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THE CHEMISTRY OF PIPERIDINES—I

3-AZABICYCLO[3.3.1]NONANES

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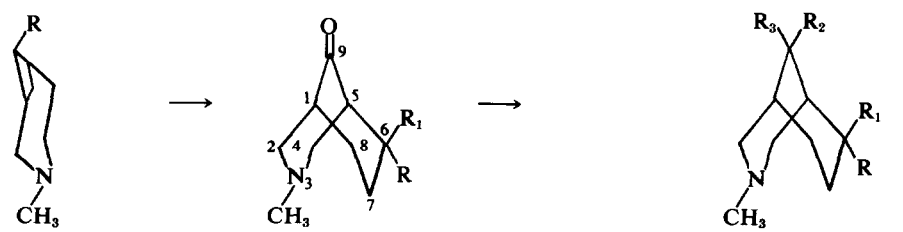
Abstract—The reaction of pyrrolidine, piperidine and morpholine enamines of 1-methyl-4-piperidone with acraldehyde is found to be a convenient route to 3-aza-3-methyl-6-cycloalkylaminobicyclo[3.3.1]-nonan-9-ones. In each case two difficultly separable ketones are obtained which on reduction give mixtures of isomeric alcohols. The alcohols are separated and their stereochemistries are determined from their physical and chemical properties.

The reaction of cycloalkanone enamines with α,β-unsaturated aldehydes has been found to be a route[1–6] to 2-cycloalkylaminobicyclo[3.3.1]nonan-9-ones. With a view to extending the information about the reactivity and conformational preferences of the piperidine system, when present in complex biologically active structures such as the benzomorphans, the reaction was applied to the enamines, **1–3**, of 1-methyl-4-piperidone. With acraldehyde and **1**, a mixture of **4** and **5** (Fig 1) was obtained.[7] The enamines **2** and **3** are now found to react with acraldehyde and give good yields of the pairs of ketones **6** with **7** and **8** with **9** respectively. (The structures in Fig 1 are configurationally correct but do not necessarily show the preferred conformations. The 6-cycloalkylamino group is referred to as 6α as in **4** and 6β as in **5**.) The presence of two ketones as in the case[7] of **4** and **5**, is demonstrated by TLC but not by GLC, and they are found to be difficult to separate chromatographically into pure single components.

The composition of the mixtures of **6** with **7** and **8** with **9** by analogy[7] with the findings for **4** and **5** is approximately in the ratio of 3–4:1 respectively. The isomers **6** and **8** as in the case[7] of **4** and **5**, in which the 6-cycloalkylamino group is in an α or *endo* position make up 70–80% of the product. This result is in agreement with the finding[3,4] for the corresponding deaza compounds (**4**, **5**, **8** and **9** in which MeN≡CH_2 or CHMe). This appears to be the expected yield based on calculations, and is in agreement with a non-stereospecific ring closure



1: R = 1-pyrrolidine(pyrld)
2: R = 1-piperidine(pip.)
3: R = 1-morpholine(morph)

4: R = pyrld. R_1 = H.
5: R = H, R_1 = pyrld.
6: R = pip. R_1 = H.
7: R = H, R_1 = pip.
8: R = morph. R_1 = H.
9: R_1 = H, R = morph.

10: R = pyrld. R_1 = H, R_2 = OH, R_3 = H
11: R = pyrld. R_1 = H, R_2 = H, R_3 = OH
12: R = H, R_1 = pyrld. R_2 = OH, R_3 = H
13: R—H, R_1 = pyrld. R_2 = H, R_3 = OH
14: R = pip, R_1 = H, R_2 = OH, R_3 = H.
15: R = pip, R_1 = H, R_2 = H, R_3 = OH.
16: R = H, R_1 = pip, R_2 = OH, R_3 = H
17: R = morph. R_1 = H, R_2 = OH, R_3 = H
18: R = morph, R_1 = H, R_2 = H, R_3 = OH
19: R = H, R_1 = morph. R_2 = OH, R_3 = H
20: R = pyrld. R_1 = H, R_2 = H, R_3 = p—O_2N—$C_6H_4CO_2$—
21: R = pyrld. R_1 = H, R_2 = p—O_2N—$C_6H_4CO_2$—R_3 = H

Fig 1.

proceeded by an intermolecular migration of the cycloalkylamino group. A thorough investigation off the course of this reaction has not been reported but some work[1] using mixtures of different enamines of cyclohexanones suggests an intermolecular process for the migration of the amino residue. The mixed pairs of ketones are reduced with $NaBH_4$ to give the series of mixtures of isomeric alcohols **10**, **11**, **12**, **13** and **14**, **15**, **16** and **17**, **18**, **19**, Fig 1. In each series GLC resolves the mixtures into only two components but TLC demonstrates three. The properties of all the isolated isomeric alcohols are summarised in the table Fig 2. In the pyrrolidine and morpholine series one pure isomer is isolated by fractional crystallisation of the crude reduction product. This isomer in each case has the longer retention time on GLC and at 0·0025M in CS_2 solution shows only free OH absorption at 3610 cm^{-1}. The stereochemistry about the 6 position of these isomers follows from their isolation in 40–50% of the total reduction product. That is, the 6 group can only be in an α or *endo* position since the 6β-substituted ketone forms at the most only 30% of the mixture. The stereochemistry about C9 is revealed by the resistance of these isomers to esterification under mild conditions. It has been reported[8] that unsubstituted 3-aza-3-methylbicyclo[3.3.1]nonan-9-ols and analogues in which the OH group is syn to the NMe group react with *p*-nitrobenzoyl chloride in chloroform at room temperature to yield the corresponding *p*-nitrobenzoates. Their anti isomers, however, are inert under these conditions. It is suggested[8] that the facile esterification of the *syn* orientated compounds proceeds by an intramolecular N to O acyl transfer through the intermediacy of an acylammonium complex as shown by 22 and 23 in Fig 3. This is confirmed in the present work by one isomeric series of alcohols being inert and another series giving the expected product. The same workers[8] also found that the *syn* OH to NMe compounds also showed a detectable degree of H-

	m.p.	Order of Elution on Carbowax 20 M	% of total reduction product	$\bar{\nu}$OH cm^{-1} $2{\cdot}5\times10^{-3}$ M in CS_2	Product with *p*-nitrobenzoyl chloride in $CHCl_3$	Hydrochloride absorption H—O—H cm^{-1}	PMR in CD_3OD for C<u>H</u>OH, NC<u>H</u>$_3$ τ	p*Ka's* in MeOH/H_2O
10	169	2nd	27	3610	No reaction	2HCl no absp^n	6·2, 7·9	10·1, 6·1
11	60	1st	20	3200	Forms Ester	2HCl 1630	6·35, 7·95	10·1, 6·6
12	135	2nd	15	3610 3335	Forms 2.HCl	Mono and 2HCl 1656 1635	6·45, 7·9 2.HCl, 6·4, 7·1 1.HCl, 6·4, 7·9	9·9, 6·6
13	215	1st	Trace	—	—	—	—	—
14	115	2nd	24	3610	No reaction	—	6·35, 8·0	10·2, 6·2
15	45	1st	15	3335	Forms Ester	—		10·1, 6·7
16	103	2nd	18	3610 3335	Forms 2.HCl	2HCl 1630		9·8, 6·3
17	99		23	3610	No reaction	—		8·8, 5·9
18	84		14	3200	Forms ester	—		8·6, 5·0
19	98		22	3610 3480	Forms 2.HCl	2HCl 1620		8·0, 5·5

Fig 2.

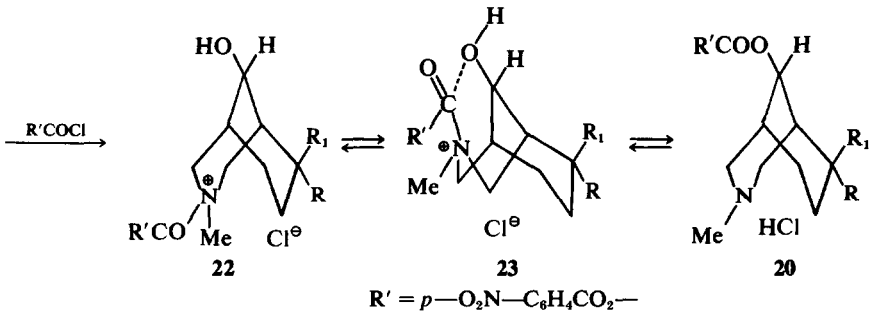


Fig 3.

bonded OH in dilute CS_2 solution, whereas their *anti* isomers showed only free OH.

The resistance to ester formation under these conditions by the present series points to their possessing an OH group *anti* to the NMe and *syn* to the 6-cycloalkylamino group. The *p*-nitrobenzoate **21** was obtained from the reaction of the lithium alkoxide salt of the alcohol, **10** and *p*-nitrobenzoyl chloride. The structures of these isomers are therefore represented, as far as their configurations are concerned, by **10**, **14** and **17** in Fig 1. It is almost certain that the carbocyclic ring with the 6β-cycloalkylamino group is in a chair form as shown. Any departure from this can only be in the direction of a tighter or puckered chair and not towards a flattened or boat form. The latter would introduce further steric crowding of this 6-*endo* group while the former reduces this crowding. On the other hand puckering will increase any interaction between the 3NMe and the $7CH_2$ positions. It is proposed here that the presence of the 6-*endo* group causes the heterocyclic ring to adopt either a half-chair or boat form in the isomers **10**, **14**, **17** and their structures are better represented by either **24** or **25** in Fig 4. Evidence for the effects of the 6-*endo* group is discussed in the section on the isomers **11**, **13**, **15** and **18**.

The reduction product residues, remaining after the removal of **10** and **17** from them, on subjection to the esterification procedure[8] described, yield in a short time, in each case, a colourless precipitate. These are found to be dihydrochloride salts of alcohols isomeric with **10**, **14**, **17**. Hydrolysis gives the parent bases isomeric with **10**, **14** and **17**. These alcohols are therefore also resistant to the esterification and so possess an OH group *anti* to the NMe and *syn* to the 6-cycloalkylamino group. Their retention time on GLC is identical with that of their corresponding isomers **10**, **14** and **17**. Their solutions in 0·0025 M CS_2 show largely free OH absorption at 3610 cm^{-1} but this is accompanied by H-bonded OH between 3335–3480 cm^{-1}, Fig 2. The latter absorption is due to intramolecular H-bonding and can only arise as a result of the proximity of the OH group to the 6-cycloalkylamino group which must occupy a 6β or *exo* position. This is further confirmed by the fact that these isomers are present in the least proportion of the total reduction product. This is to be expected since the 6β-cycloalkylamino ketone isomer is produced in lower proportion to the 6α isomer. Stereochemical models suggest that structures such as **12**, **16** and **19**, which partially describe these isomers, would be expected to have their OH and the cycloalkylamino N group so close that on the one hand the OH would exist entirely in a H-bonded form and on the other hand to be sterically overcrowded. The observation that the OH is largely free indicates a departure from a pure chair form for the carbocyclic ring of these isomers. The steric crowding can be relieved by a flattening of this ring and the structures best describing these isomers are shown by **26** and **27** in Fig 4. The latter, with a skew form for the carbocyclic ring is probably the preferred form and accounts for the large proportion of free OH and the former with a flattened chair form allows for the intramolecular H-bonding observed. The heterocyclic ring is most likely in a chair form since the flattening of the other ring should further relieve any strain due to the interaction of $7CH_2$ and 3NMe groups.

The chloroform solutions from the esterification reaction after the removal of the dihydrochlorides of **12**, **16**, **19** yield the expected *p*-nitrobenzoates **11**, **15**, **18** ($R_3 \equiv p\text{-}O_2N\text{—}C_6H_4COO\text{—}$). Acid hydrolysis of the esters gives the final group of alcohols **11**, **15**, **18**, isomeric with the other two groups. On the basis of this ready esterification these compounds have their OH group *syn* to the NMe group. This structure allows the intramolecular acyl transfer mechanism, shown in Fig 3, to become operative. As indicated in the Table, Fig 2, these isomers show only H-bonded OH at 3200–3135 cm^{-1} in 0·0025 M.CS_2 solution. The complete absence of any free OH and the large shift in the OH absorption (free OH being at about 3610 cm^{-1}) at this dilution are a clear indication of a strong intramolecular H-bond. This can only be accommodated by the existence of these isomers in CS_2 solution

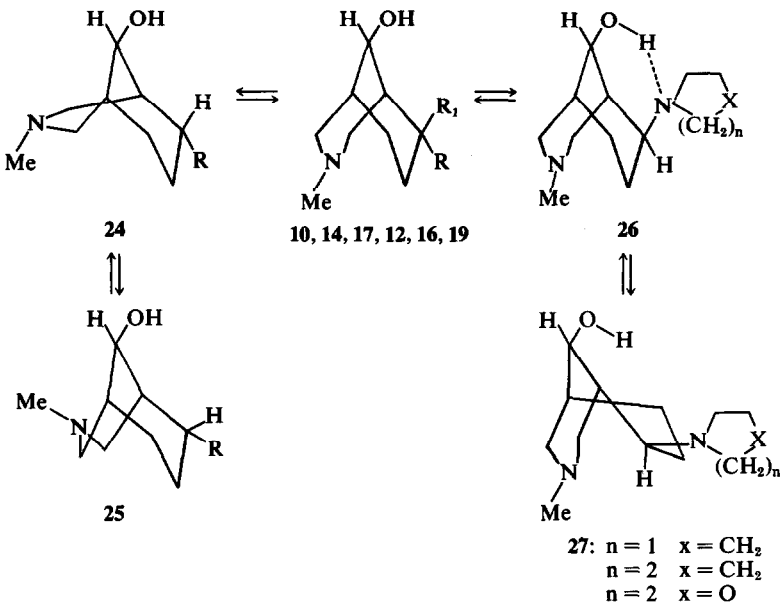


Fig 4.

with the heterocyclic ring (with NMe) in a boat form conformation. House found[8] that the corresponding 6-unsubstituted azabicyclononanols (**11**, **15**, **18** with R=R$_1$=R$_2$=H and R$_3$=OH) showed only a trace of bonded OH under these conditions, and he concluded that the effect of a possible H-bond was in itself insufficient to stabilise a boat conformation. In the present series of azabicyclononanols **11**, **15**, **18**, the placing of a 6-cycloalkylamino group has a profound effect on the conformational stability of the NMe containing heterocyclic ring. Stereochemical models show that severe steric crowding results if this group is in the 6α, or *endo* orientation. There is interaction between this group and the C4 H atoms and also the NMe group. That this group is indeed in an *endo* configuration is verified by the isolation of **11**, **15**, **18** in proportions about equal with those of **10**, **14**, **17** of the total reduction product. This again points to the origin of these compounds as the ketones **4**, **6**, **8**, respectively, in which the 6-substituent occupies a 6α or *endo* position. The interaction of the 6α group and the heterocyclic ring can to some extent be relieved by puckering the carbocyclic ring into a "tighter" chair form. However this can only result in a more severe interaction between NMe and the 7CH$_2$ group. Both the former and latter interactions are relieved by the adoption of a boat form by the heterocyclic NMe containing ring. It has already been established[10] that in 3-substituted bicyclononanes **28**, Fig 5, (X = OH, Br, Me, CO$_2$H) the ring with the substituent adopts a chair form if the substituent group is *exo* and is forced into the boat form if the group is in an *endo* configuration. The present study shows that *endo* substituents in the 2(4,6,8) position exert a transannular effect and force the ring to which they are not attached into a boat form in the bicyclononane structure. This effect should be absent in the corresponding β or *exo* isomers. If anything the presence of a 2,(4,6,8) *exo* substituent can be expected to reduce the interaction between C3 and C7 methylene groups by virtue of the flattening of the chair form of the ring to which it is attached in order to relieve the 1,3 interaction as described for **12**, **16** and **19**. To confirm this idea an effort was made to isolate the possible fourth stereoisomer **13** in the series **10**, **11** and **12**. In this isomer the 6-pyrrolidinyl group occupies an *exo* position and the OH group is *syn* to the NMe group as shown by **13**, Fig 1. This isomer can only occur in a low proportion since its production requires hydride attack from the more hindered side of the 6-*exo*-pyrrolidinylazabicyclononanone **5**, and the latter is itself present as the lesser component of the ketone product. During the purification of the *p*-nitrobenzoate **20** a small quantity of material was isolated and was found to be isomeric with the alcohols **10**, **11**, **12**. There was insufficient material for an IR dilution study but its mass fragmentation pattern and accurate molecular weight determination showed it to be the desired isomer **13**. The compound has a retention time on GLC identical with that of **11** and has the highest m.p., 215°, of all four isomers. This is in contrast to the low m.p., 60°, of **11** and since both **13** and **11** have the same configuration about C9 it appears that in **13** the OH group does not H-bond intramolecularly with the NMe group. Therefore in **13** the heterocyclic NMe containing ring is not in the boat form

but in a chair or near chair form. That the presence of a 6(2,4,8) *endo* substituent confers a characteristic stability on the boat form is evident from the total absence of any free OH in **11**, **15** and **18** and also from the magnitude of the shift of the OH absorption as compared with a free OH. This is of the order of 400 cm^{-1}. Such large shifts are only attained in intramolecularly H-bonded amino-alcohols when the OH and N groups are rigidly held close together by the stereochemistry of the structures. Examples of this order of H-bonding are found[10] in Chelidonine, **29**, and the steroidal compounds, **30**, in Fig 5. Chelidonine shows a shift of 332 cm^{-1} and the steroids 436–487 cm^{-1} to shorter wave number.

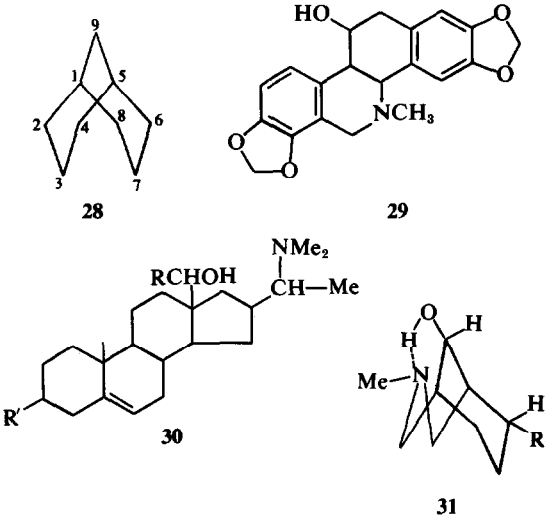


Fig 5.

The alcohols **11**, **15** and **18** are therefore best represented by structure **31**, Fig 5. The NMe heterocyclic ring is in a boat form and the N atom is H-bonded to the OH group. The carbocyclic ring is in a chair form with a 6-*endo* cycloalkylamino group. The *p*-nitrobenzoate **20**, of **11** appears to exist with its NMe ring in a chair form. This is based on the UV absorption of **20**, which is identical with the absorption of ethyl *p*-nitrobenzoate. Were there an appreciable amount of the boat form **32**, Fig 6, then an interaction between the NMe lone pair and the ester C=O as found[11] for **33**, would be expected to modify the UV absorption from that of a simple *p*-nitrobenzoate.

The structures best describing **13** are probably the same as for **12**, **16** and **19** and shown by **26** and **27**, Fig 4, with H=OH and OH=H. It is not possible to suggest the preferred conformations adopted by the parent ketones **4–9**, since these have not been isolated as single components and attempts at preparing them by oxidation of the pure isomeric alcohol pairs such as **10** and **11** have been unsuccessful. It could be argued that the IR OH absorption data does not differentiate between the series **12**, **16**, **19** and **11**, **15** and **18** and that the ready esterification could take place in the former series and not the latter. This could arise because there is a N atom of the cycloalkylamino group suitably placed for the formation of an acylammonium complex and intramolecular N to O acyl transfer. If this can occur then it invalidates the use of this reaction for assigning the configuration about C9 in these series of compounds. This possibility is unlikely on steric grounds since both the acylammonium complex and the final product would be severely crowded molecules. However this can be verified by carrying out the same esterification procedure on a 6-cycloalkylaminobicyclononanol in which the NMe group is absent but the other N centre is present together with a suitably orientated OH group. Reduction of a mixture of the known[3] 2α- and 2β-N-morpholinyl[3.3.1]bicyclononan-9-ones (**8** and **9** respectively with NMe = CH_2) yields a mixture of alcohols (**17**, **18**, **19** with NMe = CH_2). Reaction of this mixture with *p*-nitrobenzoyl chloride in chloroform produces a precipitate which is found to be a hydrochloride of one of the constituent alcohols. The residual chloroform solution yields only unreacted alcohols which on subjection to a second esterification using the same conditions again gives only starting materials. Since the mixture of alcohols is known to contain some of the isomer with the OH group *syn* to the 2β-morpholino N atom this result confirms that it is only in the series **11**, **15**, **18** in which the reaction occurs and this can only be a result of the *syn* relation of the NMe and OH groups.

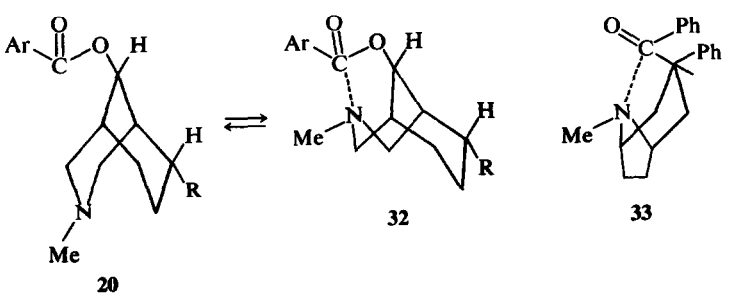


Fig 6.

An observation of potential value in stereochemical determinations is the occurrence of a medium intensity sharp band at 1640–1655 cm^{-1} in the IR of some of the hydrochlorides in this series of compounds. This band is found to occur, as recorded in the table, Fig 2, for the dihydrochlorides of **11**, **12**, **16**, **19** and the monohydrochloride of **12**. This absorption is in the correct region and of correct intensity to be assigned to the in plane bending vibration of a water molecule. The presence of such a band in the IR spectra of hydrated salts is well documented.[12] However the mono HCl and diHCl salts of **12** on elemental analysis are seen to be not hydrated. It is suggested here that this absorption arises from the presence of a "pseudo water molecule" in these compounds. This results from an intramolecular H-bond between the proton on a N atom and the OH group which is suitably placed. In the case of **12**, **16**, **19** this H-bond is between the proton on the 6-cycloalkylamino group and the *syn* OH group. This conclusion follows from the observation that the monohydrochloride of **12** is seen from NMR (and p*Ka*) data (Fig 2) to be protonated on the pyrrolidinyl N atom. This further confirms the *exo* orientation of the 6-pyrrolidinyl group and its position *syn* to the OH group. The dihydrochloride of **10** which has an OH *syn* to an *endo* pyrrolidinyl group does not show this absorption. This is presumably because the distance between the OH and NH groups is too great for intramolecular H-bonding to occur. The dihydrochloride of **11** presumably forms such a H-bond between the $HN^{\oplus}Me$ proton and the OH group.

The three structures illustrating these observations for the mono HCl salt of **12** and the di HCl of **11** and **10** are shown by **34**, **35** and **36** respectively in Fig 7.

There is no report in the literature correlating this band and this type of intramolecular H-bonding. Because of the possible value of this correlation a number of model compounds are at present being prepared to test the generality of this observation.

The NMR spectra of all the above compounds are complex at 60 MHz. At the present only a few have been determined at 220 MHz and the only clear assignment is the C9H resonance at about 6·1τ. This is confirmed by its downfield shift in the *p*-nitrobenzoates **20** and **21** and its absence in the C9D compound **10** (> CHOH = > CDOH). There is at present no reported systematic study of the NMR of the bicyclo[3.3.1]nonane skeleton. Such a study is reserved for a further publication when the 220 MHz spectra for the series of compounds **10–21**, and other model compounds, in preparation, are available.

EXPERIMENTAL

All reagents and solvents used were laboratory grade unless otherwise stated. NMR spectra were measured in CD_3OD soln using a Varian A60-A spectrometer with TMS as internal standard. IR spectra were measured with a Unicam SP200 and the dilution IR with a Grubb-Parsons spectromaster. Mass spectra were obtained using an A.E.I. MS9 instrument with direct introduction of the samples into the heated inlet system. Purity of all the isomeric alcohols was determined by TLC on neutral alumina and GLC on Carbowax 20 m KOH at 200°. p*Ka* measurements were made in MeOH/H_2O soln, titrating with N/50 HCl.

6α and 6-β-(N-Pyrrolidinyl)-3-aza-3-methylbicyclo[3.3.1]nonan-9-ones (**4** and **5**)

A soln of the pyrrolidine enamine of **1**, (8·3 g, 0·05 mole) in dioxan (15 ml) was cooled to 0–5° and acrolein (2·8 g, 0·05 mole) in dioxan (10 ml) was added dropwise with stirring during 1 hr. The mixture was stirred at 0° for 1 hr, and then allowed to stand at room temp for 1 hr. The dioxan was removed at 20 mm and the residue distilled to give a straw coloured liquid (7·8 g, 70%) b.p. 124–126°/0·75 mm, which crystallised on cooling m.p. 42–44°. (Found: C, 70·08; H, 9·88; N, 12·68; $C_{13}H_{22}N_2O$ requires: C, 70·22; H, 10·00; N, 12·61%); IR (Nujol): 2760 (N—Me), 1720 (C=O). $\tau(CHCl_3)$: 7·78 (3H, s, N—$\underline{CH_3}$).

6α and 6β-(N-Piperidinyl)-3-aza-3-methylbicyclo[3.3.1]-nonan-9-ones (**6** and **7**)

The enamine **2**, reacted with acrolein to yield the ketones **6** and **7** b.p. 158°/0·2 mm in 70·6% yield; IR (Thin Film): 2760 (N—CH_3), 1720 (C=O).

6α and 6β-(N-Morpholinyl)-3-aza-3-methylbicyclo[3.3.1]-nonan-9-ones (**8** and **9**)

To the enamine **3** (15 g, 0·07 mole) in dioxan (30 ml) was added acrolein (3·9 g, 0·07 mole) in dioxan (20 ml) and the soln was refluxed for 8 hr. The dioxan was re-

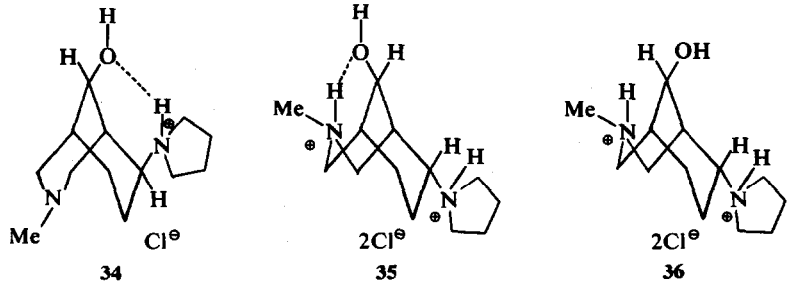


Fig 7.

moved at 20 mm and the residue distilled to give a colourless liquid (11·3 g, 57·3%) b.p. 158–160°/0·2 mm. (Found: M^+ 238·168118. $C_{13}H_{22}N_2O_2$ requires M^+, 238·169309).

6α-(N-*Pyrrolidinyl*)-3-*aza*-3-*methylbicyclo*[3.3.1]*nonan*-syn-9-*ol* (**10**)

To a soln of the ketones **4** and **5** (2·2 g, 0·01 mole) in i-PrOH (10 ml) was added $NaBH_4$ (0·33 g) and the resulting mixture stirred at room temp for 3 hr. After the excess of borohydride had been destroyed by the addition of AcOH, conc HCl (1 ml) was added. The mixture was concentrated, made basic with NaOH aq, saturated with NaCl and extracted with Et_2O. On concentrating to 20 ml the alcohol **10** precipitated m.p. 169–170° (from EtOAc). (Found: C, 69·40; H, 10·73; N, 12·66; $C_{13}H_{24}N_2O$ requires: C, 69·58; H, 10·80; N, 12·51%); IR (Nujol): 3200 (OH); 2760 (N—CH_3): IR (CS_2; 0·0025 M): 3610 (OH): τ(CD_3OD): 6·2 (1H, t, J = 2·5 Hz, > CH—O—), 7·9 (3H, S, N—CH_3).

6β-(N-*Pyrrolidinyl*)-3-*aza*-3-*methylbicyclo*[3.3.1]*nonan*-syn-9-*ol* (**12**)

(a) *The dihydrochloride of* **12**. The ethereal soln remaining after removal of **10** was evaporated and the residue dissolved in $CHCl_3$ (20 ml). To this was added *p*-nitrobenzoyl chloride (1·5 g) in $CHCl_3$ (15 ml) and the mixture stirred for 12 hr. The resulting ppt (450 mg) of the dihydrochloride of **12** was filtered and dried m.p. 271° (MeOH—Et_2O). (Found: C, 49·46; H, 8·52; N, 8·88; Cl, 22·23; $C_{13}H_{26}N_2Cl_2O$ requires: C, 49·84; H, 8·31; N, 8·95; Cl, 22·69%); IR (Nujol): 3400 (OH); 2600 (N^+H); 1635 (H—O—H): τ(D_2O): 7·1 (3H, s, N—CH_3).

(b) *The base* **12**. The dihydrochloride of **12** (450 mg) after basification with NaOH aq and extraction with Et_2O yielded **12** (0·33 g, 100%) m.p. 135–136° (from EtOAc). (Found: C, 69·67; H, 10·76; N, 12·45; $C_{13}H_{24}N_2O$ requires: C, 69·58; H, 10·80; N, 12·51%); IR (Nujol): 3200 (OH); 2760 (N—Me): IR (CS_2; 0·0025 m) 3610, 3335 (OH): τ(CD_3OD): 6·45 (1H, t, J = 3 Hz, > CH—O—), 7·9 (3H, S, N—CH_3).

(c) *The monohydrochloride of* **12**. The alcohol **12** (50 mg) in MeOH/H_2O (25 ml, 1:1) was titrated with N/50 HCl to pH 8·2. The soln was then evaporated to dryness and the residual solid (410 mg; 88%) recrystallised to yield the monohydrochloride m.p. 235°. (Found: C, 59·26; H, 9·87; N, 10·26; Cl, 13·33: $C_{13}H_{25}N_2ClO$ requires: C, 59·85; H, 9·60; N, 10·74; Cl, 13·62%); IR (Nujol): 3600 (OH); 2740 (N—Me); 1656 (H—O—H): τ(CD_3OD): 6·4 (1H, t, J = 2·5 Hz, > CH—O—), 7·9 (3H, s, N—CH_3).

6α-(N-*Pyrrolidinyl*)-3-*aza*-3-*methylbicyclo*[3.3.1]*non*-anti-9-*yl* p-*nitrobenzoate* (**20**)

The $CHCl_3$ soln after the removal of the dihydrochloride of **12** was extracted with 2N HCl, the aqueous extract was made basic with NaOH aq and extracted with Et_2O. The ethereal soln was dried ($MgSO_4$) and evaporated to yield a yellow oil the IR of which indicated a mixture with absorptions at 3300 (OH) and 1720 (C=O). This product was dissolved in Et_2O and on scratching yielded yellow needles (0·75 g) m.p. 152–153. (Found: C, 64·32; H, 7·04; N, 11·51; $C_{20}H_{27}N_3O_4$ requires: C, 64·31; H, 7·29; N, 11·26%); IR (Nujol): 2780 (N—Me); 1720 (C=O) 1535, 1350 (NO_2): τ($CDCl_3$): 1·7 (4H, s, Ph), 5·0 (1H, t, J = 2·5 Hz, > CH—O—), 7·7 (3H, S, N—CH_3).

During a large scale preparation of this ester, after removal of the bulk of the ester a small amount of **13** was obtained as colourless needles m.p. 215–216°. (Found: M^+ 224·188933. $C_{13}H_{24}N_2O$ requires: 224·188853).

6α-(N-*Pyrrolidinyl*)-3-*aza*-3-*methylbicyclo*[3.3.1]*nonan*-anti-9-*ol* (**11**)

A soln of **20** (0·75 g) in HCl aq (20 ml, 20%) was refluxed for 12 hr and then filtered from the liberated *p*-nitrobenzoic acid, made basic with NaOH aq and extracted with $CHCl_3$. The $CHCl_3$ soln was dried ($MgSO_4$) and evaporated to leave **11** (0·44 g, 100%) m.p. 60°. (Found: C, 69·57; H, 10·88; N, 12·42; $C_{13}H_{24}N_2O$ requires: C, 69·58; H, 10·80; N, 12·57%); IR (Nujol): 3200 (OH), 2760 (N—CH_3): IR (CS_2, 0·0025 M): 3200 (OH): τ(CD_3OD) 6·35 (1H, t, J = 3 Hz, > CH—O—) 7·95 (3H, S, N—CH_3).

6α-(N-*Pyrrolidinyl*)-3-*aza*-3-*methylbicyclo*[3.3.1]*nonan*-syn-9-*yl* p-*nitrobenzoate* (**21**)

To the MeLi in dry Et_2O (150 ml) generated from Li metal (0·56 g) and MeI (5·2 g), **10** (2 g) in dry Et_2O (100 ml) was added and the mixture stirred for 1 hr before adding *p*-nitrobenzoyl chloride (1·7 g) in dry Et_2O (20 ml) and the resulting mixture stirred for 16 hr. The ether soln was concentrated to half volume and extracted with H_2O. The ethereal soln was dried ($MgSO_4$) and evaporated to leave **21** (2·37 g, 71%) m.p. 135–136° (from Et_2O). (Found: C, 64·17; H, 7·43; N, 11·43; $C_{20}H_{27}N_3O_4$ requires: C, 64·31; H, 7·29; N, 11·26%); IR (Nujol): 2760 (N—Me), 1720 (C=O).

6α-(N-*Morpholinyl*)-3-*aza*-3-*methylbicyclo*[3.3.1]*nonan*-syn-9-*ol* (**17**)

The method as above for **10**, m.p. 99° (from Et_2O). (Found: C, 65·12; H, 10·08; N, 11·55; $C_{13}H_{24}N_2O_2$ requires: C, 65·00; H, 10·00; N, 11·67%); IR (Nujol): 3300 (OH); 2760 (N—Me): IR (CS_2; 0·0025 M) 3610 (OH).

6β-(N-*Morpholinyl*)-3-*aza*-3-*methylbicyclo*[3.3.1]*nonan*-syn-9-*ol* (**19**)

(a) *The dihydrochloride of* **19**. Method as above for the dihydrochloride of **12**, m.p. 230° (from MeOH/Et_2O); IR (Nujol): 3400, 3200 (OH), 2600 (N^+H), 1620 δ(H—O—H).

(b) *The base* **19**. The alcohol was obtained from the dihydrochloride by working up as for **12**. Colourless needles were obtained m.p. 98° (100%). (Found: C, 65·38; H, 9·95; N, 11·52; $C_{13}H_{24}N_2O_2$ requires: C, 65·00, H, 10·00; N, 11·67%); IR (Nujol): 3200 (OH), 2750 (N—Me): IR (CS_2, 0·0025 M) 3610, 3480 (OH).

6α-(N-*Morpholinyl*)-3-*aza*-3-*methylbicyclo*[3.3.1]*non*-anti-9-*yl* p-*nitrobenzoate*. (**20a**, R=N-morpholine)

The soln left after removal of **19** was worked up as for **20** and yielded the ester m.p. 127° (from Et_2O). (Found: C, 61·61; H, 7·12; N, 10·75; $C_{20}H_{27}N_3O_5$ requires: C, 61·70, H, 6·94; N, 10·80%); IR (Nujol): 2760 (N—Me), 1700 (C=O), 1520, 1345 (NO_2).

6α-(N-*Morpholinyl*)-3-*aza*-3-*methylbicyclo*[3.3.1]*nonan*-anti-9-*ol* (**18**)

This alcohol was prepared from **20a** by acid hydrolysis and working up as for **11**, m.p. 84° (100%). (Found: C, 65·25; H, 10·18; N, 11·40; $C_{13}H_{24}N_2O_2$ requires: C, 65·00; H, 10·00; N, 11·67%); IR (Nujol): 3100 (OH), 2750 (N—Me): IR (CS_2; 0·0025 M): 3200 (OH).

6β-(N-Piperidinyl)-3-aza-3-methylbicyclo[3.3.1]nonan-syn-9-*ol* (**16**)

The ketones **6** and **7** (14·84 g) were reduced with $NaBH_4$ and worked up as for **11** to yield a colourless oil (12·98 g, 88%) which could not be induced to crystallise. The oil was dissolved in $CHCl_3$ (50 ml) and *p*-nitrobenzoyl chloride (10 g) in $CHCl_3$ (50 ml) was added and the mixture stirred for 12 hr. The resulting ppt (3·08 g) of dihydrochloride of **16** was filtered off, dried, basified with NaOH aq and extracted with Et_2O to yield **16** (2·36 g) m.p. 102–103°. (Found: C, 70·66; H, 11·02; N, 11·69; $C_{14}H_{28}N_2O$ requires: C, 70·58; H, 10·92; N, 11·77%); IR (Nujol): 3200 (OH), 2780 (N—Me); IR (CS_2, 0·0025 M): 3610, 3355 (OH).

6α-(N-Piperidinyl)-3-aza-3-methylbicyclo[3.3.1]nonan-syn-9-*ol* (**14**)

The $CHCl_3$ soln after removal of the dihydrochloride of **16** was worked up as for **20** and yielded a yellow oil. The oil was dissolved in ether and on scratching yielded colourless needles of **14** (3·55 g, m.p. 114°. (Found: C, 70·80; H, 10·76; N, 11·56; $C_{14}H_{28}N_2O$ requires: C, 70·58; H, 10·92; N, 11·77%); IR (Nujol): 2760 (N—Me), 1710 (C=O); IR (CS_2; 0·0025 M): 3610 (OH); nDMSO): 6·35 (1H, t, J = 2 Hz, > CH—O) 8·0 (3H, s, N—Me).

6α-(N-*Piperidinyl*)-3-*aza*-3-*methylbicyclo*[3.3.1]*nonan*-anti-9-*yl* p-*nitrobenzoate* (**20b**, R=N-*piperidine*)

The ethereal soln remaining after removal of **14** was evaporated to leave a yellow oil which crystallised from light petroleum (60–80) to give pale yellow needles m.p. 114°. (Found: C, 65·21; H, 10·54; N, 7·41; $C_{21}H_{29}N_3O_4$ requires: C, 65·12; H, 10·85; N, 7·49%); IR (Nujol): 2760 (N—Me); 1710 (C=O).

6α-(N-*Piperidinyl*)-3-*aza*-3-*methylbicyclo*[3.3.1]*nonan*-anti-9-*ol* (**15**)

The alcohol was prepared from **20b** by acid hydrolysis and working up as for **11** m.p. 44–45° (1·92 g). (Found: C, 70·32; H, 10·76; N, 11·54; $C_{14}H_{28}N_2O$ requires: C, 70·58; H, 10·92; N, 11·77%); IR (Nujol): 3150 (OH), 2760 (N—Me): IR (CS_2; 0·0025 M): 3135 (OH).

Deutero-6α-(N-*pyrrolidinyl*)-3-*aza*-3-*methylbicyclo*[3.3.1]*-nonan*-syn-9-*ol* (**10**, > CH—OH = > 6DOH)

The ketones **4** and **5** were reduced with $LiAlD_4$ and worked up as for the $NaBH_4$ reduction of **4** and **5** to yield the alcohol m.p. 170°. (Found: M^+ 223. 181029, $C_{13}H_{23}D_1N_2O$ requires: 223·180854).

Deutero-6α-(N-pyrrolidinyl)-3-aza-3-methylbicyclo[3.3.1]*-nonan*-syn-9-*yl* p-*nitrobenzoate* (**21a** > C9HOR = > C9DOR)

This ester was prepared as for **21**, m.p. 152°. (Found: M^+ 374·206421, $C_{20}H_{26}D_2N_2O_4$ requires: 374·206588).

Oxidation of 6α-(N-*pyrrolidinyl*)-3-*aza*-3-*methylbicyclo*-[3.3.1]*nonan*-syn-9-*ol* (**10**)

A variety of oxidising agents all failed to oxidise **10** to the ketone. Chromic acid oxidation yielded only unchanged alcohol. DMSO/Ac_2O gave the acetate of **10** and Ruthenium tetroxide gave an intractable black tar.

Hydrochlorides of **10**, **11**. These were prepared by passing dry HCl gas through a soln of **10**, **11** in EtOH.

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[13]The mass spectra of compounds **4**–**21** are in agreement with the proposed molecular structures. A discussion of the fragmentation of these compounds under electron impact is presented in *Organic Mass Spectrometry*, in print.