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6-AZABICYCLO[3.2.1]OCTANE DERIVATIVES. SYNTHESIS OF THE 8,12-METHANOAZEPINO[2,1-*a*]ISOQUINOLINE SYSTEM.[1]

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Abstract - The synthesis of the 8,12-methanoazepino[2,1-*a*]isoquinoline system 1 by Bischler-Napieralski cyclization of an appropriate 6-phenethyl-6-azabicyclo[3.2.1]octan-7-one derivative 2 is described. Lactam 2 was prepared by three alternative procedures: (a) direct alkylation of normorphan 6, (b) alkylation of lactim ether 7 with 3,4,5-trimethoxyphenacyl bromide followed by $NaBH_4$ reduction and hydrogenolysis, and (c) lactamization of amino esters 11 or 13, which were obtained from ethyl or methyl 3-aminocyclohexanecarboxylate by direct alkylation or by acylation with 3,4,5-trimethoxyphenylacetyl chloride and further diborane reduction, respectively.

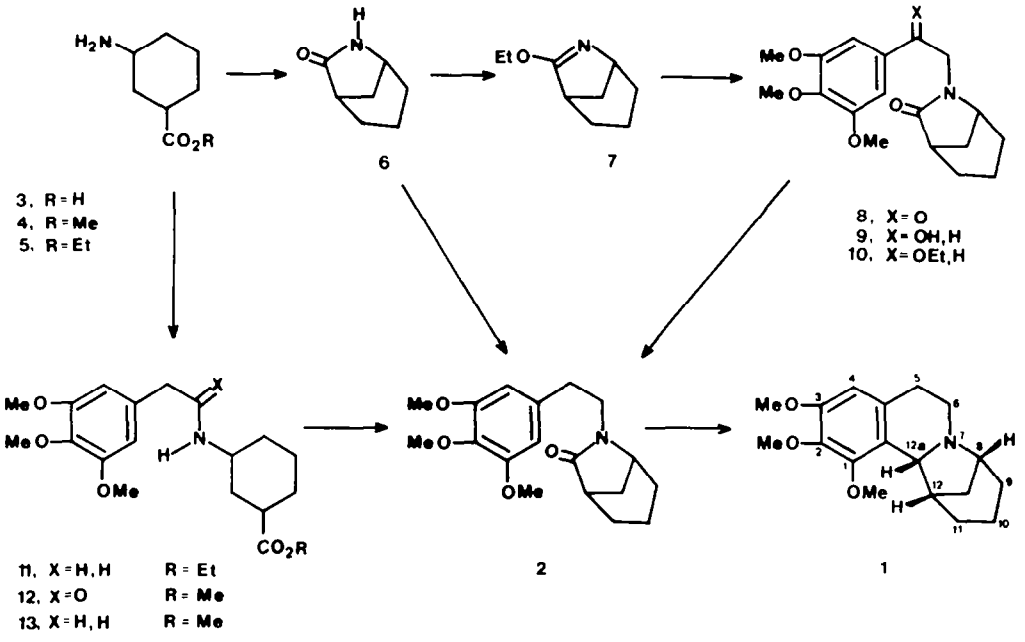
An active area of isoquinoline alkaloids research continues to be the synthesis and pharmacological evaluation of analogues. Thus, works about benzo[*a*]quinolizidines[2] and 6,7-benzomorphans,[3] which are modified structures of the alkaloids emetine and morphine, respectively, are well known. Recentely, we have described the synthesis of several compounds related to those systems, as heteromorphans,[4] 7,8-benzomorphans,[5] 2,5-methanothieno[3,2-*g*]quinolines,[6] 8,14-methanobenzo[*e*]azocino[2,1-*a*]isoquinolines,[7] pyrrolo[2,1-*a*]isoquinolines,[8] and benzo[*a*]quinolizidin-2-ones.[9]

In this paper we report the synthesis of the tetracyclic base 1 which contains simultaneously the 6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline nucleus of some peyote alkaloids[10] and the unusual 6,10-methanopyrido[1,2-*a*]azepine framework of some minor alkaloids from *Securinega* species.[11]

The synthesis of 1 was achieved by Bischler-Napieralski cyclization of the 6-azabicyclo[3.2.1]octan-7-one derivative 2 which, in turn, was prepared by three alternative routes.

There are numerous synthetic approaches to the 6-azabicyclo[3.2.1]octane nucleus.[12-24] However, only few synthesis of systems such as the alkaloid securinine,[11] *D*-normorphinans,[25] *C*-norbenzomorphans,[26] and other bridged aza-derivatives,[27] in which this nucleus is part of a more complex polycyclic structure, have been effected. Moreover, to our knowledge there are no precedents of the utilization of functionalized 6-azabicyclo[3.2.1]octanes as starting materials for the elaboration of bridged polycyclic systems.

In order to obtain the azabicyclooctanone 2 we have initially tried the allylation of the lactam 6 with 3,4,5-trimethoxyphenethyl bromide. We have used a solid/liquid two phase system consisting of pulverized KOH and THF as a solvent, together with tetrabutylammonium bromide,[28] because it is well known



that the reaction of phenethyl bromides with alkaline salts of lactams requires drastic reaction conditions and the yields of the desired *N*-phenethyl substituted products are usually low owing to the competitive formation of styrene derivatives.[29] However, the dehydrohalogenation process was still the predominant one, and compound 2 was isolated in poor yield (*ca.* 10%). The *N*-phenethyl lactam 2 was characterized, in the NMR spectrum, by the chemical shift of C-5 (δ3.50) and aromatic (δ6.35) protons, the former anisotropically affected by the amide carbonyl group.[30]

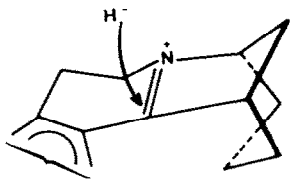
The second procedure is based in the "lactim ether method"[31] which is a helpful procedure for introducing a phenethyl substituent onto a lactam nitrogen, although it requires the alkylation with a phenacyl moiety and further two steps reduction of the ketone carbonyl group. The required lactim ether 7 was obtained by the reaction of triethyloxonium tetrafluoroborate on the lactam 6 followed by treatment of the resulting imidate salt with triethylamine.[32] When an aqueous K_2CO_3 solution was used in the work-up, as it is usual in these reactions,[33] random yields of 7 were obtained since the bridged imidate 7 turned out to be very sensitive to cleavage, affording amino ester 5. The IR spectrum of 7 showed a strong absorption at 1625 cm^{-1} corresponding to the C=N bond.

The treatment of 7 with 3,4,5-trimethoxyphenacyl bromide give lactam ketone 8 in 60% yield. In the IR spectrum the absorptions corresponding to the lactam and conjugated keto carbonyl groups are observed overlapped in the 1675-1695 cm^{-1} region, whereas the most characteristic signals in the NMR spectrum are the doublets corresponding to the diastereotopic methylene protons of the phenacyl chain, which resonate at δ5.15 and δ4.0, with J_{gem}=16 Hz. Reduction of 8 with $NaBH_4$ followed by hydrogenolysis of the resulting alcohol 9 in acidic ethanolic solution using Pd-C catalyst furnished the lactam 2 in moderate yield because of the concomitant formation of ether 10 as a by-product in the last step. Alcohol 9 was also obtained in an attempt to reduce directly the ketone carbonyl group of 8 to a methylene group with Raney Nickel W-7.[34]

A more direct and efficient synthesis of 2 involves the preparation of amino ester 11 (or 13) and its subse-

quent lactamization. Thus, alkylation of 5 with 3,4,5-trimethoxyphenethyl bromide in the presence of $NaHCO_3$ in acetonitrile[35] gave the amino ester 11 in good yield. When anhydrous K_2CO_3 was used as a base and benzene-DMF as a solvent,[36] the yield decreased to 56% due to styrene formation. Alternatively, the synthetically equivalent amino ester 13 was prepared in 40% overall yield by acylation of 4 with 3,4,5-trimethoxyphenylacetyl chloride and further diborane reduction[37] of the resulting amido ester 12. Thermal lactamization of 11 or 13 gave the required lactam 2 in near quantitative yield. The progress of the reaction could be monitored by IR spectroscopy by the decrease of the ester carbonyl signal at 1720 cm^{-1} and the appearance of a strong absorption at 1670 cm^{-1} due to the amide carbonyl group.

Finally, cyclization to the desired tetracyclic compound 1 was achieved by the Bischler-Napieralski reaction,[38] which is the most usual approach to the tetrahydroisoquinoline system.[39,40] Thus, treatment of lactam 2 with phosphoryl chloride followed by sodium borohydride reduction of the resulting iminium salt 14 led stereoselectively to the methanoazepino[2,1-*a*]isoquinoline 1. Its mass spectrum shows an intense peak at m/e (M-43) which is associated with the loss of the propano bridge, such as it has been described for other 6-azabicyclo[3.2.1]octane derivatives.[41]



14

The *cis* relationship between the hydrogen atoms at C-12 and C-12a positions was inferred taking into account that the irreversible attack of the hydride ion occurs from the more accessible face of the iminium salt 14. This stereochemical assignment, as well as the preferred conformation of the indolizidine moiety of 1, was confirmed by NMR from the chemical shift (δ4.45) and the coupling constant (J=6 Hz) of C_{12a}-H proton. Thus, it is well known that *cis*- and *trans*-conformations of benzo[*a*]quinolizidines[42] and related fused systems[43] may be distinguished from the chemical shift of the angular methine proton: the *trans* conformers are characterized by a downfield signal below δ3.8 whereas *cis* conformations show a resonance at a field higher than δ3.8. On the other hand, the vicinal coupling constant between protons on C_{12} and C_{12a} corresponds by the Karplus relation[44] to a dihedral angle (~25°) which is consistent with that observed from Drieding models in the *cis*-isomer 1. The dihedral angle (~85°) in the corresponding *trans* C_{12}-H/C_{12a}-H diastereomer should determine a very lower coupling constant.

EXPERIMENTAL

General. NMR spectra were derermined in $CDCl_3$ solution with a Perkin-Elmer R-24B (60 MHz) instrument using internal TMS (δ0) as a reference. IR spectra were taken with a Perkin-Elmer 577 spectrophotometer, and only noteworthy absorptions (reciprocal centimeters) are listed. Mass spectrum was obtained with a Hewlett-Packard 5930 A spectrometer. Melting points were determined with a Büchi capillary melting point apparatus and are uncorrected.Column and thin-layer chromatography were done by using silica gel 60 (Merck). Iodoplatinate reagent was used to locate the reaction components. Microanalyses were performed by the Instituto de Química Orgánica, Barcelona. Tetrahydrofuran was purified and dried by distillation from $LiAlH_4$. Triethylamine, benzene and acetonitrile were distilled from CaH_2. Methylene chloride and chloroform were distilled from P_2O_5.

6-[3,4,5-Trimethoxyphenacyl]-6-azabicyclo[3.2.1]octan-7-one (8). To a solution of 6-azabicyclo[3.2.1]octan-7-one[45] (6, 0.5 g, 3.9 mmol) in methylene chloride (3 ml) was added slowly triethyloxonium tetrafluoroborate (1.51 g, 7.9 mmol) dissolved in methylene chloride (7 ml). After being stirred at room temperature for 5 days, the solution was basified with triethylamine, diluted with ether, and filtered. Evaporation of filtrate gave 350 mg (71%) of *7-ethoxy-6-azabicyclo[3.2.1]oct-6-ene* (7);

NMR 1.30 (t,3H,OCH_2CH_3), 1.2-2.6 (m, 9H), 3.85 (m,1H,C_5-H), 4.20 (q,2H,OCH_2); IR (NaCl) 1625 (imino ether).

A mixture of imidate 7 (1.4 g, 9.3 mmol) and 3,4,5-trimethoxyphenacyl bromide[46] (2.69 g, 9.3 mmol) in DMF (5 ml) was kept at 60°C for 24 h. After cooling, the solvent was evaporated and the residue was dissolved in benzene (50 ml). The resulting solution was washed successively with 5% aqueous sodium hydroxide and water. The benzene extracts were dried (Na_2SO_4) and evaporated, and the residue was chromatographed on silica gel (elution with 20% benzene in chloroform) to give 1.85 g (60% yield) of keto lactam 8; NMR 1.3-2.6 (m,9H), 3.8 (m,1H,C_5-H), 3.9 (s,9H, OCH_3), 4.0 and 5.15 (2d,1H each, J_{gem}= 16 Hz,NCH_2), 7.30 (s,2H,ArH); IR ($CHCl_3$) 1675-1695 (arylketone, lactam). (Found: C, 64.85; H, 6.95; N, 4.45. Calcd.for $C_{18}H_{23}NO_5$: C, 64.84; H, 6.95; N, 4.20).

6-[2-(3,4,5-Trimethoxyphenyl)-2-hydroxyethyl]-6-azabicyclo[3.2.1]octan-7-one (9). To a stirred, ice-cooled solution of 8 (1.5 g, 4.4 mmol) in ethanol (10 ml) was added portionwise sodium borohydride (490 mg, 13 mmol). After stirring at room temperature overnight, thesolvent was removed. Water was added to the residue, and the aqueous mixture was extracted with benzene. The benzene solution was washed with water, dried (K_2CO_3), and evaporated to leave 9 (955 mg, 65% yield); NMR 1.0-2.5 (m,9H), 2.8-3.3 (m,2H,NCH_2), 3.4-4.0 (m,2H,OH and C_5-H), 3.9 (s,9H, OCH_3), 4.8 (m,1H,CHOH), 6.6 (s,2H,ArH); IR (NaCl) 3370 (alcohol), 1670 (lactam). (Found: C, 63.27; H, 7.59; N, 4.40. Calcd.for $C_{18}H_{25}NO_5.1/3H_2O$: C, 63.32; H, 7.58; N, 4.10).

Ethyl 3-(3,4,5-Trimethoxyphenethylamino)cyclohexanecarboxylate (11). A mixture of 3,4,5-trimethoxyphenethyl bromide[47] (707 mg, 2.57 mmol), ethyl 3-aminocyclohexanecarboxylate[48] (5, 441 mg, 2.57 mmol), sodium bicarbonate (894 mg) and acetonitrile (1.6 ml) was refluxed with vigorous stirring for 24 h. The mixture was diluted with water and extracted with methylene chloride. The organic extracts were dried (Na_2SO_4) and evaporated, and the residue was chromatographed on silica gel (elution with 2% methanol in chloroform) to give 770 mg (83%) of amino ester 11; NMR 1.20 (t,3H,OCH_2CH_3), 1.4-3.2 (m,15H), 3.8 (s,9H,OCH_3), 4.05 (q, 2H,OCH_2), 6.4 (s,2H,ArH); IR ($CHCl_3$) 3540 (amine), 1720 (ester). The oxalate melted at 169-170°C (ethanol). (Found: C, 57.72; H, 7.64; N, 3.09. Calcd.for $C_{22}H_{33}NO_9$: C, 58.00; H, 7.30; N, 3.07).

Methyl 3-(3,4,5-Trimethoxyphenylacetamido)cyclohexanecarboxylate (12). To a solution of methyl 3-aminocyclohexanecarboxylate[49] (4, 3.12 g, 19.8 mmol) and triethylamine (2.01 g, 19.8 mmol) in chloroform (50 ml) was slowly added a solution of 3,4,5-trimethoxyphenylacetyl chloride[50] (4.16 g, 17 mmol) in chloroform (15 ml). After being stirred overnight at room temperature, the reaction mixture was washed with water and 1N aqueous HCl. The organic phase was dried (Na_2SO_4) and evaporated to give an oil which was purified by column chromatography on silica gel. Elution with chloroform afforded 3.42 g (55% yield) of amido ester 12. An analytical sample was obtained by evaporative bulb-to-bulb distillation (b.p. 220-240°C/0.05 mm Hg)and solidified (m.p.98-100°C) on standing; NMR 1.0-3.0 (m,11H), 3.40 (s,2H,CH_2Ar), 3.58 (s,3H, CO_2CH_3), 3.74 (s,9H,OCH_3), 6.35 (s,2H, ArH); IR ($CHCl_3$) 3460 (amide), 1730 (ester), 1660 (amide). (Found: C, 62.40; H, 7.48; N, 3.86. Calcd.for $C_{19}H_{27}NO_6$: C, 62.45; H, 7.45; N, 3.83).

Methyl 3-(3,4,5-Trimethoxyphenethylamino)cyclohexanecarboxylate (13). A solution of the amido ester 12 (317 mg, 0.86 mmol) in 5 ml of THF was slowly added to 2.75 ml (3 mmol) of 1M borane in THF while stirring under nitrogen in an ice bath. The mixture was refluxed for 3 h, then cooled again in an ice bath and treated with ether saturated with HCl gas until effervescence ceased. The solvent was removed *in vacuo* to give a residue which was dissolved in methylene chloride and washed with aqueous K_2CO_3 solution. After drying, the filtrate was evaporated to give amino ester 13 (210 mg, 70% yield). An analytical sample was obtained by column chromatography on silica gel using chloroform/methanol (9:1) as the eluent; NMR 1.0-3.5 (m,15H), 3.58 (s, 3H,CO_2CH_3), 3.74 (s,9H,OCH_3), 6.35 (s, 2H,ArH); IR ($CHCl_3$) 1720 (ester). The oxalate melted at 178-180°C (ether-acetone). (Found: C, 56.75; H, 6.96; N, 3.21. Calcd.for $C_{21}H_{31}NO_9$: C, 57.13; H, 7.07; N, 3.17).

6-(3,4,5-Trimethoxyphenethyl)-6-azabicyclo[3.2.1]octan-7-one (2).

Method A: From 6. A solution of 3,4,5-trimethoxyphenethyl bromide[47] (1.09 g, 4 mmol) and 6-azabicyclo[3.2.1]octan-7-one[45] (6, 0.5 g, 4 mmol) in THF (2 ml) was added over 45 min to a suspension of pulverized KOH (0.25 g, 4.47 mmol) and tetrabutylammonium bromide (0.26 g, 0.81 mmol) in 4 ml of THF at room temperature. After completion of the addition, the reaction mixture was stirred for 6 h. The precipitate was filtered off and the filtrate was evaporated to leave an oil, to which was added methylene chloride and water. The organic phase was washed with saturated aqueous NaCl and dried. Removal of the solvent under reduced pressure left an oil which was chromatographed on silica gel (chloroform as eluent) to give 151 mg (12%) of 2: b.p. 200-210°C/0.3 mm Hg; NMR 1.1-3.2 (m,13H), 3.50 (m,1H,C_5-H), 3.75 (s,9H,OCH_3), 6.35 (s,2H,ArH); IR ($CHCl_3$) 1670 (lactam). (Found: C, 67.57; H, 7.95; N, 4.02. Calcd.for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39).

Method B: From 9. A solution of alcohol 9 (1.33 g, 3.96 mmol) in ethanol (50 ml) containing 70% aqueous $HClO_4$ (0.46 ml) was hydrogenated over 10% Pd-C (930 mg) at 5 at and 25°C for 20 h. The catalyst was removed by filtration and washed with ethanol. The filtrate

and washings were combined and evaporated to leave a jelly. The residue was partitioned by extraction with a mixture of chloroform and water. The chloroform extracts were washed successively with 5% aqueous NaOH and water, dried, and evaporated to furnish an oil which was chromatographed on silica gel. Elution with chloroform gave 756 mg (60% yield) of lactam 2, whereas elution with chloroform-methanol (98:2) furnished 287 mg (20% yield) of *6-[2-(3,4,5-trimethoxyphenyl)-2-ethoxyethyl]-6-azabicyclo[3.2.1]octan-7-one* (10); NMR 1.2-2.5 (m,9H), 1.2 (t,3H,CH_3), 3.0-3.5 (m, 5H,OCH_2,CHN and CH_2N), 3.8 (s,9H,OCH_3), 4.3 (m,1H,CHOEt), 6.5 (s,2H,ArH); IR (NaCl) 1680 (lactam). (Found: C, 66.07; H, 8.09; N, 4.16. Calcd.for $C_{20}H_{29}NO_5$: C, 66.09; H, 8.04; N, 3.85).

Method C: From 11 (or 13). Amino ester 11 (580 mg, 1.5 mmol) was heated at 230°C (17 mm Hg) for 8 h. The resulting oily residue was essentially pure lactam 2. A similar result was obtained from amino ester 13.

(8R,12S*,12aR*)-1,2,3-Trimethoxy-5,6,8,9,10,11,12,12a-octahydro-8,12-methanoazepino[2,1-a]isoquinoline* (1). To a solution of 340 mg (1.06 mmol) of lactam 2 in 10 ml of toluene was added 0.5 ml of freshly distilled phosphoryl chloride. After 2 h at reflux, the reaction mixture was evaporated, and methanol (20 ml) and sodium borohydride (420 mg, 11.1 mmol) was added. After being stirred for 2.5 h at room temperature, the solvent was removed and the residue distributed between ether and water. The ethereal layer was separated, dried and evaporated to leave an oil which was chromatographed on silica gel (10% methanol in chloroform) to yield 248 mg (76%) of 1: NMR 1.4-3.3 (m,14H), 3.75 (s,9H,OCH_3), 4.45 (d,J=6 Hz,1H, C_{12a}-H), 6.3 (s,1H,ArH); MS, m/e (relative intensity) 303(M^+,10), 302(20), 260(5), 248(9), 221(11), 220(11), 184 (23), 181(15), 170(20), 141(34), 124 (100), 109(37), 81(46). The oxalate melted at 166-168°C (acetone-ether). (Found: C, 61.14; H, 6.90; N, 3.40. Calcd.for $C_{20}H_{27}NO_7$: C, 61.05; H, 6.91; N, 3.56).

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REFERENCES

1. This work was presented in a preliminary form at the XIX Reunión Bienal de la Real Sociedad Española de Química, Santander, Spain, 1982.
2. F. D. Popp and R. F. Watts, *Heterocucles*, 1977, *6*, 1189.
3. D. L. Boger, M. Patel and M. D. Mullican, *Tetrahedron Lett.*, 1982, *23*, 4559, and references cited therein.
4. *Inter alia*, a) M. Alvarez, J. Bosch, R. Granados and F. López, *J. Heterocycl. Chem.*, 1978, *15*, 193; b) J. Bosch, J. Bonjoch and I. Serret, *Heterocycles*, 1980, *14*, 1983; c) J. Bosch, D. Mauleón and R. Granados, *An. Quim.*, 1982, *78C*, 236; d) J. Bonjoch, N. Casamitjana and J. Bosch, *Tetrahedron*, 1982, *38*, 2883.
5. J. Bosch, M. Rubiralta, N. Valls, M. Moral and G. Cao, *An. Quim.*, 1983, *79C*, 000.
6. J. Bosch, M. Alvarèz and R. Granados, *J. Heterocycl. Chem.*, 1980, *17*, 745.
7. J. Bosch, A. Domingo and R. Granados, *Ibid.*, 1983, *20*, 000.
8. J.Bosch, E. Mestre, F. López, J. Bonjoch and R. Granados, *An. Quim.*, 1983, *79C*, 000.
9. J. Bosch, A. Domingo and A. Linares, *J. Org. Chem.*, 1983, *48*, 0000.
10. G. J. Kapadia and M. B. E. Fayez, *J. Pharm. Sci.*, 1970, *59*, 1699.
11. Z. Horii, M. Hanaoka, Y. Yamawaki, Y. Tamura, S. Saito, N. Shigematsu, K. Kotera, H. Yoshikawa, Y. Sato, H. Nakai and N. Suqimoto, *Tetrahedron*, 1967, *23*, 1165, and references cited therein.
12. Pyrolysis of amino acids: a) F. R. Hewgill and P. R. Jefferies, *J. Chem. Soc.*, 1955, 2767; b) H. K. Hall, Jr., *J. Am. Chem. Soc.*, 1960, *82*, 1209; c) W. Schneider and J. Hoyer, *Arch. Pharm.*, 1971, *304*, 637; d) R. L. Agustine and L. A. Vag, *J. Org. Chem.*, 1975, *40*, 1074.
13. Lactamization of amino esters: a) V. J. Škarić, V. Turjak-Zebić and D. Škarić, *J. Chem. Soc. Perkin Trans.I*, 1974, 1406; b) M. Takeda, H. Inoue, K. Noguchi, Y. Honma, M. Kawamori, G. Tsukamoto and Y. Yamawaki, *Chem. Pharm. Bull.*, 1976, *24*, 1514.
14. Intramolecular alkylation: L. Pellacani, P. Tardella and M. A. Loreto, *J. Org. Chem.*, 1976, *41*, 1282.
15. Cyclization of γ-bromocarboxamides: M. Takeda, H. Inoue, K. Noguchi, Y. Honma, M. Kawamori, G. Tsukamoto and S. Saito, *Chem. Pharm. Bull.*, 1976, *24*, 1002.
16. Hofmann-Löffler-Freytag reaction: P. G. Gassman and B. L. Fox, *J. Org. Chem.*, 1967, *32*, 3679.
17. From *N*-Chloroamines: a) P. G. Gassman and J. H. Dygos, *Tetrahedron Lett.*, 1970, 4745, 4749; b) J. M. Surzur, L. Stella and R. Nouguier, *Ibid.*, 1971, 903; c) R. Furstoss, R. Tadayoni, G. Esposito, J. Lacrampe, A. Heumann and B. Waegell, *Can. J. Chem.*, 1976, *54*, 3569; d) J. Lacrampe, A. Heumann, R. Furstoss and B. Waegell, *J. Chem. Res. (S)*, 1978, 334.
18. Intramolecular addition of *N*-alkylamido radicals: *Inter alia*, a) R. A. Perry, S. C. Chen, B. C. Menon, K. Hanaya and Y. L. Chow, *Can. J. Chem.*, 1976, *54*, 2385; b) P. Mackiewicz, R. Furstoss, B. Waegell, R. Cote and J. Lessard, *J. Org. Chem.*, 1978, *43*, 3746.
19. Michael-type additions: a) R. Furstoss, P. Teissier and B. Waegell, *J. Chem. Soc. Chem. Comm.*, 1970, 384; b) W. J. Gensler, C. D. Gatsonis and O. A. Ahmed, *J. Org. Chem.*, 1968, *33*, 2968.

20. Molecular rearrangement of other azabicyclic systems: *Inter alia*, a) G. R. Krow, R. Rodebaugh, C. Hyndman, R. Carmosin and G. DeVicaris, *Tetrahedron Lett.*, 1973, 2175; b) R. O. Hutchins and L. Rua, Jr., *J. Org. Chem.*, 1975, *40*, 2567.
21. Palladium catalyzed allylation of amines: B. M. Trost and J. P. Genêt, *J. Am. Chem. Soc.*, 1976, *98*, 8516.
22. Diels-Alder reaction: a) H. Tomisawa, H. Kato, R. Fujita and H. Hongo, *Chem. Pharm. Bull.*, 1979, *27*, 392; b) G. R. Krow, K. M. Damodaran, D. Min Fan, R. Rodebaugh, A. Gaspari and U. K. Nadir, *J. Org. Chem.*, 1977, *42*, 2486.
23. Dieckmann cyclization of substituted pyrrolidines: W. A. M. Davies, A. R. Pinder and I. G. Morris, *Tetrahedron*, 1962, *18*, 405.
24. *Via* ω-carbinollactams: A. R. C. Oostveen, J. J. J. de Boer and W. N. Speckamp, *Heterocycles*, 1977, *7*, 171.
25. T. T. Conway, T. W. Doyle, Y. G. Perron, J. Chapuis and B. Belleau, *Can. J. Chem.*, 1975, *53*, 245.
26. a) K. Mitsuhashi, S. Shiotani, R. Oh Uchi and K. Shiraki, *Chem. Pharm. Bull.*, 1969, *17*, 434; b) G. N. Walker and D. Alkalay, *J. Org. Chem.*, 1971, *36*, 491; c) T. Kametani and S. Shiotani, *J. Med. Chem.*, 1978, *21*, 1105; d) H. Finch, *Tetrahedron Lett.*, 1982, *23*, 4393.
27. *Inter alia*: a) P. Perie, J. P. Laval, J. Roussel and A. Lattes, *Ibid.*, 1971, 4399; b) T. R. Bok and W. N. Speckamp, *Heterocycles*, 1979, *12*, 343; c) A. P. Kozikowski and R. Schimiesing, *J. Chem. Soc. Chem. Comm.*, 1979, 106; d) R. Furstoss, A. Archelas, B. Waegell, J. Le Petit and L. Deveze, *Tetrahedron Lett.*, 1981, *22*, 445.
28. H. Takahata, T. Hashizume and T. Yamazaki, *Heterocycles*, 1979, *12*, 1449.
29. T. Fujii, S. Yoshifuji and K. Yamada, *Chem. Ind.*, 1975, 177.
30. W. E. Stewart and T. H. Siddall, III, *Chem. Rev.*1970, *70*, 517.
31. T. Fujii, S. Yoshifuji and K. Yamada, *Chem. Pharm. Bull.*, 1978, *26*, 2071.
32. W. Ried and E. Schmidt, *Ann. Chem.*, 1966, *695*, 217.
33. T. Fujii and S. Yoshifuji, *Chem. Pharm. Bull.*, 1979, *27*, 1486, 2497.
34. R. H. Mitchell and Y.-H Lai, *Tetrahedron Lett.*, 1980, *21*, 2637.
35. J. E. Johansen, B. D. Christie and H. Rapoport, *J. Org. Chem.*, 1981, *46*, 4914
36. R. T. Dean and H. Rapoport, *Ibid.*, 1978, *43*, 2115.
37. D. D. Miller, P. Osei-Gymah, J. Bandin and D. R. Feller, *J. Med. Chem.*, 1975, *18*, 454.
38. S. Nagubandi and G. Fodor, *J. Heterocycl. Chem.*, 1980, *17*, 1457.
39. T. Kametani, "The Total Syntheses of Isoquinoline Alkaloids", ed. by J. ApSimon in "The Total Synthesis of Natural Products", vol. 3, Wiley, New York, 1977.
40. For synthesis of hexahydropyrrolo [2,1-*a*]isoquinolines by Bischler-Napieralski cyclization from *N*-phenethyl-2-pyrrolidinones, see: a) S. Sugosawa, K. Sakurai and N. Sugimoto, *Proc. Imp. Acad. (Tokyo)*, 1939, *15*, 82 (*Chem. Abstr.*, 1939, *33*, 6318); b) V. Boekelheide and J. C. Godfrey, *J. Am. Chem. Soc.*, 1953, *75*, 3679; c) S. Saito, T. Tanaka, K. Kotera, H. Nakai, N. Sugimoto, Z. Horii, M. Ikeda and Y. Tamura, *Chem. Pharm. Bull.*, 1965, *13*, 786.
41. R. Furstoss, A. Heumann, B. Waegell and J. Gore, *Org. Mass. Spectrom.*, 1972, *6*, 1207; See also ref. 15.
42. M. Uskoković, H. Bruderer, C. Von Planta, T. Williams and A. Brossi, *J. Am. Chem. Soc.*, 1964, *86*, 3364.
43. *Inter alia*: a) G. W. Gribble and R. B. Nelson, *J. Org. Chem.*, 1973, *38*, 2831; b) T. Kametani, K. Fukumoto, M. Thara, A. Ujiie and H. Koizumi., *Ibid.*, 1975, *40*, 3280; c) D. S. Grierson, M. Vuilhorgne, H.-P. Husson and G. Lemoine, *Ibid.*, 1982, *47*, 4439; d) ref. 8.
44. L. M. Jackman and S. Sternhell, "Applications of NMR Spectroscopy in Organic Chemistry" 2nd. ed., Pergamon Press, London, 1969.
45. Lactam 6 was prepared as previously described[12c] from *m*-aminobenzoic acid by hydrogenation over ruthenium followed by pyrolysis of the resulting amino acid 3.
46. W. J. Horton and G. Thompson, *J. Am. Chem. Soc.*, 1954, *76*, 1909.
47. E. A. Steck, L. T. Fletcher and R. P. Brundage, *J. Org. Chem.*, 1963, *28*, 2233.
48. V. Škarić, M. Kovačević and D. Škarić, *J. Chem. Soc. Perkin Trans. I*, 1976, 1199.
49. T. P. Johnston, G. S. McCaleb, P. S. Opliger, W. R. Laster and J. A. Montgomery, *J. Med. Chem.*, 1971, *14*, 600.
50. F. Benington, R. D. Morin and L. C. Clark, Jr., *J. Org. Chem.*, 1957, *22*, 227.