Tetrahedron Vol. 37, pp. 371 to 375
Pergamon Press Ltd., 1981. Printed in Great Britain

0040-4020/81/0115-0371 $02.00/0

ON *PAPAVER BRACTEATUM*—XIV†

READY ACCESS TO BENZYLIDENE PHTHALIMIDINE COMPOUNDS FROM RHOEADINE ALKALOID-DERIVED NITRILES

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(*Received in Germany 7 March 1980*)

Abstract The B/D *trans* lactole alpinigenine (**1a**) isolated from *Papaver bracteatum* Lindl. was shown to form the oxime **2a** which in turn was transformed to the nitrile **3a** by dehydration, the methiodide **4a**, and by treatment with alkali under mild conditions to the benzylidene phthalimidine derivative **5a**, whose structure was elucidated by spectral analysis as well as oxidative fragmentation into **6** and **7**.

The unique reaction leading to **5a** apparently is bound with certain structural prerequisites inherent to **3a**, including stereochemistry. When *cis*-alpinigenine (**1b**) was subjected to the same sequence, little of **5a** accordingly could be obtained, and even none of any phthalimidine was formed from the non-acetoxylated nitrile **11**.

In the preliminary report[1] on the degradation of alpinigenine (**1a**),[2] an alkaloid of the rhoeadine subgroup of the isoquinoline family,[3] it was suggested that the ready formation of the benzylidene phthalimidine derivative **5a** was favoured by any kind of concerted mechanism. We now add both complementary experiments contributing to the scope and mechanism of the novel reaction and the experimental details.

During the biosynthesis of the rhoeadine-type alkaloids[4,5] we recognized an adequate degradation scheme to be decisive for successfully evaluating radioactivity on all important positions of the benzazepine skeleton encountered in those alkaloids.

The formation of the oxime **2a** is indicative of the ready opening of ring D owing to ring-chain tautomery in the hemiacetalic structural entity. (Scheme 1). Hot acetic anhydride was chosen to dehydrate **2a** and the corresponding nitrile **3a** was formed in more than 70% yield, provided that even traces of hydrogen chloride were absent from the starting materials. Otherwise nitrile **3a** was obtained in poor yield. The NMR spectrum showed an AB-system characteristic of the two *trans* protons at C-1 and C-2 ($J = 7$ c/s) of the unaffected benzazepine structure, the relatively small coupling constant pointing to the more flexible nature of the less-connected 7-membered nitrogenous ring thus delivered from the constraints of the tetracyclic rhoeadine skeleton ($J = 9.5$ c/s in **1a**). Alkaloids comprising nitrogen as well as benzylic positions in one ring of their framework generally are not stable in the presence of carboxylic acid anhydrides. The 1-benzyl-tetrahydroisoquinoline laudanosine, for example, was found to split easily under the very conditions applied to **2a** (see Ref. 5). Mass spectrometric fragmentation of **3a** was accompanied by extensive rearrangement and high resolution analysis revealed three main peaks, *m/e* 190, 206 and 207 due to the 6,7-dimethoxyisoquinolinium cation and its N-methylated dihydro and tetrahydro derivatives, respectively (Experimental and Ref. 5).

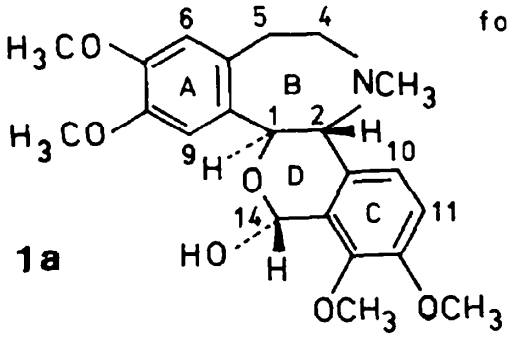
Hofmann degradation was applied to the corresponding methiodide **4a**. Although exceptionally mild conditions had been chosen, the nitrile function could not be saved. Instead, an optically inactive, yellow compound, the benzylidene phthalimidine **5a** was formed by any kind of multi-centre or concerted mechanism. Whereas tentative structure assignment based on UV (λ_{max} 211, 222, 296 and 367 nm) and IR analysis[6] ($\nu_{C=C}$ 1673, $\nu_{C=O}$ 1717 and ν_{NH} 3441 cm^{-1}) was strengthened by the singlet of the olefinic proton at $\delta = 6.36$ ppm in the NMR spectrum, the remaining uncertainty was removed after oxidative splitting into two known compounds. Osmium tetroxide catalyzed oxidation by sodium periodate according to Lemieux/Johnson at the stilbene double bond, which proceeded smoothly but very slowly even at pH 2 in aqueous medium, afforded hemipinimide (**7**)[7] and the substituted veratraldehyde **6**.[8]

Compounds representing the benzylidene phthalimidine structure, e.g. narceine imide (**5b**), have long been known[9] and have recently been isolated,[10,11] but it is still uncertain, whether or not they are original plant constituents. It should be mentioned that no correlation of either *Z* or *E* stereochemistry is intended with compounds **5**. For related work see Ref. 14.

There appears to be only one example in which a second nitrogen function in the Hofmann degradation of quaternary methohydroxides results in the formation of a new nitrogenous ring, namely the chemistry of the Codonocarpus alkaloids.[12] The obvious attack of nitrile nitrogen at the α-C atom C-1 to form the phthalimidine **5a** resembles the formation of cyclic ethers from appropriately constituted amino alcohol methohydroxides, a well-known variety occasionally observed in the course of Hofmann degradation.[13]

In two experiments planned to contribute to the scope of the phthalimidine-forming type of reaction the latter in all probability was confined to the structural prerequisites including stereochemistry comprised in the nitrile **3a**. In the first, an easily

† Part XIII. H. Rönsch and W. Schade, *Phytochemistry* **18**, 1089 (1979).



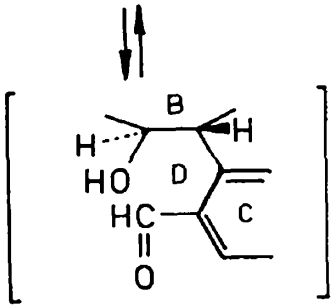
formulae 1-4:

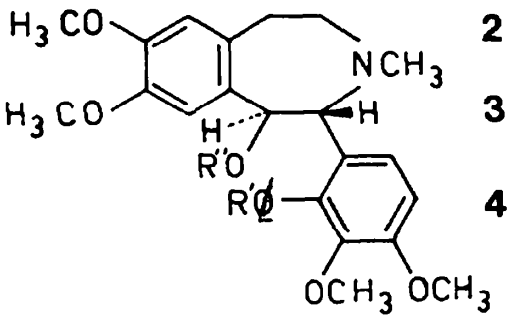
a: (1S:2R: 14R)

b: (1R:2R: 14R)

1a

1b: inversed at C-1

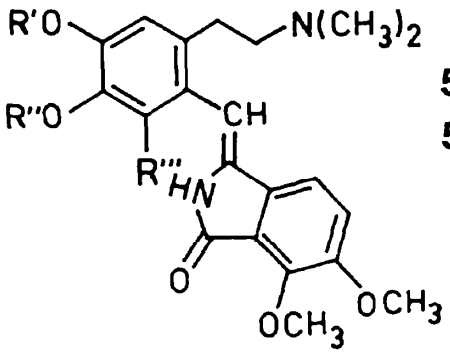




2a,b R'=CH=NOH, R''=H

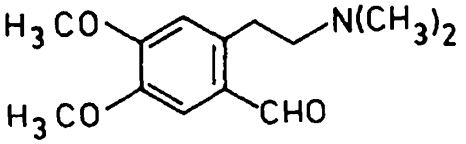
3a,b R'=C≡N, R''=CH_3CO

4a,b R'=C≡N, R''=CH_3CO, $N^+(CH_3)_3I^-$



5a R'=R''=CH_3, R'''=H

5b R'+R''=CH_2, R'''=OCH_3



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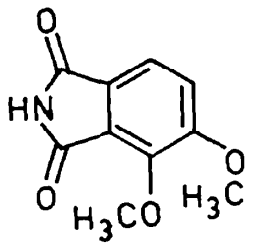
Scheme 1.



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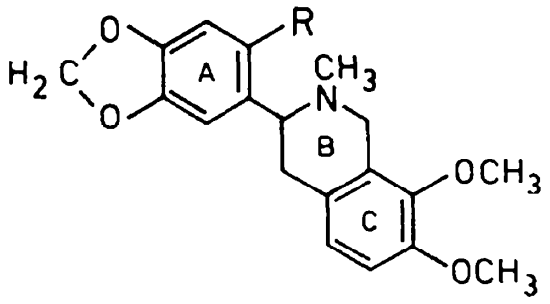
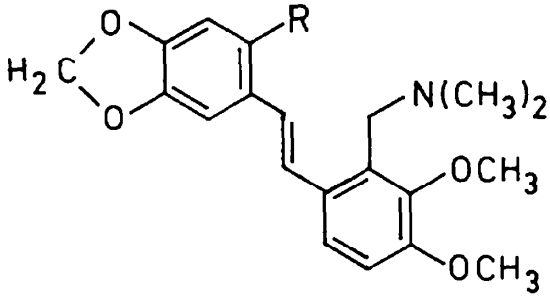
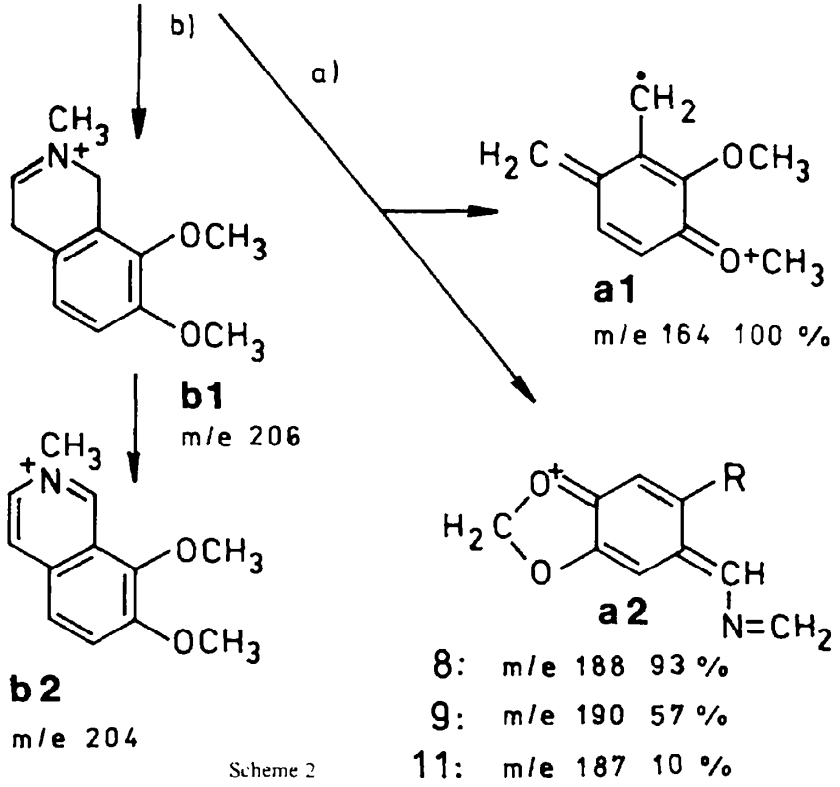


	R
8	$CH{=}CH_2$
9	CHO
10	CH=NOH
11	C≡N
12	C≡N, $N^+(CH_3)_2$



	R
13	C≡N
14	$CONH_2$

MS: **8**: M+ 353 85 %.
9: M+ 355 100 %.
11: M+ 352 54 %.



Scheme 2

obtainable model compound, the non-acetoxylated 3-(*o*-cyanobenzyl)-tetrahydroisoquinoline **11** (Scheme 2), after methiodide formation was subjected to Hofmann degradation under the conditions used for the alpinigenine derivative **4a**. The two products **13** and **14** were isolated in yields of 50% and 34%, th., respectively, and each was characterized as a stilbene derivative by their UV maxima appearing in the range of 225 and 330 nm. In the less polar **13**, which was the main product, the nitrile function ($\nu_{C\equiv N}$ 2223 cm^{-1}) was saved and **14** proved to be a primary amide (ν_{CO} 1667 cm^{-1}, ν_{NH} 3408 and 3528 cm^{-1}). In addition, there was not the slightest indication of any phthalimidine formed.

The other experiment was done with the nitrile **3b** obtained similarly from *cis*-alpinigenine[2] (**1b**) whose Hofmann degradation demonstrates the importance of an appropriate stereochemistry in the benzylidene phthalimidine-forming reaction: the same compound, **5a**, was formed, but the yield was quite low.

From the results discussed above the following prerequisites of the benzylidene phthalimidine-forming reaction appear to emerge: (i) an α-C atom substituted by an *o*-cyano-phenyl group; (ii) an adjacent β-C substituted by OH (OAc) in addition to aryl; (iii) *trans* configuration at these two reaction centres.

Finally, the preparation of the nitrile **11** from (±)-canadine via its methine base[15] **8** is described briefly. The latter reacted with sodium periodate/osmium tetroxide to afford the aldehyde **9**, ν_{CO} 1683 cm^{-1}, δ_{CHO} 10.62 ppm. The nitrile **11** was obtained by a similar reaction sequence as shown for **3a**, except for the dehydration step accomplished by heating the oxime **10** with phosphorus oxychloride, yielding **12**. $\nu_{C\equiv N}$ 2222 cm^{-1}.

The skeletal fragmentations revealed by the mass spectra of the 3-aryl-tetrahydroisoquinoline derivatives **8**, **9** and **11** are also comprised in Scheme 2. The major fragmentation mode (a) common to individual compounds is characterized by the splitting of the benzylic carbon bond, forming parent peak **a1** in addition to the various structurally specific ions **a2**. Being of variable frequency, fragmentation (b) apparently leads to the two isoquinoline species **b1** and **b2** irrelevant to the substituent R.

EXPERIMENTAL

The following equipment was applied to analysis of compounds, if not specified otherwise: A Böetius microscope hot stage for m.ps (corrected); IR spectra in $CHCl_3$ soln on a UR-10 (VEB Carl Zeiß, Jena); NMR spectra in $CDCl_3$ with TMS as internal standard on a ZKR-60 (VEB Carl Zeiß, Jena) of Varian HA-100; UV spectra in 95% ethanol using an Ultrascan (Hilger & Watts); mass spectra by a low-energy mass spectrograph (Ardenne); tlc on Kieselgel G (Merck).

Nitrile **3a** *via oxime* **2a**. A soln of **1a** (467 mg) and NH_2OH·HCl (95 mg) in 12 ml dry pyridine was heated to 100° for 30 min. The residue obtained on evaporation *in vacuo* was dissolved in 25 ml 1N KOH, and traces of **1a** were removed using ether. The pH 8 was adjusted by addn of solid NH_4Cl. Extraction with CH_2Cl_2 (4 × 20 ml) yielded amorphous **2a** (470 mg, 97%) uniform on tlc in several systems. IR (KBr): 1610 (C=N) and 3505 cm^{-1} (OH). Treatment with Ac_2O (20 ml) at 118–124° N_2 for 75 min and subsequent evaporation of reagent *in vacuo* was followed by vigorously stirring the residue in CH_2Cl_2 (50 ml) with satd $NaHCO_3$ aq (30 ml) for 20 min. The organic layer was dried (Na_2SO_4), concd to 2–3 ml and diluted with ether (200 ml) to separate brownish flocculi. Crystalline **3a** (364 mg, 70%) separated when the filtered soln was again concd. Recrystallization (CH_2Cl_2–EtOH) afforded pure **3a**, m.p. 161–162°. $[\alpha]_D^{22}$ −11.4° (*c* = 0.644, MeOH). IR: 1743 (C=O) and 2217 cm^{-1} (C≡N). UV: 233, 290 and 307 nm (log ε 4.28 sh, 3.79 and 3.74). NMR: δ 6.99 (s, 2 Ar_CH); 6.56, 6.53 (2s, 2 Ar_AH); 5.90 (d, J = 7 c/s, H-1); 3.93 (d, J = 7 c/s, H-2); 3.99, 3.87, 3.86, 3.77 (4s, 4 OCH_3); 2.38 (s, NCH_3); 2.02 ppm (s, CH_3COO). High resolution MS (JMS D 100 of JEOL, 75 ev): *m/e* 440.1957 (0.4) calc. for $C_{25}H_{28}N_2O_6$: 440.1947 (M^+), 439 (1.2), 380.1745 (16) calc. for $C_{22}H_{24}N_2O_4$: 380.1736 (M^+ − CH_3COOH), 365.1512 (7.4) calc. for $C_{21}H_{21}N_2O_4$ 365.1501 (M^+ − CH_3COOH, − CH_3), 219.1039 (4.8) calc. for $C_{12}H_{15}N_2O_2$, 219.1033, 207.1207 (>100) calc. for $C_{12}H_{15}NO_2$: 207.1207 (N-methyl-6,7-dimethoxy-tetrahydroisoquinolinium cation), 206.1183 (>100) calc. for $C_{12}H_{16}NO_2$: 206.1181 (N-methyl-6,7-dimethoxy-dihydro-isoquinolinium cation), 190.0880 (100) calc. for $C_{11}H_{12}NO_2$: 190.0868 (6,7-dimethoxy-isoquinolinium cation), 162 (43), 43 (72). (Found: C, 65.76; H, 6.58; N, 6.50. Calc. for $C_{24}H_{28}N_2O_6$: C, 65.46; H, 6.41; N, 6.36%).

Nitrile methiodide **4a**. Nitrile **3a** (285 mg) was refluxed with 5 ml of MeI in acetone (10 ml) for 3 hr. Crystalline **4a** (360 mg, 95%) was collected from the concd soln and recrystallized from MeOH, m.p. 224–228° (dec), $[\alpha]_D^{25}$ −54.2° (*c* = 0.829, $CHCl_3$ – MeOH (1:2)). IR (nujol): 1776 (C=O), 2222 cm^{-1} (C≡N). UV: 289 and 308 nm (log ε 3.76 and 3.68). MS: *m/e* 380 (25) -CH_3COOH, CH_3I, 365 (14), 206 (100), 142 (100) MeI, 127 (70) I⁺. (Found: C, 51.15; H, 5.36; N, 4.93. Calc. for $C_{26}H_{31}IN_2O_6$: C, 51.55, H, 5.37; N, 4.82%).

Benzylidene phthalimidine **5a**. A soln of **4a** (410 mg) in warm MeOH (4 ml) was mixed with 1N KOH (16 ml), heated at 80° for 5 hr, and N_2 passed through to slowly remove most of the MeOH. Crystallization started in the hot soln to afford a monohydrate of **5a** (164 mg, 75%), yellow crystals, m.p. 161–162° (MeOH), optically inactive. IR: 1673 (C=C), 1717 + 1706 sh (C=O), 3441 cm^{-1} (NH). UV: 211, 222, 296 and 367 nm (log ε 4.41, 4.37, 4.02 and 4.29); UV (N/10 KOH in EtOH): 210, 230 sh, and 368 nm (log ε 4.94, 4.73 and 4.62) indicates a pronounced alteration of the chromophoric system by base. NMR: δ 8.37 (m, NH); 7.45, 7.15 (2d, J = 8 c/s, 2 ArH); 6.86, 6.76, 6.46 (3s, 2 ArH + C=CH); 4.08, 3.94, 3.83 (3s, 4 OCH_3); 2.30 ppm (s, NCH_3). MS: *m/e* 412 (65) M^+, 367 (13) -$HN(CH_3)_2$, 220 (100). (Found: C, 66.92; H, 7.01; N, 6.67. Calc. for $C_{23}H_{28}N_2O_5$: C, 66.97; H, 6.84; N, 6.79%).

Lemieux-Johnson degradation of **5a**. Phthalimidine **5a** (143 mg) was dissolved in 8 ml water containing 0.54 mmol HCl. The soln was stirred and 9 mg of OsO_4 added. $NaIO_4$ (154 mg in 9 ml water) was introduced within 30 min. Until oxidation was complete after 15 hr, the temp was kept below 25° and pH between 2–4. Tlc control was done using $CHCl_3$–MeOH (85:15).

(a) *Hemipinimide* (**7**). The major quantity of **7** was filtered off and washed with water (50 mg, 70%). An impure portion was extracted from the acidified soln using CH_2Cl_2. Purification was achieved in turn by crystallization (EtOH, 2 ×), sublimation (0.1 mm Hg), and recrystallization, m.p. 230–232° (lit.[7] m.p. 228–230°).

(b) 6-(*β-Dimethylaminoethyl*)-*veratraldehyde* (**6**). After addition of excess NH_4OH to the foregoing soln, extraction by CH_2Cl_2 yielded 74 mg of resin. To separate a small amount of the corresponding veratric acid, the product was dissolved in 0.1 ml of MeOH + 12 ml of ether. The soln was filtered and evapd to give **6** (66 mg), approximately pure according to tlc using $CHCl_3$–MeOH (9:1 + 1% aq. NH_4). IR (film): 1685 cm^{-1} (C=O). **6**-*Methiodide* was formed by heating 66 mg of **6**, 0.5 ml of MeOH, 8 ml of ether, and 1 ml of MeI for 2 h, and collecting the crystals (92 mg, 87%), m.p. 223–225° (MeOH–ether) (lit.[8] m.p. 225°). IR (nujol): 1682 cm^{-1} (C=O). Both **6** and **7** were identical with the authentic compounds by direct comparison (mixed m.ps, IR spectra).

Nitrile **3b** was prepared from *cis*- **1b** by way of the oxime **2b** as described for **3a** except purification. The crude product was re-dissolved by means of ether CH_2Cl_2 (30:1) and then cyclohexane ether (1:1). Crystals were obtained from cyclohexane–ether (3:1) (73%) and recrystallized from acetone–water, m.p. 144 144.5°, $[\alpha]_D^{22}$ − 142.8° (c = 0.527, MeOH). IR: 1738 (C=O), 2226 cm^{-1} (C≡N). UV: 214, 219, 236 sh, 290 and 308 nm (log ε 4.49, 4.50, 4.15, 3.70 and 3.68). NMR: δ 6.86 (2d, J = 9 c/s, 2 Ar_CH), 6.61, 6.57 (2s, 2 Ar_AH); 6.02 (d, J = 2 c/s, H-1); 4.00, 3.85, 3.83, 3.74 (4s, 4 OMe); 3.10 (d, J = 2 c/s, H-2); 2.15 (s, NCH_3); 2.05 ppm (s, CH_3COO). MS: *m/e* 440 (50) M$^+$, 397 (42) M$^+$–CH_3CO, 380 (45) M$^+$ CH_3COOH, 117 (100). (Found: C, 65.30; H, 6.52; N, 6.60. Calc. for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36%).

Hofmann degradation of **3b**. The nitrile **3b** was transformed to the corresponding methiodide **4b** (54 mg, m.p. 134–140°) and the latter treated with 1N KOH as described for **4a**. There was a resinous ppt which on seeding with **5a** yielded 14 mg of impure crystals. Recrystallization from MeOH afforded 4.4 mg of **5a**, m.p. 153–155°, fairly pure and identical by IR and mixed m.p. with phthalimidine derivative **5a**.

Aldehyde **9** (*7,8-dimethoxy)-2-methyl-3-(2-formyl-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydroisoquinoline*). The starting vinyl derivative **8** was obtained in 80% yield when canadine methohydroxide was heated with 40% KOH[15] (*cf* also ref. 16), m.p. 111–113° (lit.[15] m.p. 114–115°). UV: 218, 262 and 294–302 nm sh (log ε 4.35, 4.00 and 3.70). **8** (1.52 g) was dissolved in 7 ml of AcOH, the soln diluted with water (425 ml), filtered, and combined with OsO_4 (120 mg) in 420 ml of ether. Stirring was started and a soln of 2.0 g of $NaIO_4$ in 42 ml of water added dropwise within 15 min. After 1 hr the ethereal layer was discarded and aq. soln treated for 10 min with 2 g of mannitol at pH 9 adjusted by 1N KOH. Extraction with ether (4 × 100 ml) and subsequent crystallization from i-PrOH afforded 852 mg (56.0%) of **9**, m.p. 147–148°. IR (CCl_4): 1683 cm^{-1} (C=O). UV: 208, 236, 281 and 318 nm (log ε 4.42, 4.42, 3.84 and 3.74). NMR: δ 10.62 (s, CHO); 7.50, 7.22 (2s, 2 Ar_AH); 6.92 (s, 2 Ar_CH); 6.17 (s, O CH_2 O), 4.51 (t, J = 7 c/s, ArCHN); 3.95 (s, 2 OMe), 3.06 (d, J = 7 c/s, Ar-CH_2-CH N); 2.30 ppm (s, NCH_3). (Found: C, 67.34; H, 5.93; N, 3.86. Calc. for $C_{20}H_{21}NO_5$: C, 67.58; H, 5.96; N, 3.95%).

Oxime **10** was prepared from the aldehyde **9** (555 mg) and $NH_2OH.HCl$ (131 mg) as described for **2a**. Due to lower acidity of **10**, work-up had to be modified. The residue, after evaporation, was dissolved in CH_2Cl_2, washed several times with dil. NH_4OH. The solvent was evapd and crystalline residue washed with EtOH to give **10** (546 mg, 95%), m.p. 195–197° (EtOH). UV: 217, 273 and 311 nm (log ε 4.35, 3.95, 3.60). NMR (CCl_4 + 10% pyridine-d_5): δ 8.81 (s, ArCH=NOH); 7.29, 6.90 (2s, 2 Ar_AH); 6.57 (s, 2 Ar_CH); 5.81 (s, O CH_2 O); 4.32 (t, ArCHN); 4.11 (broad, $ArCH_2N$ + ArCH CH_2Ar); 3.74, 3.68 (2s, 2 OCH_3); 2.11 ppm (s, NCH_3). (Found: C, 64.87; H, 5.83; N, 7.78. Calc. for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.99; N, 7.56%).

Nitrile **11**. The oxime **10** (557 mg) was refluxed with $POCl_3$ (15 ml) for 5 min. The reagent was evapd *in vacuo* and residue treated with toluene which was also evapd to remove most of reagent. The resin was stirred with dil NH_4OH (50 ml), the product extracted with CH_2Cl_2, the org. soln dried, concentrated to 10 ml, and passed through a layer of alumina (12 g, 5% water). The filtrate yielded uniform **11** (429 mg, 81%), crystallizing from ether, m.p. 141–142° (acetone–cyclohexane). IR: 2222 cm^{-1} (C≡N). UV: 223, 264, 286 and 300 nm (log ε 4.61, 3.86, 3.63 and 3.65). NMR: δ 6.98, 6.89 (2s, 2 Ar_AH); 6.68 (s, 2 Ar_CH); 5.97 (s, O CH_2 O); 4.16, 3.43 (2d, J = 16 cps, Ar CH_2 NMe); 3.79 (s, 2 OMe); 3.37 (t, J = 7 c/s, ArCHN); 2.88 (d, J = 7 c/s, $ArCH_2$ CHN); 2.19 ppm (s, NCH_3). (Found: C, 68.13; H, 5.63; N, 7.70. Calc. for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95%).

Hofmann degradation of nitrile **11**. The nitrile methiodide **12** was obtained as described for **3a** in 95% yield, m.p. 278–280°. IR (KBr): 2223 cm^{-1} (C≡N). (Found: C, 51.00; H, 4.90; N, 5.35. Calc. for $C_{21}H_{23}IN_2O_4$: C, 51.02; H, 4.69; N, 5.67%). Methiodide **12** (351 mg) was treated with a boiling mixture of MeOH (60 ml) and 1N KOH in H_2O (25 ml) for 5 hr. Part of MeOH was distd *in vacuo* until crystallization started. Water was added to separate the two stilbenes **13** and **14**, the latter mixture was collected and washed with water, yield: 243 mg. Chromatography on silica (12 g) with $CHCl_3$–MeOH (9:1) as solvent afforded **13** (132 mg, 51%) and **14** (93 mg, 34%). The former was recrystallized from acetone–cyclohexane, m.p. 96–97°. IR (CCl_4): 2223 cm^{-1} (C≡N). UV: 226 and 337 nm (log ε 4.25 and 4.34). NMR: δ 7.90, 7.37 (2d, J = 16 c/s, CH=CH); 7.67, 7.09 (2d, J = 8 c/s, 2 Ar_CH); 7.40, 7.16 (2s, 2 Ar_AH); 6.19 (s, O CH_2–O); 4.01, 3.94 (2s, 2 OMe); 3.68 (s, Ar-CH_2 N), 2.33 ppm (s, 2 NCH_3). MS: *m/e* 366 (65) M$^+$, 351 (21) CH_3, 322 (100) –$N(CH_3)_2$. (Found: C, 69.05; H, 5.75; N, 7.96. Calc for $C_{21}H_{22}N_2O_4$: C, 68.88; H, 6.05; N, 7.64%).

Amide **14** was recrystd from MeOH, m.p. 203–205°. IR: 1667 (C=O), 3408 + 3528 cm^{-1} (NH). UV: 225 and 326 nm (log ε 4.28 and 4.39). NMR: δ 7.50, 6.97 (2d, J = 8 c/s, 2 Ar_CH); 7.41 (s, CH=CH); 7.22, 7.19 (2s, 2 Ar_AH), 6.37 (broad, NH_2); 6.14 (s, O-CH_2 O), 4.01, 3.95 (2s, 2 OMe); 3.66 (s, Ar CH_2 N); 2.32 ppm (s, 2 NCH_3). MS: *m/e* 384 (66) M$^+$, 369 (100) CH_3, 322 (74), 206 (18), 176 (20). (Found: C, 65.70; H, 6.27; N, 7.33. Calc. for $C_{21}H_{24}N_2O_4$: C, 65.61; H, 6.29; N, 7.29%).

Acknowledgements—Thanks are due to Mrs. H. Menzky for expert technical assistance and Dr W. Schade, Jena, for High Resolution MS.

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