Synthesis of Compounds related to *endo*-6,14-Ethenotetrahydrothebaines

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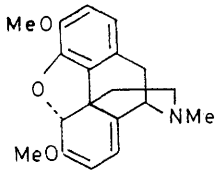
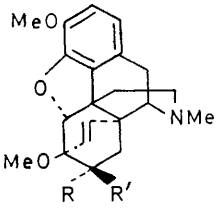
Diels–Alder adducts obtained from 6-methoxy-*N*-methyl-1,2,3,4,7,8-hexahydroisoquinoline and from 7-methoxy-*N*-methyl-1,2,3,4,5,6-hexahydroisoquinoline with ethyl acrylate, methyl vinyl ketone, and acrylonitrile are described.

DIELS–ALDER addition of suitable dienophiles to thebaine (1) [1-6] occurs readily only on the exposed face of the diene system and gives rise to derivatives of *endo*-6,14-ethenotetrahydrothebaine, in which the etheno bridge is disposed 'inside' the tetrahydrothebaine skeleton. Addition of unsymmetrical dienophiles to thebaine gives exclusively C-7 substituted derivatives which may possess either the 7α- (2; R′ = H) or 7β-configuration (2; R = H).

The introduction of the new two-carbon bridge across ring C of thebaine confers rigidity on the adduct molecules and it was hoped that the reduced flexibility and differences in peripheral shape would make such compounds unacceptable at some of the receptor surfaces and thus give rise to a separation of the various physiological



(1)



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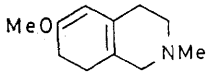

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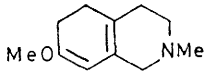


(4)

effects of morphine. In fact both epimers of (2; R,R′ = COMe,H) are potent analgetics whereas the related esters (2; R,R′ = CO_2Me or CO_2Et,H) are inactive.[1]

† The terms *exo* and *endo* are used to designate epimeric Diels–Alder adducts and have the same stereochemical connotation as for substituted *exo*- and *endo*-bicyclo[2.2.2]oct-2-enes in which the substituent is respectively *cis* and *trans* to the ethano-bridge. For convenience, the alternative symbols, α and β, are also employed to indicate *endo*- and *exo*-dispositions relative to the C=C double bond by analogy with the terminology used for thebaine adducts.

[1] K. W. Bentley and D. G. Hardy, *J. Amer. Chem. Soc.*, 1967, **89**, 3267.

[2] W. Sandermann, *Ber.*, 1938, **71**, 648.

Adducts with 7β-substituents tend to be marginally more active than the more accessible 7α-epimers.[7]

With this in mind the Diels–Alder reaction between suitable dienophiles and the dienes (3) and (4) [8] was undertaken, with the aim of producing adducts bearing structural resemblances to those (2) from thebaine. Since these would lack in particular the aromatic ring of thebaine, the number of receptor sites at which these molecules would be acceptable would be expected to be limited thus allowing a possible separation of analgetic action from unwanted side effects.

Formation of Adducts.—The dienes (3) and (4) reacted with ethyl acrylate, methyl vinyl ketone, and acrylonitrile to give in each case two adducts; data relating to these are given in Tables 1 and 2. The mixtures were separated by fractional crystallisation of the picrates (for ethyl acrylate and acrylonitrile adducts) and by column chromatography over alumina (for methyl vinyl ketone and acrylonitrile adducts). Table 3 provides details regarding the two adducts obtained from 6-ethoxy-1,2,3,4,7,8-hexahydro-2-methylisoquinoline and methyl vinyl ketone.

Assignment of Stereochemistry to Adducts.—To facilitate the argument the structure and stereochemistry assigned to the individual isomers will be presented before the discussion of the results on the basis of which the individual assignments were actually made. The adducts derived from (3) were assigned the structures (5)—(10) and from (4) the structures (11)—(16). For each pair of isomeric adducts (Tables 1—3) isomers A were *exo*-adducts and isomers B *endo*-adducts.†

(a) *Esters* [(5), (6), (11), *and* (12)]. The n.m.r. spectra of the esters (5) and (6) obtained from compound (3) and ethyl acrylate display features analogous to those re-

[3] C. Schopf, K. von Gottberg, and W. Petri, *Annalen*, 1938, **536**, 216.

[4] S. I. Kanewskaya and S. F. Mitryagina, *J. Gen. Chem. (U.S.S.R.)*, 1947, **17**, 1203.

[5] K. W. Bentley and A. F. Thomas, *J. Chem. Soc.*, 1956, 1863.

[6] J. W. Lewis, M. J. Readhead, I. A. Selby, A. C. B. Smith, and C. A. Young, *J. Chem. Soc.* (*C*), 1971, 1158.

[7] K. W. Bentley and J. W. Lewis, reported to the Committee on Problems of Drug Dependence, 1968.

[8] T. A. Crabb and J. R. Wilkinson, *J.C.S. Perkin I*, 1975, 58.

ported[9] for the *exo*- and *endo*-adducts (17) and (18). Thus shielding of the olefinic proton (δ 5.83) in the *endo*-ester (5), relative to the corresponding proton (δ 6.02) in the *exo*-ester (6), is observed. Also, the signals due to the ethyl protons occur at slightly higher field for the *endo*-ester [δ 4.07 (q) and 1.22 (t)] than for the *exo*-ester [δ 4.15 (m) and 1.26 (t)]. Shielding of the olefinic and ethyl protons in the *endo*-isomer, compared with the *exo*-isomer, is similarly encountered in the esters (11) and (12). Reference to Dreiding models of the *endo*-esters (6) and (12) indicates that, in certain conformations, the ethyl protons of the ethoxycarbonyl group will be shielded by the C=C bond. The anisotropic effect of the carbonyl of the ethoxycarbonyl group depends upon its orientation, but its net influence is apparently to shield the olefinic proton.

In the 220 MHz n.m.r. spectrum of the *endo*-ester (6), the signals representing the ethoxycarbonyl group protons are, as expected, a quartet (δ 4.07) and a triplet (δ 1.22) with J 7 Hz. However, in the *exo*-ester (5), the methylene protons of the ethoxycarbonyl group give rise to a symmetrical 16-line multiplet (δ 4.15), which must largely be a consequence of restricted rotation of the methylene group. A Dreiding model of the *exo*-ester (5) shows the methylene group of the ethoxycarbonyl function to be hindered by one of the C–H bonds of the ethano-bridge in certain conformations, whereas restriction of free rotation is less apparent in a model of the *endo*-ester (6). Another example of a complex n.m.r. splitting pattern due to a sterically hindered ethyl group has been reported recently.[10]

TABLE 1

Diels–Alder reactions of 1,2,3,4,7,8-hexahydro-6-methoxy-2-methylisoquinoline (3)

Dienophile	Adduct [a]	%	M.p. (°C)	B.p. (°C) [mmHg]	Order of elution [c]	Derivative	M.p. of deriv. (°C)
CH_2:CH·CO_2Et	A	45		120 [0.02]		Picrate	140
	B	55		120—122 [0.005]		Picrate	176
CH_2:CH·COMe	A	40		112—114 [0.02]	1	Methiodide	206 (decomp.)
	B	60	35	116—118 [0.02]	2	Picrate	190
CH_2:CH·CN	A	50	58	128—130 [0.005]	1	Picrate	186
	B	50	85		2	Picrate	143

TABLE 2

Diels–Alder reactions of 1,2,3,4,5,6-hexahydro-7-methoxy-2-methylisoquinoline (4)

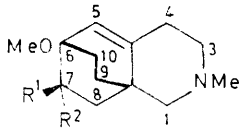
Dienophile	Adduct [a]	% [b]	M.p. (°C)	B.p. (°C) [mmHg]	Order of elution [c]	Derivative	M.p. of deriv. (°C)
CH_2:CH·CO_2Et	A	45		121 [0.01]		Picrate	140
	B	55		123—125 [0.01]		Picrate	178
CH_2:CH·COMe	A	40	50	118 [0.02]	1	Methiodide	188
	B	60		120 [0.02]	2	Methiodide	200 (decomp.)
CH_2:CH·CN	A	50	107		1	Picrate	162
	B	50	94		2	Methiodide	248 (decomp.)

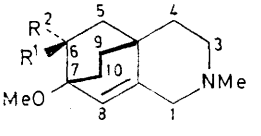
TABLE 3

Diels–Alder reaction of 6-ethoxy-1,2,3,4,7,8-hexahydro-2-methylisoquinoline

Dienophile	Adduct [a]	% [b]	M.p. (°C)	B.p. (°C) [mmHg]	Order of elution [c]	Derivative	M.p. of deriv. (°C)
CH_2:CH·COMe	A	40	38	104—106 [0.05]	1	Methiodide	216
	B	60	34	106—108 [0.05]	2	Methiodide	178

[a] A and B are respectively the *exo*- and *endo*-epimers. [b] Percentage of adduct in the initially obtained mixture. [c] Column chromatography on Wöelm neutral alumina (activity III).





(5) R^1 = CO_2Et, R^2 = H (*exo*)
(6) R^1 = H, R^2 = CO_2Et (*endo*)
(7) R^1 = COMe, R^2 = H (*exo*)
(8) R^1 = H, R^2 = COMe (*endo*)
(9) R^1 = CN, R^2 = H (*exo*)
(10) R^1 = H, R^2 = CN (*endo*)

(11) R^1 = CO_2Et, R^2 = H (*exo*)
(12) R^1 = H, R^2 = CO_2Et (*endo*)
(13) R^1 = COMe, R^2 = H (*exo*)
(14) R^1 = H, R^2 = COMe (*endo*)
(15) R^1 = CN, R^2 = H (*exo*)
(16) R^1 = H, R^2 = CN (*endo*)

In the n.m.r. spectra of the adducts (5)—(16) the AB signals due to H-8α and H-8β [in (5)—(10)] and to H-5α and H-5β [in (11)—(16)] are obscured, but the lower field X signal due to H-7α or H-7β [in (5)—(10) and to H-6α or H-6β in (11)—(16)] is clearly distinguishable. Consequently the true values of the vicinal coupling constants cannot be determined and because the observed splittings may not approximate to the true value of J, the symbol 'J' will be used to designate the appropriate splittings of the H-7α and H-7β signals for (5)—(10), and of the H-6α and H-6β signals for (11)—(16).

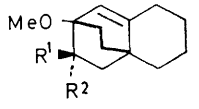
In the n.m.r. spectrum of the *exo*-ester (5) the H-7α signals are centred at δ 2.74 as a quartet ('J'$_{7\alpha,8\alpha}$ 11,

[9] A. A. Othman, M. A. Qasseem, and N. A. J. Rogers, *Tetrahedron*, 1967, **23**, 87.

[10] D. E. Caddy and J. H. P. Utley, *J.C.S. Perkin II*, 1973, 1258.

' J '$_{7\alpha,8\beta}$ 5 Hz) which is further split into doublets (' J ' 2 Hz). In the n.m.r. spectrum of the *endo*-ester (6), H-7β gives rise to a triplet at δ 2.91 (' J '$_{7\beta,8\beta}$ = ' J '$_{7\beta,8\alpha}$ = 8 Hz) with no evidence of further splitting. The shielding of an *endo*-proton relative to an *exo*-proton of otherwise similar environment has been encountered frequently in the spectra of bicyclo[2.2.2]octenes.[11-13]

The additional splitting of the H-7α quartet for the *exo*-ester (5) is attributed to long-range coupling of H-7α with the corresponding proton at C-10 for which the arrangement of the four intervening bonds is a ' planar W '. Such an arrangement does not exist for H-7β in the *endo*-ester (6) and long-range coupling is not observed. Thus convincing n.m.r. evidence for the *exo*- and *endo*-stereochemistry of (5) and (6), respectively, is provided by comparison of the olefinic and ethoxycarbonyl proton chemical shifts with those of the analogous adducts (17) and (18),[9] complex splitting for the methylene protons



(17) R^1 = CO_2R, R^2 = H
(18) R^1 = H, R^2 = CO_2R

of the ethoxycarbonyl group in (5) but not in (6), shielding of H-7α in (5) relative to H-7β in (6), and long-range coupling of H-7α with H-10 in (5), but not of H-7β with H-10 in (6).

The apparent vicinal coupling constants (' J ') also afford a useful indication of stereochemistry, although the assignment of an *exo*- or *endo*-configuration on this basis must be undertaken with caution.[14] In the adducts of thebaine with methyl vinyl ketone and with acrylonitrile coupling between *endo*-protons is reported [11] to be larger than between *exo*-protons. This apparently applies to the Diels–Alder adducts (5)—(16) and confirms the stereochemical assignments.

The 220 MHz n.m.r. spectra of the *exo*- and *endo*-esters (11) and (12) [derived from (4)] display features similar to those of the corresponding esters (5) and (6). In the *exo*-ester (11), the H-6α signal at δ 2.76 again appears as a quartet (' J '$_{6\alpha,5\alpha}$ 11, ' J '$_{6\alpha,5\beta}$ 5 Hz) showing evidence of further splitting (' J ' 2 Hz) arising from long-range coupling with H-10. The H-6β signal at δ 2.93 for the *endo*-ester (12) is a triplet (' J '$_{6\beta,5\beta}$ = ' J '$_{6\beta,5\alpha}$ = 7.5 Hz) showing no evidence of further long-range coupling.

In neither ester, (11) or (12), is a simple quartet observed for the O·CH_2·CH_3 protons. Both restricted rotation and asymmetry of the molecule may render these protons non-equivalent, but the more complex splitting observed in the spectrum of the *exo*-isomer (11) may be taken as indication of a more restrictive environment, as in the corresponding *exo*-ester (5). The position of the C=C bond relative to the ring nitrogen in isomers (11) and (12) is readily apparent from examination of the AB quartet due to the C-1 methylene protons. For both isomers, the value of J_{gem} (−15 Hz) is characteristic of N−CH_2−C=C.[15]

(b) *Ketones* [(7), (8), (13), *and* (14)]. The 220 MHz n.m.r. spectra of the ketones (7) and (8) show significant differences in the chemical shifts of the olefinic and acetyl methyl signals. The observed shielding of the acetyl methyl group (δ 2.07) in the *endo*-isomer (8), relative to the corresponding signal (δ 2.23) in the *exo*-isomer (7), is again attributable to the anisotropy of the C=C bond.[12] As in the analogous esters, the H-5 olefinic signal is at higher field (δ 5.83) for the *endo*-ketone (8) than for the *exo*-ketone (7) (δ 6.02).

Evidence for the *exo*- and *endo*-configurations of the ketones (7) and (8) is furnished by the chemical shifts and splittings of the H-7α or H-7β signals. In the n.m.r. spectrum of the *exo*-ketone (7), H-7α absorbs as a broadened quartet (centred at δ 2.91) for which the value of $J_{7\alpha,8\alpha} + J_{7\alpha,8\beta}$ is 15 Hz. If we assume that the splitting for each of the two doublets is a measure of the smaller coupling constant, $J_{7\alpha,8\beta}$, the estimated values of the vicinal coupling constants are ' J '$_{7\alpha,8\alpha}$ 11.5 and ' J '$_{7\alpha,8\beta}$ 3.5 Hz. In the n.m.r. spectrum of the *endo*-ketone (8), the H-7β signal appears as a sharper quartet at δ 2.99 (' J '$_{7\beta,8\beta}$ 9, ' J '$_{7\beta,8\alpha}$ 6 Hz). In addition further splitting of the H-6α quartet in the spectrum of (13) into an octet owing to long-range coupling (J 1.5 Hz) with H-10 (' planar W') is observed, whereas the signal of H-6β in (14) is a sharp quartet.

From a knowledge of the n.m.r. spectra of the ketones (7) and (8), the stereochemistry of the closely related adducts from methyl vinyl ketone and 6-ethoxy-1,2,3,4,-7,8-hexahydro-2-methylisoquinoline were established (see Experimental section).

(c) *Nitriles* [(9), (10), (15), *and* (16)]. In the 220 MHz n.m.r. spectrum of the *exo*-nitrile (9), the H-7α signals appear at δ 2.67 as an octet, first-order analysis of which gave values of ' J '$_{7\alpha,8\alpha}$, ' J '$_{7\alpha,8\beta}$, and $J_{7\alpha,10}$ of 12, 5, and 2.5 Hz, respectively, characteristic of an *exo*-isomer.

The H-7β signals at δ 2.92 in the 220 MHz n.m.r. spectrum of the *endo*-nitrile (10) appear as a well defined quartet arising from vicinal coupling with H-8β (' J '$_{7\beta,8\beta}$ 9.5 Hz) and H-8α (' J '$_{7\beta,8\alpha}$ 5 Hz). Unlike the *endo*-ester (6) and the *endo*-ketone (8), the *endo*-nitrile (10) gives an olefinic singlet at slightly lower field than that in the *exo*-isomer (9) (δ 6.00 *cf.* 5.93).

The stereochemistry of the isomeric nitriles (15) and (16) [derived from (4)], can also be deduced from the chemical shift and splitting of the H-6 signal in the 220 MHz spectra. In the *exo*-nitrile (15), H-6α couples vicinally with H-5α (' J '$_{6\alpha,5\alpha}$ 11.5 Hz) and H-5β

[11] W. Fulmar, J. E. Lancaster, G. O. Morton, J. J. Brown, C. H. Howell, C. T. Nora, and R. A. Hardy, *J. Amer. Chem. Soc.*, 1967, **89**, 3322.
[12] W. A. Ayer, C. E. McDonald, and J. B. Stothers, *Canad. J. Chem.*, 1963, **41**, 1113.
[13] K. Tori, Y. Takano, and K. Kitahonoki, *Chem. Ber.*, 1964, **97**, 2798.
[14] F. A. L. Anet, H. H. Lee, and J. L. Sudmeier, *J. Amer. Chem. Soc.*, 1967, **89**, 4431.
[15] R. Cahill, R. C. Cookson, and T. A. Crabb, *Tetrahedron*, 1969, **25**, 4681.

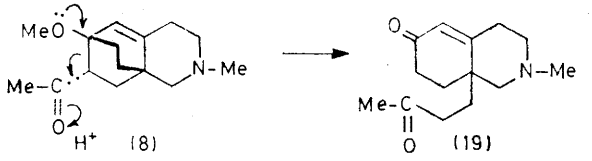
($J'_{6\alpha,5\beta}$ 5.5 Hz). Further splitting of the H-6α signal centred at δ 2.71 is attributable to long-range coupling with H-10 (J 2.5 Hz).

The H-6β signal at δ 3.00, for the *endo*-nitrile (16), appears as a quartet ($J'_{6\beta,5\beta}$ 9.5, and $J'_{6\beta,5\alpha}$ 4 Hz) showing little evidence of further splitting due to long-range coupling. The olefinic H-8 signal is again at lower field for the *endo*-nitrile (16) than for the *exo*-nitrile (15) (δ 6.03 *cf.* 5.92).

Thus again the *exo*-isomers (9) and (15) differ from the corresponding *endo*-isomers (10) and (16) in exhibiting a higher field chemical shift of the H-7 signal in (9) than in (10) and of the H-6 signal in (15) than in (16), further splitting of the H-7 signals in (9) and of the H-6 signals in (15) due to long-range coupling with H-10, and the greater magnitude of $J'_{7\alpha,8\alpha}$ compared with $J'_{7\beta,8\beta}$ in (9) and (10) and of $J'_{6\alpha,5\alpha}$ compared with $J'_{6\beta,5\beta}$ in (15) and (16).

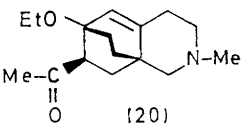
Confirmation of Stereochemical Assignments by Chemical Methods.—Although the expected products of Diels–Alder reaction between the diene (3) and methyl vinyl ketone are the 7-acetyl adducts, (7) and (8), the alternative mode of addition would give the corresponding 8-substituted derivatives. Acid-catalysed rearrangement of the *exo*-ketone (7) and the *endo*-ketone (8) demonstrated that the acetyl group was attached at C-7 since the observed ring opening is possible only for a carbonyl substituent vicinal to the bridgehead methoxy-group.[16]

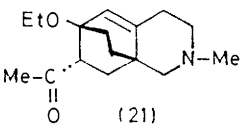
When the picrate (m.p. 190°) of the *endo*-isomer (8) was broken down on acidic alumina, a liquid was obtained which gave a n.m.r. spectrum with singlets representing an acetyl group (δ 2.13), an *N*-methyl group (δ 2.23), and one olefinic proton (δ 5.68), but no *O*-methyl singlet. The i.r. spectrum showed strong bands at 1 710 (non-conjugated C=O) and 1 670 cm^{-1} (conjugated C=O). U.v. absorption at $\lambda_{max.}$ 234 nm (ε 14 400) also indicated that the rearrangement product was an αβ-unsaturated ketone. The spectroscopic information and analytical data for the methiodide (m.p. 154°) support the assignment of structure (19) which can arise by ring-opening, as shown. Acid-catalysed rearrangements of



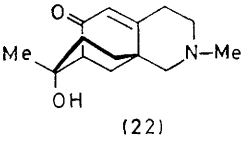
the same type have been observed with some thebaine adducts [17] and with adducts of 1,3-dihydroanisoles and methyl vinyl ketone.[16]

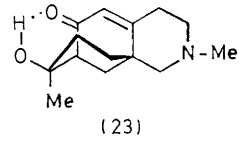
Treatment of either ethoxy-ketone (20) or (21) with 2N-hydrochloric acid at 100 °C, followed by work-up with aqueous 30% sodium hydroxide, yielded a mixture (m.p. 90—100°) of two components (ratio *ca.* 7 : 3). Two diastereoisomeric hydroxy-compounds, A and B, were isolated from this mixture by fractional crystallisation and were assigned structures (22) and (23), formed by aldol ring closure of the rearrangement product (19).





The presence of an αβ-unsaturated oxo-group in both isomers was indicated by u.v. absorption at $\lambda_{max.}$ 235 nm and a strong i.r. band at 1 660 cm^{-1}. The major constituent of the initial mixture, isomer A (m.p. 105°), showed a sharp i.r. band at 3 590 cm^{-1}, the frequency of which was independent of concentration (CCl_4 solution), whereas a corresponding much weaker band at 3 650 cm^{-1} was observed in the spectrum of the minor isomer B (m.p. 148°). These frequencies are within the range for free OH stretching in alcohols and indicate that isomer A possesses structure (22), since intramolecular hydrogen bonding with the carbonyl group in structure (23) would result in a lowered intensity of the free OH stretching band, relative to that in (22). A higher free OH stretching frequency for equatorial hydroxy-groups than for





axial hydroxy-groups in related compounds has been reported [18] and apparently also occurs in the alcohol (23) as compared with the alcohol (22), assuming that the hydroxy-substituted rings adopt chair conformations.

Both isomeric alcohols also gave broad OH stretching bands (3 410 for isomer A and 3 450 cm^{-1} for isomer B) within the range for intermolecularly hydrogen bonded hydroxy-groups, and in dilute solution isomer B showed a band at 3 510 cm^{-1} attributed to the OH stretching vibration of the intramolecularly hydrogen-bonded hydroxy-group in the alcohol (23).

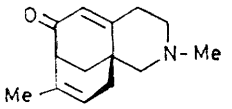
The n.m.r. spectrum of the more abundant isomer A showed singlets at δ 5.88 (1 olefinic proton), 2.33 (*N*-Me), and 1.25 [C(OH)CH_3]. In the n.m.r. spectrum of isomer B, corresponding signals respectively occurred at δ 6.02, 2.33, and 1.43. Thus the singlet due to the methyl group attached to the hydroxy-substituted carbon atom is at higher field for isomer A (δ 1.25) than for isomer B (1.43). In a Dreiding model of (22), this methyl group is situated above the plane of the C=O bond and a small shielding influence is anticipated, whereas in (23) the methyl group is unaffected. In addition, axial methyl protons normally absorb to lower field of equatorial methyl protons.[19]

Confirmation of these assignments is afforded by the relative susceptibilities of the isomers to dehydration.

[16] A. J. Birch and J. S. Hill, *J. Chem. Soc.* (*C*), 1966, 419.
[17] K. W. Bentley and J. C. Ball, *J. Org. Chem.*, 1958, **23**, 1720.
[18] I. L. Allsop, A. R. H. Cole, D. E. White, and R. L. S. Willix, *J. Chem. Soc.*, 1956, 4868.
[19] S. Brownstein and R. Miller, *J. Org. Chem.*, 1959, **24**, 1886.

During an attempted separation of the isomeric alcohols by column chromatography over Wöelm neutral alumina (activity III), a new product, $C_{14}H_{19}NO$ (m.p. 74°), was obtained. In the n.m.r. spectrum, a broad singlet at δ 5.43 and a sharper singlet at δ 5.70 represented two olefinic protons and 3-proton singlets at δ 2.33 and 1.77 were attributed to methyl protons; no OH stretching band was present in the i.r. spectrum. This compound is therefore considered to be the dehydration product (24) which also arose as a side-product from acid-catalysed rearrangement of (20) and (21).

In the hydroxy-compound (22), the axial hydroxy-group is *trans* to the axial hydrogen atom of the adjacent methylene group. It was therefore anticipated that elimination of water should occur more readily from this isomer than from the equatorial alcohol (23). Application of isomer A to an alumina column, followed by elution with ether, yielded the dehydration product (24),



(24)

whereas similar treatment of isomer B did not result in dehydration. The assignment of structure (22) to isomer A was thus confirmed.

Biological Activity.—The biological results are summarised in Table 4. Codeine has been included as a reference drug.

Of the compounds tested only the ketones (7) and (13) showed reasonable levels of antinociceptive activity. In both cases, however, this was associated with toxic side effects which precluded any further biological investigations. In neither compound was the activity of the same order of magnitude as that of thebaine. This suggests that the aromatic ring in the thebaine skeleton is essential for the intense biological action of this type of molecule.

TABLE 4

Biological activity [hot-plate test (HP) and antagonism of phenylquinone-induced writhing (PQ)] of Diels–Alder adducts

Compound	PQ (100 mg per kg)	HP (50 mg per kg)
(7)	−	+
(13)	+	−
(14)	−	−
(15) + (16)	±	±
(20)	±	−
(21)	±	−
(22) + (23)	±	+
Codeine	++ (20 mg per kg body weight)	++ (50 mg per kg body weight)

(a) *Antagonism of phenylquinone-induced writhing.* The method was based on that of Hendershot and Forsaith.[20] Test compounds were either dissolved in distilled water or suspended in 5% gum acacia solution and administered orally to groups of 3 male mice using a dose of 100 mg drug per kg body weight and a dose volume of 0.4 ml per 20 g body weight. Control mice received an equivalent volume of vehicle. After 1 h, phenylquinone (2 mg per kg) in normal saline solution was injected intraperitoneally. Immediately following phenylquinone injection the mice were observed for 20 min and the total number of writhes per group recorded. Antinociceptive activity in terms of % inhibition of writhing was expressed as follows: 25—49% = ±; 50—75% = +; >75% = ++.

(b) *Hot-plate test.* A modification of the method described by Woolfe and MacDonald [21] was used. Test compounds were dissolved in normal saline solution or suspended in 5% gum acacia solution and administered subcutaneously to groups of 3 male mice. The dose was 50 mg drug per kg body weight and the dose volume 0.2 ml per 20 g body weight. Control mice received an equivalent volume of vehicle. Thirty min after injection each mouse was placed on a hot-plate maintained at 55 °C and the reaction time noted. A maximum 'cut-off' time of 60 s was imposed. Increases in mean reaction time (R) were calculated as a percentage of this maximum from equation (i).

$$\% \text{ increase} = \frac{\text{test group } R - \text{control group } R}{60 - \text{control group } R} \times 100 \quad \text{(i)}$$

Antinociceptive activity was expressed as follows: 10—24% increase = ±; 25—50% increase = +; >50% increase = ++.

EXPERIMENTAL

Elemental analyses were carried out by Portsmouth Polytechnic analytical section. U.v. spectra were obtained (Unicam SP 800 spectrophotometer) for solutions in absolute ethanol. I.r. spectra were determined for liquid films or solutions in carbon tetrachloride with a Perkin-Elmer 237 spectrometer. N.m.r. spectra were recorded on a Varian T60 spectrometer or an HR 220 spectrometer (PCMU, Harwell) for solutions in $CDCl_3$.

Ethyl 1,2,3,4,6,7,8,8a-Octahydro-6-methoxy-2-methyl-6,8a-ethanoisoquinoline-7β- (5) and -7α-carboxylate (6).—A mixture of 70% pure 1,2,3,4,7,8-hexahydro-6-methoxy-2-methylisoquinoline (3) (3.0 g) and ethyl acrylate (15 ml) was heated under reflux in the presence of hydroquinone (0.1 g) for 8 h. Residual ethyl acrylate was removed *in vacuo* and unchanged diene (1.3 g) was recovered by vacuum distillation. The mixture of epimeric adducts (2.1 g) was distilled (b.p. 110—115° at 0.001 mmHg) to give a viscous oil. A *picrate*, m.p. 176° (1.6 g) (Found: C, 52.2; H, 5.8; N, 11.1. $C_{22}H_{28}N_4O_{10}$ requires C, 52.0; H, 5.55; N, 11.0%) was obtained by mixing hot ethanolic solutions of the freshly distilled oil (2.0 g) and picric acid (1.7 g), followed by recrystallisation from ethanol. This picrate (1.5 g) was

[20] L. C. Hendershot and J. Forsaith, *Proc. Soc. Exp. Biol. Med.*, 1959, **125**, 237.

[21] G. Woolfe and A. D. MacDonald, *J. Pharmacol. Exp. Ther.*, 1944, **80**, 300.

dissolved in acetone and applied to an alumina column (50 g Wöelm neutral; activity III). Elution with ether afforded the pure endo-*ester* (6), b.p. 120—122° at 0.005 mmHg (0.6 g), δ 5.83 (5-H), 2.29 (NMe), 3.34 (OMe), 4.07 (OCH_2·CH_3), 1.22 (OCH_2·CH_3), and 2.91 (H-7β), $J_{7\beta,8\beta}$ 8, $J_{7\beta,8\alpha}$ 8, $J_{7\beta,5} < 1$ Hz.

The picrate mother liquors gave a second *picrate* (0.7 g), m.p. 140° (from ethanol) (Found: C, 52.0; H, 5.9; N, 10.6%), which afforded the exo-*ester* (5), b.p. 120° at 0.02 mmHg (0.3 g), when broken down on alumina; δ 6.02 (5-H), 3.40 (OMe), 2.28 (NMe), 4.15 (OCH_2·CH_3), 1.26 (OCH_2·CH_3), and 2.74 (H-7α), $J_{7\alpha,8\alpha}$ 11, $J_{7\alpha,8\beta}$ 5, $J_{7\alpha,10}$ 2 Hz.

Ethyl 1,2,3,4,4a,5,6,7-*Octahydro*-7-*methoxy*-2-*methyl*-4a,7-*ethanoisoquinoline*-6β- (11) *and* -6α-*carboxylate* (12).—By the procedure described above, a mixture of epimeric esters (1.5 g), b.p. 120—125° at 0.01 mmHg, was obtained from the isomerisation mixture (3.0 g) containing 70% of 1,2,3,4,5,6-hexahydro-7-methoxy-2-methylisoquinoline and 25% of 1,2,3,4,5,8-hexahydro-7-methoxy-2-methylisoquinoline after heating under reflux with ethyl acrylate (15 ml) for 4 h. The isomeric adducts were again separated *via* the picrates. The *picrate*, m.p. 178° (1.2 g) (Found: C, 51.8; H, 5.8; N, 10.9. $C_{22}H_{28}N_4O_{10}$ requires C, 52.0; H, 5.55; N, 11.0%) of the *endo*-ester (12) afforded the pure *isomer*, b.p. 123—125° at 0.01 mmHg (0.5g), when broken down on alumina, $\nu_{max.}$ (film) 1 730 cm^{-1} (ester C=O), δ 5.82 (8-H), 3.34 (OMe), 2.28 (NMe), 4.08 (OCH_2·CH_3), 1.23 (OCH_2·CH_3), and 2.93 (6β-H), $J_{6\beta,5\beta}$ 7.5, $J_{6\beta,5\alpha}$ 7.5, $J_{6\beta,8} < 1$ Hz. A second *picrate*, m.p. 140° (0.5 g) (Found: C, 52.0; H, 5.3; N, 11.0%) isolated by fractional crystallisation from ethanol gave the exo-*ester* (11), b.p. 121° at 0.01 mmHg (0.2 g), when broken down on alumina; $\nu_{max.}$ (film) 1 725 cm^{-1} (ester C=O), δ 6.01 (8-H), 3.40 (OMe), 2.29 (NMe), 4.14 (OCH_2·CH_3), 1.26 (OCH_2·CH_3), and 2.76 (H-6α), $J_{6\alpha,5\beta}$ 5, $J_{6\alpha,10}$ 2 Hz.

7β- (7) *and* 7α-*Acetyl*-1,2,3,4,6,7,8,8a-*octahydro*-6-*methoxy*-2-*methyl*-6,8a-*ethanoisoquinoline* (8).—The isomerisation mixture (8.0 g) containing 70% of (3) was heated under reflux on a water-bath with methyl vinyl ketone (40 ml) in the presence of hydroquinone (0.1 g) for 4 h. The excess of methyl vinyl ketone was removed *in vacuo* and unchanged diene was recovered by vacuum distillation. The mixture of ketone adducts distilled over at 110—120° and 0.03 mmHg (6.4 g).

A column was prepared, in light petroleum, from Wöelm neutral alumina (activity III) (250 g). The mixture of ketone adducts (6.0 g) was dissolved in light petroleum (10 ml) and the solution was carefully applied to the surface of the alumina. Elution with light petroleum (200 ml fractions) removed aromatic impurities and starting material. Further elution with 95 : 5 light petroleum–ether afforded the exo-*ketone* (7). When the proportion of ether was increased to 10%, a mixture of ketones (7) and (8) was eventually obtained, but continued elution gave the pure *endo*-ketone (8). On further increase of eluant polarity (up to 100% ether), the remaining *endo*-ketone (8) was eluted from the column. The chromatographic fractions were readily monitored by means of t.l.c. on alumina with ether as solvent (Table 5).

The *exo*-ketone (7) (2.0 g), b.p. 112—114° at 0.02 mmHg, formed a *methiodide*, m.p. 206° (decomp.) (from ethanol) (Found: C, 49.5; H, 6.9; N, 3.2. $C_{16}H_{26}NO_2$ requires C, 49.1; H, 6.65; N, 3.6%). After distillation of the *endo*-ketone (8) (3.1 g), b.p. 116—118° at 0.02 mmHg, prolonged cooling at −40 °C induced crystallisation, and recrystallisation from a small quantity of light petroleum afforded the pure endo-*ketone* (8), m.p. 35°. When ethanolic solutions, containing equivalent amounts of the *endo*-ketone (8) and picric acid, were mixed, *picrate* was formed; m.p. 190° (from ethanol) (Found: C, 52.4; H, 5.4; N, 11.95. $C_{21}H_{26}N_4O_9$ requires C, 52.7; H, 5.4; N, 11.95%). The *exo*-ketone (7) showed $\nu_{max.}$ 1 710 cm^{-1} (C=O); δ 6.02 (5-H), 3.37 (OMe), 2.27 (NMe), 2.23 (COMe), and 2.91 (H-7α), $J_{7\alpha,8\alpha}$ 11.5,

TABLE 5

Chromatographic separation of (7) and (8)

Eluant: % Petroleum (b.p. 40—60°)	Eluant: % Ether	Fraction number (s)	Combined mass (g)	Composition of eluate
100	0	1—3	0.4	(3)
100	0	4	<0.01	and impurities
95	5	5—10	0.6	*exo*-Adduct (7)
90	10	11—16	1.4	*exo*-Adduct (7)
90	10	17—18	0.3	Mixture of adducts
90	10	19	0.1	*endo*-Adduct (8)
0	100	20—22	3.0	*endo*-Adduct (8)

$J_{7\alpha,8\beta}$ 3.5, $J_{7\alpha,10}$ 1 Hz. The *endo*-ketone (8) showed $\nu_{max.}$ 1 710 cm^{-1} (C=O); δ 5.83 (5-H), 3.31 (OMe), 2.29 (NMe), 2.07 (COMe), and 2.99 (H-7β), $J_{7\beta,8\beta}$ 9, $J_{7\beta,8\alpha}$ 6, $J_{7\beta,8} < 1$ Hz.

6β- (13) *and* 6α-*Acetyl*-1,2,3,4,4a,5,6,7-*octahydro*-7-*methoxy*-2-*methyl*-4a,7-*ethanoisoquinoline* (14).—The isomerisation mixture (3.0 g) containing 70% of (4) was heated under reflux with methyl vinyl ketone (15 ml) and hydroquinone (0.1 g) on a water-bath for 4 h. After removal of starting material, the mixture of isomeric adducts was distilled; b.p. 130—140° at 0.01 mmHg (yield 2.1 g). The *exo*- (13) and *endo*-ketone (14) were separated by chromatography on Wöelm neutral alumina (grade III), as described for the ketones (7) and (8).

The exo-*ketone* (13) (0.7 g) was distilled (b.p. 118° at 0.02 mmHg) and crystallised on cooling. The pure isomer was isolated as a white crystalline solid, m.p. 50° (from light petroleum) (Found: C, 72.55; H, 9.6; N, 5.4. $C_{15}H_{23}NO_2$ requires C, 72.25; H, 9.3; N, 5.6%). It formed a *methiodide*, m.p. 188° (from ethanol) (Found: C, 48.8; H, 6.7; N, 3.4. $C_{16}H_{26}NO_2$ requires C, 49.1; H, 6.65; N, 3.6%). The endo-*ketone* (14) (1.1 g), b.p. 120° at 0.02 mmHg, also formed a *methiodide*, m.p. 200° (from ethanol) (Found: C, 49.4; H, 6.9; N, 3.5%). The *exo*-ketone (13) showed $\nu_{max.}$ 1 710 cm^{-1} (C=O); δ 6.00 (8-H), 3.36 (OMe), 2.27 (NMe), 2.23 (COMe), and 2.93 (H-6α), $J_{6\alpha,5\alpha}$ 11, $J_{6\alpha,5\beta}$ 4, $J_{6\alpha,10}$ 1.5 Hz. The *endo*-ketone (14) showed $\nu_{max.}$ 1 710 cm^{-1} (C=O); δ 5.79 (8-H), 3.32 (OMe), 2.28 (NMe), 2.09 (COMe), and 3.02 (H-6β), $J_{6\beta,5\beta}$ 9, $J_{6\beta,5\alpha}$ 6, $J_{6\beta,8} < 1$ Hz.

1,2,3,4,6,7,8,8a-*Octahydro*-6-*methoxy*-2-*methyl*-6,8a-*ethanoisoquinoline*-7β- (9) *and* -7α-*carbonitrile* (10).—The isomerisation mixture (5.0 g) containing 70% of (3) was heated under reflux on the water-bath with acrylonitrile (15 ml) in the presence of hydroquinone (0.1 g) for 4 h. After removal of starting material, the mixture of epimeric nitriles was distilled (b.p. 120—130° at 0.002 mmHg) to give a viscous, pale yellow liquid (3.0 g). Treatment with picric acid (3.0 g) in hot, ethanolic solution yielded a picrate which was recrystallised to constant m.p. (186°) and broken down (2.5 g) on alumina to give the *exo*-isomer (9), b.p. 128—130° at 0.005 mmHg (1.0 g). The viscous oil solidified on cooling and recrystallisation from ether–light petroleum afforded

the pure exo-*nitrile* (9) as a white, crystalline solid, m.p. 58° (Found: C, 72.5; H, 8.8; N, 12.2. $C_{14}H_{20}N_2O$ requires C, 72.4; H, 8.7; N, 12.1%), δ 5.93 (5-H), 3.40 (OMe), 2.29 (NMe), and 2.67 (H-7α), $J_{7\alpha.8\alpha}$ 12.0, $J_{7\alpha.8\beta}$ 5.0, $J_{7\alpha.10}$ 2.5 Hz.

A second picrate (1.0 g), m.p. 143°, was isolated from the mother liquors and, when applied to an alumina column, produced the endo-*nitrile* (10) as colourless crystals (0.4 g). A sample of m.p. 85° was obtained by recrystallisation from ether–light petroleum (Found: C, 72.2; H, 8.7; N, 12.0%), δ 6.00 (5-H), 3.40 (OMe), 2.29 (NMe), and 2.92 (H-7β), $J_{7\beta.8\beta}$ 9.5, $J_{7\beta.8\alpha}$ 5.0, $J_{7\beta.5} < 1$ Hz. The isomeric nitriles (9) and (10) (1.0 g) were also separated by column chromatography on Wöelm neutral alumina (activity III) [elution with light petroleum–ether (4 : 1)] to give first the *exo*-adduct (9) (0.3 g) and then the *endo*-adduct (10) (0.4 g).

1,2,3,4,4a,5,6,7-*Octahydro*-7-*methoxy*-2-*methyl*-4a,7-*ethanoisoquinoline*-6β- (15) *and* -6α-*carbonitrile* (16).—The isomerisation mixture (3.0 g) containing 70% of (4) was heated under reflux on a water-bath with acrylonitrile (10 ml) and hydroquinone (0.1 g) for 4 h. After removal of starting material, the mixture of nitrile adducts was distilled (b.p. 130—140° at 0.01 mmHg) to give a viscous liquid (1.6 g). The *exo*-isomer (15) was isolated by treatment of this liquid (0.5 g) with picric acid (0.5 g) in ethanolic solution, recrystallisation of the picrate to constant m.p. (162°) (0.3 g), and breakdown on alumina. The exo-*nitrile* (15) solidified on cooling and was obtained as a white, crystalline solid (0.1 g), m.p. 107° (from ether–light petroleum) (Found: C, 72.6; H, 8.8; N, 11.8. $C_{14}H_{20}N_2O$ requires C, 72.4; H, 8.7; N, 12.1%), δ 5.92 (8-H), 3.40 (OMe), 2.27 (NMe), and 2.71 (H-6α), $J_{6\alpha.5\alpha}$ 11.5, $J_{6\alpha.5\beta}$ 5.5, $J_{6\alpha.10}$ 2.5 Hz.

The initial mixture of adducts crystallised on cooling to give a solid (m.p. 75—80°) containing approximately equal amounts of the nitriles (15) and (16). When this solid (1.0 g) was chromatographed [Wöelm neutral alumina (grade III); light petroleum–ether] the *exo*-isomer (15) (0.4 g) and the *endo*-isomer (16) (0.3 g) were obtained. Recrystallisation from ether–light petroleum afforded the pure endo-*nitrile* (16), m.p. 94° (Found: C, 72.7; H, 8.95; N, 12.3%), δ 6.03 (8-H), 3.43 (OMe), 2.32 (NMe), and 3.00 (H-6β), $J_{6\beta.5\beta}$ 10.0, $J_{6\beta.5\alpha}$ 4.0, $J_{6\beta.8} < 1$ Hz.

6-*Ethoxy*-1,2,3,4,5,8-*hexahydro*-2-*methylisoquinoline*.— A solution of 6-ethoxy-1,2,3,4-tetrahydro-2-methylisoquinoline (41.5 g) in dry methanol (300 ml) was carefully added to liquid ammonia (2 l) with dry ether (200 ml) as co-solvent. Sodium (40 g) was then carefully introduced in small portions (the blue colour was allowed to fade between additions) with stirring continuously throughout. After evaporation of ammonia, water (*ca.* 200 ml) was cautiously added and the product was extracted with ether. The dried extract was evaporated and methanol was removed *in vacuo*. The product, b.p. 102—104° at 0.7 mmHg, was an oil (38.3 g) which solidified on cooling at −40 °C to give crystals, m.p. 28°, δ 4.43 (olefinic proton), 2.27 (NMe), and 1.27 and 3.65 (OEt). It formed a methiodide, m.p. 178° (from ethanol) (Found: C, 46.5; H, 6.7; N, 4.25. $C_{13}H_{22}$-INO requires C, 46.6; H, 6.6; N, 4.2%).

6-*Ethoxy*-1,2,3,4,7,8-*hexahydro*-2-*methylisoquinoline*.— 6-Ethoxy-1,2,3,4,5,8-hexahydro-2-methylisoquinoline (38.0 g) was thoroughly mixed with a solution of potassium t-pentyl oxide (from 15 g of potassium) in t-pentyl alcohol (350 ml) and heated on a water-bath for 4 h. t-Pentyl alcohol was removed *in vacuo*, water (50 ml) was added, and the isomerisation product was extracted with ether. The dried extract was evaporated and the residual liquid distilled (b.p. 106—110° at 1 mmHg) (36.8 g). This isomerisation mixture contained the conjugated diene (65%), δ 4.62 (olefinic proton), 2.27 (NMe), 1.32 ($OCH_2{\cdot}CH_3$), and 3.37 ($OCH_2{\cdot}CH_3$), and the non-conjugated isomer (35%). The *methiodide*, m.p. 162°, of 6-ethoxy-1,2,3,4,7,8-hexahydro-2-methylisoquinoline was isolated by treatment of the isomerisation mixture with methyl iodide in ethanol solution followed by recrystallisation from ethanol (Found: C, 46.6; H, 6.5; N, 4.3. $C_{13}H_{22}INO$ requires C, 46.4; H, 6.6; N, 4.2%).

7β- (20) *and* 7α-*Acetyl*-6-*ethoxy*-1,2,3,4,6,7,8,8a-*octahydro*-2-*methyl*-6,8a-*ethanoisoquinoline* (21).—The isomerisation mixture (36.0 g) containing 65% of 6-ethoxy-1,2,3,4,7,8-hexahydro-2-methylisoquinoline was heated under reflux with methyl vinyl ketone (50 ml) and hydroquinone (0.2 g) on a water-bath for 5 h. After removal of starting material, the mixture of epimeric ketone adducts was distilled (b.p. 100—110° at 0.05 mmHg) to give a viscous oil (30.4 g). The oil (10.0 g) was dissolved in light petroleum (10 ml) and applied to an alumina column [300 g of Wöelm neutral (activity III) in light petroleum]. Elution with light petroleum removed side-products and further elution with 95 : 5 light petroleum–ether afforded the *exo*-ketone (20) (3.1 g), a mixture of ketones (20) and (21) (0.7 g), and the *endo*-ketone (21) (5.4 g).

The exo-*ketone* (20), b.p. 104—106° at 0.05 mmHg, solidified on cooling at −40 °C and was obtained as crystals, m.p. 38° (from light petroleum at 0 °C), δ 6.02 (5-H), 2.35 and 2.32 (NMe and COMe), 3.58 ($OCH_2{\cdot}CH_3$), 1.23 ($OCH_2{\cdot}CH_3$), and 2.92 (7α-H), $J_{7\alpha.8\alpha}$ 11, $J_{7\alpha.8\beta}$ 4 Hz. The *methiodide* had m.p. 216° (from ethanol) (Found: C, 52.3; H, 7.25; N, 3.7. $C_{17}H_{28}INO$ requires C, 52.4; H, 7.2; N, 3.6%). The endo-*ketone* (21), b.p. 106—108° at 0.05 mmHg, similarly solidified at −40 °C and was isolated as a low-melting crystalline solid by suction on sintered glass. A pure sample, m.p. 34° (from light petroleum) showed δ 5.85 (5-H), 2.17 (COMe), 2.35 (NMe), 3.58 ($OCH_2{\cdot}CH_3$), 1.23 ($OCH_2{\cdot}CH_3$), and 3.07 (7β-H), $J_{7\beta.8\beta}$ 9, $J_{7\beta.8\alpha}$ 6 Hz. The *methiodide* had m.p. 178° (from ethanol) (Found: C, 52.5; H, 7.3; N, 3.5%).

1,3,4,7,8,8a-*Hexahydro*-2-*methyl*-8a-(3-*oxobutyl*)*isoquinolin*-6(2H)-*one* (19).—The picrate, m.p. 190° (0.5 g), of the *endo*-adduct (8) was dissolved in acetone and applied to an alumina (type H) column. Elution with ether afforded the rearrangement product (19) as a viscous liquid (0.1 g), $\nu_{max.}$ (film) 1 710 (C=O) and 1 670 cm^{-1} (conj. C=O), $\lambda_{max.}$ 234 nm (ε 14 400), δ 2.13 (COMe), 2.23 (NMe), and 5.68 (olefinic proton). The *methiodide* had m.p. 154° (from ethanol) (Found: C, 47.6; H, 6.4; N, 3.6. $C_{15}H_{24}INO_2$ requires C, 47.8; H, 6.4; N, 3.7%).

Acid-catalysed Rearrangement of the Ethoxy-ketones (20) *and* (21).—Each ethoxy-ketone (0.5 g) was heated separately in 3N-hydrochloric acid (15 ml) on a water-bath for 3 h. The mixture was basified with 30% sodium hydroxide solution and extracted with ether, and the dried extract was evaporated. The rearrangement product derived from each ketone [and from the analogous ketones (7) and (8)] was a solid (*ca.* 0.35 g), m.p. 90—100°, containing two major components, as indicated by t.l.c. on alumina (ether as eluant). Fractional crystallisation from ether afforded the two diastereoisomeric 10-*hydroxy*-3,10-*dimethyl*-3-*azatricyclo*-[7.3.1.$0^{1,6}$]*tridec*-6-*en*-8-*ones* (22), m.p. 105° (Found: C, 71.3; H, 9.1; N, 5.9. $C_{14}H_{21}NO_2$ requires C, 71.45;

H, 9.0; N, 5.95%), and (23), m.p. 148° (Found: C, 71.6; H, 8.8; N, 5.7%).

The alcohol (22) (0.2 g) was dissolved in ether (1 ml) and applied to an alumina column [10 g of Wöelm neutral (activity III)]. Elution with ether gave 3,10-*dimethyl*-3-*azatricyclo*[7.3.1.$0^{1,6}$]*trideca*-6,10-*dien*-8-*one* (24) (*ca.* 0.1 g), m.p. 74° (Found: C, 77.2; H, 8.9; N, 6.4. $C_{14}H_{19}NO$ requires C, 77.4; H, 8.8; N, 6.45%). The alcohol (23) (0.2 g) was not dehydrated to the olefinic enone (24) under these conditions.

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