Compound **IIa** is formed on treatment of acetyl derivative **IIIa** with phosphoryl chloride, hydrochloric acid, or



X = H (**a**), F (**b**).

† Deceased.

acetic anhydride. The formation of imidazoquinoline systems from *N*-(isoquinolin-2-ylmethyl) amides was reported previously [2]; however, these reactions required such strong condensing agents as phosphoryl chloride.

Thus we have demonstrated the possibility for the cyclization of *N*-acyl-α-aminopapaverine derivatives into methylimidazoisoquinolines to occur under very mild conditions.

1-(3,4-Dimethoxyphenyl)-8,9-dimethoxy-3-methylimidazo[5,1-*a*]isoquinoline hydrochloride (IIa·HCl). *a*. Acetyl chloride, 100 mmol, was added to a solution of 10 mmol of α-aminopapaverine (**I**) [1] in 100 ml of anhydrous ethyl acetate. The mixture was stirred for 24 h, and the precipitate was filtered off and recrystallized. mp 210–212°C (from ethanol). ^{1}H NMR spectrum, δ, ppm: 3.00 s (3H, CH_3), 3.60 s (3H, OCH_3), 3.90 s (9H, $3OCH_3$), 7.11 d (1H, H_{arom}, J = 7 Hz), 7.30 m (4H, H_{arom}), 7.47 s (1H, H_{arom}), 8.09 d (1H, H_{arom}, J = 7 Hz). Found, %: C 63.68; H 5.61; N 6.83. $C_{22}H_{23}ClN_2O_4$. Calculated, %: C 63.69; H 5.59; N 6.75.

b. A mixture of 10 mmol of *N*-acetyl-α-aminopapaverine **IIIa** and 50 ml of phosphoryl chloride was heated for 12 h under reflux. The mixture was evaporated, and the precipitate was filtered off and recrystallized. Yield 70%.

c. A mixture of 10 mmol of *N*-acetyl-α-aminopapaverine **IIIa**, 20 ml of 37% hydrochloric acid, and 40 ml of water was heated for 12 h under reflux. The mixture was evaporated, and the residue was recrystallized. Yield 90%.

1-(3,4-Dimethoxyphenyl)-8,9-dimethoxy-3-methylimidazo[5,1-*a*]isoquinoline (IIa). A mixture of 10 mmol of compound **IIIa** and 50 ml of acetic anhydride was heated for 5 h under reflux. The mixture was poured into water and made alkaline by adding aqueous ammonia, and the precipitate was filtered off and recrystallized. Yield 95%, mp 112–114°C (from toluene). ^{1}H NMR spectrum, δ, ppm: 2.62 s (3H, CH_3), 3.59 s (3H, OCH_3), 3.85 s (9H, $3OCH_3$), 6.79 d (1H, H_{arom}, J = 7 Hz), 6.99 d (1H, H_{arom}, J = 7 Hz), 7.09 s (1H, H_{arom}), 7.18 m (2H, H_{arom}), 7.51 s (1H, H_{arom}), 7.69 d (1H, H_{arom}, J = 7 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 378 (100) $[M]^+$, 363 (33), 189 (40). Found, %: C 69.93; H 5.98; N 7.38. $C_{22}H_{22}N_2O_4$. Calculated, %: C 69.83; H 5.86; N 7.40.

1-(3,4-Dimethoxyphenyl)-8,9-dimethoxy-3-trifluoromethylimidazo[5,1-*a*]isoquinoline (IIb). Trifluoroacetic anhydride, 100 mmol, was added to a solution of 10 mmol of α-aminopapaverine (**I**) [1] in 100 ml of anhydrous ethyl acetate. The mixture was stirred for 24 h, and the precipitate was filtered off and recrystallized. mp 109–111°C (from acetone). ^{1}H NMR spectrum, δ, ppm: 3.57 s (3H, CH_3), 3.87 t (9H, $3OCH_3$), 7.03 d (1H, H_{arom}, J = 7 Hz), 7.18 m (4H, H_{arom}), 7.46 s (1H, H_{arom}), 7.95 d (1H, H_{arom}, J = 7 Hz). Found, %: C 61.18; H 4.44; N 6.47. $C_{22}H_{19}F_3N_2O_4$. Calculated, %: C 61.11; H 4.43; N 6.48.

***N*-[6,7-Dimethoxyisoquinolin-1-yl(3,4-dimethoxyphenyl)methyl]acetamide (IIIa, *N*-acetyl-α-aminopapaverine).** *a*. Acetic anhydride, 30 mmol, was added to a solution of 10 mmol of oxime **IV** [1] in 80 ml of acetic acid. Zinc dust, 40 mmol, was then added in small portions under stirring, maintaining the temperature at 40°C. The mixture was heated to the boiling point, cooled to room temperature, and filtered, the filtrate was evaporated under reduced pressure, and the residue was recrystallized. Yield 70%, mp 189–191°C (from toluene). ^{1}H NMR spectrum, δ, ppm: 1.94 s (3H, $COCH_3$), 3.71 s (6H, OCH_3), 3.91 s (6H, OCH_3), 6.75 d (2H, H_{arom}, J = 8 Hz), 6.86 d (1H, α-C**H**NH, J = 8 Hz), 7.03 s (1H, H_{arom}), 7.23 s (1H, H_{arom}), 7.48 s (1H, H_{arom}), 7.53 d (1H, H_{arom}, J = 6 Hz), 8.29 d (1H, H_{arom}, J = 6 Hz), 8.65 d (1H, NH, J = 8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 23,46 (1C), 59.91 (1C), 56.15 (4C, OCH_3), 103.89 (1C), 106.18 (1C), 112.16 (1C), 112.75 (1C), 119.76 (1C), 120.76 (1C), 121.92 (1C), 133.70 (1C), 135.07 (1C), 140.25 (1C), 148.63 (1C), 149.30 (1C), 150.62 (1C), 153.13 (1C), 157.06 (1C), 168.60 (1C, **C**$COCH_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 396 (51) $[M]^+$, 353 (100), 215 (20), 166 (24), 43 (22). Found, %: C 66.70; H 6.26; N 7.14. $C_{22}H_{24}N_2O_5$. Calculated, %: C 66.65; H 6.10; N 7.07.

b. Acetic anhydride, 10 mmol, was added to a solution of 10 mmol of α-aminopapaverine (**I**) [1] in 100 ml of ethyl acetate. After 24 h, the precipitate of amide **IIIa** was filtered off and recrystallized. Yield 99%, mp 189–191°C (from toluene).

***N*-[6,7-Dimethoxyisoquinolin-1-yl(3,4-dimethoxyphenyl)methyl]-2,2,2-trifluoroacetamide (IIIb, *N*-trifluoroacetyl-α-aminopapaverine).** Trifluoroacetic anhydride, 10 mmol, was added to a solution of 10 mmol of α-aminopapaverine (**I**) [1] in 100 ml of ethyl acetate. After 24 h, the mixture was evaporated under reduced pressure, the residue was dissolved in acetone, and 5 ml of aqueous ammonia was added to the solution. The precipitate was filtered off and recrystallized. Yield 50%, mp 129–131°C (from MeOH).

^{1}H NMR spectrum, δ, ppm: 3.77 s (3H, OCH_3), 3.81 s (3H, OCH_3), 3.88 s (3H, OCH_3), 3.99 s (3H, OCH_3), 6.60 d (1H, α-C**H**NH, J = 6 Hz), 6.75 d (1H, H_{arom}, J = 8 Hz), 6.93 m (2H, H_{arom}), 7.07 s (1H, H_{arom}), 7.19 s (1H, H_{arom}), 7.53 d (1H, H_{arom}, J = 8 Hz), 8.41 d (1H, NH, J = 6 Hz). Found, %: C 58.73; H 4.82; N 6.19. $C_{22}H_{21}F_3N_2O_5$. Calculated, %: C 58.67; H 4.77; N 6.33.

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-500 spectrometer at 500 and 125 MHz, respectively, from 1% solutions in DMSO-d_6. The elemental compositions were determined on a Perkin–Elmer 240 analyzer. The mass spectra (electron impact, 70 eV) were run on an MKh-1321 instrument (vaporizer temperature 120°C, ion source temperature 200°C). The melting points were determined on an NMK melting point apparatus. The progress of reactions was monitored by TLC on Silufol UV-254 plates using benzene–anhydrous ethanol (9 : 1) as eluent.

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