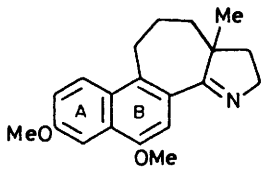
Synthesis and Stereochemical Studies on the Reductions of Some Pyrrole Derivatives

Sudin Bhattacharya, Asok N. Mandal, Swadesh R. Ray Chaudhuri, and Amareshwar Chatterjee *
Department of Chemistry, Jadavpur University, Calcutta-700032, India

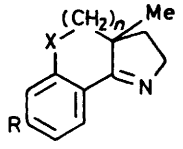
Total syntheses of the unique pyrrole derivatives (2a—d) and the steroid analogue (1) are reported. Reductions of the above imines with sodium borohydride or by a catalytic procedure have been found to be stereospecific, yielding only the *trans*-amine in each case. Metal–ammonia reductions of the benzoxepino- (2a) and benzocycloheptenopyrrole (2d) provided a 2 : 1 mixture of the corresponding *trans*- and the *cis*-amine respectively. Reductions of the indole derivative (2e) with lithium aluminium hydride, sodium in liquid ammonia, or by a catalytic method furnished in each case the *cis*-amine (22b). The rate of reduction of (2e) with sodium borohydride was much slower, and under special conditions it afforded a 3 : 1 mixture of the *cis*- (22b) and the *trans*-amine (22a) respectively. The reasons for the completely different stereochemical results observed in the reductions of the imines (2a—d) and (2e) have been briefly discussed.

Many modified steroids having one or more heteroatoms in the rings have been synthesised, and compounds, particularly those containing nitrogen, have been shown to possess a wide range of physiological activity. The equilenin-like 15-aza-[2] and 6,15-diaza-steroids,[3] having steroid and indole nuclei in a single structure, have been synthesised, and the former is reported [2] to have antibacterial activity.

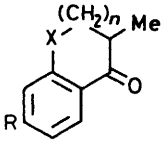
We wish to report here the complete synthesis and characterisation of the 15-aza-c-homoequilenin (steroid nomenclature) derivative (1), as well as the unique pyrrole derivatives where the pyrrole ring is fused to seven-membered heterocyclic and carbocyclic rings, such as (2a—d). The main objective † of this work was to investigate in detail the stereochemistry of reduction of the above imines ‡ (1) and (2a—d) with various reducing agents. Such reductions of the related six-membered analogue (2e) was also undertaken to find out the conformational effects of the six- and seven-membered rings on the stereochemical outcome of the reductions of these imines.



(1)

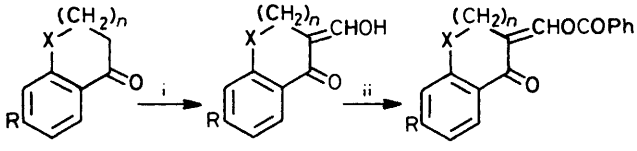


(2)



(3)

a; R = H, X = O, n = 2
b; R = OMe, X = O, n = 2
c; R = H, X = S, n = 2
d; R = OMe, X = CH_2, n = 2
e; R = OMe, X = CH_2, n = 1
f; R = OH, X = CH_2, n = 2
g; R = OH, X = O, n = 2
h; R = OH, X = CH_2, n = 1



(4) (5) (6)

iii

(3a–c) and (3e)*

* a—c and e as in formulae (1)—(3)

Scheme 1. *Reagents:* i, HCO_2Et, NaOMe; ii, PhCOCl, pyridine; iii, PtO_2, H_2

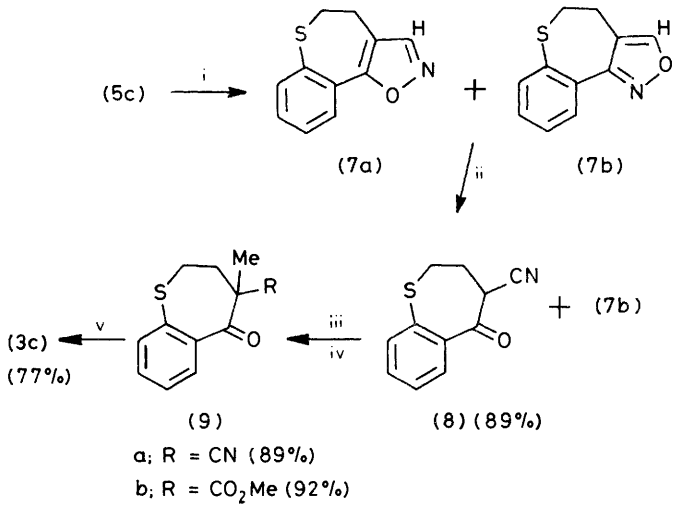
Preparation of the Imines (2a—e) and (1).—The required α-methyl ketones (3a—b) and (3e) were prepared in good overall yields from the known ketones (4a), (4b), and (4e) respectively following essentially the procedure (Scheme 1) reported [4] for a related system.

The preparation of the sulphur ketone (3c) by the above procedure (Scheme 1) was complicated, probably owing to poisoning of the catalyst during hydrogenation of the benzoyloxy derivative (6c). This ketone was finally prepared in good overall yield following the method [5] depicted in Scheme 2. The undesired isoxazole derivative (7b) was isolated in the pure state in low yield after treatment of the crude isoxazole mixture (7a—b) with base (see Experimental section). The special feature of the ^1H n.m.r. spectra of the isoxazoles (7a—b) is that the aromatic hydrogen of the isoxazole ring in (7b) resonated as a singlet at slightly lower field [6] (δ 8.30) than that (δ 8.20) in (7a). The structures assigned for the β-oxonitriles (8), (9a) and the β-oxoester (9b) were confirmed by elemental analyses and spectral data.

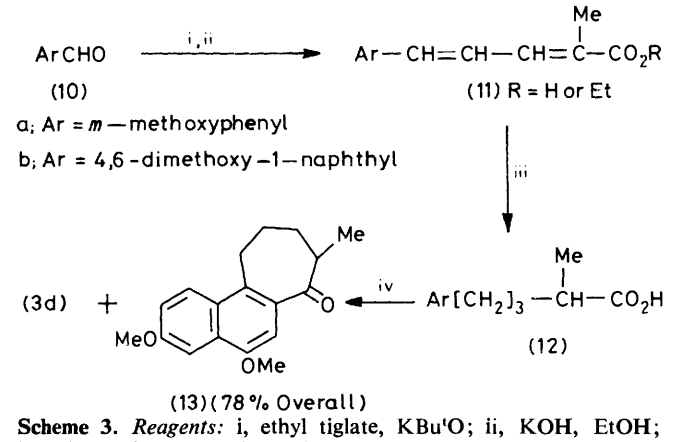
The benzosuberanone derivative (3d) was directly synthesised in good overall yield starting from *m*-methoxybenzaldehyde (10a) as shown in Scheme 3. The crystalline tricyclic ketone (13) was finally available from 4,6-dimethoxy-1-naphthaldehyde [7] (10b) following the reaction sequences shown in Scheme 3.

† The other interest was to find out whether the modification of the ring size and the presence of an extra heteroatom have any effect on the direction of the change in biological activity of the imines (1), (2a—d), and the corresponding reduced products.

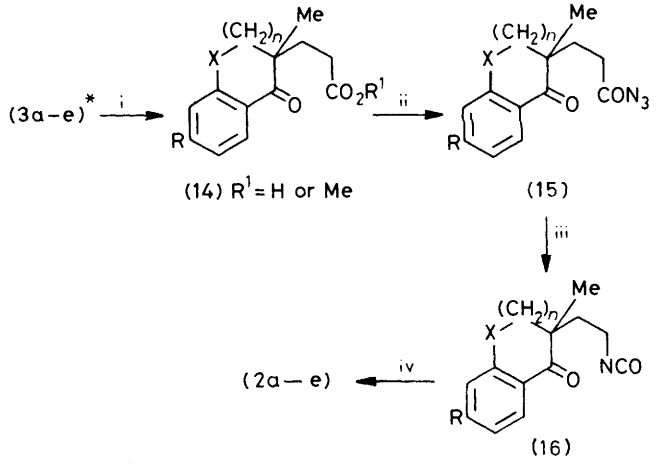
‡ As far as we know similar stereochemical studies on the reductions of this type of imine have not been reported earlier in the literature.



Scheme 2. *Reagents:* i, NH_2OH, AcOH; ii, NaOMe, Et_2O; iii, NaOMe, MeOH, MeI; iv, MeOH, HCl gas; v, AcOH, HCl, H_2O

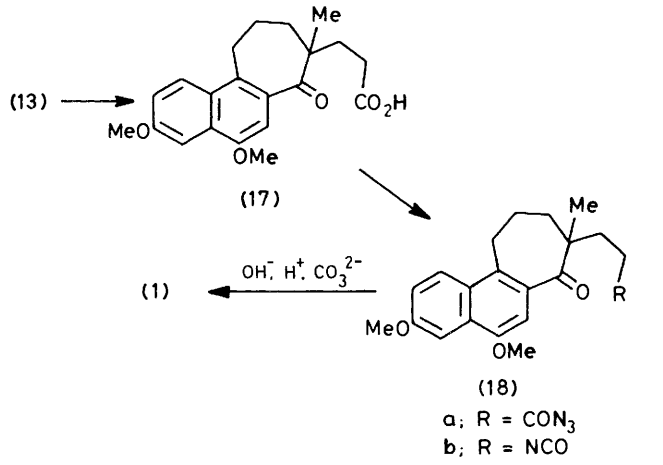


Scheme 3. *Reagents:* i, ethyl tiglate, KBu^{t}O; ii, KOH, EtOH; iii, Ni–Al alloy, OH^-; iv, PPA



* a—e as in formulae (1)—(3)

Scheme 4. *Reagents:* i, CH_2=CHCN, OH^-; ii, $ClCO_2Et$, Et_3N, NaN_3; iii, toluene/heat; iv, HCl, AcOH, reflux



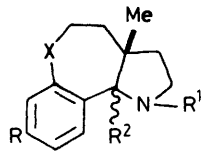
The synthesis of the imines (2a—e) (Scheme 4) involved a modified Curtius rearrangement [2,3,8] of the oxo-acids (14a—e; R^1 = H) which were in turn prepared in excellent yields from the corresponding α-methyl ketones (3a—e) reported above. All the oxo-acids (14a—e; R^1 = H) were fully characterised through their methyl esters. The oily acids (14c; R^1 = H) and (14e; R^1 = H), which failed to crystallise, were sufficiently pure for conversion into the imines (2c) and (2e). The crude isocyanates (16d) and (16e) on refluxing with acids, furnished, besides the main products (2d) and (2e), two phenolic compounds characterised as (2f) and (2h) in low yield. The methoxy-imines (2b) and (2d) on direct demethylation with hydrobromic acid also provided, respectively, the phenols (2g) and (2f). For the preparation of the steroidal imine (1), the crystalline ketone (13) was converted into the oxo-acid (17) as before (Scheme 4).

The acid azide (18a) obtained as a crystalline solid was rearranged to the isocyanate (18b). Hydrolysis of this isocyanate and subsequent cyclisation of the resulting amine with acids as before (Scheme 4) was not satisfactory as it provided a nonhomogeneous high melting phenolic product(s) which could not be fully characterised. Alkaline hydrolysis of the crude isocyanate (18b) and subsequent processing of the reaction mixture (see Experimental section) finally provided the desired imine (1) in good yield.

Results and Discussion

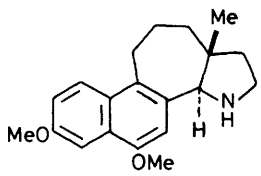
Chemical and Catalytic Reductions of the Imines (2a—e) *and* (1).—It is interesting to note that all the tricyclic imines (2a—d) and the steroid analogue (1) on reduction with sodium borohydride in methanol afforded respectively the saturated amines (19a—d) and (20) as a single stereoisomer and the stereochemistry in each case was found to be *trans*. It may be mentioned here that reduction of the imine (1) with a more powerful reducing agent, such as lithium aluminium hydride, also furnished a single amine characterised as the *trans*-amine (20). Dreiding molecular models of the above saturated amines clearly reveal that in the *trans*-isomer, the angular methyl group is more shielded by the ring current of the benzene ring than that in the case of the corresponding *cis*-isomer. This is supported by the fact that the ^{1}H n.m.r. spectra of the *trans*-amines (19a—d) and (20) displayed high field singlets at δ 0.40—0.67 for the angular methyl groups. The other special features of the spectra are the characteristic singlets for the benzylic hydrogen atoms at the point of ring fusion (see Experimental section). These singlets for (19a—b) were not clearly discernible as they merged with the signals for the methylene groups adjacent to the oxygen atom. The crystalline acetyl derivatives (19e—h) of the above amines also furnished the expected spectral data.

Sodium–liquid ammonia reductions of the imines (2a) and (2d) were next studied in detail, and the results were found to

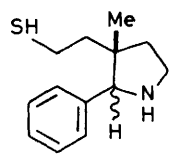


(19)

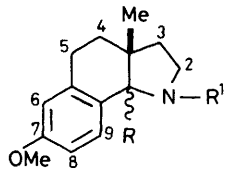
	R	R^1	R^2	X
a;	H	H	α-H	O
b;	OMe	H	α-H	O
c;	H	H	α-H	S
d;	OMe	H	α-H	CH_2
e;	H	COMe	α-H	O
f;	OMe	COMe	α-H	O
g;	H	COMe	α-H	S
h;	OMe	COMe	α-H	CH_2
i;	OMe	H	β-H	CH_2
j;	H	H	β-H	O
k;	OMe	COMe	β-H	CH_2
l;	H	COMe	β-H	O



(20)



(21)



(22)

a; R = α-H, R^1 = H
b; R = β-H, R^1 = H
c; R = α-H, R^1 = COMe
d; R = β-H, R^1 = COMe

be very useful for unambiguous stereochemical assignments of the amines. Such a reduction of (2d), using diethyl ether as the co-solvent and ammonium chloride as the proton source, furnished a mixture of saturated amines (19d) and (19i). The integration curves for the two angular methyl singlets at δ 0.47 and 1.10 indicated the product to be a 2 : 1 mixture of the *trans*-amine (19d) and its *cis*-isomer (19i) respectively. This mixture on acetylation afforded a crude acetyl derivative also as a 2 : 1 mixture (from g.l.c.) of the *trans*-acetyl derivative (19d) and its *cis*-isomer (19k). Similar metal–ammonia reduction of the amine (2a) afforded again a mixture of amines showing angular methyl singlets at δ 0.63 and 1.20 for the *trans* (19a) and the *cis*-isomer (19j) respectively. The crude acetyl derivative, prepared from this mixture, was shown to be a 2 : 1 mixture (from g.l.c.) of the *trans*- (19e) and the *cis*-acetyl derivative (19l) respectively.

Sodium–liquid ammonia reduction of the imines (2c) and (1) did not proceed in the expected way; reduction of (2c) which has a heterocyclic ring containing sulphur was complicated. The ^{1}H n.m.r. spectrum of the crude reduction product showed no characteristic angular methyl singlet for the expected *trans*-amine (19c). Two sharp singlets for angular methyls at δ 0.96 and 1.00, and two other singlets assignable for the benzylic hydrogen atoms at δ 4.56 and 4.64 (counting for one proton) indicated that the C=N of (2c) has been completely reduced. The other characteristic features of the spectrum are the two multiplets at δ 3.00—2.60 and δ 3.54—3.20, each accounting for two protons. From this spectral behaviour, the structure (21) has been tentatively assigned for the reduction product. The aryl–sulphur bond cleavage of (2c) to form (21) probably proceeds through prior reduction [9] of the aromatic ring.

Metal–ammonia reduction of the tetracyclic imine (1) as above afforded a nonhomogeneous material (from ^{1}H n.m.r. and i.r.) and this was not investigated further.

Catalytic reductions of the imines (2d) and (1) were briefly investigated, and this resulted only in the isolation of the corresponding *trans*-amine in each case.

Reduction of the indole derivative (2e) with sodium borohydride as before afforded mainly a mixture of the imine (2e) (from ^{1}H n.m.r.) and a small amount of reduced product. Use of ethanol under reflux or isopropyl alcohol at 60 °C for a long period in the above reduction also provided mainly the unchanged imine (2e). Treatment of (2e) with a more powerful hydride-donating agent, such as lithium aluminium hydride, furnished a saturated amine, identical in all respects with the single stereoisomer obtained through sodium–liquid ammonia or catalytic reduction of (2e). The ^{1}H n.m.r. signal for the angular methyl group at δ 1.18 of this saturated amine when compared with that (δ 1.02) of the related carbocyclic analogue [10] with *cis*-ring fusion suggested the amine to have *cis*-stereochemistry as shown in (22b). The crystalline acetyl derivative (22d) was shown to be homogeneous (g.l.c.) but its ^{1}H n.m.r. spectrum was informative as it depicted two close signals (see Experimental section) for each of the angular methyl groups, the methoxy group, and the acetyl methyl. The behaviour of the benzylic hydrogen atom adjacent to the amide nitrogen is of special significance as it exhibited two sharp singlets at δ 4.20 and 4.93. Conformational isomerism * or restricted rotation around the $-C(O)-N\lesssim$ bond of (22d) may rationalise the multiple signals in its n.m.r. spectrum. It may be mentioned in this connection that the related seven-membered ring acetyl compounds mentioned before showed normal ^{1}H n.m.r. spectra. Reduction of the imine (2e) with a large excess of sodium borohydride for a long period (see Experimental section) was rewarding as this provided a 3 : 1 mixture (from ^{1}H n.m.r.) of the above *cis*-amine (22b) and its *trans*-isomer (22a) respectively. The special features of the ^{1}H n.m.r. spectrum of this mixture are the two characteristic singlets for the angular methyl groups at δ 1.18 and 0.60 respectively for the *cis*- (22b) and the *trans*-amine (22a). The crude acetyl derivative, obtained from this mixture as a viscous oil, showed the expected spectral behaviour for a stereoisomeric mixture of the acetyl derivatives (22c) and (22d).

The very slow rate of reduction observed for the imine (2e) with the less powerful reagent sodium borohydride, resulting in less stereoselectivity, may possibly be due to the less electrophilic character of the benzylic carbon of C=N which is in the same plane as the benzene ring. Lithium aluminium hydride, being a more powerful reducing agent, is very stereoselective giving only the *cis*-amine (22b). The C=N moiety of the seven-membered ring analogues (2a—d) is somewhat out of the plane of the benzene ring, and this accounts for their ease of reduction with sodium borohydride under normal conditions. This reasoning gets further support from the u.v. spectrum of (2d), $\lambda_{max.}$ 255 nm (ε 11 450) when compared with that of the imine (2e), $\lambda_{max.}$ 268 nm (ε 18 050).

* One of the referees suggested the following: ' multiple signals were shown in the n.m.r. spectrum owing to isomerisation.'

The reason for the completely different stereoselectivity observed in the reductions of the imines (2e) and (2a—d) is not completely clear. From an inspection of molecular models, it seems probable that in the case of (2e), the *trans*-attack by hydride ion (or an equivalent species) is hindered owing to the concave nature of the *trans*-face and this accounts for the stereospecificity observed in the reduction of (2e) with metal–ammonia, lithium aluminium hydride, or by a catalytic procedure. In case of the imines (2a—d) having a flexible seven-membered ring, the angular methyl group and the out-of-plane *peri*-hydrogen adjacent to an sp^2 hybridized carbon probably hinder the *cis*-face, and therefore reductions of these imines with hydride or by a catalytic method proceed exclusively from the *trans*-side. However, the possibility of other unspecified minor steric and electronic factors in the transition state of all these reductions cannot be fully excluded.

Experimental

M.p.s were determined on a sulphuric acid bath. U.v. spectra were measured for solutions in ethanol with a Unicam SP 500 spectrophotometer, i.r. spectra for solutions in $CHCl_3$ with a Perkin-Elmer 337 instrument, and n.m.r. spectra for solutions in $CDCl_3$ (unless otherwise stated) with a Varian T-60 spectrometer (tetramethylsilane as internal standard). G.l.c. was carried out on a Hewlett-Packard-5730A chromatograph using 10% UCW-982 on W.AW-DMCS (80—100 mesh, 20 in × 1/8 in) column at 170 °C. Extracts were dried over Na_2SO_4, and light petroleum refers to the fraction of b.p. 60—80 °C.

Preparation of α-*Methyl Ketones* (3a—e).—*4-Benzoyloxymethylene-3,4-dihydro-1-benzoxepin-5(2H)-one* (6a). The homochromanone [11] (4a) (5 g) on condensation with ethyl formate in the presence of dry NaOMe under dry benzene according to the reported procedure [5] afforded the crude formyl derivative (5a) as an oil (5.75 g). This material was directly converted by the literature procedure [4] into the desired benzoyloxy derivative (6a) obtained as a brown solid. Recrystallisation of this product furnished the pure material as *needles* (5.3 g, 60%), m.p. 98—99 °C (EtOH); $\nu_{max.}$ 1 745, 1 680, 1 620, and 1 600 cm^{-1} (Found: C, 73.5; H, 4.9. $C_{18}H_{14}O_4$ requires C, 73.46; H, 4.79%).

4-Methyl-3,4-dihydro-1-benzoxepin-5(2H)-one (3a). A solution of the benzoyloxy derivative (6a) (8.2 g) in dry isopropyl alcohol (182 ml) containing triethylamine (7 ml) was hydrogenated over PtO_2 (0.1 g). Work-up of the reaction mixture by the usual procedure [4] gave the desired *ketone* (3a) (3.3 g, 67%), b.p. 110—115 °C (bath)/2 mmHg; $\nu_{max.}$ 1 685 and 1 600 cm^{-1}; δ (CCl_4) 7.83—6.77 (4 H, m), 4.71—4.27 (1 H, m), 3.84 (1 H, dt, *J* 12 and 5 Hz), 3.37—2.10 (2 H, m), 1.95—1.37 (1 H, m), and 1.17 (3 H, d, *J* 6 Hz) (Found: C, 75.1; H, 6.8. $C_{11}H_{12}O_2$ requires C, 74.98; H, 6.86%).

4-Benzoyloxymethylene-8-methoxy-3,4-dihydro-1-benzoxepin-5(2H)-one (6b). The known [5] hydroxymethylene derivative (5b) (4 g) on treatment with benzoyl chloride in pyridine according to the prescribed [4] procedure afforded the *benzoyloxy derivative* (6b) (5 g, 83%), m.p. 110 °C (EtOH), $\nu_{max.}$ 1 740, 1 675, and 1 600 cm^{-1} (Found: C, 70.2; H, 5.1. $C_{19}H_{16}O_5$ requires C, 70.36; H, 4.97%).

8-Methoxy-4-methyl-3,4-dihydro-1-benzoxepin-5(2H)-one (3b). Catalytic hydrogenation of the above benzoyloxy derivative (6b) (8 g) over PtO_2 as before afforded the desired *ketone* (3b) (4.4 g, 86%), b.p. 140—145 °C/2 mmHg; $\nu_{max.}$ 1 665 cm^{-1}; δ (CCl_4) 7.75 (1 H, d, *J* 8.5 Hz), 6.60—6.43 (2 H, m), 4.36—3.61 (2 H, m), 3.80 (3 H, s) 3.29—2.20 (2 H, m), 1.96—1.54 (1 H, m), and 1.15 (3 H, d, *J* 6 Hz) (Found: C, 70.2; H, 6.9. $C_{12}H_{14}O_3$ requires C, 69.89; H, 6.84%).

4-Formyl-3,4-dihydro-1-benzothiepin-5(2H)-one (5c). Condensation of homothiochromanone (4c) [12] (2 g) with ethyl formate by the literature procedure [5] furnished the crude formyl derivative (5c) (2.1 g, 92%), m.p. 50—55 °C. A part of this material on recrystallisation afforded an analytical *sample* of (5c), m.p. 55—56 °C (Et_2O–light petroleum), $\nu_{max.}$ 1 635 cm^{-1} (Found: C, 63.8; H, 5.1. $C_{11}H_{10}O_2S$ requires C, 64.08; H, 4.89%).

4-Benzoyloxymethylene-3,4-dihydro-1-benzothiepin-5(2H)-one (6c). The above crude formyl compound (5c) (7 g) furnished as before a crude benzoyl derivative which on recrystallisation afforded a pure *sample* of (6c) (8 g, 75%), m.p. 131—132 °C (EtOH); $\nu_{max.}$ 1 740 and 1 680 cm^{-1} (Found: C, 69.8; H, 4.7. $C_{18}H_{14}O_3S$ requires C, 69.67; H, 4.55%).

4-Cyano-3,4-dihydro-1-benzothiepin-5(2H)-one (8). A solution of the crude formyl derivative (5c) (10.3 g, 0.05 mol) in glacial AcOH (167 ml) was treated with $NH_2OH{\cdot}HCl$ (6.95 g, 0.1 mol) and the mixture was heated under reflux for 15 min. Work-up by the reported procedure [5] afforded an isomeric mixture of the iso-oxazole derivatives (7a) and (7b) (9.5 g), m.p. 85—88 °C with shrinking at 70—71 °C. Several recrystallisations of this material finally provided an analytical sample of the desired *iso-oxazole derivative* (7a), m.p. 90—91 °C (Et_2O–light petroleum); $\nu_{max.}$ 1 615 and 1 600 cm^{-1}; δ 8.20 (1 H, s), 8.14—7.91 (1 H, m), 7.64—7.14 (3 H, m), and 3.27—2.81 (4 H, m) (Found: C, 65.2; H, 4.5. $C_{11}H_9NOS$ requires C, 65.02; H, 4.46%).

A solution of the above crude iso-oxazole derivative (9.5 g) in dry diethyl ether (70 ml) was treated with a solution of NaOMe (from 2.2 g of Na) in dry MeOH (35 ml) as reported earlier.[5] Usual work-up of the reaction mixture furnished the desired β-*oxonitrile* (8) [9.1 g, 83% based on ketone (4c)], m.p 105—106 °C (Et_2O–light petroleum); $\nu_{max.}$ 2 250 and 1 689 cm^{-1} (Found: C, 64.9; H, 4.6. $C_{11}N_9NSO$ requires C, 65.02; H, 4.46%).

The above cleavage of the crude iso-oxazole derivative (mixture) with base provided a neutral solid material [0.4 g, 4% based on (5c)]. Recrystallisation of this solid afforded a pure sample of the isomeric *iso-oxazole derivative* (7b), m.p. 70—71 °C (Et_2O–light petroleum); $\nu_{max.}$ 1 615 and 1 600 cm^{-1}; δ 8.30 (1 H, s), 8.09—7.84 (1 H, m), 7.67—7.20 (3 H, m), and 3.24—2.81 (4 H, m) (Found: C, 65.0; H, 4.7. $C_{11}H_9NSO$ requires C, 65.02; H, 4.46%).

4-Cyano-4-methyl-3,4-dihydro-1-benzothiepin-5(2H)-one (9a). Methylation of the β-oxonitrile (8) (4.06 g) by the well-known [13] procedure afforded the methylated β-oxonitrile (9a) (3.7 g, 89%), b.p. 170 °C/0.1 mmHg; m.p. 55 °C. Recrystallisation of this material provided an analytical *sample* of (9a), m.p. 58—59 °C (Et_2O–light petroleum); $\nu_{max.}$ 2 240, 1 685, and 1 600 cm^{-1}; δ 7.60—7.13 (4 H, m), 3.23—2.83 (2 H, m), 2.83—1.91 (2 H, m), and 1.66 (3 H, s) (Found: C, 66.3; H, 5.2. $C_{12}H_{11}NOS$ requires C, 66.35; H, 5.10%).

4-Methoxycarbonyl-4-methyl-3,4-dihydro-1-benzothiepin-5(2H)-one (9b). A solution of (9a) (2.4 g) in dry MeOH (66 ml) was cooled in an ice–salt bath, and was saturated with dry HCl gas keeping the temperature of the reaction mixture at 0 °C. The resulting reaction mixture was left at −5 °C for 16 h and then poured into ice–water (400 ml). The diluted solution was allowed to stand at room temp. for 4 h, and the product was extracted with a mixture of diethyl ether–methylene dichloride (3 × 100 ml). Usual processing of the solvent afforded the β-*oxoester* (9b) (2.55 g, 92%), b.p. 135—140 °C (bath)/0.1 mmHg; $\nu_{max.}$ 1 730 and 1 680 cm^{-1}; δ (CCl_4) 7.62—7.36 (1 H, m), 7.35—7.03 (3 H, m), 3.51 (3 H, s), 3.25—2.81 (2 H, m), 2.75—1.81 (2 H, m), and 1.47 (3 H, s) (Found: C, 62.2; H, 5.7. $C_{13}H_{14}SO_3$ requires C, 62.39; H, 5.64%).

4-Methyl-3,4-dihydro-1-benzothiepin-5(2H)-one (3c). The above β-oxoester (9b) (2.35 g) was hydrolysed and decarboxyl-

ated by being heated under reflux for 7 h with a mixture of AcOH (20 ml), conc. HCl (10 ml), and water (2 ml). Uusal work-up of the reaction mixture gave the desired α-methyl ketone (3c) (1.37 g, 77%), b.p. 110 °C (bath)/0.1 mmHg (lit.,[14] b.p. 124—126 °C/0.8 mmHg); $\nu_{max.}$ 1 675 and 1 600 cm^{-1}; δ (CCl_4) 7.86—7.56 (1 H, m), 7.42—6.99 (3 H, m), 3.76—1.56 (5 H, m), and 1.18 (3 H, d, *J* 7 Hz) (Found: C, 68.5; H, 6.3. Calc. for $C_{11}H_{12}OS$: C, 68.74; H, 6.29%).

5-(m-*Methoxyphenyl*)-2-*methylpenta*-2,4-*dienoic acid* (11a; R = H). An intimate mixture of (10a) (13.8 g, 0.1 mol) and ethyl tiglate[15] (22 g, 0.17 mol) was added dropwise to a stirred solution of Bu^{t}OK, prepared from potassium metal (3.9 g, 0.1 mol) and Bu^{t}OH (62 ml), maintained at 25 °C. The resulting reaction mixture was left at 25—30 °C for 40 h, and then acidified with dil. AcOH (15 ml, 50%). Excess of t-butyl alcohol was then removed under reduced pressure and the residue was diluted with saturated brine. The product was extracted with diethyl ether (3 × 100 ml). The combined extract was washed with water, and any acidic material present was extracted with aq. NaOH (6 × 30 ml; 5%). Usual processing of the neutral solvent afforded a neutral product as an oil (15.3 g). The above alkaline solution on acidification afforded solid acid which was extracted with a mixture of diethyl ether–ethyl acetate (4 × 75 ml). Usual processing of the solvent furnished the solid acid (11a) (13 g), m.p. 140—145 °C. The above neutral material (15.3 g) on hydrolysis with dil. ethanolic KOH and usual work-up provided an additional amount of the acid (11a) (9 g), m.p. 140 °C. The total yield of the acid (11a) was therefore 22 g (quantitative). A part was recrystallised to furnish a pure sample of the *acid* (11a), m.p. 153—155 °C (acetone–light petroleum); $\nu_{max.}$ 1 680 and 1 625 cm^{-1} (Found: C, 71.3; H, 6.2. $C_{13}H_{14}O_3$ requires C, 71.54; H, 6.47%).

5-(m-*Methoxyphenyl*)-2-*methylpentanoic acid* (12a). Reduction of the above crude unsaturated acid (11a; R = H) (22 g) with Ni–Al alloy (50 : 50) in the presence of alkali and usual work-up as reported[16] in the literature gave the saturated *acid* (12a) [13.7 g, 63% based on (10a)], b.p. 169—170 °C/0.2 mmHg; $\nu_{max.}$ 1 700 cm^{-1} (Found: C, 70.1; H, 8.3. $C_{13}H_{18}O_3$ requires C, 70.24; H, 8.16%).

2-*Methoxy*-6-*methyl*-6,7,8,9-*tetrahydro*-5H-*benzocyclohepten*-5-*one* (3d). The above acid (12a) (3 g) was added in one portion to polyphosphoric acid (PPA), prepared from P_2O_5 (18 g) and H_3PO_4 (12 ml, 85%). The reaction mixture was then heated to 100 °C with stirring for 2 h, and then left at room temp. for 16 h. Usual work-up of the reaction mixture afforded the desired *ketone* (3d) (2.2 g), b.p. 136—140 °C/0.2 mmHg; $\nu_{max.}$ 1 670 cm^{-1}; δ (CCl_4) 7.66 (1 H, d, *J* 8 Hz), 6.70 (1 H, dd, *J* 8 and 2.5 Hz), 6.60 (1 H, d, *J* 2.5 Hz), 3.78 (3 H, s), 3.10—2.46 (3 H, m), 2.16—1.50 (4 H, m), and 1.14 (3 H, d, *J* 7 Hz) (Found: C, 76.4; H, 7.8. $C_{13}H_{16}O_2$ requires C, 76.44; H, 7.9%).

Ethyl 5-(4,6-*dimethoxy*-1-*naphthyl*)-2-*methylpenta*-2,4-*dienoate* (11b; R = Et), *and the corresponding carboxylic acid* (11b; R = H). Condensation of the naphthaldehyde (10b)[7] (9 g) with ethyl tiglate[15] in the presence of Bu^{t}OK as before afforded the unsaturated ethyl ester (11b; R = Et) (6.1 g), m.p. 98—101 °C, and the corresponding acid (11b; R = H) (4.2 g), m.p. 215—216 °C. A part of the ethyl ester was recrystallised to furnish an analytical sample of the *ester* (11b; R = Et), m.p. 107—108 °C (Et_2O–light petroleum); $\nu_{max.}$ 1 700 and 1 625 cm^{-1}; δ 8.11—6.61 (8 H, m), 4.22 (2 H, q, *J* 7 Hz), 3.97 (3 H, s), 3.91 (3 H, s), 2.06 (3 H, s), and 1.32 (3 H, t, *J* 7 Hz) (Found: C, 73.4; H, 6.7. $C_{20}H_{22}O_4$ requires C, 73.60; H, 6.79%).

The crude ester (11b; R = Et) (6 g) on alkaline hydrolysis as before provided the acid (11b; R = H) (5.6 g). Therefore the crude yield of the acid (11b; R = H) was 9.8 g (79%). A portion of this acid was recrystallised to afford a pure sample of the *acid* (11b; R = H), m.p. 223—224 °C (acetone–light petroleum); $\nu_{max.}$ 1 670 and 1 610 cm^{-1} (Found: C, 72.3; H, 6.4. $C_{18}H_{18}O_4$ requires C, 72.47; H, 6.08%).

5-(4,6-*Dimethoxy*-1-*naphthyl*)-2-*methylpentanoic acid* (12b). The above crude acid (11b; R = H) (3.2 g) was reduced with Ni–Al alloy by the prescribed procedure[16] to furnish the saturated acid (12b) (3.1 g, 95%), m.p. 93—96 °C. Recrystallisation of this acid afforded an analytical sample of the *acid* (12b), m.p. 99—100 °C (Et_2O–light petroleum); $\nu_{max.}$ 1 704 and 1 630 cm^{-1} (Found: C, 71.6; H, 7.2. $C_{18}H_{22}O_4$ requires C, 71.50; H, 7.33%).

3,5-*Dimethoxy*-8-*methyl*-8,9,10,11-*tetrahydro*-7H-*cyclohepta*[a]*naphthalene* (13). The above saturated acid (12b) (3 g) on cyclisation with PPA afforded a neutral material (2.77 g) which on chromatography over alumina (30 g) and elution of the chromatogram with diethyl ether–light petroleum (1 : 3) furnished the desired ketone (13) [2.65 g, 78% based on (10b)], m.p. 104—105 °C. Recrystallisation of this material gave an analytical sample of *product* (13), m.p. 107—108 °C (Et_2O–light petroleum; $\nu_{max.}$ 1 665 and 1 620 cm^{-1}; δ 8.03 (1 H, d, *J* 9 Hz), 7.59 (1 H, d, *J* 3 Hz), 7.23 (1 H, dd, *J* 9.5 and 3 Hz), 7.16 (1 H, s), 4.00 (3 H, s), 3.93 (3 H, s), 3.58—1.51 (7 H, m), and 1.24 (3 H, d, *J* 6.5 Hz) (Found: C, 75.8; H, 7.1. $C_{18}H_{20}O_3$ requires C, 76.03; H, 7.09%).

6-*Methoxy*-2-*methyl*-3,4-*dihydronaphthalen*-1(2H)-*one* (3e). This ketone was prepared by the reported procedure[4] as shown in Scheme 1.

Synthesis of the Oxo-acids (14a—e).—4-(2-*Methoxycarbonylethyl*)-4-*methyl*-3,4-*dihydro*-1-*benzoxepin*-5(2H)-*one* (14a; R^1 = Me) *and the corresponding carboxylic acid* (14a; R^1 = H). Michael condensation of the ketone (3a) (2.7 g) with acrylonitrile by the reported[2] procedure afforded a crude nitrile which on alkaline hydrolysis (aq. KOH; 20%) provided a crude carboxylic acid as an oil (3.2 g). This acid was purified by esterification with methanol and sulphuric acid to give the *methyl ester* (14a; R^1 = Me) [2.4 g, 60% based on (3a)], b.p. 150 °C (bath)/0.1 mmHg; $\nu_{max.}$ 1 738, 1 678, and 1 601 cm^{-1}; δ (CCl_4) 7.67—6.80 (4 H, m), 4.23 (2 H, t, *J* 6 Hz), 3.60 (3 H, s), 2.17—1.73 (6 H, m), and 1.20 (3 H, s) (Found: C, 68.4; H, 7.3. $C_{15}H_{18}O_4$ requires C, 68.69; H, 6.92%).

The above oxo-ester (14a; R^1 = Me) (1.6 g) after alkaline hydrolysis and usual work-up afforded the corresponding oxo-acid (14a; R^1 = H) (1.5 g), m.p. 60—62 °C. Recrystallisation provided an analytical sample of the *acid* (14a; R^1 = H) (1.3 g, 85%), m.p. 63—64 °C (Et_2O–light petroleum); $\nu_{max.}$ 1 710, 1 680, and 1 601 cm^{-1} (Found: C, 67.7; H, 6.5. $C_{14}H_{16}O_4$ requires C, 67.73; H, 6.50%).

4-(2-*Carboxyethyl*)-8-*methoxy*-4-*methyl*-3,4-*dihydro*-1-*benzoxepin*-5(2H)-*one* (14b; R^1 = H) *and the corresponding methyl ester* (14b; R^1 = Me). Condensation of the ketone (3b) (2 g) with acrylonitrile and subsequent alkaline hydrolysis of the resulting oxonitrile by the reported procedure,[2] afforded a crystalline acid (2.7 g) which on one recrystallisation furnished the desired *oxo-acid* (14b; R^1 = H) (2.2 g, 81%), m.p. 72—74 °C (Et_2O–light petroleum). Further recrystallisation provided an analytical sample of (14b; R^1 = H), m.p. 67—77 °C; $\nu_{max.}$ 1 710, 1 670, and 1 600 cm^{-1}; δ 9.43 (1 H, bs), 7.57 (1 H, d, *J* 9 Hz), 6.73—6.37 (2 H, m), 4.23 (2 H, t, *J* 6 Hz), 3.80 (3 H, s), 2.37—1.73 (6 H, m), and 1.23 (3 H, s) (Found: C, 64.6; H, 6.6. $C_{15}H_{18}O_5$ requires C, 64.74; H, 6.52%).

The crude acid (14b; R^1 = H) (2.7 g) on esterification as before afforded the corresponding *methyl ester* (14b; R^1 = Me) (2.55 g, 90%), b.p. 175—180 °C (bath)/0.1 mmHg; $\nu_{max.}$ 1 738, 1 670, and 1 600 cm^{-1}; δ (CCl_4) 7.45 (1 H, d, *J* 10 Hz), 6.60—6.27 (2 H, m), 4.17 (2 H, t, *J* 6 Hz), 3.77 (3 H, s), 3.53 (3 H, s), 2.20—1.70 (6 H, m), and 1.17 (3 H, s) (Found: C, 65.6; H, 6.9. $C_{16}H_{20}O_5$ requires C, 65.74; H, 6.90%).

4-(2-*Methoxycarbonylethyl*)-4-*methyl*-3,4-*dihydro*-1-*benzothiepin*-5(2H)-*one* (14c; R^1 = Me) *and the acid* (14c; R^1 = H). Michael condensation of the ketone (3c) (4.3 g) with acrylonitrile and subsequent alkaline hydrolysis as before afforded a crude acid (5.75 g). This acid on esterification furnished the *oxoester* (14c; R^1 = Me) [4.95 g, 79% based on (3c)], b.p. 175—180 °C/0.1 mmHg; $\nu_{max.}$ 1 730 and 1 675 cm^{-1}; δ (CCl_4) 7.33—7.07 (4 H, m), 3.57 (3 H, s), 3.03—2.73 (2 H, m), 2.40—1.60 (6 H, m), and 1.20 (3 H, s) (Found: C, 64.7; H, 6.6. $C_{15}H_{18}O_3S$ requires C, 64.74; H, 6.52%).

Alkaline hydrolysis of the above ester (14c; R^1 = Me) furnished the corresponding oxo-acid (14c; R^1 = H) as an oil, and this was used directly in the next step.

6-(2-*Carboxyethyl*)-2-*methoxy*-6-*methyl*-6,7,8,9-*tetrahydro*-5H-*benzocyclohepten*-5-*one* (14d; R^1 = H). Condensation of the ketone (3d) (2.6 g) with acrylonitrile as before gave a crude nitrile which on alkaline hydrolysis afforded crude acidic material as an oil (3.7 g). Purification of this acid with aq. $NaHCO_3$ afforded a crystalline *acid* characterised as (14d; R^1 = H) [2.2 g, 62% based on (3d)], m.p. 93—95 °C (Et_2O–light petroleum); $\nu_{max.}$ 1 715 and 1 680 cm^{-1} (Found: C, 69.4; H, 7.2. $C_{16}H_{20}O_4$ requires C, 69.55; H, 7.30%).

Esterification of the above crude acid (2 g) with MeOH–H_2SO_4 afforded the *oxo-ester* (14d; R^1 = Me) (1.46 g, 69%), b.p. 160—165 °C (bath)/0.1 mmHg; $\nu_{max.}$ 1 735 and 1 675 cm^{-1}; δ (CCl_4) 7.30—6.44 (3 H, m), 3.78 (3 H, s), 3.60 (3 H, s), 2.94—2.57 (2 H, bt), 2.40—1.46 (8 H, m), and 1.12 (3 H, s) (Found: C, 70.3; H, 7.6. $C_{17}H_{22}O_4$ requires C, 70.32; H, 7.64%).

8-(2-*Carboxyethyl*)-3,5-*dimethoxy*-8-*methyl*-8,9,10,11-*tetrahydro*-7H-*cyclohepta*[a]*naphthalene* (17). Michael condensation of the tricyclic ketone (13) with acrylonitrile and subsequent alkaline hydrolysis as stated above provided a gummy acid which was extracted with diethyl ether–methylene chloride. Evaporation of the dry solvent and trituration of the residue with Et_2O–light petroleum afforded the *oxo-acid* (17) [2 g, 80% based on (13)], m.p. 122—125 °C. Further recrystallisation of this acid furnished an analytical *sample* of (17), m.p. 126—127 °C (Et_2O–light petroleum); $\nu_{max.}$ 1 710 and 1 670 cm^{-1}; δ 9.70—9.32 (1 H, bs), 7.97 (1 H, d, *J* 9.5 Hz), 7.57 (1 H, d, *J* 3 Hz), 7.18 (1 H, dd, *J* 9.5 and 3 Hz), 6.70 (1 H, s), 3.97 (3 H, s), 3.92 (3 H, s), 3.38—2.87 (2 H, bt), 1.45—2.57 (8 H, m), and 1.21 (3 H, s) (Found: C, 70.6; H, 6.9. $C_{21}H_{24}O_5$ requires C, 70.77; H, 6.79%).

Methyl β-(1,2,3,4-*tetrahydro*-6-*methoxy*-2-*methyl*-1-*oxo*-2-*naphthyl*)*propionate* (14e; R^1 = Me) *and the corresponding acid* (14e; R^1 = H). Michael condensation of the ketone (3e) (3.5 g) with acrylonitrile and subsequent alkaline hydrolysis as before afforded a crude oily acid which was directly esterified as before to furnish the pure *methyl ester* (14e; R^1 = Me) [4 g, 79% based on (3e) used], b.p. 170 °C/0.1 mmHg; $\nu_{max.}$ 1 740 and 1 665 cm^{-1}; δ (CCl_4) 7.89 (1 H, d, *J* 8.5 Hz), 6.76 (1 H, dd, *J* 8.5 and 2.5 Hz), 6.56 (1 H, d, *J* 2.5 Hz), 3.82 (3 H, s), 3.59 (3 H, s), 2.91 (2 H, t, *J* 6 Hz), 2.48—1.42 (6 H, m), and 1.14 (3 H, s) (Found: C, 69.4; H, 7.4. $C_{16}H_{20}O_4$ requires C, 69.55; H, 7.30%).

Usual alkaline hydrolysis of the above ester (4 g) afforded an acid which was purified through $NaHCO_3$ to furnish the desired acid (14e; R^1 = H) as a liquid, $\nu_{max.}$ 1 715 and 1 665 cm^{-1}, and this was used directly in the next step.

Preparation of the Cyclic Imines (2).—2,3,4,5-*Tetrahydro*-3a-*methyl*-3aH-[1]*benzoxepino*[5,4-b]*pyrrole* (2a). A typical procedure is described for the conversion of the oxo-acid (14a; R^1 = H) into the cyclic imine (2a).

A solution of the oxo-acid (14a; R^1 = H) (1.2 g, 0.0048 mol) in dry acetone (35 ml) was cooled to −5 °C. To this solution was added triethylamine (1.1 ml, 0.008 mol) with stirring under N_2, and the reaction mixture kept below 0 °C. Dry ethyl chloroformate (0.76 ml, 0.008 mol) was then added dropwise to the reaction mixture which was maintained below 0 °C. After complete addition, the reaction mixture was stirred at 0 °C for 30 min. A solution of NaN_3 (0.65 g, 0.01 mol) in H_2O (2.6 ml) was next added dropwise under N_2 so that the temperature did not rise above 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was poured into ice–water (150 ml), and the product was extracted with diethyl ether (3 × 50 ml). The solvent was washed with water, aq. $NaHCO_3$, and finally with water. Evaporation of the dry solvent afforded a viscous oil (1.3 g) as a mixture of the azide (15a) and the isocyanate (16a), $\nu_{max.}$ 2 270, 2 140, 1 710, 1 675, and 1 600 cm^{-1}. This crude mixture (1.3 g) was rearranged by heating it in toluene (50 ml) for 2 h on a steam bath. Removal of toluene under reduced pressure furnished the crude isocyanate (16a) (1.25 g), $\nu_{max.}$ 2 270, 1 675, and 1 600 cm^{-1}.

The above crude isocyanate (1.25 g) was then heated under reflux for 24 h under N_2 with HCl–AcOH–water (1 : 1 : 1; 30 ml). The reaction mixture was then diluted with cold water (175 ml), and the neutral product, if any, was extracted with diethyl ether (2 × 50 ml). The aqueous acidic solution was then treated with excess of solid $NaHCO_3$. The liberated product was extracted with a mixture of diethyl ether–ethyl acetate (3 × 50 ml). The combined extract was washed with water, dried, and evaporated to furnish the desired *imine* (2a) [0.84 g, 87% based on (14a; R^1 = H)], b.p. 95—110 °C (bath)/0.1 mmHg; $\nu_{max.}$ 1 605 cm^{-1}; $\lambda_{max.}$ 245 nm (ε 6 866); δ (CCl_4) 7.65 (1 H, dd, *J* 8 and 2 Hz), 7.37—6.70 (3 H, m), 4.27—3.70 (4 H, m), 2.17—1.70 (4 H, m), and 1.17 (3 H, s) (Found: C, 77.8; H, 7.5. $C_{13}H_{15}NO$ requires C, 77.58; H, 7.51%).

2,3,4,5-*Tetrahydro*-8-*methoxy*-3a-*methyl*-3aH-[1]*benzoxepino*[5,4-b]*pyrrole* (2b). The oxo-acid (14b; R^1 = H) (2 g) was converted into the azide and then into the isocyanate (16b), $\nu_{max.}$ 2 260 and 1 660 cm^{-1}, as described above. Hydrolysis of this isocyanate and cyclisation of the resulting amine was carried out as before. After treatment of the acidic solution with excess of solid $NaHCO_3$, the product was extracted with diethyl ether (3 × 100 ml). The ether extract was washed with aq. NaOH (3 × 50 ml, 5%) to remove any phenolic material present. The solvent was then washed with water, dried and evaporated to give the desired imine (2b) (1.4 g, 84% based on oxo-acid), b.p. 130—140 °C (bath)/0.1 mmHg; m.p. 62—63 °C. Recrystallisation of this material provided a pure sample of the *imine* (2b), m.p. 62—63 °C (Et_2O–light petroleum), $\nu_{max.}$ 1 605 cm^{-1}; $\lambda_{max.}$ 260 nm (ε 11 600); δ 7.63 (1 H, d, *J* 8 Hz), 6.72—6.37 (2 H, m), 4.33—3.80 (4 H, m), 3.77 (3 H, s), 2.17—1.77 (4 H, m), and 1.20 (3 H, s); *m/z* 231 (M^+), 216 (M^+ − 15), and 203 ($M^+ - C_2H_4$) (Found: C, 72.7; H, 7.5. $C_{14}H_{17}NO_2$ requires C, 72.70; H, 7.41%).

The above alkaline extract was just acidified with HCl, and then made alkaline with solid $NaHCO_3$. The liberated product was extracted with diethyl ether (3 × 50 ml). Usual processing of the extract furnished phenolic material as a viscous oil (0.1 g).

2,3,4,5-*Tetrahydro*-8-*hydroxy*-3a-*methyl*-3aH-[1]*benzoxepino*[5,4-b]*pyrrole* (2g). The above methoxy-imine (2b) (0.45 g) was demethylated by being heated under reflux for 12 h under N_2 with HBr (25 ml, 48%). Processing of the acidic solution as before and extraction of the phenol with diethyl ether–methylene dichloride (4 × 75 ml) afforded the solid phenol (2g) (0.3 g, 71%), m.p. 269—275 °C. Recrystallisation of this material furnished pure *phenol* (2g), m.p. 271 °C (acetone–light petroleum); $\nu_{max.}$ 3 600 cm^{-1} (Found: C, 71.9; H, 6.8; N, 6.8. $C_{13}H_{15}NO_2$ requires C, 71.87; H, 6.96; N, 6.45%).

2,3,4,5-*Tetrahydro*-3a-*methyl*-3aH-[1]*benzothiepino*[5,4-b]-

pyrrole (2c). The oxo-acid (14c; R^1 = H) (3.25 g) was converted into the imine (2c) (1.75 g, 61%) following exactly the same procedure as that reported for (2a). The *imine* (2c) had b.p. 110—115 °C (bath)/0.1 mmHg; $\nu_{max.}$ 1 625 cm^{-1}; $\lambda_{max.}$ 228 (ε 10 230) and 267 nm (4 129); δ (CCl_4) 7.42—7.00 (4 H, m), 3.85 (2 H, t, *J* 7 Hz), 2.95—2.68 (2 H, m), 2.22—1.65 (4 H, m), and 1.15 (3 H, s) (Found: C, 71.6; H, 7.0. $C_{13}H_{15}NS$ requires C, 71.87; H, 6.96%).

2,3-*Dihydro*-8-*methoxy*-3a-*methyl*-3aH-*benzocyclohepteno*-[5,6-b]*pyrrole* (2d). The oxo-acid (14d; R^1 = H) (2.1 g) was converted into the acid azide and then into the isocyanate (16d) following the typical procedure described for (2a). Acid hydrolysis of the isocyanate (16d) and work-up of the reaction mixture as described before afforded the desired imine (2d) (1.3 g, 76%) and a crude phenolic product (90 mg). The *imine* (2d) had b.p. 130—135 °C (bath)/0.1 mmHg, $\nu_{max.}$ 1 605 cm^{-1}; $\lambda_{max.}$ 255 nm (ε 11 450); δ (CCl_4) 7.23 (1 H, d, *J* 8 Hz), 6.56 (1 H, dd, *J* 8 and 3 Hz), 6.46 (1 H, d, *J* 3 Hz), 3.84 (2 H, dd, *J* 7.5 and 2.5 Hz), 3.70 (3 H, s), and 2.86—2.48 (2 H, bt), 2.07—1.66 (6 H, m), and 0.93 (3 H, s) (Found: C, 78.6; H, 8.1. $C_{15}H_{19}NO$ requires C, 78.56; H, 8.35).

The above phenolic material (90 mg) on recrystallisation furnished the pure phenol (2f) (50 mg, 5%), m.p. 200 °C (acetone–light petroleum), $\nu_{max.}$ 3 600 cm^{-1}, and this was identical with the demethylation product of (2d).

2,3-*Dihydro*-8-*hydroxy*-3a-*methyl*-3aH-*benzocyclohept-eno*[5,6-b]*pyrrole* (2f). Demethylation of the imine (2d) (0.45 g) as before afforded crude phenolic material (0.45 g), m.p. 185—195 °C. Recrystallisation of this product gave the pure *phenol* (2f) (0.3 g, 71%), m.p. 200 °C (acetone–light petroleum), $\nu_{max.}$ 3 600 and 1 604 cm^{-1} (Found: C, 78.3; H, 8.1; N, 6.7. $C_{14}H_{17}NO$ requires C, 78.10; H, 7.96; N, 6.51%).

2,3-*Dihydro*-9,11-*dimethoxy*-3a-*methyl*-3aH-*naphtho*[a]-*cycloheptheno*[7,8-b]*pyrrole* (1). The oxo-acid (17) (1.52 g) was converted into the corresponding acid azide (18a) (1.72 g), m.p. 82—84 °C (decomp.); $\nu_{max.}$ 2 150, 1 715, and 1 670 cm^{-1}. This azide was rearranged to the isocyanate (18b) by heating it in dry toluene (32 ml) as before. To the resulting toluene solution of (18b) was added aq. KOH (10 ml, 50%), and the reaction mixture was kept at 100 °C for 2 h under N_2 with stirring. Toluene was removed under reduced pressure, and the residue thus obtained was dissolved in cold dil. HCl (6M), and the acidic solution was extracted with diethyl ether–benzene (2 × 50 ml) to remove any neutral material present. The acidic solution was then made alkaline with solid Na_2CO_3, and the separated product was extracted with diethyl ether–methylene dichloride (5 × 75 ml). Usual processing of the extract afforded a solid product which on re-recrystallisation furnished the pure *imime* (1) [0.55 g, 63% based on (17)], m.p. 109—111 °C (Et_2O–light petroleum); $\nu_{max.}$ 1 625 cm^{-1}; δ 7.94 (1 H, d, *J* 9.0 Hz), 7.57 (1 H, d, *J* 3 Hz), 7.13 (1 H, dd, *J* 9 and 3 Hz), 6.85 (1 H, s), 4.20—3.73 (2 H, overlapping with the two OMe signals), 3.96 (3 H, s), 3.89 (3 H, s), 3.43—2.63 (2 H, bt), 2.16—1.60 (6 H, m), and 1.00 (3 H, s) (Found: C, 77.6; H, 7.2; N, 4.6. $C_{20}H_{23}NO_2$ requires C, 77.64; H, 7.49; N, 4.53%).

In another experiment the crude isocyanate (18b) was hydrolysed with acid by the typical procedure. Usual work-up gave a solid product (1.6 g), m.p. 306—310 °C with earlier shrinking, and this could not be purified.

3,3a,4,5-*Tetrahydro*-7-*methoxy*-3a-*methyl*-2H-*benz*[g]*in-dole* (2e). The oxo-acid (14e; R = H (2.2 g) was converted into the acid azide and then into the isocyanate as before. Acid hydrolysis of this isocyanate (16e) as stated before afforded mainly the crystalline cyclic imine (2e) (1.22 g, 67.6% based on oxo-acid used), b.p. 120 °C (bath)/0.1mmHg, m.p 57—59 °C; and phenolic material as a gummy solid. A portion of the above imine was recrystallised to furnish an analytical sample of the pure *imine* (2e) as colourless, short needles, m.p. 59—61 °C (light petroleum, b.p. 40—60 °C), $\nu_{max.}$ 1 600 cm^{-1}; $\lambda_{max.}$ 268 nm (ε 18 050); δ (CCl_4) 7.92 (1 H, d, *J* 8.5 Hz), 6.83—6.47 (2 H, m), 3.97—3.60 (2 H, m), 3.75 (3 H, s), 2.97—2.70 (2 H, m), 2.03—1.43 (4 H, m), and 1.03 (3 H, s) (Found: C, 78.2; H, 8.0; N, 6.7. $C_{14}H_{17}NO$ requires C, 78.10; H, 7.96; N, 6.51%).

The above phenolic product on crystallisation provided a pure sample of the phenol (2h) (50 mg, 3%), m.p. 199—201 °C (acetone–light petroleum); $\nu_{max.}$ 3 610 cm^{-1} (Found: C, 77.4; H, 7.7; N, 7.2. $C_{13}H_{15}NO$ requires C, 77.58; H, 7.51; N, 6.96%).

Chemical and Catalytic Reduction of the Imines (2a—e).—trans-2,3,3a,10b-*Tetrahydro*-8-*methoxy*-3a-*methylbenzocyclo-hepteno*[5,6-b]*pyrrole* (19d) *and the* N-*acetyl derivative* (19h). (*a*) *By* $NaBH_4$ *reduction of the imine* (2d). A solution of the imine (2d) (0.3 g, 0.0013 mol) in MeOH (9 ml) containing 3—4 drops of water was cooled in ice–water. To the cold solution was then added $NaBH_4$ (0.15 g, 0.0039 mol) in small portions with stirring. After complete addition (1—2 h), the reaction mixture was stirred under cold conditions for 3—4 h, and then left at 30 °C for 16 h. The mixture was then poured into ice–water (200 ml) and the diluted solution was allowed to stand at room temp. for 2 h. The product was then extracted with a mixture of diethyl ether–methylene dichloride (3 × 50 ml). The solvent was washed with water, dried, and evaporated to furnish the desired *amine* (19d) (0.3 g, 99%), b.p. 115—120 °C (bath)/0.1 mmHg; $\nu_{max.}$ 1 604 cm^{-1}; δ (CCl_4) 7.29 (1 H, d, *J* 9 Hz), 6.61—6.45 (2 H, m), 3.95 (1 H, s), 3.67 (3 H, s), 3.25—2.82 (2 H, bt), 2.82—2.45 (2 H, bt), 2.08—1.33 (7 H, m), and 0.47 (3 H, s) (Found: C, 77.3; H, 9.4. $C_{15}H_{21}NO$ requires C 77.88; H, 9.15%).

A cold solution of the above amine (19d) (0.29 g) in dry pyridine (3 ml) was treated with Ac_2O (3 ml). The reaction mixture was stirred at 30 °C for 40 h, and then poured into cold dil. HCl (200 ml). The neutral product was then extracted with diethyl ether (3 × 50 ml). Usual processing of the solvent afforded crude solid (0.32 g, 93%); $\nu_{max.}$ 1 620 cm^{-1}. Recrystallisation of the product afforded the pure *acetyl derivative* (19h) as colourless microcrystals (0.2 g, 57%), m.p. 90—92 °C (diethyl ether–light petroleum), $\nu_{max.}$ 1 625 cm^{-1}; δ 7.01 (1 H, d, *J* 9 Hz), 6.76—6.55 (2 H, m), 4.83 (1 H, s), 3.77 (3 H, s), 3.64—1.36 (13 H, m), and 0.45 (3 H, s) (Found: C, 74.5; H, 8.6; N, 5.2. $C_{17}H_{23}NO_2$ requires C, 74.69; H, 8.48; N, 5.12%).

(*b*) *By catalytic reduction of the imine* (2d). A solution of the imine (2d) (0.3 g) in MeOH (14 ml) was hydrogenated over Pd–C (65 mg, 10%) at 30 °C and ordinary pressure. After complete absorption of hydrogen (4 h), the reaction mixture was worked up in the usual way to furnish a saturated amine (0.28 g, 93%) identical in all respects with (19d) described above.

Sodium–liquid ammonia reduction of the imine (2d); *formation of a mixture of the stereoisomeric amines* (19d) *and* (19i). To stirred liquid ammonia (250 ml, directly from the tank) was added a small piece of Na-metal. To the resulting mixture was then added in a slow stream a solution of the imine (2d) (0.3 g, 0.0013 mol) in dry diethyl ether (25 ml). The rest of the Na-metal (total Na used 0.15 g, 0.0065 g-atom) was added in small pieces during 2—3 min. The reaction mixture was then stirred for 3 min, and then excess of NH_4Cl (1 g) was added in one portion. Ammonia was allowed to evaporate, the residue was diluted with water (200 ml), and the product was extracted with diethyl ether (3 × 50 ml). Usual processing of the extract provided the saturated *amine* as a mixture (not resolvable by g.l.c.) of (19d) and (19i) (0.27 g, 89%), b.p. 115—120 °C (bath)/0.1 mmHg. The special features of the ^1H

n.m.r. spectrum are two benzylic hydrogen singlets at δ 3.99 [for (19d)] and 3.81 [for (19i)], and two angular methyl singlets at δ 0.47 [for (19d)] and 1.10 [for (19i)] (Found: C, 77.9; H, 9.3. $C_{15}H_{21}NO$ requires C, 77.68; H, 9.15%).

The above mixtures of amines (0.34 g) was converted into the acetyl derivative as before to give an oil (0.4 g), $\nu_{max.}$ 1 620 cm^{-1}. G.l.c. of this mixture showed it to be a 1 : 2 mixture of *cis*- (19k) and the *trans*-acetyl derivative (19h) respectively. The above oil was distilled to give a mixture of (19k) and (19h), b.p. 170 °C (bath)/0.1 mmHg, $\nu_{max.}$ 1 620 cm^{-1}. The special characteristics of ^1H n.m.r. spectrum are two benzylic hydrogen singlets at δ 4.84 [for (19h)] and 4.51 [for (19k)], and two angular methyl singlets at δ 0.46 [for (19h)] and 1.18 [for (19k)].

trans-2,3,3a,4,5,10b-*Hexahydro*-3a-*methyl*-[1]*benzoxepino*-[5,4-b]*pyrrole* (19a) *and its* N-*acetyl derivative* (19e). Reduction of the imine (2a) (0.45 g) with $NaBH_4$ by the procedure described for (2d) afforded the *trans*-amine (19a) (0.4 g, 90%), b.p. 120 °C (bath)/0.1 mmHg, $\nu_{max.}$ 1 615 cm^{-1}; δ 7.48—6.92 (4 H, m), 4.40—4.16 (2 H, m), 3.88—3.56 (1 H, m), 3.32—3.08 (2 H, m), 2.16—1.72 (5 H, m), and 0.67 (3 H, s).

The above amine (19a) (0.4 g) furnished as before a crude crystalline acetyl derivative (0.34 g, 68%). Recrystallisation of this material afforded the pure *acetyl compound* (19e) as colourless short needles (0.27 g, 55%), m.p. 140—142 °C (acetone–light petroleum), $\nu_{max.}$ 1 630 cm^{-1}; δ 7.30—6.76 (4 H, m), 5.08 (1 H, s), 4.47—3.17 (4 H, m), 2.50—1.57 (4 H, m), 1.83 (3 H, s), and 0.61 (3 H, s) (Found: C, 73.4; H, 8.0; N, 5.8. $C_{15}H_{19}O_2N$ requires C, 73.44; H, 7.81; N, 5.71%).

Sodium–liquid ammonia reduction of the imine (2a); *formation of a mixture of the saturated amines* (19a) *and* (19j). Reduction of the imine (2a) (0.3 g) with Na-metal in liquid ammonia as before afforded a stereoisomeric *mixture* (not resolvable by g.l.c.) of (19a) and (19j) (0.21 g, 68%), b.p. 110 °C (bath)/0.1 mmHg, $\nu_{max.}$ 1 600 cm^{-1}; the special features of its ^1H n.m.r. spectrum are two angular methyl singlets at δ 0.63 and 1.20 respectively for (19a) and (19j) (Found: C, 76.7; H, 8.6. $C_{13}H_{17}NO$ requires C, 76.81; H, 8.43%).

Acetylation of the above amine mixture (310 mg) as before provided an acetyl derivative as an oily solid (350 mg, 93%), $\nu_{max.}$ 1 630 cm^{-1}. The special characteristics of its ^1H n.m.r. spectrum are two benzylic hydrogen singlets at δ 5.11 and 4.91, and two angular methyl singlets at δ 0.61 and 1.30 respectively for the *trans*-acetyl derivative (19e) and its *cis*-isomer (19l). G.l.c. of this mixture showed it to be a 1 : 2 mixture of (19l) and (19e) respectively.

trans-2,3,3a,4,5,10b-*Hexahydro*-8-*methoxy*-3a-*methyl*[1]-*benzoxepino*[4,5-b]*pyrrole* (19b) *and its* N-*acetyl derivative* (19f). Reduction of the imine (2b) (0.2 g) with $NaBH_4$ as described for (2d), afforded the *trans*-amine (19b) (0.15 g, 76%), b.p. 120 °C (bath)/0.1 mmHg; $\nu_{max.}$ 1 612 cm^{-1}; δ (CCl_4) 7.17 (1 H, bd, *J* 8 Hz), 6.57—6.33 (2 H, m), 4.33—3.97 (2 H, m), 3.70 (3 H, s), 3.80—3.53 (1 H, m), 3.10 (2 H, bt, *J* 8 Hz), 2.03—1.53 (5 H, m), and 0.63 (3 H, s).

The above amine on acetylation afforded a crystalline acetyl derivative (0.3 g, 75%), m.p. 170—172 °C. Recrystallisation of this product furnished the pure *acetyl derivative* (19f) as short colourless needles, m.p. 172—173 °C, $\nu_{max.}$ 1 625 cm^{-1}; δ 7.00 (1 H, d, *J* 9 Hz), 6.76—6.43 (2 H, m), 4.98 (1 H, s), 4.56—3.16 (4 H, m), 3.77 (3 H, s), 2.26—1.13 (4 H, m), 1.85 (3 H, s), and 0.62 (3 H, s) (Found: C, 69.9; H, 7.8; N, 5.3. $C_{16}H_{21}O_3N$ requires C, 69.79; H, 7.69; N, 5.09%).

trans-2,3,3a,4,5,10b-*Hexahydro*-3a-*methyl*[1]*benzothiepino*-[4,5-b]*pyrrole* (19c) *and its* N-*acetyl derivative* (19g). The imine (2c) (1 g) was reduced with $NaBH_4$ following the procedure described for (2d) to afford the solid amine (19c) (0.9 g, 75%), b.p. 120—125 °C (bath)/0.2 mmHg, m.p. 63—64 °C. Recrystallisation provided an analytical sample of (19c), m.p. 64—65 °C (diethyl ether–light petroleum); $\nu_{max.}$ 1 610 cm^{-1}; δ 7.40—6.97 (4 H, m), 4.57 (1 H, bs), 3.30—2.93 (2 H, m), 2.80—2.47 (2 H, m), 2.20—1.60 (5 H, m), and 0.57 (3 H, s) (Found: C, 71.2; H, 7.9. $C_{13}H_{17}NS$ requires C, 71.21; H, 7.81%).

The above amine (19c) (0.3 g) on acetylation as before afforded the crystalline acetyl derivative (19g) (0.35 g, 98%), m.p. 169—173 °C. Recrystallisation of this material furnished an analytical sample of (19g), m.p. 175—176 °C (acetone–light petroleum), $\nu_{max.}$ 1 630 cm^{-1}; δ 7.75—6.94 (4 H, m), 5.50 (1 H, s), 4.47—3.10 (2 H, m), 2.90—2.60 (2 H, m), 2.33—1.76 (4 H, m), 1.70 (3 H, s), and 0.56 (3 H, s) (Found: C, 68.8; H, 7.5; N, 5.5. $C_{15}H_{19}NOS$ requires C, 68.94; H, 7.33; N, 5.36%).

trans-2,3,3a,12b-*Tetrahydro*-9,11-*dimethoxy*-3a-*methyl*-*naphtho*[a]*cyclohepta*[7,8-b]*pyrrole* (20). (*a*) *By reduction with* $NaBH_4$. Reduction of the tetracyclic imine (1) (0.2 g) with $NaBH_4$ as before afforded a crude solid (175 mg) which on recrystallisation furnished the pure trans-*amine* (20) (140 mg, 70%), m.p. 153—154 °C (Et_2O–light petroleum), *m/z* 311 (M^+), 296 ($M^+ - 15$), 282 ($M^+ - C_2H_4$) and 268 ($M^+ - 43$); δ 7.96 (1 H, d, *J* 9.5 Hz), 7.56 (1 H, d, *J* 3 Hz), 7.22 (1 H, s), 7.12 (1 H, dd, *J* 9.5 and 3 Hz), 4.34 (1 H, s), 3.97 (3 H, s), 3.90 (3 H, s), 3.83—2.33 (5 H, m), 2.10—1.40 (6 H, m), and 0.46 (3 H, s) (Found: C, 77.3; H, 8.0; N, 4.6. $C_{20}H_{25}NO_2$ requires C, 77.14; H, 8.09; N, 4.50%).

(*b*) *By catalytic hydrogenation of the imine* (1). A solution of (1) (100 mg) in MeOH (10 ml) was hydrogenated over PtO_2 (50 mg). After the complete absorption of hydrogen (4 h), the reaction mixture was worked up in the usual way to furnish the above saturated amine (20) (50 mg, 50%), m.p. 153—154 °C.

(*c*) *By reduction of the imine* (1) *with lithium aluminium hydride* (LAH). A solution of (1) (200 mg) in dry diethyl ether (15 ml) was added dropwise to a stirred suspension of LAH (50 mg) in dry diethyl ether (5 ml) at 25 °C. After being stirred for 22 h at 25 °C, the reaction mixture was refluxed for 3 h. The reaction mixture was then decomposed with moist diethyl ether, and filtered. The filtrate was extracted with diethyl ether (3 × 75 ml). Usual work-up then provided only the pure saturated amine (20) (130 mg, 65%), m.p. 153—154 °C.

cis-2,3,3a,4,5,9b-*Hexahydro*-7-*methoxy*-3a-*methyl*-1H-*benz*-[g]*indole* (22b) *and its* N-*acetyl derivative* (22d). (*a*) *By metal–ammonia reduction of the imine* (2e). Reduction of the imine (2e) (300 mg) with Na-metal in liquid ammonia as before afforded the saturated amine (240 mg, 79%), b.p. 110 °C (bath)/0.1 mmHg, $\nu_{max.}$ 1 600 cm^{-1}; δ 7.22 (1 H, d, *J* 8 Hz), 6.87—6.50 (2 H, m), 3.76 (3 H, s), 3.55 (1 H, s), 3.18—2.54 (4 H, m), 2.05—1.41 (5 H, m), and 1.18 (3 H, s) (Found: C, 77.2; H, 8.9. $C_{14}H_{19}NO$ requires C, 77.38; H, 8.89%).

Acetylation of the above amine (350 mg) as before furnished the crude acetyl derivative (22d) (350 mg, 83%), m.p. 86—90 °C. A portion was recrystallised to provide an analytical sample of (22d), m.p. 91—93 °C; $\nu_{max.}$ 1 625 cm^{-1}; δ 7.50 (1 H, d, *J* 8 Hz), 6.80—6.46 (2 H, m), two singlets at 4.93 and 4.20 (1 H), two close singlets at 3.78 and 3.75 (3 H), 3.61—3.33 (2 H, m), 2.93—2.50 (2 H, m), two close singlets at 2.16 and 2.12 (3 H), 2.00—1.43 (4 H, m), and two close singlets at 1.15 and 1.13 (3 H) (Found: C, 74.1; H, 8.3. $C_{16}H_{21}NO_2$ requires C, 74.10; H, 8.16%).

(*b*) *By catalytic hydrogenation of the imine* (2e). A solution of the imine (2e) (150 mg) in MeOH (6 ml) was hydrogenated over Pd–C (100 mg, 10%) as before to afford a single (from ^1H n.m.r.) saturated amine (120 mg, 79%), identical in all respects with (22b) reported above.

(*c*) *By reduction of the imine* (2e) *with lithium aluminium hydride*. Reduction of the imine (2e) (200 mg) with LAH (75

mg) in dry diethyl ether, as described for (1) before, afforded only the *cis*-amine (22b) (135 mg, 67%) reported above.

Reduction of the imine (2e) *with* $NaBH_4$ *under special conditions; formation of a stereoisomeric mixture of the saturated amines* (22a) *and* (22b). Sodium borohydride (200 mg) was added in portions during 7 h to a stirred solution of the imine (2e) (200 mg) in MeOH (6 ml) and H_2O (3—4 drops) at 25 °C. The reaction mixture was then stirred at 25 °C for 16 h. Fresh $NaBH_4$ (200 mg) was then added in portions as above, and the reaction mixture was stirred for 16 h. Further $NaBH_4$ (100 mg) was again added and the reaction mixture refluxed for 1 h; it was then poured into water (150 ml), and after standing at room temp. for 2 h, the product was extracted with diethyl ether (3 × 75 ml). Usual processing of the extract finally afforded a saturated amine (160 mg, 79%), b.p. 110 °C (bath)/0.1 mmHg as a 3 : 1 mixture (from ^1H n.m.r.) of the cis- (22b) and trans-*amine* (22a) respectively. The special features of the ^1H n.m.r. spectrum are two characteristic singlets for angular methyl groups at δ 1.08 and 0.59 respectively for the *cis*- (22b) and the *trans*-isomer (22a); a singlet at δ 3.50 can be assigned to benzylic hydrogen at the ring junction for *cis*- (22b), the corresponding singlet for the *trans*-isomer (22a) overlapped with the signal for the methoxy group (Found: C, 77.3; H, 9.1. $C_{14}H_{19}NO$ requires C, 77.38; H, 8.81%).

The above mixture of amines (240 mg) on usual acetylation as before provided an acetyl derivative as an oil (250 mg, 87%), b.p. 160 °C (bath)/0.1 mmHg; $\nu_{max.}$ 1 630 cm^{-1}; *m/z* 259 (M^+), 244 ($M^+ - 15$), 231 ($M^+ - 28$) and 216 ($M^+ - 43$); the special characteristics of the ^1H n.m.r. spectrum are two close singlets at δ 1.15 and 1.10 for the angular methyl of the *cis*-isomer (22d), and a singlet at δ 0.40 is assigned to the angular methyl of the *trans*-acetyl (22c). The benzylic hydrogen at the ring-junction for *cis*- (22d) showed two singlets at δ 4.91 and 4.21; the corresponding hydrogen of the *trans*-isomer (22c) showed only one singlet at δ 4.27.

Reduction of the imine (2e) with $NaBH_4$ by the normal procedure described for the seven-membered case [see for (2d)] gave a mixture of the starting imine (major) and the reduced amine. Attempted reduction of (2e) with $NaBH_4$ in ethanol, or in isopropyl alcohol at 60 °C, or at reflux gave always a mixture of products.

Acknowledgements

We thank the C.S.I.R., New Delhi, for financial assistance, and Professor D. Nasipuri for useful discussions.

References

1 M. Alauddin and M. Martin-Smith, *J. Pharm. Pharmacol.*, 1962, **14**, 325; M. Martin-Smith and F. Surgue, *ibid.*, 1964, **16**, 568; S. Padmanabhan and V. Parashar, *J. Proc. Inst. Chem., India*, 1967, **39**, 54.
2 J. G. Morgan, K. D. Berlin, N. N. Durham, and R. W. Chesnut, *J. Org. Chem.*, 1971, **36**, 1599.
3 D. Nasipuri and S. K. Ghosh, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2720.
4 A. P. G. Kieboom and H. Van Bekkum, *Synthesis*, 1970, 476.
5 *Cf.* A. Chatterjee, D. Roy, and S. K. Chatterjee, *Synthesis*, 1981, 499.
6 *Cf.* J. P. Ferris and R. W. Trimmer, *J. Org. Chem.*, 1976, **41**, 13.
7 Ng. Ph. Buu-Hoi and D. Lavit, *J. Org. Chem.*, 1956, **21**, 1257.
8 J. Weinstock, *J. Org. Chem.*, 1961, **26**, 3511.
9 *Cf.* A. J. Birch and D. Nasipuri, *Tetrahedron*, 1959, **6**, 148.
10 D. K. Banerjee, T. R. Kasturi, and G. Govindon, *Indian J. Chem., Sect. B*, 1976, **14**, 312.
11 G. Fontaine, *Chem. Abstr.*, 1968, **69**, 106536u.
12 V. J. Traynelis, W. L. Hergenrother, J. R. Livingston, and J. A. Valicenti, *J. Org. Chem.*, 1962, **27**, 2377.
13 W. S. Johnson, J. W. Peterson, and C. D. Gutsche, *J. Am. Chem. Soc.*, 1947, **69**, 2942.
14 D. Huckle, I. M. Lockhart, and N. E. Webb, *J. Chem. Soc. C*, 1971, 2252.
15 R. E. Buckles and G. V. Mock, *J. Org. Chem.*, 1950, **15**, 680.
16 A. G. Anderson, Jr., and Shih Yi Wang, *J. Org. Chem.*, 1954, **19**, 277.

Received 28*th March* 1983; *Paper* 3/483