Photocyclisation of Enamides. Part XI.[1] Syntheses of Benzo[*i*]phenanthridines related to Aza-steroids

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Photocyclisation of various types of *N*-(1-naphthoyl)enamines (IIa, b, and d) prepared from the corresponding cyclohexanones provides a general route to benzo[*i*]phenanthridines [(III)—(V), (VII), (VIII), and (XIV)—(XVI)] related to 6-aza-steroids.

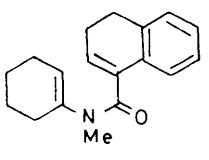
DURING investigations to establish the scope and limitations of photocyclisation of enamides,[1,2] we found that various types of benzo[*i*]phenanthridine could be obtained, providing a potential preparative route to 6-aza-steroids.[3] Three routes to the benzo[*i*]phenanthridine system were considered: (1) photocyclisation of *N*-(αβ-unsaturated acyl)enamines, (2) that of *N*-(1-naphthoyl)enamines, and (3) that of *N*-(3,4-dihydro-1-naphthoyl)anilines.[2] This paper deals with routes (1) and (2), and subsequent approaches to the synthesis of the 6-aza-steroid skeleton.

[1] Part X, I. Ninomiya, T. Naito, and H. Takasugi, preceding paper.

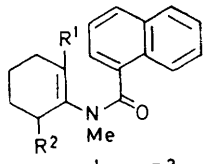
[2] I. Ninomiya, S. Yamauchi, T. Kiguchi, A. Shinohara, and T. Naito, *J.C.S. Perkin I*, 1974, 1747.

[3] Z. Horii, K. Morikawa, and I. Ninomiya, *Chem. and Pharm. Bull. (Japan)*, 1969, **17**, 2230.

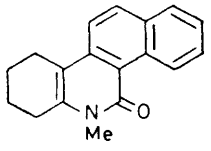
Photocyclisation to Benzo[i]*phenanthridines.*—The enamides (I) and (IIa) were readily prepared by acylation



(I)



(II) a; R^1 = H, R^2 = H
b; R^1 = CO_2Et, R^2 = H
c; R^1 = H, R^2 = Me
d; R^1 = Me, R^2 = H



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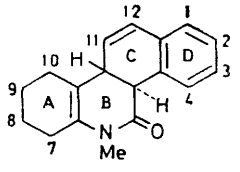

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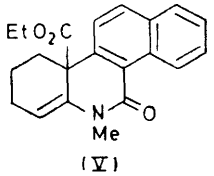

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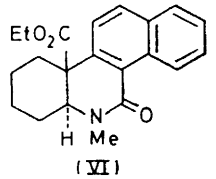

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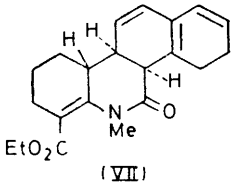

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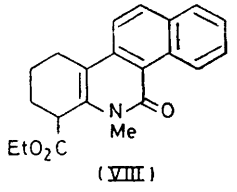

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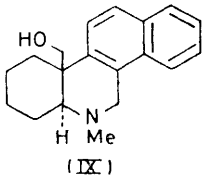

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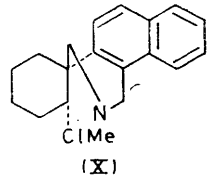
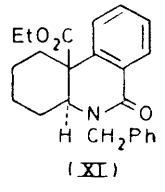
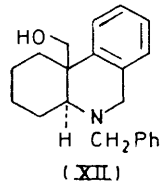


(X)



(XI)



(XII)

(XIII)

of *N*-cyclohexylidenemethylamine with 3,4-dihydro-1-naphthoyl chloride and 1-naphthoyl chloride, respectively. Photochemical experiments were carried out with a 0.02M-solution of the enamide in an appropriate solvent (usually methanol or ether) and a low-pressure mercury lamp at room temperature. The photoproducts were isolated by either column or preparative thin-layer chromatography.

Irradiation of the enamide (I), under oxidative or non-oxidative conditions, afforded a complex mixture of products (t.l.c.), from which only the lactam (III) was isolated. Similarly, photocyclisation of the *N*-naphthoylenamine (IIa), which is expected to proceed stereospecifically as in the case of *N*-benzoylenamines,[4] gave the lactam (III) as major product in only 10% yield, along with a trace of the dihydro-analogue (IV), which was shown to have a BC-*trans*-structure from its n.m.r. spectrum [4b- and 10b-H signals both as doublets, *J* 9 Hz, and two olefinic proton signals (11- and 12-H)]. The formation of the product (IV) is indicative of the stability of an aromatic ring system during photocyclisation.

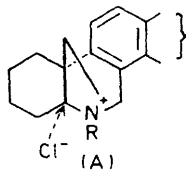
As described previously,[4] an *ortho*-ester group in the enamide showed a marked accelerating effect on the photocyclisation, affording a lactam [*e.g.* (XI)] with an ester group at the ring junction. In addition, transformation of the ester into a methyl group would provide a useful approach to 6-aza steroids. The enamide (IIb) was therefore prepared and irradiated. Three photocyclisation products (V)—(VII) were detected (t.l.c.) but separation proved difficult and only 8% of (VII) was isolated. The structure of (VII) was deduced from its n.m.r. spectrum. On the other hand, oxidative photocyclisation of the enamide (IIb) proceeded smoothly though slowly to afford two photocyclisation products, (V) and (VIII), in 58 and 17% yields, respectively.

The ready and stereospecific conversion of the major product (V) into the AB-*trans*-lactam (VI) by catalytic hydrogenation over palladium–charcoal confirmed the structure of both compounds. The formation of these two types of photoproducts, (VII) and (VIII), is presumably due to steric hindrance by the ester group at the site of cyclisation, which causes a double bond shift at an intermediate stage of the photocyclisation.

With the route to the lactam (VI) [(IIb) ⟶ (V) ⟶ (VI)] established, we next attempted conversion of the angular ester group into a methyl group. Reduction of the ester (VI) with lithium aluminium hydride afforded the amino-alcohol (IX) in good yield. Tosylation of the alcohol (IX) at room temperature was unsuccessful, so it was treated with tosyl chloride in pyridine at reflux temperature; however the isolated product was the chlorospiran (X). This type of transformation was also observed in the case of the model compound (XII), obtained from the photocyclisation product (XI) prepared previously,[4] upon reduction with lithium aluminium hydride. Similar treatment of the amino-alcohol (XII) with tosyl chloride in pyridine afforded the rearrangement product (XIII) in 26% yield. The structure of this spiro-derivative (XIII) was deduced from its n.m.r. spectrum which showed the presence of an axial chlorine atom

[4] I. Ninomiya, T. Naito, and T. Kiguchi, *J.C.S. Perkin I*, 1973, 2257.

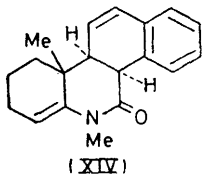
[δ 4.75 ($W_{\frac{1}{2}}$ 5.5 Hz) (CHCl)] and from a positive Beilstein test. The formation of compounds (X) and (XIII) can be explained in terms of rearrangement of an intermediate cation (A).



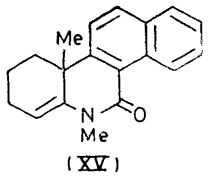
(A)

Approaches to 6-*Aza-steroids.*—After our failure to convert an angular ester goup into a methyl group, we investigated the photocyclisation of an enamide carrying an *ortho*-methyl group.

Acylation of *N*-(2-methylcyclohexylidene)methylamine with 1-naphthoyl chloride yielded the enamide (IIc) in good yield [δ 5.82 (:CH) and 1.02 (d, *Me*CH)]. Irradiation of the neat enamide (IIc) with a high-pressure mercury lamp for 40 min caused quantitative isomerisation to the enamide (IId).[4] This isomerisation also occurred in part during the gentle distillation of the enamide (IIc), but the photochemical procedure was much superior. Irradiation of the enamide (IId) and chromatography afforded three photoproducts, (XIV)—(XVI), in 44, 5, and 8% yields, respectively, in ratios dependent on the solvent employed; the lactam (XV) was obtained predominantly in methanol, whereas the lactam (XIV) was the major product in ether. The structures of these photoproducts were deduced from their n.m.r. spectra and confirmed from their chemical interconversion.



(XIV)



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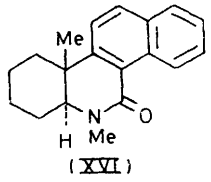

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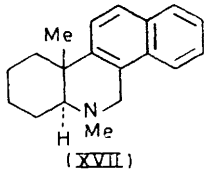

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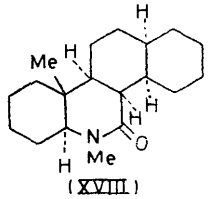

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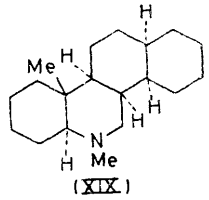

(XIX)

Heating the lactam (XIV) with 10% palladium–charcoal afforded the lactam (XV), which was hydrogenated over 10% palladium–charcoal to yield the *trans*-lactam (XVI) in good yield; these processes established a preparative route to the lactam (XVI) from the enamide (IId). Furthermore, reduction of the *trans*-lactam (XVI) with lithium aluminium hydride afforded the *trans*-amine (XVII).

Catalytic hydrogenation of the lactam (XIV) over platinum oxide in a hydrogen stream at 5 atm pressure gave the lactam (XVIII). The stereochemistry of this lactam (XVIII) was assigned on the basis of favoured addition of hydrogen from the less hindered α-side of the molecule. The saturated amine (XIX) was prepared by reduction of the lactam (XVIII) with lithium aluminium hydride.

EXPERIMENTAL

^{1}H N.m.r. spectra were measured for solutions in deuteriochloroform with a Varian A60-D instrument (tetramethylsilane as internal reference), i.r. spectra for solutions in chloroform, unless otherwise stated, and mass spectra with a JEOL JMS OlSG machine. M.p.s were determined with a Kofler hot-stage apparatus. Photochemical reactions were carried out as described in Part I.[5]

The Enamides (I) *and* (IIa—d).—The method of preparation of the enamides (I) and (IIa—c) is exemplified as follows. To a solution of *N*-cyclohexylidenemethylamine (5 g) and triethylamine (3.6 g) in anhydrous benzene (50 ml), a solution of freshly prepared 3,4-dihydro-1-naphthoyl chloride (8 g) in anhydrous benzene (50 ml) was added dropwise with stirring. After refluxing for 2 h, the cooled mixture was filtered to remove triethylamine hydrochloride. The filtrate was washed with water, dried, and evaporated to give an oily residue, which solidified and was recrystallised from ether to give N-(*cyclohex*-1-*enyl*)-3,4-*dihydro*-N-*methyl*-1-*naphthamide* (I) (9 g, 81%), m.p. 100—102.5°, $\nu_{max.}$ 1 625 cm^{-1} (C=C–CO·N–C=C), δ 6.16 (1 H, approx. t, HC=C·CO), 3.11 (3 H, s, NMe), and 5.78—5.33 (1 H, m, HC=CN), *m/e* 263 (M^+) (Found: C, 81.15; H, 7.55; N, 5.4. $C_{18}H_{21}NO$ requires C, 80.85; H, 7.9; N, 5.25%).

N-(*Cyclohex*-1-*enyl*)-N-*methyl*-1-*naphthamide* (IIa) (100%) had m.p. 128—129.5° (from methanol), $\nu_{max.}$ 1 622 cm^{-1} (C=C·N·CO), δ 5.45 (1 H, m, HC=CN) and 3.23 (3 H, s, NMe), *m/e* 265 (M^+) (Found: C, 81.45; H, 6.95; N, 5.2. $C_{18}H_{19}NO$ requires C, 81.45; H, 7.2; N, 5.3%). *Ethyl* 2-(N-*methyl*-1-*naphthamido*)*cyclohex*-1-*enecarboxylate* (IIb) (93%) had b.p. 140—170° (bath temp.) at 6 × 10^{-3} mmHg, $\nu_{max.}$ 1 700 (CO_2-Et) and 1 625 cm^{-1} (C=C·N·CO), δ 4.17 (2 H, q, *J* 7 Hz, OCH_2Me), 3.31 (3 H, s, NMe), and 1.27 (3 H, t, 7 Hz, $O{\cdot}CH_2Me$), *m/e* 337 (M^+) (Found: C, 74.85; H, 7.05; N, 4.45. $C_{21}H_{23}NO_3$ requires C, 74.75; H, 6.85; N, 4.15%). N-*Methyl*-N-(6-*methylcyclohex*-1-*enyl*)-1-*naphthamide* (IIc) (97%) had m.p. 84—84.5° (from ether), $\nu_{max.}$ 1 633—1 620br (C=C·N·CO·C=C) cm^{-1}, δ 5.82 (1 H, m, HC=CN), 3.30 (3 H, s, NMe), and 1.02 (3 H, d, *J* 7 Hz, CMe), *m/e* 279 (M^+) (Found: C, 81.8; H, 7.55; N, 5.25. $C_{19}H_{21}NO$ requires C, 81.7; H, 7.6; N, 5.0%). Irradiation [4] of the enamide (IIc) with a high-pressure mercury lamp for 40 min afforded N-*methyl*-N-(2-*methylcyclohex*-1-*enyl*)-1-*naphthamide* (IId) (100%), m.p. 104—104.5° (from ether), $\nu_{max.}$ 1 633—1 620br cm^{-1} (C=C·N·CO·C=C), δ 3.27 (3 H, s, NMe) and 1.58 (3H, s, C=CMe), *m/e* 279 (M^+) (Found: C, 81.8; H, 7.3; N, 5.25. $C_{19}H_{21}NO$ requires C, 81.7; H, 7.6; N, 5.0%).

Photoproducts (III)—(V), (VII), (VIII), *and* (XIV)—

[5] I. Ninomiya, T. Naito, and T. Mori, *J.C.S. Perkin I*, 1973, 505.

(XVI).—Irradiation of the enamides (I) and (IIa, b, and d) is exemplified by that of the enamide (I). An ethereal 0.02M-solution of the enamide (I) (4.3 g) was irradiated for 28 h, then evaporated, and the residue was chromatographed on silica gel. Elution with chloroform containing 1% methanol gave an oil (200 mg) which was crystallised from methanol to give yellow crystals, m.p. 157.5—158°, of 7,8,9,10-*tetrahydro*-6-*methylbenzo*[i]*phenanthridin*-5(6H)-*one* (III), $\nu_{max.}$ 1 645 (C=C·N·CO) and 1 593 cm^{-1} (C=C), δ 10.11 (1 H, m, 4-H) and 3.73 (3 H, s, NMe), *m/e* 263 (M^+) (Found: C, 82.0; H, 6.6; N, 5.4. $C_{18}H_{17}NO$ requires C, 82.1; H, 6.5; N, 5.3%). The lactam (III) was also obtained from the enamide (IIa) (10%) and from the enamide (I) under oxidative conditions in the presence of iodine.[4] Data for the other photoproducts are collected in Tables 1 and 2.

(3 H, s, NMe), and 1.13 (3 H, t, *J* 7 Hz, OCH_2Me) (Found: C, 74.55; H, 7.15; N, 4.05%; M^+, 337.168. $C_{21}H_{23}NO_3$ requires C, 74.75; H, 6.85; N, 4.15%; *M*, 337.167).

2′-*Chloro*-2,3-*dihydro*-2-*methylspiro*[*benzo*[h]*isoquinoline*-4(1H),1′-*cyclohexane*] (X).—To an ice-cooled solution of the lactam (VI) (557 mg) in anhydrous ether (50 ml) was added lithium aluminium hydride (300 mg) in small portions. The mixture was heated under reflux for 1.5 h. Treatment as usual gave a pale yellow oil (IX) (543 mg), $\nu_{max.}$ 2 800—2 700 cm^{-1}. Toluene-*p*-sulphonyl chloride (550 mg) was added in portions and the mixture was dissolved in pyridine (20 ml) and heated under reflux for 2 h. The solution was then evaporated and the residue was dissolved in chloroform. The chloroform extract was washed with sodium hydrogen carbonate solution, and water, dried, and evaporated and the residue was recrystallised

TABLE 1

Photoproducts

Compd.	Yield (%) [starting enamide : solvent]	M.p. (°C) (solvent)	Formula	Analysis (%) * C	H	N
(IV)	Trace [(IIa) : MeOH]	(Amorphous)	$C_{18}H_{19}NO$			
(V)	58 [(IIb) : MeOH(I_2)]	(Yellow oil, b.p. 180° at 6×10^{-3} mmHg)	$C_{21}H_{21}NO_3$	75.5 (75.2	6.3 6.3	3.95 4.2)
(VII)	8 [(IIb) : Et_2O]	146—147 (C_6H_6–n-C_6H_{14})	$C_{21}H_{23}NO_3$	74.95 (74.75	6.8 6.85	4.4 4.15)
(VIII)	17 [(IIb) : MeOH(I_2)]	97—98 (Et_2O–petroleum)	$C_{21}H_{21}NO_3$	75.1 (75.2	6.15 6.3	4.15 4.2)
(XIV)	44 [(IId) : Et_2O]	134.5—135.5 (petroleum)	$C_{19}H_{21}NO$	81.5 (81.7	7.65 7.6	4.95 5.0)
(XV)	5 [(IId) : Et_2O]	144—145 (Et_2O)	$C_{19}H_{19}NO$	82.5 (82.3	6.8 6.9	4.95 5.05)
(XVI)	8 [(IId) : Et_2O]	156—157 (C_6H_6–n-C_6H_{14})	$C_{19}H_{21}NO$	81.4 (81.7	7.45 7.6	5.3 5.0)

* Required values in parentheses.

TABLE 2

Spectral data for photoproducts

Compd.	$\nu_{max.}$/cm^{-1}(NCO)	M^+	δ(CDl_3)
(IV)	1 660	265	7.97 (1 H, m, 4-H), 6.50 (1 H, dd, *J* 9.5 and 2 Hz, 12-H), 5.73 (1 H, dd, *J* 9.5 and 2 Hz, 11-H), 4.09 (1 H, d, *J* 9 Hz, 4b-H), 3.17 (3 H, s, NMe), and 2.83 (1 H, approx d, *J* 9 Hz, 10b-H)
(V)	1 728 (CO_2Et), 1 643	335	9.35 (1 H, m, 4-H), 5.55 (1 H, t, *J* 4 Hz, HC=CN), 4.06 (2 H, q, *J* 7 Hz, OCH_2Me), 3.45 (3 H, s, NMe), and 1.15 (3 H, t, *J* 7 Hz, OCH_2Me)
(VII)	1 700 (CO_2Et), 1 663, 1 625 (C=C)	337	6.57 (1 H, dd, *J* 10 and 2 Hz, 12-H), 5.80br (1 H, d, *J* 10 Hz, 11-H), 4.18 (2 H, q, *J* 7 Hz, OCH_2Me), 3.71 (1 H, d, *J* 7 Hz, 4b-H), 3.02 (3 H, s, NMe), 2.90 (1 H, m, 10a-H), 2.67 (1 H, m, 10b-H), and 1.23 (3 H, t, *J* 7 Hz, OCH_2Me)
(VIII)	1 728 (CO_2Et), 1 643	335	10.33 (1 H, m, 4-H), 4.05—3.67 (1 H, m, 7-H), 4.25 (2 H, q, *J* 7 Hz, OCH_2Me), 3.61 (3 H, s, NMe), and 1.26 (3 H, t, *J* 7 Hz, OCH_2Me)
(XIV)	1 630	279	7.55 (1 H, m, 4-H), 6.68 (1 H, d, *J* 10 Hz, 12-H), 5.92 (1 H, dd, *J* 10 and 6 Hz, 11-H), 5.10 (1 H, t, *J* 4 Hz, 7-H), 4.13 (1 H, d, *J* 8.5 Hz, 4b-H), 3.25 (3 H, s, NMe), 2.60 (1 H, dd, *J* 8.5 and 6 Hz, 10b-H), and 0.72 (3 H, s, CMe)
(XV)	1 640	277	5.31 (1 H, approx t-like, HC=CN), 3.40 (3 H, s, NMe), and 1.43 (3 H, s, CMe)
(XVI)	1 643	279	9.33 (1 H, m, 4-H), 3.50 (1 H, dd, *J* 13 and 4 Hz, 6a-H), 3.17 (3 H, s, NMe), and 1.15 (3 H, s, CMe)

Ethyl trans-5,6,6a,7,8,9,10,10a-*octahydro*-6-*methyl*-5-*oxobenzo*[i]*phenanthridine*-10a-*carboxylate* (VI). A solution of lactam (V) (1.4 g) in acetic acid (70 ml) was shaken over 10% palladium–charcoal (696 mg) under a hydrogen atmosphere (*ca.* 5 atm. at 50 °C for 21 h). The catalyst was filtered off and the filtrate was evaporated; the residue was dissolved in chloroform and the extracts were washed with water, dried, and evaporated. Chromatography of the residue on silica gel afforded the trans-*lactam* (VI) (1.1 g, 81%), b.p. 170° (bath temp.) at 6×10^{-3} mmHg, $\nu_{max.}$ 1 728 (CO_2Et) and 1 643 cm^{-1} (N·CO), δ 9.25 (1 H, m, 4-H), 4.08 (2 H, q, *J* 7 Hz, OCH_2Me), 3.77 (1 H, dd, *J* 10 and 7 Hz, 6a-H), 3.25

from ethanol to afford the spiro-compound (X). Recrystallisation of the picrate of (X) from ethanol afforded yellow crystals, m.p. 130—132° (Found: M^+ — Cl, 264.174. $C_{19}H_{22}ClN$ requires M^+ — Cl, 264.176); Beilstein test positive.

2′-*Benzyl*-2-*chloro*-2′,3′-*dihydrospiro*[*cyclohexane*-1,4′(1′H)-*isoquinoline*] (XIII).—By the procedure given for (X), reduction of the lactam (XI) [4] followed by tosylation gave the *spiro-compound* (XIII) (26%), m.p. 145—147° (from ether), $\nu_{max.}$ 2 800— 2700 cm^{-1}, δ 4.75br (1 H, $W_{\frac{1}{2}}$ 5.5 Hz, CHCl), 4.1 and 3.5 (2 H, ABq, *J* 15 Hz), 3.75 and 3.48 (2 H, ABq, *J* 13 Hz), and 3.40 and 2.15 (2 H, ABq, *J* 12 Hz)

(3 × CH_2N), *m/e* 325 (M^+) (Found: C, 77.55; H, 7.15; N, 4.05. $C_{21}H_{24}ClN$ requires C, 77.4; H, 7.4; N, 4.3%); Beilstein test positive.

Dehydrogenation of cis-4b,8,9,10,10a,10b-*Hexahydro*-6,10a-*dimethylbenzo*[i]*phenanthridin*-5(6H)-*one* (XIV).—A mixture of the photoproduct (XIV) (100 mg) and 10% palladium–charcoal in *p*-cymene (10 ml) was heated under reflux for 5 h. The catalyst was filtered off and the solution was evaporated; the residue was extracted with chloroform. Evaporation left a crystalline residue, which was recrystallised from ether to afford yellow crystals (90 mg, 91%), identical with the photoproduct (XV) (i.r. spectrum, g.l.c., and mixed m.p.s).

trans-5,6,6a,7,8,9,10,10a-*Octahydro*-6,10a-*dimethylbenzo*[i]*phenanthridine* (XVII).—By the procedure given for (IX), reduction of the lactam (XVI) (100 mg), which was also obtained from (XV) as described for (VI), with lithium aluminium hydride (50 mg) gave the *amine* (XVII) (50 mg, 53%) as an oil, b.p. 140° (bath temp.) at 7 × 10^{-3} mmHg, $\nu_{max.}$ 2 800—2 700 cm^{-1}, δ 4.45 and 3.70 (2 H, ABq, *J* 16 Hz, NCH_2), 2.40 (3 H, s, NMe), and 1.28 (3 H, s, CMe) (Found: C, 86.3; H, 8.45; N, 4.95. $C_{19}H_{23}N$ requires C, 86.0; H, 8.75; N, 5.3%).

1,2,3,4,4aα,4bα,6aα,7,8,9,10,10aβ,10bα,11,12,12aα-*Hexadecahydro*-6,10aβ-*dimethylbenzo*[i]*phenanthridin*-5(6H)-*one* (XVIII).—By the procedure given for (VI), the lactam (XIV) (500 mg) in acetic acid (30 ml) was hydrogenated over platinum oxide at *ca.* 40 °C for 16 h to give the *lactam* (XVIII) (500 mg, 95%) as needles (from ether), m.p. 160—161.5°, $\nu_{max.}$ 1 622 cm^{-1} (N·CO), δ 2.93 (3 H, s, NMe) and 0.75 (3 H, s, CMe), *m/e* 289 (M^+) (Found: C, 78.8; H, 10.65; N, 5.05. $C_{19}H_{31}NO$ requires C, 78.85; H, 10.8; N, 4.85%).

1,2,3,4,4aα,4bα,5,6,6aα,7,8,9,10,10aβ,10bα,11,12,12aα-*Octadecahydro*-6,10aβ-*dimethylbenzo*[i]*phenanthridine* (XIX).—By the procedure given for (XVII), reduction of the lactam (XVIII) (100 mg) with lithium aluminium hydride (50 mg) gave the *amine* (XIX) (80 mg, 85%) as a pale yellow oil, b.p. 150° (bath temp.) at 6 × 10^{-3} mmHg, $\nu_{max.}$ 2 800—2 700 cm^{-1}, δ 2.15 (3 H, s, NMe) and 0.98 (3 H, s, CMe) (Found: C, 83.1; H, 11.95; N, 5.45. $C_{19}H_{33}N$ requires C, 82.85; H, 12.1; N, 5.1%).

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