A Novel and Efficient Synthesis of the Aspidosperma Alkaloid Ring System: *N*(a)-Benzyldeethylaspidospermidine[1]

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Nonoxidative photocyclization of the aryl enaminone **3** led to the formation of the hexahydrocarbazol-4-one **4**. Alkylation of the anion derived from **4** with iodoacetamide and dehydration gave the tetracyclic enamide **9**, which was reduced to the imine **10** with $LiAlH_4$. Reaction of the metalated imine **10** with 1-bromo-3-chloropropane afforded the pentacyclic enamine **11**, which was converted into (±)-*N*(a)-benzyldeethylaspidospermidine (**12**) by catalytic hydrogenation. The compound **12** was synthesized in 57% overall yield from *N*-benzylaniline and 1,3-cyclohexanedione.

A great deal of work has been devoted to the synthesis of the aspidosperma alkaloids due to their importance in the preparation of biologically active compounds (e.g., vincamine and vincaleucoblastine).[2-4] Although these alkaloids represent a structurally diverse class of compounds, many possess, as a common structural feature, a hexahydrocarbazole ring system. The chemistry of this tricyclic dihydroindole system has received little or no attention in terms of alkaloid synthesis[5] due to the fact that these molecules rapidly oxidize to their tetrahydro derivatives whose exploitation as synthon for aspidosperma alkaloid synthesis is limited.

Recently we have developed a photochemical approach for the formation of C-4a-substituted carbazol-4-one (see Scheme II, **6** → **7**).[6] If the C-4a-unsubstituted hexahydrocarbazol-4-one could also be prepared by this method, their alkylation at C-4a would allow for an efficient synthesis to aspidospermidine (**1**) or pseudoaspidospermidine (**2**) (Chart I).

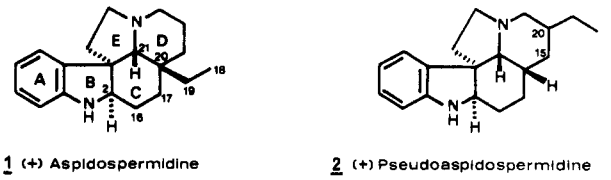
We now describe our preliminary results aimed at a potentially general approach, from a common starting material, for the synthesis of aspidosperma alkaloids.

Results and Discussion

Irradiation of a deoxygenated benzene solution of the aryl enaminone **3**[7] (Scheme I) afforded the hexahydrocarbazol-4-one **4** in nearly quantitative yield. On the basis of our previous results (Scheme II) a trans relationship between H-4a and H-9a was anticipated.[6] The reaction conditions were thus established that prevented the usual oxidation of hexahydrocarbazol-4-one.[8]

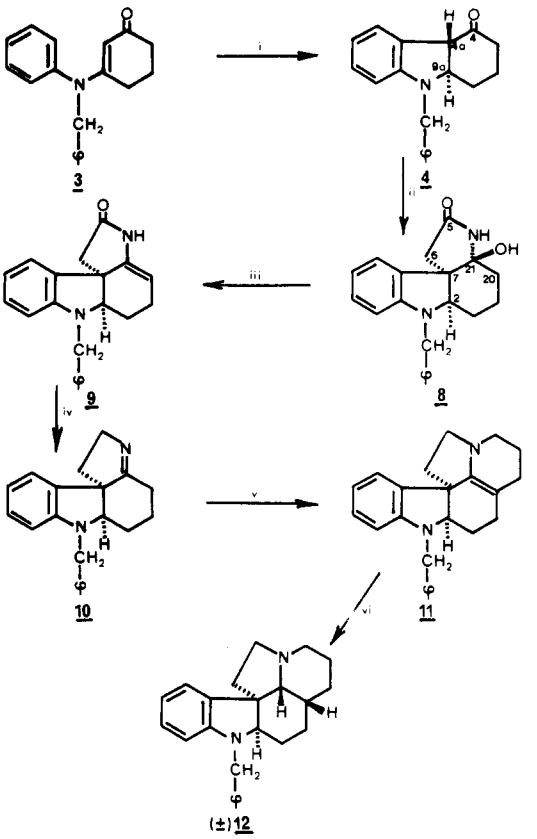
A critical step in our approach was the formation of the thermodynamic enolate of **4** followed by its alkylation with a reagent suitable for the construction of the five-membered ring. By use of standard equilibrating conditions[9] (*t*-BuOK, *t*-BuOH, reflux) the oxidation product, i.e., the tetrahydrocarbazol-4-one, was the only derivative observed. We found that a highly efficient procedure for producing the required enolate was the treatment of **4** with KH in THF.[10] In a model reaction, alkylation of this enolate with CH_3I gave the new *cis*-4a-methylhexahydrocarbazol-4-one **5**[11] in 92% yield. Thus, having in hand the conditions for regio- and stereospecific reaction of the carbazolone **4**, the latter was treated, without further purification after photocyclization, with KH in THF and subsequently alkylated with iodoacetamide. A single cyclized product **8** was obtained in excellent yield (93%). Assignment of structure **8** was inferred from examination of the spectral data. Because the alkylation of **4** with CH_3I was shown

Chart I



1 (+) Aspidospermidine **2** (+) Pseudoaspidospermidine

Scheme I



Reagents: (i) *hν*, argon; (ii) KH, THF, ICH_2CONH_2; (iii) molecular sieves (4 Å), CH_2Cl_2, Δ; (iv) LAH, THF; (v) *t*-BuLi, $Br(CH_2)_3Cl$; (vi) H_2, Pt/Al_2O_3, EtOH, HCl.

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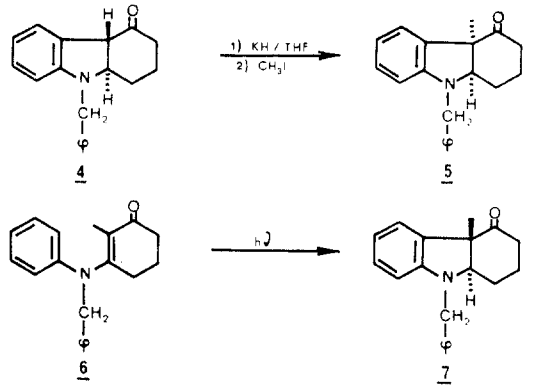
(1) This work was presented as preliminary communication at the "Journées de Chimie Organique de la Société Chimique de France", Palaiseau, September 1984.
(2) For recent developments in indole alkaloid synthesis, see: *Tetrahedron Symposia*-In-Print 1983, *39*(12), 3627.

0022-3263/85/1950-5517$01.50/0

Scheme II



4 5 6 7

to produce a cis B/C ring junction (see above), it was assumed that **8** also possesses a cis B/C ring junction. Thermodynamic considerations led to postulating a cis C/E ring junction.

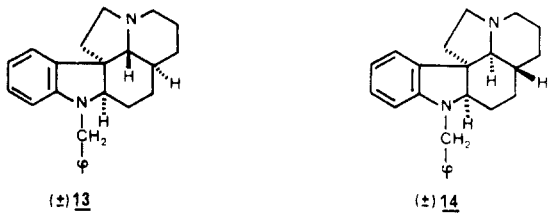
Dehydration of the carbinol amide **8** occurred in CH_2Cl_2 solution in the presence of molecular sieves to give the enamide **9** (yield $\simeq$ 100%). Compound **9**, a stable crystalline derivative, showed strong IR absorptions at 3450, 1720, and 1680 cm^{-1}. The ^1H and ^{13}C NMR spectra of **9** were straightforward. The H-20[12] enamide signal occurred at δ 5.2 (t, J = 3.5 Hz), and the characteristic absorptions for C-20 (δ 102.3) and C-21 (δ 140) were observed.

Selective reduction of the amide function of **9** with $LiAlH_4$ gave the imine **10** (yield = 95%). The structure of this compound was deduced from the disappearance of the carbonyl absorption in the IR and ^{13}C NMR spectra and from observation of an imine function (IR 1650 cm^{-1} and ^{13}C NMR C-21 at δ 178.3).

The method developed by Evans[13] for the synthesis of the tetrahydropyridine ring system appeared to be a particularly attractive strategy for formation of ring D of the aspidosperma skeleton. Indeed, the reaction of the imine **10** with LDA in THF at −78 °C followed by treatment of the resultant anion with 1-bromo-3-chloropropane led to the formation of a single product, **11**, although in poor yield (15%).

However by a modification of Evans' conditions for metalation of **10**, i.e., *t*-BuLi, ether, −20 °C followed by reaction with 1-bromo-3-chloro propane, compound **11** was obtained in nearly quantitative yield. This enamine **11** proved to be very unstable but could be purified by rapid filtration through a short column of silica gel. The fragmentations observed in mass spectrometry are in good agreement with the expected pentacyclic structure.[14] The fragmentation of the ring D following a retro-Diels–Alder mechanism gave a fragment at m/z 314.

Chart II



(±)**13** (±)**14**

It was expected that catalytic hydrogenation of **11** in EtOH would give the required cis D/C ring junction of pseudoaspidosperma alkaloids **2** (Chart I). However, these conditions led to recovery of the starting material. Protonation of **11** (EtOH/HCl) followed by catalytic hydrogenation in the presence of platinum supported on alumina in a Parr apparatus led to the formation of three of the four possible diastereomers. These were readily separated by column chromatography on silica gel.

The major reaction product was identified as the expected *N*(a)-benzyl-20-deethylaspidospermidine (**12**) (yield = 70%). The other two products were identified as its isomers, **13** (yield = 7%) and **14** (yield = 12%), depicted in Chart II.

The position of the H-21 absorption in the 250-MHz ^1H NMR spectrum (δ 2.4) and its negligible coupling ($J \simeq 1$ Hz) with H-20 suggested a cis C/D ring junction. Finally the presence of Bohlmann–Wenkert[15] bands in the IR spectrum was in further agreement with structure **12**, i.e., a *trans*-indolizidine. Comparison of these spectral data with the literature data for 20-deethylaspidospermidine[16] allowed us to conclude that **12** was *N*(a)-benzyl-20-deethylaspidospermidine.

The complete absence of Bohlmann–Wenkert bands in the IR spectrum of **13** (*cis*-indolizidine configuration) and the characteristic coupling of H-21 [δ 2.28 (J = 10 Hz)] gave direct indications that the molecule belonged to the 20-iso series[17] (trans C/D ring junction). Definitive proof for the structure of **13** was obtained by a chemical correlation with 20-deethyl-20-isoaspidospermidine[18] by debenzylation.

The 400-MHz ^1H NMR spectrum of the third product **14** was highly resolved, permitting also the assignment of H-21 signal [δ 1.8 (J = 10 Hz)]. The presence of Bohlmann–Wenkert bands in the IR spectrum supported a *trans*-indolizidine configuration. These data strongly suggested the 21-iso structure as depicted for **14**[19] (Chart II).

(3) "The Monoterpenoid Indole Alkaloids", in: Saxton, J. E., Ed. "Heterocyclic Compounds"; Wiley: New York, 1983; Vol. 25.
(4) For leading references to the syntheses of the aspidosperma nucleus, see: Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35.
(5) Recently a photochemical approach leading to 3-acylindolenines by a photo-Fries rearrangement of 1-acylindoles has been described: Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T. *J. Am. Chem. Soc.* **1981**, *103*, 6990.
(6) Gramain, J. C.; Husson, H.-P.; Troin, Y. *Tetrahedron Lett.* **1985**, *26*, 2323.
(7) Schultz, A. G.; Dittami, J. P.; Myong, S. O.; Sha, C. K. *J. Am. Chem. Soc.* **1983**, *105*, 3273.
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(9) d'Angelo, J. *Tetrahedron* **1976**, *32*, 2979 and references therein cited.
(10) Negishi, E.; Chatterjee, S.; *Tetrahedron Lett.* **1983**, *24*, 1341.
(11) The stereochemistry of **5** was inferred from comparison with the trans epimer obtained by photocyclization of the corresponding aryl enaminone.[6]
(12) C-20 and C-21 positions using the aspidosperma alkaloids numbering which will be used for the synthetic intermediates throughout this paper.
(13) Evans, D. A. *J. Am. Chem. Soc.* **1970**, *92*, 7593.
(14) Biemann, K.; Spiteller-Friedmann, M.; Spiteller, G. *J. Am. Chem. Soc.* **1963**, *85*, 631.
(15) Wenkert, E.; Roychaudhuri, D. K. *J. Am. Chem. Soc.* **1956**, *78*, 6417.
(16) Wenkert, E.; Orito, K.; Simmons, D. P.; Kunesh, N.; Ardisson, J.; Poisson, J. *Tetrahedron* **1983**, *22*, 3719.
(17) For the nomenclature of C-20 and C-21 isomers see ref 18.
(18) Wenkert, E.; Bindra, J. S.; Chauncy, B. *Synth. Commun.* **1972**, *2*, 285.
(19) Several features in the ^1H NMR spectrum of **14** were in agreement with the assigned structure. The H-21 signal (δ 1.8) was observed upfield from the corresponding signals of **12** and **13** whose position are nearly identical (δ 2.4 and 2.28, respectively) despite different stereochemistry of the nitrogen lone pair of electron.[15] Examination of Dreiding models strongly suggests that this difference is probably due to the relative position of H-21 in **12**–**14** with respect to the indole aromatic ring. Related to this interaction was the observation that H-9 aromatic absorption for these epimers was shifted markedly downfield from δ 6.95 (**12**) and 7.2 (**13**) to 7.8 (**14**). This shift could be attributed to the deshielding effect of the N(b) lone pair.

In conclusion, the unprecedented nonoxidative photocyclization of the aryl enaminone **3** to the hexahydrocarbazolone **4** provides an efficient method for the synthesis of the aspidosperma nucleus in 57% overall yield by a seven-step procedure. Work is now in progress to introducing the correct substitution at C-20 position to achieve the total synthesis of a number of alkaloids in the series.

Experimental Section

Infrared spectra (IR) were recorded in solution on a Perkin-Elmer 377 spectrophotometer. Infrared absorption bands are expressed in reciprocal centimeters with polystyrene calibration. Peaks yielding structural information are reported. ^1H nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ (tetramethylsilane as an internal standard, δ 0) on the IEF (Institut d'Electronique Fondamentale, Université de Paris-Sud, Orsay, France) 400-MHz spectrometer, a Brucker WM 250 or a JEOL C60H. Chemical shift data are reported in parts per million downfield from tetramethylsilane, where s, d, dd, t, q, or m designate singlet, doublet, doublet of doublet, triplet, quadruplet, and multiplet, respectively. ^{13}C NMR spectra were recorded in $CDCl_3$ (δ 0, Me_4Si) on a JEOL FX 60 (15.08 MHz) instrument. Low-resolution (70 eV) and high-resolution mass spectrometry was performed on a Varian CH5 instrument.

All melting points were determined on a micro hot stage Reichert apparatus. Reagent grade THF and ether were distilled from sodium–benzophenone prior to use. All the samples used for spectroscopic measurements were obtained by flash chromatography on Merck 40–63-μm silica gel. Irradiations were performed in a Pyrex glass vessel using a medium-pressure mercury lamp (Philips, 400 W). Before irradiation the reaction mixture was flushed with a stream of argon for 10 min in order to remove oxygen. Potassium hydride was carefully washed with hexane before use and dried under argon.

Preparation of Enaminone 3. A mixture of *N*-phenylbenzylamine (5.5 g, 30 mmol), 1,3-cyclohexanedione (3.36 g, 30 mmol), *p*-toluenesulfonic acid (0.050 g), and toluene (100 mL) was refluxed under a Dean–Stark head for 8 h. After neutralization with solid K_2CO_3 the toluene solution was filtered and evaporated under vacuum to give a residue. The crude product was purified by simple filtration through a column of alumina (elution with AcOEt). The enaminone **3**[7] was obtained as a viscous oil (8.10 g, yield = 97%): IR ν_{max} (CCl_4) 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.5–2.1 (m, 2 H), 2.1–2.5 (m, 4 H), 4.7 (s, 2 H), 5.3 (s, 1 H), 6.9–7.5 (10 H); ^{13}C NMR ($CDCl_3$) δ 197.4, 165.0, 144.1, 136.1, 129.4, 128.4, 127.6, 127.5, 127.3, 127.2, 126.6, 101.2, 56.4, 35.8, 28.3, 22.2; MS, exact mass m/z 277.1459 (calcd for $C_{19}H_{19}NO$ m/z 277.1459).

Photocyclization of 3 → 4. A solution of **3** (1.2 g, 4.33 mmol) in benzene (200 mL) was irradiated for 1 h. under an atmosphere of argon. The solvent was then concentrated, and the crude product was purified by flash chromatography on silica gel eluting with hexane–ethyl acetate (8–2). The carbazolone **4** was obtained as a white solid (1.15 g, yield = 95%): mp 165–166 °C (recrystallization from ether); IR ν_{max} (CCl_4) 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.4–2.6 (m, 6 H), 3.4–3.6 (m, 2 H), 4.2 (s, 2 H), 6.3–7.6 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 205.6, 152.6, 138.6, 128.5, 127.9, 127.2, 124.9, 119.5, 108.9, 73.0, 57.6, 52.7, 40.9, 29.4, 23.7; MS, exact mass m/z 277.1466 (calcd for $C_{19}H_{19}NO$ m/z 277.1462).

Preparation of Compound 5. A solution of **4** (0.7 g, 2.53 mmol) in THF (10 mL) was added to a suspension of potassium hydride (35% in oil; 0.304 g, 2.66 mmol) in THF (5 mL) and stirred at room temperature for 5 min under an atmosphere of nitrogen. The resultant medium was then added to a solution of methyl iodide (0.37 g, 2.60 mmol) in THF (20 mL). After the mixture was stirred for an additional 10 min, water was added to the reaction mixture in order to solubilize the precipitate. The majority of THF was distilled, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed with water, dried over sodium sulfate, and concentrated. The crude product was purified by filtration through a column of silica gel (elution with AcOEt). The pure compound **5** (0.66 g, yield = 90%) was obtained as crystals from ether: mp 129–130 °C; IR (CCl_4) ν_{max} 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.4 (s, 3 H), 1.6–2.5 (m, 6 H), 3.7 (m, 1 H), 4.3 (2 H, J_{AB} = 15 Hz, $\Delta\nu$ = 13 Hz), 6.4–7.5 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 212.1, 151.1, 138.3, 131.4, 128.5, 127.0, 124.2, 118.1, 107.5, 72.6, 56.6, 50.3, 38.1, 24.4, 23.1, 19.4; MS, exact mass m/z 291.1615 (calcd for $C_{20}H_{21}NO$ m/z 291.1618).

Preparation of Tetracyclic Compound 8. A solution of **4** (0.6 g, 2.16 mmol) in THF (10 mL) was added to a suspension of potassium hydride (35% in oil; 0.248 g, 2.25 mmol) in THF (5 mL) and stirred at room temperature for 5 min under an atmosphere of nitrogen. The resultant medium was then added to a solution of iodoacetamide (0.41 g, 2.21 mmol) in THF (20 mL). After the mixture was stirred for an additional 10 min, water was added to the reaction mixture in order to solubilize the precipitate. The majority of THF was distilled, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed with water, dried over sodium sulfate, and concentrated. The crude product was purified by filtration through a column of silica gel (elution with AcOEt).

Compound **8** (0.67 g, yield = 93%) was obtained as a white solid: mp 131–132 °C (recrystallization from ether); IR ($CHCl_3$) ν_{max} 3540 (OH), 3420 (NH), 1700 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.1–2.0 (m, 7 H), 2.7 (s, 2 H), 3.35 (m, 1 H), 3.4 (m, 1 H, exchangeable with D_2O), 4.3 (2 H, J_{AB} = 15 Hz, $\Delta\nu$ = 21.5 Hz), 6.4–7.5 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 175.8, 152.5, 138.3, 129.4, 129.0, 128.7, 124.7, 118.8, 108.4, 88.7, 69.1, 53.7, 50.3, 42.1, 34.9, 23.4, 17.5; MS, m/z (relative intensity) 334 (2), 316 (25), 225 (25), 185 (55), 142 (25), 127 (20), 91 (5), 58 (100), exact mass m/z 334.1682 (calcd for $C_{21}H_{22}N_2O_2$ m/z 334.1681).

Preparation of Enamide 9. (±)-10-Camphorsulfonic acid (0.010 g) was added to a solution of **8** (0.4 g, 1.2 mmol) in CH_2Cl_2 (50 mL). The resultant solution was refluxed in the presence of molecular sieves (4 Å) for 8 h. The reaction mixture was then neutralized at room temperature with anhydrous K_2CO_3. After filtration and concentration of the organic phase compound **9** (0.375 g) was purified by crystallization from ether: mp 184–185 °C; IR ($CHCl_3$) ν_{max} 3450 (NH), 1695–1720 cm^{-1} (enamide); ^1H NMR ($CDCl_3$, 60 MHz) δ 1.3–2.3 (m, 2 H), 2.6 (s, 2 H) 3.8 (m, 1 H), 4.3 (2 H, J_{AB} = 16.5 Hz, $\Delta\nu$ = 10.5 Hz), 5.2 (t, 1 H, J = 3.5 Hz), 6.2–7.4 (m, 9 H), 9.1 (s, 1 H, exchangeable with D_2O, NH); ^{13}C NMR ($CDCl_3$) 175.2, 150.3, 140.4, 138.6, 134.6, 128.6, 127.5, 127.2, 121.7, 117.7, 106.7, 102.3, 67.2, 50.3, 49.8, 47.0, 26.4, 19.4; MS, exact mass m/z 316.1575 (calcd for $C_{21}H_{20}N_2O$ m/z 316.1576).

Preparation of Imine 10. A solution of crude enamide **9** (0.4 g, 1.26 mmol) in THF (20 mL) was added to a suspension of $LiAlH_4$ (0.15 g, 3.78 mmol) in THF (10 mL). The resultant mixture was then refluxed for 7 h. After addition of water (1 mL) and filtration of inorganic salts, the filtrate was concentrated to give a crude product, which was purified by filtration through a column of silica gel (elution with AcOEt). The pure imine **10** (0.36 g, yield = 95%) was obtained as crystals from hexane: mp 132–133 °C; IR (CCl_4) ν_{max} 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.1–2.8 (m, 8 H), 3.5 (m, 1 H), 3.7–4.1 (m, 2 H), 4.3 (2 H, J_{AB} = 15 Hz, $\Delta\nu$ = 16 Hz), 6.3–7.6 (m, 9 H); ^{13}C NMR ($CDCl_3$) 178.3, 149.2, 138.2, 132.0, 128.5, 127.4, 127.1, 126.8, 122.2, 117.6, 107.4, 72.2, 61.3, 57.1, 48.9, 40.9, 29.4, 25.4, 20.9; MS, exact mass m/z 302.1776 (calcd for $C_{21}H_{22}N_2$ m/z 302.1778).

Preparation of Enamine 11. A pentane solution of *t*-BuLi (0.93 mmol) was added to a solution of imine **10** (0.13 g, 0.43 mmol) in anhydrous ether (100 mL) at −20 °C under an atmosphere of argon. The mixture was stirred for 1 h at −20 °C and cooled at −70 °C before addition of 1-bromo-3-chloropropane (0.068 g, 0.43 mmol) in ether (2 mL). The resultant solution was warmed to room temperature over 30 min and stirred for 12 h. The solvent was then evaporated, and normal extraction with CH_2Cl_2 gave nearly pure enamine **11** as an amorphous solid (0.145 g, yield ~ 100%): IR (CCl_4) ν_{max} 1640, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2–2.3 (m, 10 H), 3.3–4.6 (m, 7 H), 6.3–7.5 (m, 9 H); MS, m/z (relative intensity) 342 (44), 314 (2) 313 (3), 251 (44), 234 (12), 223 (9), 160 (11), 91 (100).

Catalytic Hydrogenation of 11: (±)-*N*(a)-Benzyl-20-deethylaspidospermidine (12) + 13 and 14. Enamine **11** (0.1 g, 0.29 mmol) in ethanol (10 mL) acidified to pH 4 with aqueous HCl was hydrogenated for 40 h, at 40 psi (Parr apparatus) and room temperature by using 5% platinum on alumina (50 mg) as catalyst. The reaction mixture was then neutralized with anhydrous K_2CO_3 and filtered through a Celite bed and concentrated

to give a residue, which was purified by flash chromatography on silica gel eluting with $CHCl_3$–CH_3OH (95:5).

The *first fraction* gave compound **14** (yield = 12%) as an amorphous solid: IR (CCl_4) ν_{max} 2860, 2840, and 2760 (Bohlmann–Wenkert bands), 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.95 (m, 1 H), 1.0–2.1 (m, 8 H), 2.3 (m, 1 H), 3.3 (m, 2 H), 3.5 (dd, 1 H, J = 6 and 9 Hz), 4.3 (2 H, J_{AB} = 15 Hz, $\Delta\nu$ = 115 Hz), 6.4 (d, 1 H, J = 8 Hz), 6.8 (t, 1 H, J = 8 Hz), 7.1 (t, 1 H, J = 8 Hz), 7.2–7.5 (m, 5 H), 7.8 (d, 1 H, J = 8 Hz); ^{13}C NMR ($CDCl_3$) 150.7, 139.8, 130.9, 127.2, 125.6, 117.8, 107.9, 72.8, 68.5, 54.5, 51.4, 49.2, 37.7, 34.0, 30.4, 29.8, 26.2, 25.9; MS, m/z (relative intensity) 344 (76), 316 (20), 253 (6), 234 (12), 220 (20), 124 (10), 96 (100), 91 (72).

The *second fraction* gave compound **12** (yield = 70%) as an amorphous solid: IR (CCl_4) 2860, 2790, and 2730 (Bohlmann–Wenkert bands), 1605 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.9–2.0 (m, 11 H), 2.0–2.35 (m, 2 H), 2.4 (d, 1 H, J = 1.25 Hz), 3.0–3.2 (m, 2 H), 3.35 (dd, 1 H, J = 5 Hz, J' = 10 Hz), 4.25 (2 H, J_{AB} = 15 Hz, $\Delta\nu$ = 68 Hz), 6.35 (d, 1 H, J = 8 Hz), 6.7 (t, 1 H, J = 8 Hz), 6.95 (d and t, 2 H, J = 8 Hz), 7.2–7.5 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 151.0, 138.8, 135.5, 127.1, 121.9, 117.6, 106.9, 70.0, 68.1, 54.4, 53.9, 52.7, 48.9, 38.4, 32.3, 29.5, 25.4, 22.0, 21.3; MS, m/z (relative intensity) 344 (83), 316 (5), 277 (10), 253 (8), 234 (6), 220 (11), 162 (17), 124 (12), 96 (100), 91 (41), exact mass m/z 344.2269 (calcd for $C_{24}H_{28}N_2$ m/z 344.2259).

The *third fraction* gave compound **13** (yield = 7%) as an amorphous solid: IR (CCl_4) [no Bohlmann–Wenkert bands] 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.9–1.9 (m, 9 H), 1.9–2.25 (m, 2 H), 2.28 (d, 1 H, J = 10 Hz), 2.8–3.2 (m, 4 H), 3.45 (dd, 1 H, J = 2 Hz, J' = 4 Hz), 4.20 (2 H, J_{AB} = 16 Hz, $\Delta\nu$ = 70 Hz), 6.35 (d, 1 H, J = 8 Hz), 6.70 (t, 1 H, J = 8 Hz), 6.95 (t, 1 H, J = 8 Hz), 7.2 (d, 1 H, J = 8 Hz), 7.2–7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$) 151.1, 139.8, 126.9, 123.5, 118.5, 107.6, 71.3, 69.5, 52.9, 52.3, 48.1, 46.4, 33.4, 33.3, 31.6, 26.0, 25.2, 21.0; MS, m/z (relative intensity) 344 (34), 316 (4), 220 (4), 162 (3), 124 (4), 96 (100), 91 (22), exact mass m/z 344.2259 (calcd for $C_{24}H_{28}N_2$ m/z 344.2259).

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Oxidation of 1-Aminopyrazoles and Synthesis of 1,2,3-Triazines

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Unsubstituted and various substituted monocyclic 1,2,3-triazines were synthesized from 1-aminopyrazoles by oxidation with lead tetraacetate, lead dioxide–CF_3CO_2H, and/or nickel peroxide–AcOH.

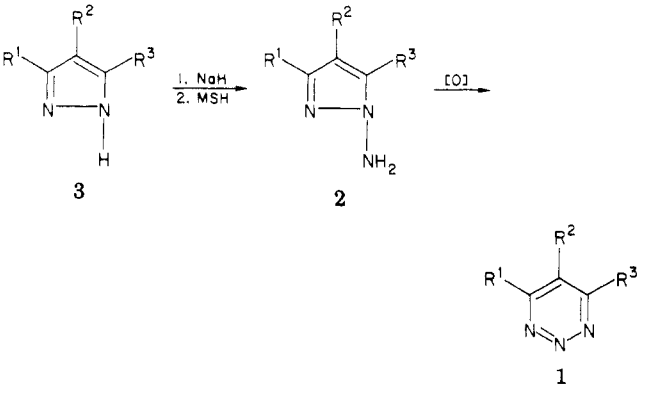
In previous papers,[1,2] we have dealt briefly with the syntheses of unsubstituted[1] and substituted[2] monocyclic 1,2,3-triazines (**1**) by oxidation of *N*-aminopyrazoles (**2**). This paper describes detailed data and additional findings concerning the synthesis of the triazines **1**.

In earlier 1,2,3-triazine synthesis, the substituents on the triazine rings have been mostly limited to be $R^1 = R^2 = R^3$ = alkyl, aryl, or halogen, and this depends on the availability and stability of cyclopropenyl compounds as the synthetic intermediates.[3]

Results and Discussion

We found that alkyl- and/or phenyl-substituted 1,2,3-triazines (**1a–h**) could be synthesized from *N*-aminopyrazoles by oxidation. Unexpectedly, N-amination of pyrazoles **3** did not proceed by Rees and Storr's method[4] using hydroxylamine-*O*-sulfonic acid or chloramine with which N-amination of indazoles has successfully carried out. However, the 1-aminopyrazoles were obtained in medium to high yields from appropriate pyrazoles through a deprotonation by sodium hydride followed by amination using (*O*-mesitylenesulfonyl)hydroxylamine (MSH).[5] The

Scheme I



3 2 1

a, $R^1 = R^2 = R^3 = H$
b, R^1 = Me, $R^2 = R^3 = H$
b', $R^1 = R^2 = H$, R^3 = Me
c, $R^1 = R^3 = H$, R^2 = Me
d, $R^1 = R^3$ = Me, $R^2 = H$
e, $R^1 = R^2 = R^3$ = Me
f, R^1 = Ph, $R^2 = R^3 = H$
f', $R^1 = R^2 = H$, R^3 = Ph
g, R^1 = Ph, $R^2 = H$, R^3 = Me
g', R^1 = Me, $R^2 = H$, R^3 = Ph
h, $R^1 = R^3$ = Ph, $R^2 = H$

yields and some properties of **2** are shown in Table I.

In the N-amination of asymmetrical pyrazoles, a mixture of the isomeric 1-aminopyrazoles due to the positions of the N-amination was obtained. In cases of **2f** and **2f'**, and **2g** and **2g'**, their separations were possible, although their respective distinctions were not accomplished. The ratio **2b**/**2b'** in the product mixture from **3b** was shown to be

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