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AZASTEROIDS—VI

A FACILE TOTAL SYNTHESIS OF DL-8-AZAESTRONE METHYL ETHER AND RELATED SYSTEMS[1]

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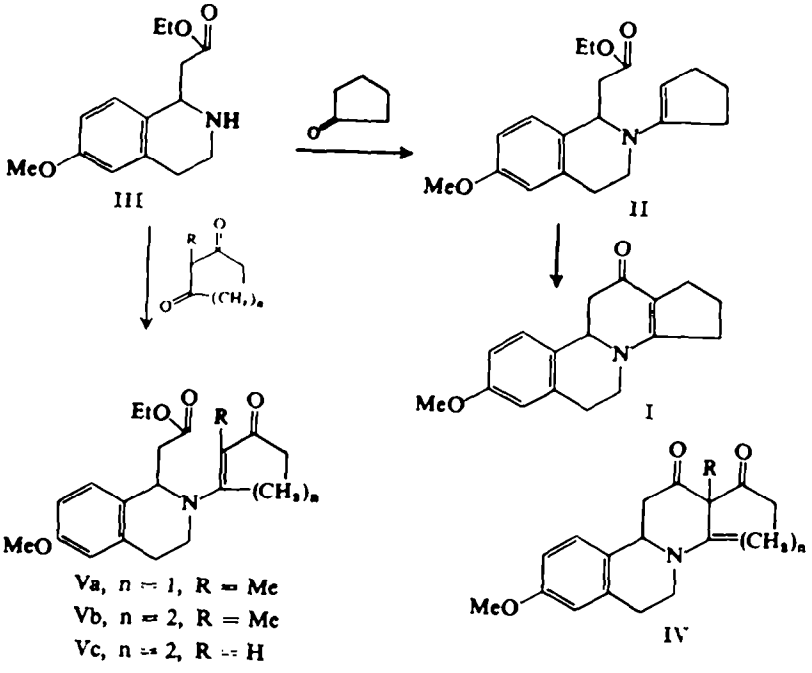
Abstract—A three step (four operational) synthesis of DL-8-azaestrone methyl ether (IX) was accomplished in 43% overall yield from known, readily available starting materials. Condensation of the tetrahydroisoquinoline alcohol, VI, with 2-methyl-1,3-cyclopentanedione gave the enaminoketone, VIIa, in 94% yield which was quantitatively transformed into the corresponding bromide, VIIb. The latter was cyclized in acetonitrile to give the unstable iminium salt, VIII, which was reduced to 55:45 mixture of (DL)-14α- and 14β-8-azaestrone methyl ether (IXa, IXb).

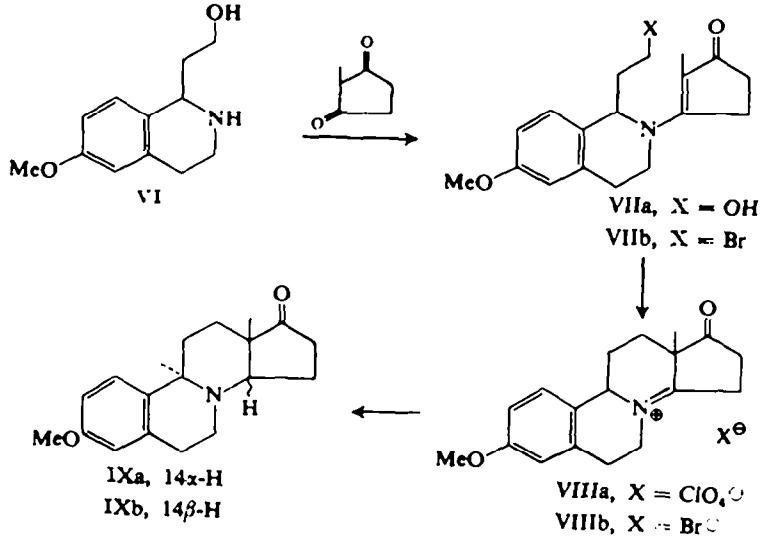
Related steroidal systems have also been prepared by utilization of previously reported methods. An attempt to extend this approach to the D-homo-8-azaestrone series proved unsatisfactory.

IN an earlier report,[2] a general route to the 8- and 9-azasteroid ring systems, I, was outlined utilizing an enamine acylation as the key step. The method was recently published in detail[3] and shown to proceed in good yield involving the spontaneous cyclization of the enamine, II. The logical extension of this process, namely, the use of cyclic diketones and the isoquinoline ester, III, was investigated in the anticipation of obtaining, by a process similar to III → I, the diketosteroid system, IV. The latter would serve a useful precursor to many interesting azasteroids. When III was treated with 2-methyl-1,3-cyclopentanedione and water azeotropically removed, a poor yield of crystalline product was obtained which possessed an UV max at 286 mμ. Further examination confirmed that the product was the enamino ketone, Va, and no trace of the desired IV could be found. Similar results were obtained when 2-methyl-1,3-cyclohexanedione and 1,3-cyclohexanedione were reacted with III, giving only poor yields of the enaminoketone Vb and Vc, respectively. The failure to obtain IV by cyclization of V(a–c) is attributed to the reluctance of the stable *transoid* enaminoketones to exchange their conjugated linkages for the less conjugated system present in IV. Several unsuccessful attempts to convert the carbonyl group in V to its ethylenedioxy derivative were made although similar transformations have been reported.[4] The low yields obtained in the formation of V (a–c) is difficult to explain in the light of the good yields reported by Kessar[5] using tetrahydroisoquinolines and related bases with cyclic diketones.

[1] The authors gratefully acknowledge the support of the National Institutes of Health (NIGMS-06248-05) and the Eli Lilly Co., Indianapolis, Indiana.
[2] A. I. Meyers, G. G. Munoz, W. Sobotka and K. Baburao, *Tetrahedron Letters* No. 4, 255 (1965).
[3] W. Sobotka, W. N. Beverung, G. G. Munoz, J. C. Sircar and A. I. Meyers, *J. Org. Chem.* **30**, 3667 (1965).
[4] F. Bohlmann, E. Winterfeldt, O. Schmidt and W. Reusche, *Chem. Ber.* **94**, 1767 (1961).
[5] S. V. Kessar, A. L. Rampal, K. Kumar and R. R. Jogi, *Indian J. Chem.* 240 (1964).



An alternative approach to the 8-azasteriod system took its cue from the previous observation[5] that an alkyl halide is capable of C-alkylating enaminoketones in good yield. Starting with the known[6] isoquinoline alcohol, VI, obtained from the ester (III) already in hand, it was possible to convert it to the enaminoketone, VIIa, using 2-methyl-1,3-cyclopentanedione. The yield of VIIa was 94%, in contrast to the poor (15%) conversion obtained with the ester, III, using this diketone. VIIa was

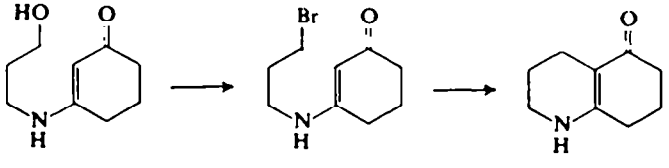


[6] N. A. Nelson, K. Gellotte, Y. Tamara, N. B. Sinclair, J. M. Schuck, V. J. Bauer and R. W. White, *J. Org. Chem.* **26**, 2599 (1961).

obtained as a crystalline material which possessed a maximum at 294 mμ. The alcohol was quantitatively transformed into the bromide, VIIb, using phosphorus tribromide in chloroform. Attempts to cyclize the bromide to VIIIb using the method reported for a related system[7] gave no readily identifiable products. Similar results were obtained when the alcohol, VIIa, was converted to its tosylate and heated in ethanol. However, when VIIb was heated in anhydrous acetonitrile and aliquots periodically examined in the UV, its max at 294 mμ steadily decreased until, after 54 hr, it had reached 10–15% of its original value. The iminium salt, VIIIb, proved to be unstable and was, therefore, reduced without purification in the presence of platinum oxide to 8-azaestrone methyl ether, IX, obtained in 46% yield from VIIb. The cyclization of VIIb was also accomplished in comparable yield after 18 hr, if 1–1·5 equivalents of silver perchlorate were employed. The perchlorate, VIIIa, was likewise unstable and hydrogenated without isolation to IX (a,b). The 8-azasteroid was obtained as a mixture of 14α-(IXa) and 14β-(IXb) isomers in the ratio 55:45. The mixture was conveniently separated by fractional crystallization from ethyl acetate or acetone to afford pure 14α- and 14β-isomers.[8,9] Since no epimers at C-9 and C-13 were encountered through this sequence, it represents a rather highly stereoselective synthesis, and surely a convenient one for 8-azasteroids. It should be noted that Clarkson has reported that his synthesis of 8-azaestrone gave only the 14α-isomer, but this must be due to the relatively planar molecule ($\Delta^{9(11)}$, $\Delta^{14(15)}$) which served as the steroid precursor.

The stereochemical assignments of IXa and IXb were based upon their IR and PMR spectra. Both IXa and IXb exhibited prominent absorption at 3·56 and 3·64 μ (Bohlmann bands[10]) and chemical shifts for the C-9 proton at 6·80–6·82 τ which have been ascribed to *trans*-quinolizidines and *trans*-benzo-quinolizidines,[11] respectively. Since IXa and IXb both possessed *trans*-B/C rings, their difference must lie in the C/D-ring junction (C-13, C-14 configuration). The configuration of the angular methyl group was readily established by comparison of the chemical shift of the

[7] A recent report [H. Dugas, R. A. Allison, Z. Valenta, K. Wiesner, C. M. Wong, *Tetrahedron Letters* No. 18, 1279 (1965)] described the conversion of the enaminoketone, **1**, to the bromide, **2**, and then cyclization in EtOH to **3**, in poor yields with difficulty. We thank Professor Wiesner for making his experimental details available to us.



1 **2** **3**

[8] R. E. Brown, D. M. Lustgarten, R. J. Stanaback and R. I. Meltzer, *J. Org. Chem.* **31**, 1489 (1966). We gratefully acknowledge receiving samples of IXa and IXb from Dr. R. E. Brown for comparison with our material.

[9] R. Clarkson, *J. Chem. Soc.* 4900 (1965).

[10] F. Bohlmann, *Chem. Ber.* **91**, 2157 (1958).

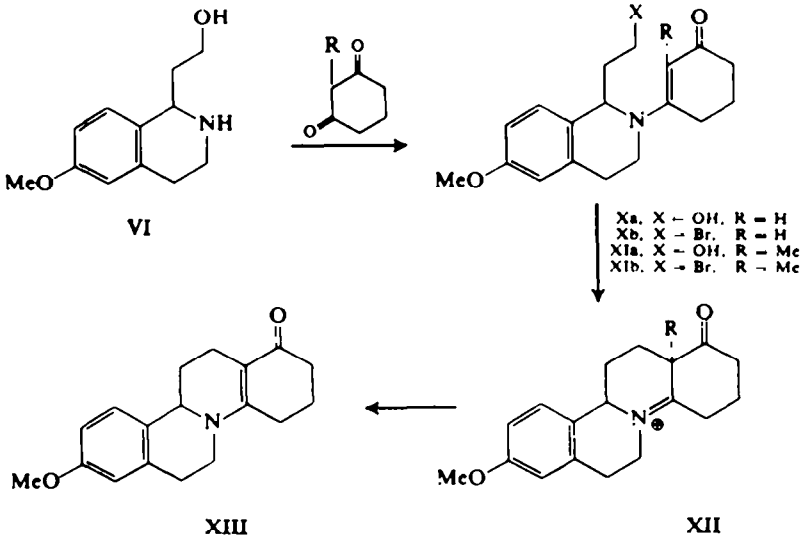
[11] M. Uskakovic, H. Bruderer, C. von Planta, T. Williams and A. Brossi, *J. Amer. Chem. Soc.* **86**, 3364 (1964).

methyl singlet in deuteriochloroform and benzene solvents. Both IXa and IXb exhibited upfield shifts for the methyl singlet in going to benzene as a solvent:

	$\tau(CDCl_3)$	$\tau(C_6H_6)$	$\Delta\tau$
IXa	8·99	9·12	0·13
IXb	8·98	9·20	0·22

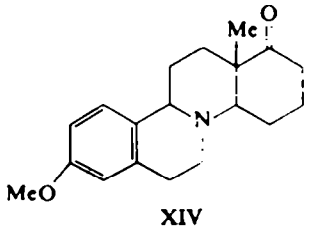
These results are in accord[12] with the observations reported for axially situated methyl groups whereas equatorially placed angular methyl groups would exhibit slight, if any, upfield shifts. No reason is immediately apparent why these correlations from the homocyclic steroids should not hold in this case. On the basic of these spectral results, IXa and IXb must therefore be epimeric at C-14. The higher melting isomer was assigned the 14α-configuration whereas the lower melting isomer was assigned as the 14β-configuration.[13]

In order to determine the scope of the cyclization, VII → VIII, the isoquinoline alcohol, VI, was treated with 1,3-cyclohexanedione and afforded the enaminoketone, Xa, which was converted in the usual manner to the corresponding bromide, Xb. When the latter was heated in acetonitrile in the presence of silver perchlorate, it was quantitatively converted into the tetracyclic derivative, XII (R = H), in 20 hr (as evidenced by the decrease in the UV absorbance). Neutralization of this salt produced the tetracyclic enaminoketone XIII[14] in 95% yield from Xb.



The excellent conversion leading to XIII prompted the investigation leading to the D-homo-8-azasteroid, XIV. This derivative has recently been reported[9] in an elegant study on azasteroids. Although the enaminoketone alcohol, XIa, and the corresponding bromide, XIb, were prepared without any undue difficulty, the cyclization leading to XII (R = Me) was only partially successful. Only trace quantities

[12] D. H. Williams and N. S. Bhacca, *Tetrahedron* **21**, 2021 (1965).
[13] Ref. 6, and private communication from Dr. R. E. Brown.
[14] N. A. Nelson and Y. Tamura, *Canad. J. Chem.* **43**, 1323 (1965).



XIV

of the desired product could be obtained and in an impure state. Studies to further accomplish this goal are still in progress as well as studies leading to the total synthesis of 9-azasteroids.

EXPERIMENTAL

M.ps determined on a Fisher-Johns m.p. apparatus were corrected. UV and IR spectra were taken on Beckman DB and IR-5A instruments, respectively, while NMR spectra were obtained on a Varian A-60[15] using TMS as internal standard and $CDCl_3$ as solvent. TLC (analytical and preparative) was carried out using silica gel PF_{254} (Merck). Thin layer plates for analytical purposes were developed with I vapor, whereas thick layer preparative techniques used UV detection. The preparative plates employed were 1·0–2·0 mm in thickness. Analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

2-*Methyl*-3-N(1-*carboethoxymethyl*-6-*methoxy*-1,2,3,4-*tetrahydroisoquinoline*)*cyclopent*-2-*ene*-1-*one* (Va). A soln containing III[9] (5·8 g), 2-methyl-1,3-cyclopentanedione[4] (3·0 g), toluene (90 ml), and trifluoroacetic acid (0·1 ml) was refluxed in a N atm for 70 hr with continuous water removal. On cooling the soln, there was obtained a crystalline product, 1·1 g, m.p. 181–182° (AcOEt); UV (EtOH), 286 mμ (43,858), 233 mμ (11,255); IR (chf), 5·83 μ (ester carbonyl), 6·20 μ (enamine carbonyl); NMR, 8·50 τ ($-\overset{|}{C}=\overset{|}{C}-CH_3$). (Found: C, 69·74; H, 7·47; N, 4·23. $C_{20}H_{25}O_4N$ requires: C, 69·95; H, 7·34; N, 4·08%.) A picrate was formed in the usual manner, m.p. 161–162° (EtOH).

2-*Methyl*-3-N(1-*carboethoxymethyl*-6-*methoxy*-1,2,3,4-*tetrahydroisoquinoline*)*cyclohex*-2-*ene*-1-*one* (Vb). A soln of III (3·8 g), 2-methyl-1,3-cyclohexanedione (2·53 g), toluene (70 ml) and trifluoroacetic acid (0·1 ml) was refluxed in a N atm for 68 hr with continuous removal of water. The soln was concentrated to a small volume and allowed to stand in the refrigerator where a pale yellow solid crystallized. After filtration, the solid was washed with ether and dried, m.p. 125–135°. Fractional crystallization from chf gave unreacted dione, m.p. 200–205° and the desired product, m.p. 152–154°. The mother liquor was evaporated to dryness and the residue dissolved in a minimum quantity of AcOEt and cooled at 0° overnight. The crystalline ppt was collected and recrystallized from AcOEt, m.p. 154°. Total combined yield was 0·385 g. UV (EtOH) 305 mμ (46,900), 233 mμ (10,050); IR (chf) 5·86 μ (ester carbonyl), 6·22 μ (enamine carbonyl), 6·40 μ (aromatic); NMR, 8·40 τ ($C=C-CH_3$). (Found: C, 70·29; H, 7·82; N, 3·75. $C_{21}H_{27}O_4N$ requires: C, 70·56; H, 7·61; N, 3·92%.)

3-N(1-*carboethoxymethyl*-6-*methoxy*-1,2,3,4-*tetrahydroisoquinoline*)*cyclohex*-2-*en*-1-*one* (Vc). This reaction was carried out in the manner described for Vb using III (5·0 g), dihydroresorcinol[16] (2·8 g), toluene (75 ml) and trifluoroacetic acid (0·1 ml). Removal of the solvent gave Vc (7·5 g) as a viscous yellow oil. UV (EtOH) 302 mμ (44,400), 225 mμ (10,000); IR (chf) 5·78, 6·0, 6·15, 6·20 μ.

2-*Methyl*-3-N[6-*methoxy*-1(2-*hydroxyethyl*)1,2,3,4-*tetrahydroisoquinolyl*]*cyclopent*-2-*ene*-1-*one* (VIIa). A mixture of VI[9] (1·04 g; 5·0 mmoles), 2-methyl-1,3-cyclopent-1,3-dione (0·81 g; 7·3 mmoles), *p*-toluenesulfonic acid (1–5 mg) and dry toluene (20 ml) was refluxed for 20 hr in a N atm with continuous water removal. The solvent was removed *in vacuo* and the brown viscous oil chromatographed on neutral alumina (25 g) using chf as the eluent. The fractions containing crystalline material were combined and recrystallized from chf–ether to give 1·38 g (93·5%) VIIIa, m.p. 137–139°. The analytical sample melted at 139–140°. UV (EtOH) 294 mμ (38,000); IR (chf)

[15] We wish to acknowledge funds granted by the National Science Foundation for the purchase of this instrument. N.S.F. No. GP-3674.

[16] J. C. Sircar and A. I. Meyers, *J. Org. Chem.* 30, 3206 (1965). In this preparation, reagent quality resorcinol must be employed for best results.

2·95 μ (OH), 6·05 μ (N—C=C), 6·21 μ (C=O), 6·45 μ (aromatic); NMR (τ), 2·85–3·35, 3-protons (aromatic); 4·74, one-proton (triplet, benzylic); 6·25, three-protons (singlet, Me); 6·30, two-protons (triplet, CH_2—OH); 5·85 τ, one-proton, exchangeable with D_2O (OH); 8·05, three-protons (singlet, Me). (Found: C, 71·49; H, 7·77; N, 4·79. $C_{18}H_{23}O_3N$ requires: C, 71·73; H, 7·69; N, 4·65%.) The picrate (EtOH) melted at 141–143° (Found: C, 54·25; H, 5·12; N, 10·56. $C_{24}H_{26}O_{10}N_4$ requires: C, 54·34; H, 4·94; N, 10·56%.)

2-*Methyl*-3-N[6-*methoxy*(2-*bromoethyl*)1,2,3,4-*tetrahydroisoquinolyl*]*cyclopent*-2-*ene*-1-*one* (VIIb). To an ice-cold soln of VIIa (1·05 g, 3·5 mmoles) in chf (30 ml) was added slowly, with stirring, a soln of PBr_3 (6·5 g) in chf (20 ml). The mixture was kept at 0–5° for 16 hr and then heated at 50–60° for 1 hr. Upon cooling and dilution with ice (100 g) the mixture was rendered alkaline with K_2CO_3. The chf layer was separated and dried over Na_2SO_4 and concentrated to yield 1·26 g (99%) of a light yellow viscous oil, VIIb. UV (EtOH), 294 mμ (30,860); IR (chf) 6·05 μ (N—C=C), 6·20 μ (C=O), 6·45 μ (aromatic); NMR (τ), 2·9–3·4, three-protons (multiplet, aromatic); 4·79, one-proton (triplet, benzylic); 6·25, three-protons (singlet, methoxy); 6·55, two-protons (triplet, CH_2Br); 8·05, three-protons (singlet, Me). Attempts to crystallize this compound were unsuccessful and it was therefore used without further purification for the subsequent step.

DL-8-*Azdestrone methyl ether* (IXa *and* IXb). The bromide VIIb (0·276 g, 0·76 mmole) was dissolved in acetonitrile[17] (28 ml) and stirred in a N atm for 15 min after which anhydrous silver perchlorate[18] (0·250 g) was added in a single portion. The mixture was stirred under N for 22 hr at reflux temp and aliquots removed periodically during this time. When the absorption of the enaminoketone bromide (294 mμ) decreased to 10–15% of its original value, the heating was discontinued. The solvent was removed *in vacuo* and the dark residue was taken up in EtOH, and insoluble salts removed by filtration. The EtOH soln was hydrogenated in the presence of PtO_2 (110 mg) in a Paar apparatus for 8 hr. After removal of the catalyst and solvent, the residue was dissolved in CH_2Cl_2 (20 ml) and shaken with 5% NaOH (10 ml) followed by water. The organic soln was dried (Na_2SO_4) and concentrated to give a brown oil (220 mg). The crude product (IXa, IXb) was redissolved in CH_2Cl_2 (2 ml) and pipetted onto a thick layer (1·0 mm) silica gel plate (20 × 20 cm). The plate was eluted vertically with AcOEt giving 3 bands which were visualized by an UV lamp. The middle band was cut from the plate and extracted repeatedly with AcOEt which upon concentration produced a colorless solid (98·5 mg, 46%) m.p. 150–160°. The latter was fractionally crystallized from AcOEt (or acetone) to give the 14α-isomer (41 mg), m.p. 170–172° (reported[4,9] 171–172°). The analytical sample melted at 175–176°. IR (CCl_4) 3·56 and 3·64 μ (Bohlmann bands[10]), 5·73 μ (C—O); NMR (τ), 2·90–3·40, three-protons (m, aromatic); 6·25, three-protons (s, MeO); 8·99, three-protons (s, C-18 protons). In benzene the C-18 protons appeared at 9·12 τ. (Found: C, 75·88; H, 7·98; N, 5·04. Calc. for $C_{18}H_{23}NO_3$: C, 75·76; H, 8·12; N, 4·91%.) The hydrobromide salt melted at 248–251° (dec) which showed no depression when mixed with authentic 14α-hydrobromide.[4]

The AcOEt mother liquor was concentrated to give a viscous oil which was converted to the HBr salt. Fractional crystallization of the latter in MeOH gave IXb. HBr (53 mg) m.p. 282–286° (dec). (Found: C, 59·12; H, 6·70; Br, 22·01. Calc. for $C_{18}H_{24}NO_3Br$; C, 59·02; H, 6·56; Br, 21·86%.) The MeOH soln also deposited 12 mg of IXa, HBr, m.p. 249–251° (dec).[4] Neutralization of IXb, HBr, in dil NaOH produced IX, m.p. 122–124°. IR (CCl_4), 3·55, 3·64 μ (Bohlmann bands), 5·74 μ (C=O). NMR (τ), 3·0–3·60 (m, aromatic), 6·20 (s, MeO); 8·98 (s, C-18 protons). In benzene the C-18 protons appeared at 9·30 τ. Recrystallization from pet. ether gave the analytical sample, m.p. 125–126°. (Found: C, 76·05; H, 8·34. Calc. for $C_{18}H_{23}NO_3$; C, 75·76; H, 8·12%.)

Compounds IXa *and* IXb *without use of silver perchlorate.* A soln of VIIb, (550 mg) in anhydrous acetonitrile (55 ml) was refluxed under N for 54 hr. After this period, no further changes were noted from aliquots in the UV. The reaction mixture was treated as above to yield 414 mg crude products.

The crude product (314 mg) was applied to a thick layer plate (2·0 mm, Silica) Gel. and eluted with 30% EtOH–chf. The middle band, after being cut from the plate afforded the mixture of 14α-, 14β-isomers (167 mg, 45%).

3-N[6-*Methoxy*-2(2-*hydroxyethyl*)1,2,3,4-*tetrahydroisoquinoline*]*cyclohex*-2-*ene*-1-*one* (Xa). A mixture containing 1·0 g of VI, 0·814 g 1,3-cyclohexanedione, toluene (20 ml), and a trace of *p*-toluenesulfonic acid was refluxed under N with continuous water removal for 20 hr. Evaporation of the

[17] Freshly distilled over P_2O_5 just prior to use.

[18] Commercial salt dried 36 hr *in vacuo* over P_2O_5.

solvent left a dark oil which was chromatographed over alumina (30 g). The column was eluted initially with 30% chf–pet. ether to remove a deep yellow product (λ_{Max}^{EtOH} 433 mμ) and then with chf to yield 0·728 g of a pale yellow oil, Xa. UV (EtOH) 304 mμ (31,650); IR (chf) 3·0, 6·22, 6·32, 6·45μ; NMR (τ) 2·75–3·35, three-protons (m, aromatic); 4·55, one-proton (s, vinyl); 4·75–5·05, one-proton (t, C-9); 5·83, one-proton (broad, exchangeable with D_2O); 6·20, three-protons (s, MeO).

A picrate was prepared in the usual manner, m.p. 181–182° (abs. EtOH). (Found: C, 54·34; H, 5·14; N, 10·39. $C_{34}H_{36}O_{10}N_4$ requires: C, 54·34; H, 4·94; N, 10·56%.)

3-N[6-*Methoxy*-2(2-*bromoethyl*)1,2,3,4-*tetrahydroisoquinoline*]*cyclohex*-2-*ene*-1-*one* (Xb) *and cyclization to* 9-*methoxy*-2,3,4,6,7,11b,12,13-*octahydro*-1H-*dibenzo*[*a*,*f*]*quinolizin*-1-*one* (XIII). A soln of 0·720 g of Xa in 15 ml chf was cooled in an ice bath and treated with 5 g PBr_3 in 20 ml chf. The reaction mixture was stirred at 0° for 20 hr and heated at 55–60° for 1 hr and then decomposed in ice. After neutralization with solid K_2CO_3, the product was extracted with chf and dried over Na_2SO_4. The solvent was removed at room temp[10] *in vacuo* to give an oil, λ_{Max}^{EtOH} 308 mμ which was immediately used for the cyclization to XIII. A soln containing 0·318 g of the crude bromide in 45 ml dry acetonitrile was treated with 0·42 g silver perchlorate and refluxed under N for 24 hr. An aliquot removed from the reaction vessel indicated no absorption at 308 mμ and the heating was discontinued and the solvent evaporated. The residue was dissolved in chf and washed with 5% NaOHaq and then with water. The chf soln was dried over Na_2SO_4 and then passed through a small column containing 1·6 g alumina. The solvent was concentrated to give an amber oil, XIII, (0·274 g, 95%); UV (EtOH) 318 mμ (22,490);[14] IR (chf); 6·20, 6·48 μ; NMR (τ) 2·75–3·35, three-protons (m, aromatic); 5·64, one-proton (qu, C-9 benzylic); 6·22, three-protons (s, MeO).

The viscous oil was transformed into a picrate, m.p. 174–175° (reported[14] 174–175). (Found: C, 56·23; H, 4·76; N, 11·03. Calc. for $C_{34}H_{34}N_4O_9$; C, 56·25; H, 4·72; N, 10·93%.)

2-*Methyl*-3-N[6-*methoxy*-1(2-*hydroxyethyl*)1,2,3,4-*tetrahydroisoquinoline*]*cyclohex*-2-*ene*-1-*one* (XIa). A mixture of VI (1·00 g), 2-methyl-1,3-cyclohexanedione (0·734 g), *p*-toluenesulfonic acid, and toluene (50 ml) was refluxed for 60 hr under N, with continuous water removal. Upon cooling, unreacted diketone crystallized out (0·416 g) and the filtrate was concentrated yielding a viscous oil. The latter was chromatographed through alumina (30 g) using chf as the eluent. The yield of XIa, m.p. 135–138° (0·430 g) was 50% based on diketone recovery. The analytical sample melted at 143–144° (chf–pet. ether). UV (EtOH), 326 mμ (27,240); IR (chf), 2·90 μ (OH), 6·19 and 6·48 μ (carbonyl); NMR (τ) 2·85–3·40, three-protons (m, aromatic); 5·05, one-proton (t, C-9 benzylic); 5·88, one-proton (exchangeable with D_2O); 6·28, three-protons (s, MeO); 8·20, three-protons (s, Me). (Found: C, 72·13; H, 8·07; N, 4·60. $C_{19}H_{25}NO_3$ requires: C, 72·35; H, 7·99; N, 4·44%.)

2-*Methyl*-3-N[6-*methoxy*-1(2-*bromoethyl*)1,2,3,4-*tetrahydroisoquinoline*]*cyclohex*-2-*ene*-1-*one* (XIb). The alcohol, XIa, (0·417 g) was treated as above with PBr_3 in chf at 0° for 20 hr. After the usual work-up, there was obtained an oil (0·440 g, λ_{Max}^{EtOH} 320 mμ, λ^{chf} 6·19, 6·40 μ) which slowly decomposed and was therefore utilized immediately.

[10] The bromide, Xb, was unstable to heat or prolonged standing and slowly formed an ionic salt, whose exact nature is currently under investigation.