thus demonstrated in this always up-to-date field of nucleophilic substitution.[21]

Experimental Section

The preparation of the *p*-OMe-substituted derivatives and the techniques for identifying products and measuring rates have already been described.[6] The same procedures are used here.

Products. 1,2-Dichloro-3-arylpropanes 2c and 1,3-Dichloro-2-arylpropanes 3c. The mixture of **2c** and **3c** dichlorides obtained by the action of chlorine on $XC_6H_4CH_2CH{=}CH_2$ (K & K) contains 18% and 27% of **3c** for X = H and X = *p*-Me, respectively (50% for X = *p*-OMe).[6]

1-Bromo-3-chloro-2-arylpropanes 3b. Of the bromo chlorides obtained by the action of a mixture of bromine and chlorine on $XC_6H_4CH_2CH{=}CH_2$, **3b** represents 22% and 45% for X = H and X = *p*-Me, respectively (50% for X = *p*-OMe).[6]

2-Bromo-1-chloro-3-arylpropanes 2d. The procedure given for **2d**-OMe is used.[6] The amount of bromo chloride **2d** in the crude product is the same (86%) whatever the aromatic substituent.

1,2-Dibromo-3-phenylpropane (2a-H). To 3-phenylpropene (0.1 mol) in $CHCl_3$ (50 mL) is added bromine (0.1 mol) in the same solvent (25 mL). After the crude product is washed with a $NaHCO_3$ solution and dried on $MgSO_4$ and the solvent evaporated, the crude product, which contains 95% 1,2-dibromo-3-phenylpropane, is purified by GLC.

Kinetic Studies. For unreactive compounds, sealed tubes containing substrate (4 μL), $SnCl_4$ (200 μL), and a reference substance are suspended in a steam bath for the appropriate time. Because of the slow rate of reaction of **2d**-H, product formation for this compound was only followed up to 60% conversion. The equilibrium mixture of **3c**-H and **2c**-H in $SnCl_4$ was obtained from each dichloride by heating, first for 90 h at 161 °C, then for 80 days at 100 °C. The formation of **3b** in the reaction of **2d** with $SnCl_4$ was determined by GLC on a Varian 1400 chromatograph (0.125 in. × 10 ft column packed with 10% DEGS on Chromosorb).

Supplementary Material Available: Derivation of rate constants $k_{3b\rightarrow 2d}$, $k_{3b\rightarrow 3c}$, and $k_{2d\rightarrow 3b}$ and eq 4 (5 pages). Ordering information is given on any current masthead page.

(21) (a) Allen, A. D.; Kanagasabapathy, V. M.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 4513. (b) Paradisi, C.; Bunnett, J. F. *J. Am. Chem. Soc.* **1985**, *107*, 8223.

Functionalized 2-Azabicyclo[3.3.1]nonanes. 6.[1] Studies Directed to the Synthesis of Pentacyclic *Strychnos* Indole Alkaloids[2]

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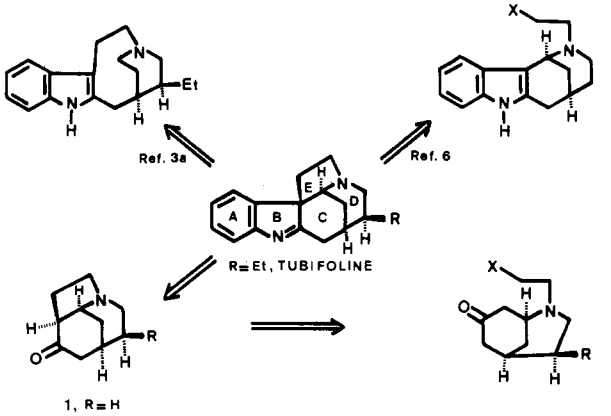
A new synthetic entry to the pentacyclic ring system of *Strychnos* indole alkaloids, based on the elaboration of the indolenine ring by Fischer indole synthesis in the last step, is investigated. The required tricyclic amino ketone **1** was prepared from N-(hydroxyethyl) ketone **2g** by closure of the five-membered ring by treatment with mesyl chloride and further base-catalyzed cyclization. In turn, morphan **2g** was obtained through a new method for the synthesis of 2-azabicyclo[3.3.1]nonan-7-ones, consisting in the oxidative cyclization of 4-piperidineacetoacetates **4**. Unfortunately, indolization of unsymmetrical ketone **1** afforded the unnatural regioisomer **11** instead of the *Strychnos*-type indolenine **12**.

Pentacyclic *Strychnos* indole alkaloids, exemplified by tubifoline, possess a characteristic 4-azatricyclo-[5.2.2.$0^{4,8}$]undecane ring system fused to the indole nucleus. These alkaloids have been synthesized by means of a common strategy based on the elaboration of a tetracyclic stemmadenine-type system followed by its transanular cyclization through an iminium salt.[3,4] In our search to new and general synthetic entries to pentacyclic *Strychnos* alkaloids,[5] we recently reported[6] an alternative route for the elaboration of the ring skeleton of these alkaloids consisting in the closure of the five-membered E ring by cyclization upon the indole 3-position from an appropriately N-substituted 1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole system.



With the same synthetic goal, we decided to explore another synthetic alternative to the *Strychnos* alkaloids based on the elaboration of the indolenine moiety in the

(1) For part 5 in this series, see: Bosch, J.; Casamitjana, N.; Bonjoch, J.; Rubiralta, M. *An. Quím.* **1987**, *83C*, 000.

(2) Presented in part at the 4th European Symposium on Organic Chemistry, Aix-en-Provence, France, 1985.

(3) (a) Schumann, D.; Schmid, H. *Helv. Chim. Acta* **1963**, *46*, 1996. (b) Harley-Mason, J. *Pure Appl. Chem.* **1975**, *41*, 167 and references cited therein. (c) Wu, A.; Snieckus, V. *Tetrahedron Lett.* **1975**, 2057. (d) Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T. *J. Am. Chem. Soc.* **1981**, *103*, 6990. (e) Takano, S.; Hirama, M.; Ogasawara, K. *Tetrahedron Lett.* **1982**, *23*, 881. (f) Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T.; Takeda, E. *Tetrahedron* **1983**, *39*, 3657.

(4) (a) A different approach was used in a synthesis of geissoschizoline, which constituted the first synthesis of a pentacyclic *Strychnos* indole alkaloid: Van Tamelen, E. E.; Dolby, L. J.; Lawton, R. G. *Tetrahedron Lett.* **1960**, 30. (b) For a recent unsuccessful approach, see: Overman, L. E.; Angle, S. R. *J. Org. Chem.* **1985**, *50*, 4021.

(5) (a) Feliz, M.; Bosch, J.; Mauleón, D.; Amat, M.; Domingo, A. *J. Org. Chem.* **1982**, *47*, 2435. (b) Bosch, J.; Rubiralta, M.; Domingo, A.; Bolós, J.; Linares, A.; Minguillón, C.; Amat, M.; Bonjoch, J. *J. Org. Chem.* **1985**, 50, 1516. (c) Bosch, J.; Amat, M.; Sanfeliu, E.; Miranda, M.-A. *Tetrahedron* **1985**, *41*, 2557.

(6) Bosch, J.; Amat, M. *Tetrahedron Lett.* **1985**, *26*, 4951.

0022-3263/87/1952-0267$01.50/0

Table I. ^{13}C NMR Chemical Shifts[a,b] of 2-Azabicyclo[3.3.1]nonan-7-ones

	compd (R =)						
	2a	2b	2d	2e	2g	2h ($COCH_2Cl$)	
carbon	(CH_3)	($CH_2C_6H_5$)	(H)	($CH_2CH_2OCH_2C_6H_5$)	(CH_2CH_2OH)	Z	E
1	55.9	53.9	49.4	54.8	55.4	46.2	51.3
3	46.5	44.7	38.0	46.2	43.8	39.7	35.1
4	31.1	31.1	31.9	31.0	31.1	30.9	30.3
5	28.0	28.7	28.9	28.4	28.4	28.3	28.2
6	47.0	47.1	41.7	41.7	47.0	46.3	46.6
7	212.2	211.5	211.2	211.3	211.1	209.8	208.6
8	39.2	40.1	48.5	40.3	41.0	45.8	46.2
9	33.1	33.0	32.7	32.8	32.9	31.2	32.1
Cα-N	43.1	59.5[c]		54.9	56.6	165.4	164.9
CH_2X				68.4[d]	57.7	41.4	41.0

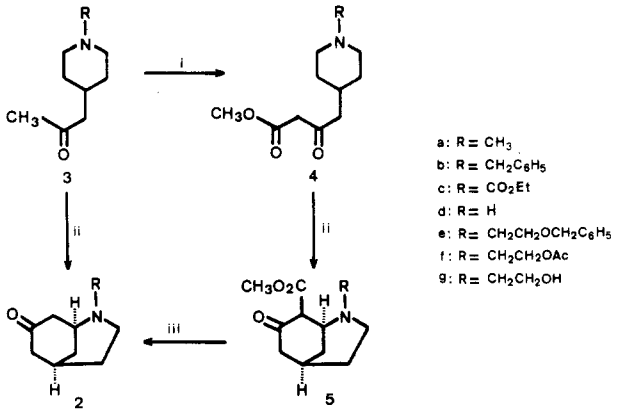
[a] In ppm relative to Me_4Si. Measured in $CDCl_3$ solution at 50.3 MHz. [b] The assignments are in agreement with off-resonance spectra. [c] Phenyl ring carbons were found at δ 126.9 (p-C); 128.2, 128.6 (m- and o-C); 138.8 (ipso-C). [d] Benzyl group: δ 73.0 (CH_2); 127.6 (p-C); 127.6, 128.3 (m- and o-C); 138.4 (ipso-C).

last synthetic step by Fischer indole synthesis from a polycyclic ketone having the appropriate functionalization and stereochemistry. A similar methodology has been used for the synthesis of *Aspidosperma*[7] and *Iboga*[8] alkaloids.[9] Accordingly, 4-azatricyclo[5.2.2.0^{4,8}]undecan-11-one (1), which possesses rings C, D, and E of *Strychnos* alkaloids, was chosen as the key intermediate since it was expected that further indolization would give rise to the pentacyclic framework of these alkaloids.

Results and Discussion

Synthesis of 2-Azabicyclo[3.3.1]nonan-7-ones. Our synthetic approach to azatricyclo 1 implies the intramolecular alkylation of a suitably 2-substituted 2-azabicyclo[3.3.1]nonan-7-one. In contrast to the preparation of the 2-azabicyclo[3.3.1]nonan-8-one ring system, for which many routes have been described,[10] only two syntheses in the 7-oxo series had been reported[11] at the beginning of our studies,[12] and both utilize 3,5-dihydroxyphenylacetic acid as starting material and the intramolecular addition of an amino group upon an α,β-unsaturated ketone as the last step.[13] Thus, initially we planned to examine a direct and potentially broader approach to the 2-azabicyclo-[3.3.1]nonan-7-one system involving the oxidative cyclization of a 4-acetonylpiperidine derivative.

Scheme I. Synthesis of 2-Azabicyclo[3.3.1]nonan-7-ones[a]



[a] Reagents: (i) Me_2CO_3, NaH, Et_2O or THF, reflux; (ii) $Hg(AcO)_2$, H_2O, reflux; then H_2S; (iii) aq HCl, reflux.

In a previous paper[12] we described the preparation of morphans **2a** and **2b** by mercuric acetate oxidation of 4-acetonylpiperidines **3a** and **3b**, respectively.[14] The process implies an intramolecular cyclization between an iminium salt[15] and the α-position of a ketone group. In order to improve this cyclization we intended to operate from 4-piperidineacetoacetates **4a** and **4b** (Scheme I), in which the nucleophile carbon atom is activated by two electron-withdrawing functions. To our knowledge there are no precedents for cyclizations of β-keto esters upon iminium salts generated by mercuric acetate oxidation of amines. The required β-keto esters **4a** and **4b** were obtained by methoxycarbonylation[16] of the corresponding ketones **3a** and **3b** which, in turn, were prepared as previously described[12] from the appropriate N-substituted 4-piperidinone by Wadsworth–Emmons condensation with diethyl (2-oxopropyl)phosphonate followed by catalytic

(7) (a) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872. (b) Ban, Y.; Sato, Y.; Inoue, I.; Nagai, M.; Oishi, T.; Terashima, M.; Yonemitsu, O.; Kanaoka, Y. *Tetrahedron Lett.* **1965**, 2261. (c) Ban, Y.; Iijima, I. *Tetrahedron Lett.* **1969**, 2523. (d) Inoue, I.; Ban, Y. *J. Chem. Soc. C* **1970**, 602. (e) Klioze, S. S.; Darmory, F. P. *J. Org. Chem.* **1975**, *40*, 1588. (f) Lawton, G.; Saxton, J. E.; Smith, A. J. *Tetrahedron* **1977**, *33*, 1641. (g) Pearson, A. J.; Rees, D. C. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2467.

(8) (a) Sallay, S. I. *J. Am. Chem. Soc.* **1967**, *89*, 6762. (b) Ikezaki, M.; Wakamatsu, T.; Ban, Y. *J. Chem. Soc., Chem. Commun.* **1969**, 88. (c) Augustine, R. L.; Pierson, W. G. *J. Org. Chem.* **1969**, *34*, 1070.

(9) For other examples in alkaloid synthesis, see: (a) Langlois, Y.; Langlois, N.; Potier, P. *Tetrahedron Lett.* **1975**, 955. (b) Kökösi, J.; Hermecz, I.; Szász, G.; Mészáros, Z. *Tetrahedron Lett.* **1981**, *22*, 4861. (c) Cloudsdale, I. S.; Kluge, A. F.; McClure, N. L. *J. Org. Chem.* **1982**, *47*, 919. (d) Haeflinger, W. E. *Helv. Chim. Acta* **1984**, *67*, 1942. (e) Smith, A. B., III; Mewshaw, R. *J. Am. Chem. Soc.* **1985**, *107*, 1769.

(10) (a) For a review on the synthesis of 2-azabicyclo[3.3.1]nonanes (morphans), see: Bosch, J.; Bonjoch, J. *Heterocycles* **1980**, *14*, 505. (b) See also: Katsuura, K.; Mitsuhashi, K. *Chem. Pharm. Bull.* **1983**, *31*, 2094. (c) For more recent syntheses of 6-oxo derivatives, see: Bosch, J.; Bonjoch, J. *J. Org. Chem.* **1981**, *46*, 1538. Boger, D. L.; Patel, M.; Mullican, M. D. *Tetrahedron Lett.* **1982**, *23*, 4559.

(11) (a) Mokotoff, M.; Cavestri, R. C. *J. Org. Chem.* **1974**, *39*, 409. (b) Adachi, J.; Nomura, K.; Mitsuhashi, K. *Chem. Pharm. Bull.* **1976**, *24*, 85.

(12) Bonjoch, J.; Casamitjana, N.; Bosch, J. *Tetrahedron* **1982**, *38*, 2883.

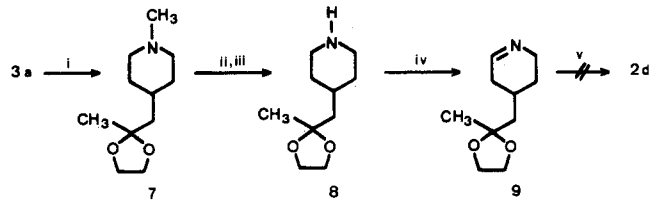
(13) In a recent synthesis of an oxide-bridged 5-phenylmorphan, an intermediate 2-azabicyclo[3.3.1]nonan-7-one was prepared by using the same ring closure: Burke, T. R., Jr.; Jacobson, A. E.; Rice, K. C.; Silverton, J. V. *J. Org. Chem.* **1984**, *49*, 1051.

(14) (a) Related cyclizations with a methyl ketone group as nucleophile, leading either to fused[14b,c] or to bridged[14d] systems, have been reported: (b) Openshaw, H. T.; Whittaker, N. *J. Chem. Soc.* **1963**, 1449. (c) Schneider, W.; Dechow, H. J. *Arch. Pharm.* **1966**, *299*, 279. (d) Noguchi, K.; Takeda, M.; Nurimoto, S. *Chem. Pharm. Bull.* **1977**, *25*, 890.

(15) For other procedures leading to bridged β-amino ketones through iminium salts, see: (a) By Mannich reaction: Findlay, S. P. *J. Org. Chem.* **1957**, *22*, 1385. Petersen, J. S.; Töteberg-Kaulen, S.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 2948. (b) By decarbonylation of α-amino acids: Bates, H. A.; Rapoport, H. *J. Am. Chem. Soc.* **1979**, *101*, 1259. Petersen, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539. (c) From α-amino nitriles: Gnecco Medina, D. H.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1983**, *24*, 2099.

(16) (a) Krapcho, A. P.; Diamanti, J.; Cayen, C.; Bingham, R. *Org. Synth.* **1967**, *47*, 20. (b) LaLonde, R. T.; Muhammad, N.; Wong, C. F. *J. Org. Chem.* **1977**, *42*, 2113.

Scheme II[a]



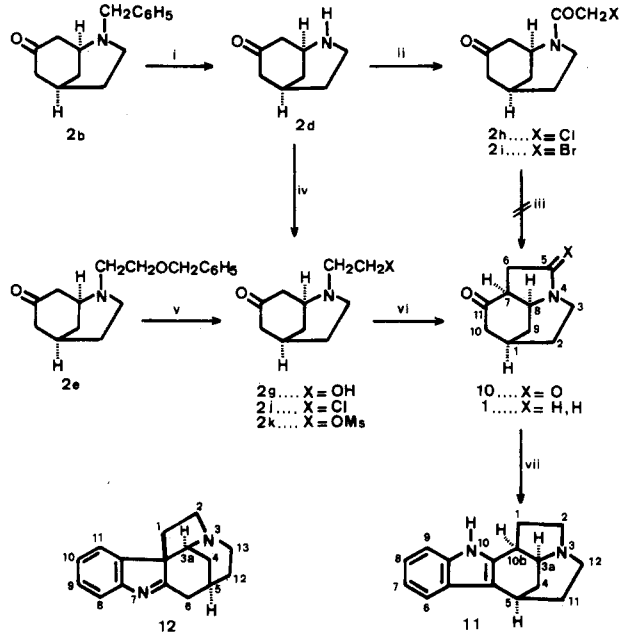
[a] Reagents: (i) $(CH_2OH)_2$, *p*-TsOH–C_6H_6 or Me_3SiCl–CH_2Cl_2; (ii) $ClCO_2Et$, C_6H_6, reflux; (iii) KOH, EtOH, reflux; (iv) NCS, Et_2O; then KOH–EtOH; (v) see ref 26.

hydrogenation of the resultant adduct.[17] Treatment of 4-piperidineacetoacetates **4a** and **4b** with mercuric acetate in aqueous solution at reflux temperature, followed by removal of the excess oxidizing reagent with hydrogen sulfide and hydrolysis (and decarboxylation) with dilute hydrochloric acid, furnished pure azabicyclic ketones **2a** or **2b** in 35% yield. The method appears to be better than the direct oxidative cyclization of 4-acetonylpiperidines[12] due to the slightly higher overall yield and, more important, to the higher purity of the azabicyclo derivatives obtained in this way.[18] When the final hydrolytic treatment was omitted, the corresponding β-keto esters **5a** and **5b** were isolated. They appeared to be mainly enolic, as cyclic β-keto esters normally are,[19] unlike acyclic ones[20] such as **4a** and **4b**.

Our next goal was to convert azabicyclic compounds **2a** or **2b** into N-unsubstituted derivative **2d** in order to introduce later the two-carbon chain necessary for the elaboration of the five-membered ring. However, N-demethylation of azabicyclo **2a** failed. Thus, reaction of **2a** with ethyl chloroformate in refluxing benzene afforded α,β-unsaturated ketone **6**,[21] coming from a retro-Michael reaction, instead of the desired carbamate **2c**. On the contrary, hydrogenolysis of N-benzyl derivative **2b** afforded in excellent yield the secondary amine **2d** (Scheme III), which proved to be moderately unstable.[22] In its ^{13}C NMR spectrum, as compared with those of *N*-alkyl-2-azabicyclo[3.3.1]nonan-7-ones (see Table I), are noteworthy the upfield shift of the signals corresponding to carbons 1 and 3, α to nitrogen, and the downfield shift[23] of the signal due to carbon 8.

At this point, it is worth commenting upon the attempts to prepare azabicyclo **2d** by direct acidic cyclization of imino ketal **9**. Although to our knowledge there are no precedents of intramolecular reactions between Δ^1-piperideines and active methylene groups, the intermolecular version of this process has received considerable attention.[24] On the other hand, it is well-known that, under acidic conditions, ketal α-positions can act as nucleophilic centers upon iminium salts.[25] However, cyclization[26] of imine **9**, which was obtained as a trimer[27] (see Experimental Section) from piperidine **3a** through the reaction sequence depicted in Scheme II,[28] failed.

Scheme III[a]



[a] Reagents: (i) H_2, Pd–C, HCl–EtOH; (ii) $XCOCH_2X$, Et_3N; (iii) see ref 33; (iv) ICH_2CH_2OH, K_2CO_3, Me_2CO; (v) BF_3·Et_2O, Me_2S, CH_2Cl_2; (vi) from **2g**: MsCl, Et_3N, THF, −20 °C; then *t*-BuOK, −20 °C → room temperature; (vii) $C_6H_5NHNH_2$, reflux; then glacial AcOH or HCOOH, reflux.

Synthesis of Azatricyclo 1. Initially, closure of the pyrrolidine ring present in azatricyclo **1** was intended by base-catalyzed cyclization of *N*-chloroacetyl derivative **2h**, in a similar way to that described in the *Aspidosperma* series.[7]

The required chloroacetamide **2h** was obtained in excellent yield by acylation of **2d**·HCl with chloroacetyl chloride in the presence of triethylamine (Scheme III) and shown to be a mixture of two rotamers due to restricted rotation of the amide group.[29] The two rotamers were assignable both in ^1H (see Experimental Section) and in the ^{13}C NMR spectra[30] (see Table I) on the basis of the multiplicity and chemical shift of signals corresponding to methine and methylene groups adjacent to nitrogen of the chloroacetamide group.[31,32] However, when chloro-

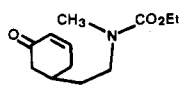
(17) For other procedures to elaborate an acetoacetate side chain from cyclic ketones, see: (a) Bodalski, R.; Pietrusiewicz, K. M.; Monkiewicz, J.; Koszuk, J. *Tetrahedron Lett.* **1980**, *21*, 2287. (b) Van den Goorbergh, J. A. M.; Van der Gen, A. *Recl. Trav. Chim. Pays-Bas* **1984**, *103*, 90 and earlier papers in this series. (c) Corbel, B.; Medinger, L.; Haelters, J.-P.; Sturtz, G. *Synthesis* **1985**, 1048.

(18) Direct cyclization of 4-acetonylpiperidines **3a** and **3b**, as well as of **3e** and **3f**, led to mixtures of the corresponding azabicyclic ketones and the starting piperidines, whose separation proved to be difficult.

(19) Rhoads, S. J. *J. Org. Chem.* **1966**, *31*, 171.

(20) Burdett, J. L.; Rogers, M. T. *J. Am. Chem. Soc.* **1964**, *86*, 2105.

(21) **6**: IR (NaCl) 1685 cm^{-1}; ^1H NMR δ 1.2 (t, 3 H), 1.0–2.6 (m, 7 H), 2.83 (s, 3 H), 3.30 (t, 2 H), 4.06 (q, 2 H), 5.96 (d, 1 H), 6.7–7.1 (m, 1 H).



6

(22) The unstability of secondary β-amino ketones has been previously observed: see ref 11b and 13.

(23) For a related observation in *N*-demethylmorphine derivatives, see: (a) Terui, Y.; Tori, K.; Maeda, S.; Sawa, Y. K. *Tetrahedron Lett.* **1975**, 2853. (b) Casy, A. F.; Ogundaini, A. O.; Parfitt, R. T. *Org. Magn. Reson.* **1982**, *20*, 254.

(24) See inter alia: (a) Bender, D. R.; Bjeldanes, L. F.; Knapp, D. R.; Rapoport, H. *J. Org. Chem.* **1975**, *40*, 1264. (b) Grisar, J. M.; Claxton, G. P.; Stewart, K. T.; MacKenzie, R. D.; Kariya, T. *J. Med. Chem.* **1976**, *19*, 1195. (c) Quick, J.; Oterson, R. *Synthesis* **1976**, 745. (d) Fukawa, H.; Terao, Y.; Achiwa, K.; Sekiya, M. *Chem. Pharm. Bull.* **1983**, *31*, 94.

(25) Bosch, J.; Rubiralta, M.; Moral, M.; Valls, M. *J. Heterocycl. Chem.* **1983**, *20*, 595 and references cited therein.

(26) We tried cyclization under hydrolytic (*p*-TsOH, C_6H_6, 3 h, reflux or HCl, citrate buffer, pH 4.6-4.8, 22 h, 40-50 °C) and anhydrous (dry HCl, CH_2Cl_2, 21 h, reflux) conditions.

(27) For related imine trimers, see: (a) Schöpf, C. *Chem. Ber.* **1956**, 1821. (b) Grundon, M. F.; Reynolds, B. E. *J. Chem. Soc.* **1964**, 2245. (c) Claxton, G. P.; Allen, L.; Grisar, J. *Org. Synth.* **1977**, *56*, 118.

(28) For NCS oxidation of secondary amines, see: (a) ref 24a,c. (b) Ruenitz, P. C.; Smissman, E. E. *J. Org. Chem.* **1977**, *42*, 937. (c) Uskoković, M. R.; Henderson, T.; Reese, Ch.; LinLee, H.; Grethe, G.; Gützwiller, J. *J. Am. Chem. Soc.* **1978**, *100*, 571.

(29) Stewart, W. E.; Siddall, T. H. *Chem. Rev.* **1970**, *70*, 517.

(30) It has been pointed out that the carbon syn to the carbonyl oxygen of an amide is shielded relative to the corresponding carbon anti: Hirsch, J. A. *J. Org. Chem.* **1979**, *44*, 3225 and references cited therein.

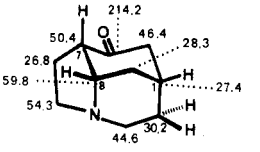
acetamide **2h** was subjected to base treatment,[33] instead of the desired tricyclic system **10**, a polymeric amorphous material was obtained.

In the belief that this result was due to an unfavorable distance for bond formation between the methylene carbon of the chloroacetamide group and the ketone α-position as a consequence of the sp^2-hybridization of the exocyclic carbon atom linked to the piperidine nitrogen, we turned our attention to the intramolecular alkylation of hydroxyethyl ketone **2g**, in which this carbon atom is sp^3-hybridized.[34] However, alkylation of secondary amine **2d** with 2-iodoethanol took place in low yield.[35] For this reason, in order to prepare **2g** we applied our previously established procedure for the synthesis of 2-azabicyclo-[3.3.1]nonan-7-ones, from 4-acetonylpiperidine **3e**. 2-(Benzyloxy)ethyl instead of 2-hydroxyethyl[36] was chosed as the substituent on the nitrogen atom because an hydroxyl group would compete as nucleophile toward the iminium salt during the cyclization step.[37] Piperidine **3e** was prepared (Scheme I) from N-benzyl derivative **3b** by formation of carbamate **3c**,[38] subsequent hydrolysis with 5 N aqueous sulfuric acid, and further alkylation of the resultant secondary amine **3d** with 2-bromoethyl benzyl ether. In the anticipated manner, methoxycarbonylation of acetonylpiperidine **3e** followed by mercuric acetate oxidation, hydrolysis, and decarboxylation furnished azabicyclic ketone **2e** in 27% overall yield. When cyclization was directly effected from **3e**, without activation of the acetonyl moiety, the yield was lower and the desired azabicyclo **2e** was contaminated with the starting piperidine **3e**.[18] Finally, removal of O-benzyl protecting group[39] was effected with boron trifluoride etherate and dimethyl sulfide[41] to give **2g** in high yield.

An alternative route to the target compound **2g** from piperidine **3d** (Scheme I) was investigated, although it proved to be less efficient. This route consisted in alkylation of secondary amine **3d** with 2-bromoethyl acetate, treatment of the resultant 4-acetonylpiperidine **3f** with mercuric acetate in aqueous solution and, finally, hydrolysis of the ester group.

With the requisite morphan **2g** in hand, the next step of the synthesis was closure of the five-membered ring by intramolecular alkylation upon the ketone α-position. For this purpose, alcohol **2g** should be converted into the corresponding mesylate.[42] However, treatment of **2g** with mesyl chloride in the presence of triethylamine under usual conditions led to the unstable[43] chloride **2j** instead of the required mesylate. Its formation can be accounted for by considering the nucleophilic attack of the chloride anion upon the initially formed mesylate with anchimeric assistance exerted by the piperidine nitrogen atom. In the mass spectrum of **2j** the molecular peak at m/e 201 and the base peak at m/e 144, corresponding to a loss of 57 mass units to give a 2,3-dihydropyridinium ion, were observed. A similar fragmentation pattern is evident in all 2-azabicyclo[3.3.1]nonan-7-ones prepared in this work.[44] A peak at m/e 152, resulting from the fragmentation of the carbon–carbon bond α both to nitrogen and chlorine, which leads to the base peak in morphans **2e** and **2g**, was also observed.

Taking into account the above result, we carried out the mesylation at −20 °C and, without trying to isolate the mesylate, the resultant mixture was subjected to potassium *tert*-butoxide treatment at the same temperature. When operating under these conditions the desired azatricyclo **1** was isolated in 21% yield. The ^1H NMR spectrum of **1** showed only two isolated signals, at δ 3.18 and 1.60, assigned to the C-8 methine and equatorial C-2 protons, respectively. The ^{13}C NMR spectrum fully confirmed the



1

structure of **1** since three signals corresponding to tertiary carbons were observed. One of these signals, assigned to the bridgehead carbon adjacent to nitrogen, appears downfield (δ 59.8) with respect to its precursor, alcohol **2g** (δ 55.4), thus indicating a new neighboring substitution. This fact clearly establishes that cyclization has taken place

(31) For ^1H NMR analysis of *N*-acylpiperidines, see: (a) Paulsen, H.; Todt, K. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 899. (b) Johnson, R. A. *J. Org. Chem.* **1968**, *33*, 3627. (c) See also ref 5c.

(32) The relative integration of signals due to the C-1 proton allowed us to calculate a 70% population of rotamer *Z*, in which the bulkier substituent on amide nitrogen atom is located syn with respect to the carbonyl group.

(33) We tried the following experimental conditions: *t*-BuOK, C_6H_6, rt, 7 h; NaH, glyme, reflux, 5 h; KH, THF, 60–70 °C, 90 min; LICA, THF, −78 °C, 30 min and then −78 °C → rt, 2 h. When we used bromoacetamide **2i** we tried the first experimental conditions.

(34) In fact, molecular models allow to observe a shorter distance between the potential electrophilic carbon and the ketone α-position when the exocyclic carbon atom attached to the piperidine nitrogen is sp^3-hybridized. See also ref 6.

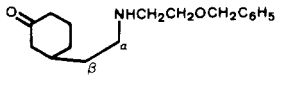
(35) It has been reported that alkylation of **2d** with methyl iodide leads to a complex mixture: see ref 11b.

(36) For the protection of the hydroxyl group as a benzyl ether in mercuric acetate promoted oxidations, see: Kutney, J. P.; Abdurahman, N.; Gletsos, C.; Le Quesne, P.; Piers, E.; Vlattas, I. *J. Am. Chem. Soc.* **1970**, *92*, 1727 and preceding papers.

(37) (a) Both the formation of 2-piperidinones[37b] and oxazolidines[37c] by mercuric acetate oxidation of *N*-(2-hydroxyethyl)piperidines have been reported: (b) Fujii, T.; Yoshifuji, S. *Chem. Pharm. Bull.* **1972**, *20*, 1451. (c) Leonard, N. J.; Musker, W. K. *J. Am. Chem. Soc.* **1960**, *82*, 5148.

(38) (a) Schwartz, M. A.; Wallace, R. A. *J. Med. Chem.* **1981**, *24*, 1525. (b) Kapnang, H.; Charles, G. *Tetrahedron Lett.* **1983**, *24*, 3233.

(39) (a) Catalytic hydrogenolysis of **2e** under usual acidic conditions afforded the desired alcohol **2g** in low yield,[39b] whereas under neutral conditions failed.[40] (b) Cyclohexanone **13**, formed by a retro-Michael reaction followed by hydrogenation of the carbon–carbon double bond in the resultant α,β-unsaturated ketone, was isolated as the major product.



13

IR ($CHCl_3$) 1710 (ketone) cm^{-1}; ^1H NMR (200 MHz) δ 1.2–2.5 (m, 11 H), 2.67 (t, J = 7.2 Hz, 2 H, NCH_2), 2.84 (t, J = 4.8 Hz, 2 H, NCH_2), 3.62 (t, J = 4.8 Hz, 2 H, OCH_2), 4.53 (s, 2 H, $ArCH_2$), 7.2–7.4 (m, 5 H, Ar H); ^{13}C NMR δ 25.1 (5-C), 31.3 (β-C), 36.7 (4-C), 37.0 (3-C), 41.3 (6-C), 47.1 (2-C), 48.0 (NCH_2), 49.3 (α-C), 69.4 (OCH_2), 73.2 (Ar CH_2), 127.6 (*p*-C), 127.7 (*m*-C), 128.3 (*o*-C), 138.2 (ipso-C), 211.2 (CO).

(40) Recent work indicates that amines inhibit, both in a intra- and intermolecular manner, hydrogenolysis of *O*-benzyl groups: Czech, B. P.; Bartsch, R. A. *J. Org. Chem.* **1984**, *49*, 4076.

(41) Fuji, K.; Kawabata, T.; Fujita, E. *Chem. Pharm. Bull.* **1980**, *28*, 3662.

(42) (a) There are relatively few references for the use of *O*-mesyl derivatives of ethanolamines: Natsume, M.; Utsunomiya, I. *Heterocycles* **1982**, *17*, 111. Natsume, M.; Utsunomiya, I.; Yamaguchi, K.; Sakai, S.-I. *Tetrahedron* **1985**, *41*, 2115. (b) For isolation of 1-(2-hydroxyethyl)-piperidinemesylate, see: Zikolova, S.; Konstantinova, R.; Zhelyazkov, L. *Farmatsiya (Sofia)* **1967**, *17*, 6; *Chem. Abstr.* **1968**, *69*, 18531*h*.

(43) It has been reported that 1-(2-chloroethyl)piperidine shows a similar behavior: Mason, J. P.; Block, H. W. *J. Am. Chem. Soc.* **1940**, *62*, 1443.

(44) An intense peak associated to the loss of a propano bridge in related azabicyclic systems has been observed: (a) Furstoss, R.; Heumann, A.; Waegell, B.; Gore, J. *Org. Mass. Spectrom.* **1972**, *6*, 1207. (b) Takeda, M.; Inoue, H.; Noguchi, K.; Honma, Y.; Kawamori, M.; Tsukamoto, G.; Saito, S. *Chem. Pharm. Bull.* **1976**, *24*, 1002. (c) Bonjoch, J.; Mestre, E.; Cortés, R.; Granados, R.; Bosch, J. *Tetrahedron* **1983**, *39*, 1723. (d) Sánchez, I. H.; Larraza, M. I.; Flores, H. J.; Díaz, E.; Jankowski, K. *Heterocycles* **1985**, *23*, 593.

at the C-8 morphan nucleus. Similarly, the carbonyl carbon appears more deshielded (δ 214.2) than in the morphan systems prepared in this work, as could be expected when introducing a substituent at the α-position of a ketone group.[45] Moreover, a good correlation is observed between the chemical shift values for the methylene carbons of the morphan moiety of **1** and those corresponding to all 2-azabicyclo[3.3.1]nonanes reported in this work (Table I).[46] The only noticeable deviation was the chemical shift of carbon 9, which undergoes a shielding effect (~5 ppm) since the piperidine ring is included in a *cis*-indolizidine moiety.[47]

The relative configuration of azatricyclo **1** follows from steric grounds since (i) substituents at bridgehead carbons 1 and 8 must necessarily adopt a cis relationship and (ii) the fused octahydroindole moiety cannot be trans as a consequence of the axial disposition of the nitrogen substituent with respect to the carbocyclic ring (see **1**).

Attempts To Elaborate the Pentacyclic Skeleton of *Strychnos* Alkaloids. The last step of the synthesis was the Fischer indolization[48] with azatricyclo **1** as the ketonic moiety. It is well-known that, in the Fischer indole synthesis of phenylhydrazones derived from unsymmetrical ketones, the use of weak (i.e., carboxylic) acids promotes cyclization toward the more branched α-carbon atom.[49] However, surprisingly, when **1** phenylhydrazone was treated with glacial acetic acid, only the unnatural regioisomer **11** coming from cyclization upon the methylene group was obtained. The desired indolenine **12**, having the pentacyclic ring system of *Strychnos* alkaloids, was not detected. The structure of **11** was ascertained from the ^{13}C NMR spectrum, which showed a typical indole pattern and only five signals attributable to methylene carbons.

In order to decrease the acidity of the cyclization medium and, consequently, to favor the indolenine rather than the indole formation, sodium acetate was added to the acetic acid reaction medium.[50] The indole derivative **11** was also isolated as the only identifiable product.

The above results are in contrast with the earlier reports on the synthesis of *Aspidosperma* alkaloids.[7] In such cases, the Fischer indolization from a fused hydrolulolidin-9-one ring system leads to the corresponding indolenine.[51] An account of this different behavior could be the instability of the desired indolenine **12** under the acidic reaction conditions. Since the use of formic acid in the Fischer indole synthesis allows the isolation of formylindolines as stable products,[52] we tried the indolization under these conditions. Unfortunately, the indole **11** was again obtained.

A possible alternative explanation for the observed regioselectivity in the above Fischer indole synthesis could stem from the greater stability of the intermediate enehydrazine leading to the indole **11** as compared with the more substituted double-bond isomer required for cyclization to the indolenine **12**, as a consequence of the steric strain of the bridged system when carbon-7 is sp^2-hydridized.[53]

Further efforts to prepare the pentacyclic skeleton of *Strychnos* alkaloids by construction of the indolenine ring at the last synthetic step will require the previous preparation of a tricyclic ketone similar to **1**, having a suitable aryl substituent at C-7, in which the C_7–aryl bond has been formed. Recent work by Overman[54] on the synthesis of *Aspidosperma* alkaloids has established the usefulness of this strategy.

Experimental Section

General Methods. Melting points were determined in a capillary tube on a Büchi or a CTP-MP 300 hotplate apparatus and are uncorrected. ^1H NMR spectra were recorded on a Perkin-Elmer R-24B (60 MHz) instrument or, when indicated, on a Varian XL-200 spectrometer. ^{13}C NMR spectra were recorded with a Varian XL-200 spectrometer. Unless otherwise noted, NMR spectra were taken in $CDCl_3$, and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. IR spectra were taken on a Perkin-Elmer 1430 spectrophotometer. Except for compound **1**, mass spectra were determined on a Hewlett-Packard 5930A mass spectrometer. The mass spectrum of compound **1** was recorded on a MS-9 AEI mass spectrometer up-dated by VG. Distillations were effected on a Büchi GKR-50 Kugelrohr apparatus and the temperatures cited are the maximum temperatures of the oven during the distillation. Column chromatography was carried out on SiO_2 (silica gel 60, 63–200 μm, Merck) or Al_2O_3 (aluminium oxide 90, neutral, activity I, 63–200 μm, Merck). Flash column chromatography was carried out on SiO_2 (silica gel 60, 40–63 μm, Macherey-Nagel). TLC was performed on SiO_2 (silica gel 60 F_{254}, Merck) or Al_2O_3 (aluminium oxide 150 F_{254}, neutral, Type T, Merck), using 70:30:5 Et_2O–acetone–DEA as developing solvent, and the spots were located with UV light or iodoplatinate reagent. Preparative TLC was performed on silica gel plates 60 F_{254} (Merck), layer thickness 2 mm. Purification of reagents and solvents was effected according to standard methods.[55] In the oxidative cyclizations, "Hyflo Supercel" (Macherey Nagel) was used as filtering agent. Prior to concentration, under reduced pressure, all organic extracts were dried over anhydrous $MgSO_4$ or Na_2SO_4 powder. Microanalyses were performed on a Carlo Erba 1106 analyzer by Instituto de Química Bio-Orgánica, Barcelona.

Methyl 1-Methyl-4-piperidineacetoacetate (4a). Dimethyl carbonate (16.3 mL, 194 mmol) was added under N_2 to a suspension of NaH (6.57 g, 274 mmol) in anhydrous Et_2O (20 mL). The resulting mixture was heated at reflux, and then some drops of absolute MeOH and a solution of piperidine **3a**[12,56] (15 g, 96.7 mmol) in anhydrous Et_2O (100 mL) were added dropwise. The mixture was refluxed for 8 h, cooled, and brought to pH 6–7 by careful addition (0 °C) of concentrated AcOH. Cold water was added and the mixture was basified with concentrated NH_4OH. The ethereal layer was decanted and the aqueous phase extracted with $CHCl_3$. The combined ethereal and chloroformic solutions were dried and evaporated. Purification by flash chromatography (SiO_2, 95:5 $CHCl_3$–MeOH) afforded 13.6 g (66%) of β-keto ester

(45) Langford, G. E.; Auksi, H.; Gosbee, J. A.; MacLachlan, F. N.; Yates, P. *Tetrahedron* **1981**, *37*, 1091.

(46) These assignments have been effected on the basis of the two-dimensional proton–carbon chemical shift correlation of benzylmorphan **2b**: see ref 1.

(47) A common characteristic of fused azabicyclic systems having the nitrogen atom in a fusion position is that the carbon atom adjacent to the fused carbon undergoes a shielding effect when the fusion is cis. (a) Quinolizidines: Tourwé, D.; Van Binst, G. *Heterocycles* **1978**, *9*, 507. (b) Hexahydrojulolidines: Bohlmann, F.; Zeisberg, R. *Chem. Ber.* **1975**, *108*, 1043. (c) Benzo[*a*]quinolizidines: Sugiura, M.; Takao, N.; Iwasa, K.; Sasaki, Y. *Chem. Pharm. Bull.* **1979**, *27*, 3144. (c) Indolo[2,1-*a*]quinolizidines: Gribble, G. W.; Nelson, R. B.; Johnson, J. L.; Levy, G. C. *J. Org. Chem.* **1975**, *40*, 3720. (e) Dibenzo[*a*,*g*]quinolizidines: Kametani, T.; Fukumoto, K.; Ihara, M.; Ujiie, A.; Koizumi, H. *J. Org. Chem.* **1975**, *40*, 3280.

(48) Robinson, B. *The Fischer Indole Synthesis*; John Wiley: Chichester, 1982.

(49) Miller, F. M.; Schinske, W. N. *J. Org. Chem.* **1978**, *43*, 3384.

(50) For the successful use of this procedure, see: Bird, C. W.; Wee, A. G. H. *Tetrahedron* **1985**, *41*, 2019.

(51) For a notable exception, see: Akagi, M.; Oishi, T.; Ban, Y. *Tetrahedron Lett.* **1969**, 2063.

(52) (a) Ban, Y.; Oishi, T.; Kishio, Y.; Iijima, I. *Chem. Pharm. Bull.* **1967**, *15*, 531. (b) Shimizu, J.; Murakami, S.; Oishi, T.; Ban, Y. *Chem. Pharm. Bull.* **1971**, *19*, 2561. (c) See also ref 7c,d,f.

(53) For the synthesis of pyrrolocarbazoles related to **11** and **12**, lacking the ethano bridge, by Fischer indolization, see: Fritz, H.; Rubach, G. *Liebigs Ann. Chem.* **1968**, *715*, 135.

(54) Overman, L. E.; Sworin, M.; Burk, R. M. *J. Org. Chem.* **1983**, *48*, 2685.

(55) Perrin, D. D.; Amarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*; Pergamon Press: Oxford, 1980.

(56) Bosch, J.; Bonjoch, J.; Díez, A.; Linares, A.; Moral, M.; Rubiralta, M. *Tetrahedron* **1985**, *41*, 1753.

4a: IR ($CHCl_3$) 1735 (strong, ester), 1710 (strong, ketone), 1650 (weak, enol ester), 1620 (weak, enol) cm^{-1}; ^1H NMR (200 MHz) δ 1.0–2.3 (m, 7 H), 2.18 (s, 3 H, NCH_3), 2.40 (d, J = 6 Hz, 2 H, $COCH_2$), 2.75 (dm, J = 11 Hz, 2 H, 2-H_e and 6-H_e), 3.33 (s, 2 H, $COCH_2CO$), 3.61 (s, 3 H, OCH_3). For the picrate: mp 105–106 °C (EtOH). Anal. Calcd for $C_{17}H_{22}N_4O_{10}\cdot{}^1/_2C_2H_6O$: C, 46.45; H, 5.41; N, 12.03. Found: C, 46.82; H, 5.10; N, 12.35.

Methyl 1-Benzyl-4-piperidineacetoacetate (4b). Operating as above, from NaH (5.85 g, 244 mmol), dimethyl carbonate (14.56 mL, 172 mmol), some drops of absolute MeOH, and benzylpiperidine **3b**[12,56] (20 g, 86 mmol), the piperidine **4b** (20.7 g, 83%) was obtained as an oil after flash chromatography (SiO_2, $CHCl_3$ as eluent): IR ($CHCl_3$) 1740 (strong, ester), 1710 (strong, ketone), 1660 (weak, enol ester), 1630 (weak, enol) cm^{-1}; ^1H NMR (200 MHz) δ 1.40 (qm, J = 12, 12, and 12 Hz, 2 H, 3-H_a and 5-H_a), 1.71 (dm, J = 12 Hz, 2 H, 3-H_e and 5-H_e), 1.7–2.0 (m, 1 H, 4-H_a), 2.11 (tm, J = 12 and 12 Hz, 2 H, 2-H_a and 6-H_a), 2.51 (d, J = 6.5 Hz, 2 H, $COCH_2$), 2.96 (dm, J = 12 Hz, 2 H, 2-He and 6-He), 3.43 (s, 2 H, $COCH_2CO$), 3.60 (s, 2 H, $ArCH_2$), 3.73 (s, 3 H, OCH_3), 7.2–7.3 (m, 5 H, Ar H); ^{13}C NMR δ 31.1 (4-C), 31.3 (3-C and 5-C), 49.3 and 49.5 ($COCH_2$), 52.3 (OCH_3), 53.2 (2-C and 6-C), 62.9 (Ar CH_2), 127.5 (p-C), 128.3 (m-C), 129.6 (o-C), other signals were not recorded.

2-Methyl-2-azabicyclo[3.3.1]nonan-7-one (2a). A solution of β-keto ester **4a** (1 g, 4.7 mmol) and $Hg(AcO)_2$ (14.95 g, 47 mmol) in H_2O (50 mL) was refluxed under N_2 with vigorous stirring for 3 h. The resulting mixture was cooled and filtered. The residue was washed with H_2O and the combined filtrate and washings were saturated with H_2S for 20 min. The precipitated salts were filtered through "Hyflo Supercel" and washed with H_2O. The combined filtrate and washings were concentrated and 12 N aqueous HCl was added to obtain an approximately 3.6 N solution. After being refluxed under N_2 for 2 h, the solution was cooled, basified with aqueous 20% NaOH solution, and extracted with $CHCl_3$. Evaporation of the dried extracts gave 0.25 g (34%) of **2a**:[12] ^1H NMR (200 MHz) δ 1.51 (dsex, J = 13, 3.6, 3.6 and 2 Hz, 1 H, 4-H_e), 1.8–1.9 (m, 3 H, 9-H and 4-H_a), 2.05 (dd, J = 17 and 4.8 Hz, 1 H, 8-H_a), 2.20 (td, J = 13, 13 and 4 Hz, 1 H, 3-H_a), 2.2–2.3 (m, 1 H, 5-H_e), 2.35 (s, 3 H, CH_3), 2.38 (m, 2 H, 6-H), 2.52 (qd, J = 13, 6 and 2 Hz, 1 H, 3-H_e), 2.80 (dq, J = 17, 4.8 and 2 Hz, 1 H, 8-H_e), 3.20 (m, 1 H, 1-H_e); MS (m/e, relative intensity) 153 (M^+, 37), 138 (3), 110 (36), 97 (25), 96 (M^+ - 57, 100), 94 (37), 70 (46), 56 (10), 44 (11), 43 (13), 42 (43). When the acid treatment was omitted, **methyl 2-methyl-7-oxo-2-azabicyclo[3.3.1]nonane-8-carboxylate (5a)** was obtained. Thus, the filtrate obtained after bubbling a H_2S stream was basified with aqueous 20% NaOH solution and extracted with CH_2Cl_2. Drying and evaporation of the extracts gave an oil which was purified by column chromatography (SiO_2). Elution with 70:30:5 Et_2O–acetone–DEA afforded **5a** as a white solid: 0.17 g (17%);[57] mp 70–72 °C (Et_2O); IR ($CHCl_3$) 1640 (enol ester), 1605 (enol) cm^{-1}; ^1H NMR δ 1.3–2.8 (m, 9 H), 2.06 (s, 3 H, NCH_3), 3.63 (s, 3 H, OCH_3), 3.7 (m, 1 H, 1-H). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.55; H, 8.05; N, 6.63. Found: C, 62.14; H, 8.10; N, 6.62.

2-Benzyl-2-azabicyclo[3.3.1]nonan-7-one (2b). β-Keto ester **4b** (3 g, 10.3 mmol) was allowed to react, as in the above methyl series, with $Hg(AcO)_2$ (33 g, 103 mmol) in H_2O (75 mL). After the usual workup and acid hydrolysis, an oil was obtained, which was chromatographed through Al_2O_3. Elution with 9:1 hexane–AcOEt afforded 0.83 g (35%) of **2b**:[12] ^1H NMR (200 MHz) δ 1.54 (dsex, J = 13.5, 3.6, and 2.7 Hz, 1 H, 4-H_e), 1.86 (dq, J = 13, 3.6, 3.6, and 3.6 Hz, 1 H, 9-H anti), 1.9–2.0 (m, 2 H, 4-H_a and 9-H syn), 2.15 (dd, J = 17 and 5 Hz, 1 H, 8-H_a), 2.30 (td, J = 13.5, 13, and 4 Hz, 1 H, 3-H_a), 2.3–2.5 (m, 3 H, 5-H_e and 6-H), 2.60 (qd, J = 13, 6 and 2 Hz, 1 H, 3-H_e), 2.88 (dq, J = 17, 3.8, 1.2, and 1.2 Hz, 1 H, 8-H_e), 3.26 (m, 1 H, 1-H_e), 3.53 and 3.70 (2d, 1 H each, J = 14 Hz, 2 H, Ar CH_2), 7.2–7.3 (m, 5 H, Ar H); MS (m/e, relative intensity) 230 (4), 229 (M^+, 14), 186 (9), 173 (9), 172 (M^+ - 57, 54), 170 (6), 92 (11), 91 (100), 80 (7), 65 (16), 42 (12), 41 (10), 39 (12).

(57) The fact that the yield of β-keto ester **5a** was lower than the yield of ketone **2a** can be attributed to the partial hydrolysis of the ester group under the lightly acidic cyclization conditions to give a water-soluble amino acid. This interpretation was confirmed since ketone **2a** could be obtained after refluxing the aqueous solution once acidified.

4-[2,2-(Ethylenedioxy)propyl]-1-methylpiperidine (7). Method A. A stirred solution of methylpiperidine **3a** (10 g, 64 mmol) as its hydrochloride, p-TsOH monohydrate (6 g, 32 mmol), and ethylene glycol (11 mL, 0.19 mol) in anhydrous C_6H_6 (50 mL) was refluxed for 40 h with removal of H_2O by a Dean–Stark trap. The reaction mixture was poured into H_2O and basified with concentrated NH_4OH. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried and evaporated to give acetal **7** (9.8 g, 76%): bp 70 °C (0.1 mmHg); ^1H NMR δ 1.26 (s, 3 H, CCH_3), 1.1–1.9 (m, 7 H, 3-H, 4-H, 5-H, and $CHCH_2$), 2.13 (s, 3 H, NCH_3), 2.0–2.5 (m, 2 H, 2-H_a and 6-H_a), 2.70 (dm, J = 12 Hz, 2 H, 2-H_e and 6-H_e), 3.76 (s, 4 H, OCH_2). For the picrate: mp 146–147 °C (EtOH). Anal. Calcd for $C_{17}H_{24}N_4O_9$: C, 47.66; H, 5.60; N, 13.08. Found: C, 47.67; H, 5.47; N, 13.20.

Method B. To a solution of **3a** (10 g, 64.5 mmol) and ethylene glycol (11 mL, 0.19 mol) in anhydrous CH_2Cl_2 (160 mL), Me_3SiCl (38 mL, 0.28 mol) was added under N_2. After being refluxed for 48 h, the mixture was poured into H_2O, basified with K_2CO_3, and extracted with CH_2Cl_2. Evaporation of the dried organic extracts gave acetal **7** (12.3 g, 95%).[58]

4-[2,2-(Ethylenedioxy)propyl]piperidine (8). To a solution of acetal **7** (3 g, 15 mmol) in anhydrous C_6H_6 under N_2 was added ethyl chloroformate (15 mL, 0.15 mol) dropwise. After being refluxed for 18 h, the reaction mixture was acidified with aqueous 1.2 N HCl solution and extracted with C_6H_6. Evaporation of the dried extracts afforded **ethyl 4-[2,2-(ethylenedioxy)propyl]-1-piperidinecarboxylate** (3.3 g, 85%): bp 130 °C (0.05 mmHg); IR (NaCl) 1690 (carbamate) cm^{-1}; ^1H NMR δ 1.20 (t, 3 H, CH_2CH_3), 1.28 (s, 3 H, CH_3), 0.8–1.9 (m, 7 H), 2.70 (td, J = 12, 12 and 2 Hz, 2 H, 2-H_a and 6-H_a), 3.81 (s, 4 H, OCH_2), 4.01 (q, 2 H, CH_3CH_2), 3.7–4.3 (masked, 2 H, 2-H_e and 6-H_e). To a mixture of aqueous 50% KOH (33.8 mL) and EtOH (68 mL) was added this carbamate (3.3 g, 3.9 mmol). The resulting solution was refluxed for 48 h and, after evaporation of EtOH, was extracted with Et_2O. The ethereal extracts were dried and evaporated to give piperidine **8** (2 g, 85%): bp 220 °C (0.05 mmHg); ^1H NMR δ 1.26 (s, 3 H, CH_3), 0.9–2.2 (m, 7 H), 1.83 (s, 1 H, NH), 2.55 (td, J = 12, 12 and 2 Hz, 2 H, 2-H_a and 6-H_a), 2.8–3.2 (m, 2 H, 2-H_e and 6-H_e), 3.81 (s, 4 H, OCH_2). Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.86; H, 10.27; N, 7.56. Found: C, 64.70; H, 10.16; N, 7.27.

4-[2,2-(Ethylenedioxy)propyl]-2,3,4,5-tetrahydropyridine (9). Piperidine **8** (2.17 g, 11 mmol) was added under N_2 to a cooled solution (0 °C) of N-chlorosuccinimide (1.7 g, 12 mmol) in anhydrous Et_2O (30 mL). The mixture was stirred at room temperature for 2 h. The precipitate was filtered off and the filtrate was washed with H_2O, dried, and concentrated to a third of its volume. The resulting ethereal solution was added under N_2 to a solution of KOH (0.6 g, 11 mmol) in absolute EtOH (40 mL) cooled at 5 °C. After being stirred at room temperature for 4 h, the reaction mixture was filtered and evaporated to afford piperidine **9** as a trimer (2 g): ^1H NMR δ 1.30 (s, CH_3), 1.0–3.6 (m), 3.86 (s, OCH_2); MS (m/e, relative intensity) 550 (M^+ + 1, 18), 549 (M^+, 18), 366 (34), 277 (22), 236 (11), 198 (16), 184 (97), 183 (98), 168 (93), 140 (47), 138 (83), 95 (54), 88 (85), 87 (100), 80 (80). Anal. Calcd for $C_{30}H_{51}N_3O_6\cdot{}^3/_4H_2O$: C, 64.00; H, 9.33; N, 7.46. Found: C, 63.91; H, 9.38; N, 7.42.

2-Azabicyclo[3.3.1]nonan-7-one (2d). A suspension of benzylmorphan **2b** (0.83 g, 3.6 mmol) and 10% Pd/C (249 mg) in MeOH, acidified with a solution of HCl in MeOH, was hydrogenated until total disappearance of the starting compound was observed by TLC. When long reaction times were required (24 h), additional 10% Pd/C was added. The catalyst was filtered off and the filtrate was evaporated to dryness to give 0.62 g (97%) of **2d**·HCl as a white solid: mp 185–187 °C (EtOH) (lit.[11b] picrate mp 222–226 °C). A sample of **2d**·HCl was basified with aqueous 10% K_2CO_3 solution and extracted with $CHCl_3$ to afford morphan **2d** as a free base, which was unstable and polymerized on standing: IR ($CHCl_3$) 1690 (ketone) cm^{-1}; ^1H NMR (200 MHz) δ 1.58 (dsex, J = 13, 4.8, 4.8, and 2.4 Hz, 1 H, 4-H_e), 1.7–2.1 (m, 3 H, 4-H_a and 9-H), 2.3–2.7 (m, 5 H, 8-H_a, 3-H_a, 5-H_e, and 6-H), 2.7–2.9 (m, 2 H, 3-H_e and 8-H_e), 3.56 (m, 1 H, 1-H_e); MS (m/e, relative intensity)

(58) For this procedure of acetalization, see: Chan, T. H.; Brook, M. A.; Chaly, T. *Synthesis* **1983**, 203.

140 (1.5), 139 (M^+, 11), 96 (6), 83 (5), 82 (M^+ - 57, 100), 80 (7.5), 60 (5), 56 (13), 55 (5), 43 (5), 42 (5), 41 (6), 39 (5), 36 (5).

2-(Chloroacetyl)-2-azabicyclo[3.3.1]nonan-7-one (2h). A solution of chloroacetyl chloride (0.52 mL, 6.5 mmol) in dry $CHCl_3$ (25 mL) was added dropwise under N_2 to a stirred solution of amine **2d**·HCl (1.05 g, 5.9 mmol) and triethylamine (1.72 mL, 12.4 mmol) in dry $CHCl_3$ (50 mL) at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was diluted with $CHCl_3$ (30 mL) and washed with aqueous 1.2 N HCl (80 mL), aqueous 5% K_2CO_3 solution (80 mL), and water (80 mL). Evaporation of the dried organic extract afforded 1.24 g (90%) of chloroacetamide **2h** as a white solid: mp 126–128 °C (Et_2O); IR ($CHCl_3$) 1710 (ketone), 1645 (amide) cm^{-1}; ^1H NMR (200 MHz) δ 1.6–2.1 (m, 4 H, 4-H, and 9-H), 2.4–2.7 (m, 5 H, 5-H_e, 6-H, and 8-H), 2.72 (td partially masked, 0.3 H, 3-H_a rotamer *E*), 3.21 (td, J = 15, 13 and 4 Hz, 0.7 H, 3-H_a rotamer *Z*), 3.65 (dd, J = 15 and 5 Hz, 0.7 H, 3-H_e rotamer *Z*), 3.98 and 4.05 (2d, J = 12 Hz, 0.7 H each, $ClCH_2$ rotamer *Z*), 4.01 and 4.08 (2d, J = 12 Hz, 0.3 H each, $ClCH_2$ rotamer *E*), 4.43 (dd partially masked, 0.3 H, 3-H_e rotamer *E*), 4.45 (m, 0.3 H, 1-H_e rotamer *E*), 5.21 (m, 0.7 H, 1-H_e rotamer *Z*); MS (*m/e*, relative intensity) 217 (5), 215 (M^+, 12), 180 (13), 160 (19), 158 (M^+ - 57, 100), 152 (15), 138 (5), 82 (32), 77 (9), 67 (7), 55 (10), 49 (13), 42 (20). Anal. Calcd for $C_{10}H_{14}ClNO_2$: C, 55.68; H, 6.49; Cl, 16.93; N, 6.49. Found: C, 55.51; H, 6.53; Cl, 16.61; N, 6.52.

Operating as above, from amine **2d**·HCl (0.61 g, 3.4 mmol), triethylamine (1.0 mL, 7.3 mmol), and bromoacetyl bromide (0.33 mL, 3.8 mmol), **2-(bromoacetyl)-2-azabicyclo[3.3.1]nonan-7-one (2i)** was obtained as a white solid (0.84 g, 93%): ^1H NMR δ 1.6–2.1 (m, 4 H), 2.4–2.7 (m, 5 H), 2.9–3.5 (m, 1 H, 3-H_a), 3.5–3.8 (m, 0.7 H, 3-H_e rotamer *Z*), 3.75 (s, 1.4 H, CH_2Br rotamer *Z*), 3.95 (s, 0.6 H, CH_2Br rotamer *E*), 4.1–4.6 (m, 0.6 H, 3-H_e and 1-H_e rotamer *E*), 5.0–5.2 (m, 0.7 H, 1-H_e rotamer *Z*).

Ethyl 4-Acetonyl-1-piperidinecarboxylate (3c). To a solution of benzylpiperidine **3b** (28.4 g, 0.12 mmol) in dry C_6H_6 (200 mL) under N_2 was added ethyl chloroformate (14.6 mL, 0.12 mmol). After being refluxed for 19 h, the reaction mixture was cooled, acidified with aqueous 1.2 N HCl solution, and extracted with C_6H_6. Evaporation of the dried organic extracts gave an oil from which benzyl chloride was removed by distillation to afford carbamate **3c** (21.2 g, 81%): bp 140 °C (0.1 mmHg); IR (NaCl) 1705 (ketone), 1690 (carbamate) cm^{-1}; ^1H NMR (200 MHz) δ 1.12 (qd, J = 12, 12, 12, and 4.2 Hz, 2 H, 3-H_a and 5-H_a), 1.26 (t, 3 H, CH_2CH_3), 1.68 (dm, J = 12 Hz, 2 H, 3-H_e and 5-H_e), 1.9–2.3 (m, 1 H, 4-H_a), 2.14 (s, 3 H, $COCH_3$), 2.38 (d, J = 6.6 Hz, 2 H, $COCH_2$), 2.78 (tm, J = 12 Hz, 2 H, 2-H_a and 6-H_a), 4.12 (q, 2 H, CH_3CH_2), 4.0–4.2 (masked, 2 H, 2-H_e and 6-H_e); ^{13}C NMR δ 14.6 (CH_3), 30.5 ($COCH_3$), 31.6 (4-C), 31.8 (3-C and 5-C), 43.8 (2-C and 6-C), 50.0 ($COCH_2$), 61.1 (OCH_2), 155.5 (CO carbamate), 207.5 (CO ketone). Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.97; H, 8.92; N, 6.57. Found: C, 61.57; H, 8.76; N, 6.46.

Formation of carbamate **3c** from *N*-methylpiperidine **3a** took place in lower yield (47%).

4-Acetonylpiperidine (3d). A solution of carbamate **3c** (48 g, 0.255 mol) in aqueous 5 N H_2SO_4 solution (1.15 L) was stirred at 90–100 °C overnight. The reaction mixture was cooled and extracted with Et_2O. The resulting aqueous phase was basified with concentrated NH_4OH and extracted with $CHCl_3$ in a continuous extractor for 12 h. The chloroformic extracts were dried and evaporated to yield **3d**: 30.6 g (96%); IR ($CHCl_3$) 1700 (ketone) cm^{-1}; ^1H NMR (200 MHz) δ 1.30 (qd, J = 12, 12, 12, and 4 Hz, 2 H, 3-H_a and 5-H_a), 1.74 (dm, J = 12 Hz, 2 H, 3-H_e and 5-H_e), 1.96 (m, 1 H, 4-H_a) 2.14 (s, 3 H, $COCH_3$), 2.39 (d, J = 7 Hz, 2 H, $COCH_2$), 2.72 (td, J = 12, 12 and 2.8 Hz, 2 H, 2-H_a and 6-H_a), 3.16 (dm, J = 12 Hz, 2 H, 2-H_e and 6-H_e), 3.90 (br, 1 H, NH); ^{13}C NMR δ 30.6 (CH_3), 32.3 (4-C), 33.2 (3-C and 5-C), 46.5 (2-C and 6-C), 50.9 ($COCH_2$), 208.1 (CO). For the picrate: mp 137–138 °C (EtOH). Anal. Calcd for $C_{14}H_{18}N_4O_8$: C, 45.40; H, 4.86; N, 15.13. Found: C, 45.66; H, 4.85; N, 14.85.

4-Acetonyl-1-[2-(benzyloxy)ethyl]piperidine (3e). Benzyl 2-bromoethyl ether[59] (26.73 g, 124 mmol) was added dropwise under N_2 to a suspension of piperidine **3d** (14.47 g, 102 mmol) and anhydrous K_2CO_3 (17.2 g, 123 mmol) in dry C_6H_6 (250 mL). The mixture was heated at 90–100 °C for 14 h, cooled, and acidified with aqueous 1.2 N HCl solution. The benzene solution was discarded and the aqueous layer was extracted with Et_2O, basified with concentrated NH_4OH, and extracted with $CHCl_3$. Evaporation of the dried chloroformic extracts gave **3e**: 23.5 g (83%). An analytical sample was obtained by distillation: bp 170 °C (0.01 mmHg); IR ($CHCl_3$) 1700 (ketone) cm^{-1}; ^1H NMR (200 MHz) δ 1.29 (qd, J = 12, 12, 12, and 3.6 Hz, 2 H, 3-H_a and 5-H_a), 1.67 (dm, J = 12 Hz, 2 H, 3-H_e and 5-H_e), 1.7–1.9 (m, 1 H, 4-H_a), 2.02 (td, J = 12, 12, and 2.4 Hz, 2 H, 2-H_a and 6-H_a), 2.12 (s, 3 H, CH_3), 2.34 (d, J = 7 Hz, 2 H, $COCH_2$), 2.60 (t, J = 6 Hz, 2 H, NCH_2), 2.91 (dm, J = 12 Hz, 2-H_e and 6-H_e), 3.58 (t, J = 6 Hz, 2 H, OCH_2), 4.53 (s, 2 H, Ar CH_2), 7.32 (s, 5 H, Ar H); ^{13}C NMR δ 30.5 (CH_3), 31.6 (4-C), 32.1 (3-C and 5-C), 50.4 ($COCH_2$), 54.0 (2-C and 6-C), 58.2 (NCH_2), 67.8 (OCH_2), 73.1 (Ar CH_2), 127.5 (*p*-C), 127.7 (*m*-C), 128.3 (*o*-C), 138.4 (ipso-C), 208.1 (CO). For the oxalate: mp 156–157 °C (acetone). Anal. Calcd for $C_{19}H_{27}NO_6$: C, 62.46; H, 7.39; N, 3.83. Found: C, 62.37; H, 7.44; N, 3.80.

1-(2-Acetoxyethyl)-4-acetonylpiperidine (3f). Operating as above, from piperidine **3d** (6.36 g, 45 mmol), anhydrous K_2CO_3 (7.48 g, 54 mmol), and 2-bromoethyl acetate (7.41 mL, 67.6 mmol) in dry C_6H_6 (100 mL), piperidine **3f** was obtained: 7.37 g (72%). An analytical sample was obtained by distillation: bp 225–230 °C (0.05 mmHg); IR ($CHCl_3$) 1735–1705 (ketone, ester) cm^{-1}; ^1H NMR (200 MHz) δ 1.28 (qd, J = 12, 12, 12, and 3.6 Hz, 2 H, 3-H_a and 5-H_a), 1.69 (dm, J = 12 Hz, 2 H, 3-H_e and 5-H_e), 1.87 (s, 3 H, $OCOCH_3$), 2.14 (s, 3 H, $COCH_3$), 1.6–2.3 (m, 3 H, 4-H_a, 2-H_a, and 6-H_a), 2.37 (d, J = 6.6 Hz, 2 H, $COCH_2$), 2.62 (t, J = 6 Hz, 2 H, NCH_2), 2.90 (dm, J = 12 Hz, 2 H, 2-H_e and 6-H_e), 4.18 (t, J = 6 Hz, 2 H, OCH_2); ^{13}C NMR δ 20.9 ($OCOCH_3$), 30.5 ($COCH_3$), 31.5 (4-C), 32.0 (3-C and 5-C), 50.2 ($COCH_2$), 53.8 (2-C and 6-C), 56.8 (NCH_2), 61.9 (OCH_2), 170.8 (CO ester), 208.0 (CO ketone). For the picrate: mp 135–137 °C (EtOH). Anal. Calcd for $C_{18}H_{24}N_4O_{10}$: C, 47.36; H, 5.26; N, 12.28. Found: C, 47.49; H, 5.25; N, 12.27.

Methyl 1-[2-(Benzyloxy)ethyl]-4-piperidineacetoacetate (4e). Operating as in the above N-methyl series, piperidine **3e** (23.5 g, 85 mmol) was allowed to react with NaH (6 g, 250 mmol) and dimethyl carbonate (21.5 mL, 255 mmol) in dry THF (350 mL). The mixture was quenched with AcOH, diluted with cold water, and extracted with Et_2O. The ethereal extract was discarded, the aqueous layer was basified at 0 °C with concentrated NH_4OH, and the product was isolated by Et_2O extraction. Flash chromatography (SiO_2, 97:3 $CHCl_3$–DEA) gave pure β-keto ester **4e** (21.2 g, 75%) as an oil: IR (NaCl) 1740 (strong, ester), 1710 (strong, ketone), 1645 (weak, enol ester), 1630 (weak, enol) cm^{-1}; ^1H NMR (200 MHz) δ 1.32 (qd, J = 12, 12, 12, and 4 Hz, 2 H, 3-H_a and 5-H_a), 1.68 (dm, J = 12 Hz, 2 H, 3-H_e and 5-H_e), 1.7–1.9 (m, 1 H, 4-H_a), 2.04 (td, J = 12, 12, and 3 Hz, 2 H, 2-H_a and 6-H_a), 2.46 (d, J = 6.5 Hz, 2 H, $COCH_2$), 2.60 (t, J = 6 Hz, 2 H, NCH_2), 2.92 (dm, J = 12 Hz, 2 H, 2-H_e and 6-H_e), 3.43 (s, 2 H, $COCH_2CO$), 3.58 (t, J = 6 Hz, 2 H, OCH_2), 3.73 (s, 3 H, OCH_3), 4.53 (s, 2 H, Ar CH_2), 7.3–7.4 (m, 5 H, Ar H); ^{13}C NMR δ 31.3 (4-C), 31.8 (3-C and 5-C), 49.5 and 49.6 ($COCH_2$), 52.3 (OCH_3), 53.9 (2-C and 6-C), 58.1 (NCH_2), 67.6 (OCH_2), 73.1 (Ar CH_2), 127.6 (*p*-C), 127.7 (*m*-C), 128.4 (*o*-C), 138.3 (ipso-C), 167.5 (CO ester), 201.9 (CO ketone). Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.40; H, 8.10; N, 4.20. Found: C, 68.16; H, 8.50; N, 4.45.

2-[2-(Benzyloxy)ethyl]-2-azabicyclo[3.3.1]nonan-7-one (2e). Method A. A solution of β-keto ester **4e** (3.65 g, 10.9 mmol) in H_2O (200 mL) was allowed to react, as in the above N-methyl series, with $Hg(AcO)_2$ (35 g, 109 mmol). The resulting mixture was filtered and the precipitate was washed with H_2O. Concentrated AcOH (6.3 mL) and aqueous 20% ammonium polysulfide (37 mL) were added to the combined filtrate and washings. The precipitated salts were filtered through "Hyflo Supercel" and washed with aqueous 1.2 N HCl solution. The combined filtrate and washings were acidified with concentrated HCl to obtain an approximately 1.2 N solution and refluxed for 2 h. After cooling, the solution was basified with aqueous 50% NaOH solution and extracted with Et_2O. Evaporation of the dried ethereal extract furnished an oil which was purified by flash chromatography (SiO_2, 98:2 $CHCl_3$–DEA) to afford **2e**: 1.1 g (36%); IR ($CHCl_3$) 1705 (ketone cm^{-1}; ^1H NMR (200 MHz) δ 1.54 dsex, J = 13, 3.6, 3.6, and 1 Hz, 1 H, 4-H_e), 1.90 (dq, J = 13, 13, 5.4, and 3 Hz, 1 H, 9-H

(59) Grobelny, D.; Maślak, P.; Witek, S. *Tetrahedron Lett.* **1979**, 2639.

anti), 2.03 (m, 2 H, 4-H_a and 9-H syn), 2.12 (dd, J = 17 and 4.8 Hz, 1 H, 8-H_a), 2.28 (td, J = 13, 13, and 3.6 Hz, 1 H, 3-H_a), 2.4–2.5 (m, 3 H, 5-H_e and 6-H), 2.6–2.7 (masked, 1 H, 3-H_e), 2.70 (t, J = 6 Hz, 2 H, NCH_2), 2.80 (dm, J = 17 Hz, 1 H, 8-H_e), 3.38 (m, 1 H, 1-H_e), 3.56 (t, J = 6 Hz, 2 H, OCH_2), 4.52 (s, 2 H, Ar CH_2), 7.30 (m, 5 H, Ar H); MS (m/e, relative intensity) 273 (M^+, 2), 216 (M^+ – 57, 7), 167 (19), 153 (12), 152 (100), 139 (13), 124 (9), 110 (5), 108 (7), 95 (6), 91 (31), 82 (15), 81 (6), 79 (8), 77 (6). For the picrate: mp 122–123 °C (EtOH). Anal. Calcd for: $C_{23}H_{26}N_4O_9$: C, 54.90; H, 5.17; N, 11.15. Found: C, 55.05; H, 5.10; N, 10.97. The above aqueous solution was extracted with $CHCl_3$. Drying and evaporation of the extracts gave an oil which, by preparative TLC (SiO_2, 70:30:5 Et_2O–acetone–DEA) afforded 80 mg (4%) of alcohol **2g**.[60]

Method B. A solution of piperidine **3e** (3.1 g, 11.3 mmol) and $Hg(AcO)_2$ (17.96 g, 56 mmol) in H_2O (100 mL) was refluxed under N_2 for 3 h 30 min. The workup indicated in the preparation of **2a**, except for the acid treatment, furnished an oil which was chromatographed (Al_2O_3, 9:1 C_6H_6–$CHCl_3$) to give 470 mg (15%) of **2e** and 480 mg of a 1:1 mixture of **2e** and **3e** (23% overall yield of **2e**).

2-(2-Hydroxyethyl)-2-azabicyclo[3.3.1]nonan-7-one (2g). Method A. From Benzyl Ether 2e. Dimethyl sulfide (13.2 mL) and BF_3·Et_2O (8.1 mL) were added under N_2 to a solution of benzyl ether **2e** (1.71 g, 6 mmol) in dry CH_2Cl_2 (14 mL). The resulting mixture was stirred at 30 °C for 10 h. Then, BF_3·Et_2O (8.1 mL) was added and the mixture was stirred for 14 h. The reaction solution was evaporated to dryness and the oily residue was distributed between Et_2O and H_2O. The aqueous layer was basified with concentrated NH_4OH and extracted with $CHCl_3$. The chloroformic extracts were dried and evaporated to give an oil which on flash chromatography (SiO_2, 29:1 CH_2Cl_2–DEA) afforded 922 mg (84%) of alcohol **2g**: IR ($CHCl_3$) 3610–3150 (alcohol), 1705 (ketone) cm^{-1}; ^1H NMR (200 MHz) δ 1.61 (dsex, J = 13, 3.6, 3.6, and 1 Hz, 1 H, 4-H_e), 1.8–2.1 (m, 3 H, 4-H_a and 9-H), 2.24 (dd, J = 17 and 4.8 Hz, 1 H, 8-H_a), 2.33 (td, J = 13, 13, and 3.6 Hz, 1 H, 3-H_a), 2.4–2.5 (m, 3 H, 5-H_e and 6-H), 2.5–2.6 (m, 1 H, 3-H_e), 2.58–2.70 (AA'XX' system, 2 H, NCH_2), 2.78 (AA'XX' system, 2 H, OCH_2); MS (m/e, relative intensity) 184 (3), 183 (M^+, 12), 182 (2), 153 (10), 152 (100), 128 (9), 126 (M^+ – 57, 42), 124 (12), 100 (9), 95 (10), 91 (33), 82 (14), 67 (10), 56 (11), 55 (11). For the picrate: mp 143–145 °C (EtOH). Anal. Calcd for $C_{16}H_{20}N_4O_9 \cdot {}^1/_2C_2H_6O$: C, 46.89; H, 5.32; N, 12.86. Found: C, 47.25; H, 4.99; N, 13.17.

Method B. From Amine 2d. 2-Iodoethanol (0.15 mL, 1.9 mmol) was added under N_2 to a solution of **2d**·HCl (140 mg, 0.79 mmol) and anhydrous K_2CO_3 (300 mg, 2.17 mmol) in MeOH (5 mL). The resulting mixture was stirred at 60 °C for 2 h, MeOH was evaporated, and the residue was acidified with aqueous 1.2 N HCl solution and extracted with Et_2O. The aqueous phase was basified with 10% aqueous K_2CO_3 solution and extracted, first with Et_2O and then with CH_2Cl_2. The combined organic extracts were dried and evaporated to afford 30 mg (20%) of alcohol **2g**.

Method C. From Acetonylpiperidine 3f. A solution of piperidine **3f** (2 g, 8.8 mmol) and $Hg(AcO)_2$ (14 g, 44 mmol) in H_2O (50 mL) was refluxed under N_2 for 3 h. The usual workup (see preparation of **2a**) was effected, except that "Hyflo Supercel" was washed with aqueous 20% AcOH solution and that concentrated AcOH was added to the combined filtrate and washings to obtain an aqueous 50% AcOH solution, which was refluxed for 2 h. The resulting oil was chromatographed through Al_2O_3. On elution with 2:1 hexane–AcOEt, acetate **2f** (30 mg) was obtained: IR ($CHCl_3$) 1735 (ester), 1700 (ketone) cm^{-1}; ^1H NMR δ 1.95 (s, 3 H, $COCH_3$), 1.8–2.8 (m, 13 H), 3.35 (br, 1 H, 1-H), 4.0 (t, 2 H, OCH_2). On further elution with 1:1 hexane–AcOEt, azabicyclic alcohol **2g** (290 mg, 18%) was obtained. Finally, elution with 2:3 hexane–AcOEt afforded (hydroxyethyl)piperidine **3g** (30 mg).

2-(2-Chloroethyl)-2-azabicyclo[3.3.1]nonan-7-one (2j). To a chilled (0 °C) solution of alcohol **2g** (245 mg, 1.3 mmol) in dry CH_2Cl_2 were added, under N_2, Et_3N (0.27 mL, 2 mmol) and mesyl chloride (0.11 mL, 1.4 mmol). The mixture was stirred at 0 °C for 5 min and at room temperature for 4 h. The solution was diluted with CH_2Cl_2 (10 mL) and washed with saturated aqueous $NaHCO_3$ solution (2 × 20 mL) and H_2O (3 × 10 mL). The organic phase was dried and evaporated at room temperature to give the chloride **2j** (0.23 g, 90%), which was unstable and polymerized on standing: ^1H NMR (200 MHz) δ 1.58 (dsex, J = 13, 3.6, 3.6, and 1 Hz, 1 H, 4-H_e), 1.92 (tq, J = 13, 13, 5.6, and 2.4 Hz, 1 H, 4-H_a), 1.8–2.1 (m, 2 H, 9-H), 2.20 (dd, J = 17 and 4.5 Hz, 1 H, 8-H_a), 2.38 (td, J = 13, 13, and 3.2 Hz, 1 H, 3-H_a), 2.4–2.5 (m, 3 H, 5-H_e and 6-H), 2.6–2.8 (m, 2 H, 3-H_e and 8-H_e), 2.72 and 2.82 (m, 2 H, NCH_2), 3.34 (br, 1 H, 1-H_e), 3.52 (t, J = 7 Hz, 2 H, $ClCH_2$); MS (m/e, relative intensity) 203 (7), 201 (M^+, 19), 152 (44), 146 (35), 145 (10), 144 (M^+ – 57, 100), 142 (13), 118 (15), 108 (10), 95 (12), 82 (15), 79 (11), 67 (13), 63 (13), 55 (15), 54 (11), 42 (15), 41 (17), 40 (10). For the hydrochloride: mp 145–147 °C (acetone). Anal. Calcd for $C_{10}H_{17}Cl_2NO$: C, 50.42; H, 7.14; Cl, 29.83; N, 5.88. Found: C, 50.51; H, 7.40; Cl, 29.39; N, 5.65.

4-Azatricyclo[5.2.2.0^{4,8}]undecan-11-one (1). Triethylamine (0.57 mL, 1.9 mmol) and mesyl chloride (0.23 mL, 1.4 mmol) were added under N_2 to a solution of alcohol **2g** (0.5 g, 1.27 mmol) in dry THF (15 mL) at –20 °C. The mixture was stirred at –20 °C for 2 h and then freshly sublimed t-BuOK (0.66 g, 2.8 mmol) was added. After being stirred at –20 °C for 2 h and at room temperature for 2 h 30 min, the reaction mixture was poured into brine (25 mL) and extracted first with Et_2O and then with $CHCl_3$. The combined organic extracts were dried and evaporated to give an oil which was chromatographed (Al_2O_3). On elution with 4:1 hexane–$CHCl_3$, azatricyclo **1** (95 mg, 21%) was obtained: IR ($CHCl_3$) 1690 (ketone) cm^{-1}; ^1H NMR (200 MHz) δ 1.60 (m, 1 H, 2-H_e), 1.8–3.0 (m, 13 H), 3.18 (m, 1 H, 8-H_e); MS (m/e, relative intensity) 166 (8), 165 (M^+, 76), 164 (33), 149 (13), 137 (6), 136 (6), 124 (20), 122 (11), 120 (5), 110 (6), 108 (6), 96 (32), 95 (100), 94 (14), 83 (9), 82 (35), 71 (15), 70 (8), 69 (11), 68 (9), 67 (12), 55 (21), 44 (61), 42 (19), 41 (26). For the picrate: mp 209–210 °C dec (EtOH). Anal. Calcd for $C_{16}H_{18}N_4O_8$: C, 48.71; H, 4.56; N, 14.21. Found: C, 48.84; H, 4.65; N, 14.00.

Fischer Indolization of Ketone 1 Phenylhydrazone. Method A. A mixture of ketone **1** (435 mg, 2.63 mmol) and freshly distilled phenylhydrazine (284 mg, 2.9 mmol) in absolute EtOH (6 mL) was refluxed under N_2. After 2 days, more phenylhydrazine (284 mg, 2.9 mmol) in absolute EtOH (3 mL) was added to the reaction mixture and the reflux was prolonged for 5 days. The reaction was maintained until total disappearance of the starting ketone (monitored by TLC, SiO_2). The EtOH was evaporated and the residue was taken up with dry C_6H_6. After evaporation of the C_6H_6 solution, the excess of phenylhydrazine was distilled (100–110 °C, 0.5 mmHg) to leave 670 mg of crude **1** hydrazone as an oil: IR (NaCl): 1600 (C=N) cm^{-1}. A solution of this hydrazone (112 mg, 0.43 mmol) in glacial AcOH (5 mL) was refluxed for 50 min. After cooling, the AcOH was evaporated in vacuo and aqueous $HNaCO_3$ solution was added to the resulting residue until pH 8–9. The aqueous solution was extracted with CH_2Cl_2. Evaporation of the dried extracts left an oil which was chromatographed (Al_2O_3). On elution with 1:1 hexane–$CHCl_3$, the indole **11**[61] (34 mg, 32%) was obtained: IR (NaCl) 3450 (NH) cm^{-1}; ^1H NMR δ 3.25–3.5 (m, 2 H, 3a-H and 10b-H), 6.9–7.4 (m, 4 H, indole), 8.1 (br, 1 H, NH); ^{13}C NMR δ 23.4 (5-C), 27.8 (1-C), 29.4 (4-C and 11-C), 35.3 (10b-C), 45.3 (12-C), 54.2 (2-C), 59.7 (3a-C), 110.7 (9-C), 117.4 (6-C), 119.0 (7-C), 121.0 (8-C); MS (m/e, relative intensity) 239 (18), 238 (M^+, 100), 237 (24), 195 (8), 194 (15), 183 (5), 182 (20), 181 (11), 180 (14), 169 (15), 168 (35), 167 (34), 156 (5), 154 (5), 143 (5), 119 (11), 95 (69), 71 (10). For the picrate: mp 194–195 °C dec (MeOH). Anal. Calcd for $C_{22}H_{21}N_5O_7 \cdot {}^3/_2H_2O$: C, 53.44; H, 4.89; N, 14.15. Found: C, 53.62; H, 4.49; N, 13.82.

Method B. Anhydrous sodium acetate (241 mg, 2.93 mmol, recrystallized from AcOH) and freshly distilled glacial AcOH (8 mL) were added to crude **1** phenylhydrazone (375 mg, 1.47 mmol),

(60) Its formation can be explained by cleavage of the ether bond under the acidic hydrolytic conditions.

(61) Systematic name: 2,3,3a,4,5,10b-hexahydro-1*H*-3,5-ethanopyrrolo[3,2-*a*]carbazole (**11**). **Note Added in Proof**: ^1H NMR (200 MHz) δ 1.60 (br d, J = 12 Hz, 1 H, 4-H_e), 1.98 (m, 1 H, 4-H_a), 2.14 (m, 2 H, 11-H), 2.26 (m, 2 H, 1-H), 2.0–2.4 (masked, 1 H, 12-H_a), 2.75 (br d, J = 12 Hz, 1 H, 12-H_e), 2.6–2.8 (masked, 1 H, 5-H), 2.90 (m, 2 H, 2-H), 3.32 (br s, 1 H, 3a-H), 3.44 (br s, 1 H, 10b-H), 7.12 (m, 2 H, 7- and 8-H), 7.30 and 7.45 (2 m, 1 H each, 6- and 9-H), 8.7 (br, 1 H, NH).

prepared as above, and the mixture was stirred at 95–100 °C for 2 h 30 min. After the usual workup and chromatographic purification, the indole 11 was obtained: 83 mg (20%).

Method C. A solution of crude 1 phenylhydrazone (670 mg, 2.63 mmol) in freshly distilled 98–100% HCOOH (1 mL, 26.3 mmol) was refluxed for 1 h. After cooling, AcOEt (10 mL) was added, the mixture was made alkaline with saturated aqueous $HNaCO_3$ solution and extracted with AcOEt. Evaporation of the dried extracts gave a dark red oil (530 mg) which was chromatographed as above to give the indole 11 (250 mg, 26%).

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Notes

An Expedient Synthesis of Bis(trimethylsilyl)carbodiimide

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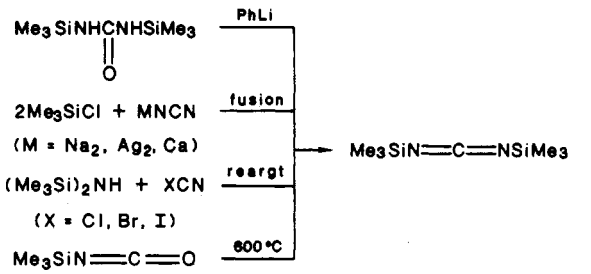
We have recently reported the preparation of a number of silylated compounds using alkylsilyl cyanides as silylating agents.[1] We now wish to describe an extension of this work involving the preparation of bis(trimethylsilyl)carbodiimide (BTMSC), which in turn is a very useful versatile synthetic intermediate.[2-9]

In general, BTMSC can be prepared either by the dehydration of bis(trimethylsilyl)urea,[10,11] by the condensation of a metal cyanamide with trimethylsilyl chloride,[12-15] by the reaction of hexamethyldisilazane with cyanogen halide followed by rearrangement,[16] or by heating trimethylsilyl isocyanate at 600 °C[17] (Scheme I). Very recently, a patent was issued for the preparation of this carbodiimide.[18]

Scheme I



As seen in Scheme I, the reactions take place only under forcing conditions. We wish to report here that BTMSC can be prepared in 90% yield by the reaction of trimethylsilyl cyanide (Me_3SiCN) with cyanamide (eq 1). The reaction proceeds extremely fast and is complete within seconds. This is a pleasantly unexpected result since it has been reported that Me_3SiCN reacts with amines only at higher temperature (70 °C) and over prolonged periods of time (30 min).[1]

$$N{\equiv}CNH_2 + Me_3Si \xrightarrow{\text{neat, 1 min, room temperature}} Me_3SiN{=}C{=}NSiMe_3 \quad (1)$$

Experimental Section

Bis(trimethylsilyl)carbodiimide. Performance of the reaction under an inert gas atmosphere is not necessary, but exposure of the reaction mixture or the product to moistue should be avoided.

In a well-ventilated hood, Me_3SiCN (12 g, 0.12 mol) was slowly added to cyanamide (2.1 g, 0.05 mol). A vigorous reaction was observed intantaneously as gaseous hydrogen cyanide was vented and trapped in a bottle containing caustic solution. After the exothermic reaction subsided (20 s), the homogeneous clear oil was distilled at atmospheric pressure to afford a colorless oil: yield, 11 g (91.7%); bp 158–162 °C; ^1H NMR (neat, with Me_4Si as internal standard) δ 018; IR spectrum indicates a very strong band typical for carbodiimide at 2190 cm^{-1} (lit.[10] bp 164 °C, IR 2190 cm^{-1}).

It should be noted that when only 1 equiv of Me_3SiCN was used, two clear layers were observed. Surprisingly enough, distillation also gave the bis(trimethylsilyl)carbodiimide in 80% yield instead of the expected *N*-mono(trimethylsilyl)cyanamide. Also after

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