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Azabicycloalkanes as Analgetics. II.[1] An Improved Synthesis of 1-Phenyl-6-azabicyclo[3,2,1]octane Derivatives

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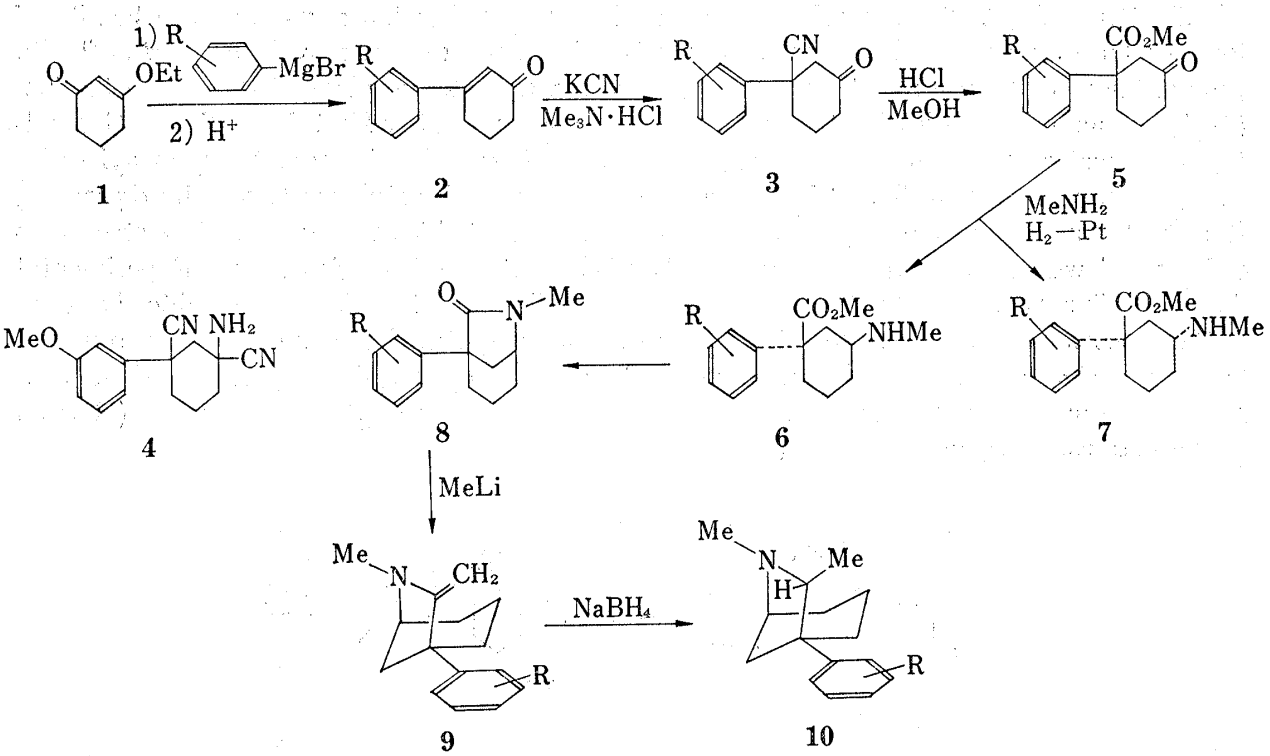
An improved synthesis of 6,7*endo*-dimethyl-1-(3-hydroxyphenyl)-6-azabicyclo[3,2,1]-octane (**10c**), a new analgetic agent with a low addiction liability, is described. Grignard reaction of 3-ethoxy-2-cyclohexen-1-one(**1**) with *m*-methoxyphenylmagnesium bromide gave the α,β-unsaturated ketone (**2b**). Hydrocyanation of the latter followed by methanolysis yielded the keto ester (**5b**). The bicyclic lactam (**8b**), a key intermediate in the original synthesis was obtained by reductive amination of **5b** with methylamine. As a result of this sequence of reactions, **10c** could be obtained in 7 steps from **1** in 42% overall yield. By an application of this new method, a number of 1-phenyl-6-azabicyclo[3,2,1] octane derivatives with various substituents on benzene ring (**10d—k**), nitrogen (**31**), and C_8 (**39—46**) have been prepared for pharmacological evaluation.

The preceding paper[1] of this series described the synthesis of 6,7 *endo*-dimethyl-1-(3-hydroxyphenyl)-6-azabicyclo[3,2,1]octane (**10c**), a good mixture of agonist (analgetic) and narcotic antagonist components with a low grade of physical dependence capacity, from 1-(3-methoxyphenyl)-4-oxocyclohexanecarbonitrile. The rather long sequence of the reactions (10 steps in 16% overall yield) and less accessibility to the starting material prompted us to study a more practical synthesis of **10c**.

Thermal cyclization of 3-aminocyclohexanecarboxylic acid has been known to give 6-azabicyclo[3,2,1]octan-7-one effectively.[3] Therefore, reductive amination of methyl 1-(3-methoxyphenyl)-3-oxocyclohexanecarboxylate (**5b**) appeared to be most feasible route to the lactam (**8b**), a key intermediate in the above synthesis. Although one cannot easily predict the stereochemistry of the hydrogenation step (**5**→**6** and/or **7**), the scheme outlined in Chart 1 was thus chosen as a potential route to **10c**.

Reaction of 3-ethoxy-2-cyclohexen-1-one (**1**), readily obtained from resorcinol in 2 steps,[4] with *m*-methoxyphenylmagnesium bromide in tetrahydrofuran (THF) followed by quenching the Grignard mixture with dil. H_2SO_4[5] gave a quantitative yield of 3-(3-methoxyphenyl)-2-cyclohexen-1-one (**2b**). Various methods for the conjugate addition of CN^- ion to the α,β-unsaturated ketone (**2**) were investigated. In a model experiment, heating of **2a**[5] with acetone cyanohydrine in the presence of sodium carbonate in aqueous methanol[6] gave the cyano ketone (**3a**, 25.4%), 1-phenyl-3-oxocyclohexanecarboxamide (20%) and an unknown dimeric product together with the starting material (15%). Reaction of **2a** with potassium cyanide in the presence of acetic acid in aqueous ethanol[7] for 80 hr yielded **3a** in 61% yield.

1) Part I: M. Takeda, H. Inoue, K. Noguchi, Y. Honma, M. Kawamori, G. Tsukamoto and S. Saito, *Chem. Pharm. Bull.* (Tokyo), **24**, 1002 (1976).
2) Location: *2–2–50, Kawagishi, Toda, Saitama, Japan; a)* To whom correspondence should be addressed.
3) *a)* W. Schneider and J. Hoyer, *Arch. Pharm.*, **304**, 637 (1971); *b)* F.R. Hewgill and P.R. Jefferies, *J. Chem. Soc.*, **1955**, 2767.
4) R. Grewe, E. Nolte and R.H. Rotzoll, *Chem. Ber.*, **89**, 600 (1956).
5) G.F. Woods and I.W. Tucker, *J. Am. Chem. Soc.*, **70**, 2174 (1948).
6) M.P. Mertes, A.A. Ramsey, P.E. Hanna and D.D. Miller, *J. Med. Chem.*, **13**, 789 (1970).
7) C.F.H. Allen and R.H. Kimball, "Organic Syntheses," Coll. Vol. II, ed. by A.H. Blatt, John Wiley and Sons, Inc., New York, N.Y. 1943, p. 498.



a,R=H; **b**,R=3-OMe; **c**,R=3-OH; **d**,R=2-OMe; **e**,R=2-OH; **f**,R=4-OMe; **g**,R=4-OH; **h**,R=3,4-diOMe; **i**,R=3,4-diOH; **j**,R=3,5-diOMe; **k**,R=3,5-diOH

Chart 1

However, the reaction was rather difficult to control and the yield was not reproducible because of the formation of dimeric products[7] on prolonged reaction. Finally, hydrocyanation of **2b** was carried out according to the procedure described by Nagata, *et al.*[8] Thus, when heated with potassium cyanide in the presence of ammonium chloride in aqueous dimethylformamide (DMF), **2b** afforded the cyano ketone (**3b**) in 53% yield together with the amino dinitrile (**4**) (18% yield). The structure of **4** was confirmed by elemental and spectral analyses. **4** was apparently formed through **3b** by the further addition of ammonia and CN^- ion to the carbonyl group. On substitution of trimethylamine hydrochloride for ammonium chloride in the reaction, therefore, **3b** was obtained in a satisfactory yield (77%). Heating of **3b** in methanolic hydrogen chloride gave the keto ester (**5b**) in 88% yield. Platinum-catalized hydrogenation of **5b** in the presence of aqueous methylamine in methanol followed by heating of the reduction product at 110° gave the N-methyl lactam (**8b**) in 72.3% yield together with the non-cyclizing *trans* amino ester (**7b**, 17%). Accordingly, by this new method, **10c** could be obtained in 7 steps from **1** in much increased overall yield (42%) (Chart 1).

As an alternative route to the lactam (**8**), 3-hydroxyimino-1-phenylcyclohexanecarboxylic acid (**12**) prepared from **3a** was hydrogenated over Raney Nickel. Heating of the resultant amino acids in boiling xylene gave a 1:1 mixture of the lactam (**13**)[1] and the *trans* amino acid (**14**). Therefore, there is no stereoselectivity in the hydrogenation step in this case (Chart 2).

For pharmacological evaluation, 6,7-dimethyl-1-phenyl-6-azabicyclo[3,2,1]octanes (**10d**—**k**) with a hydroxy group at various positions of the benzene ring were synthesized by an application of the new method described above (Chart 1). The cyano ketones (**3d** and **3j**) with 2-methoxy- and 3,5-dimethoxyphenyl group behaved anomalously in the methanolysis step (Chart 2). Heating of **3d** in methanolic hydrogen chloride for 4 hr in the usual manner gave the expected keto ester (**5d**), the hydroxy-lactam (**15**), and the methoxy-lactam (**16**) in yields

8) W. Nagata, S. Hirai, H. Itazaki and K. Takeda, *J. Org. Chem.*, **26**, 2413 (1961).

of 9.5, 31.2 and 33.9%, respectively. Formation of a similar hydroxy-lactam, a hemiketal form of keto amide, and its methoxy derivative has been reported by Nagata, *et al.*[8] On prolongation of the reaction time to 20 hr, however, a moderate yield of the keto ester (**5d**) (67%) was achieved, indicating that **15** and **16** were convertible to **5d** in this condition. Generally, prolonged reaction time was required for the each step in the 2-methoxyphenyl series owing to the sterical crowding. Similar treatment of **3j** yielded mainly the two cyclized product, **17** and **18**, together with a very small amount of the expected keto ester (**5j**). The structures of **17** and **18** were deduced from their spectral and elemental analyses given in the Experimental Section. This type of cyclization[9] is apparently ascribable to the high nucleophilic character of the 2-position of 3,5-dimethoxyphenyl group. By an application of the procedure reported by Pfeffer, *et al*,[10] the keto acid (**21**) obtained by alkaline hydrolysis of **3j** was esterified with methyl iodide and potassium hydroxide in alcoholic hexamethylphosphoramide (HMPA) to the keto ester (**5j**) in good yield (76%).

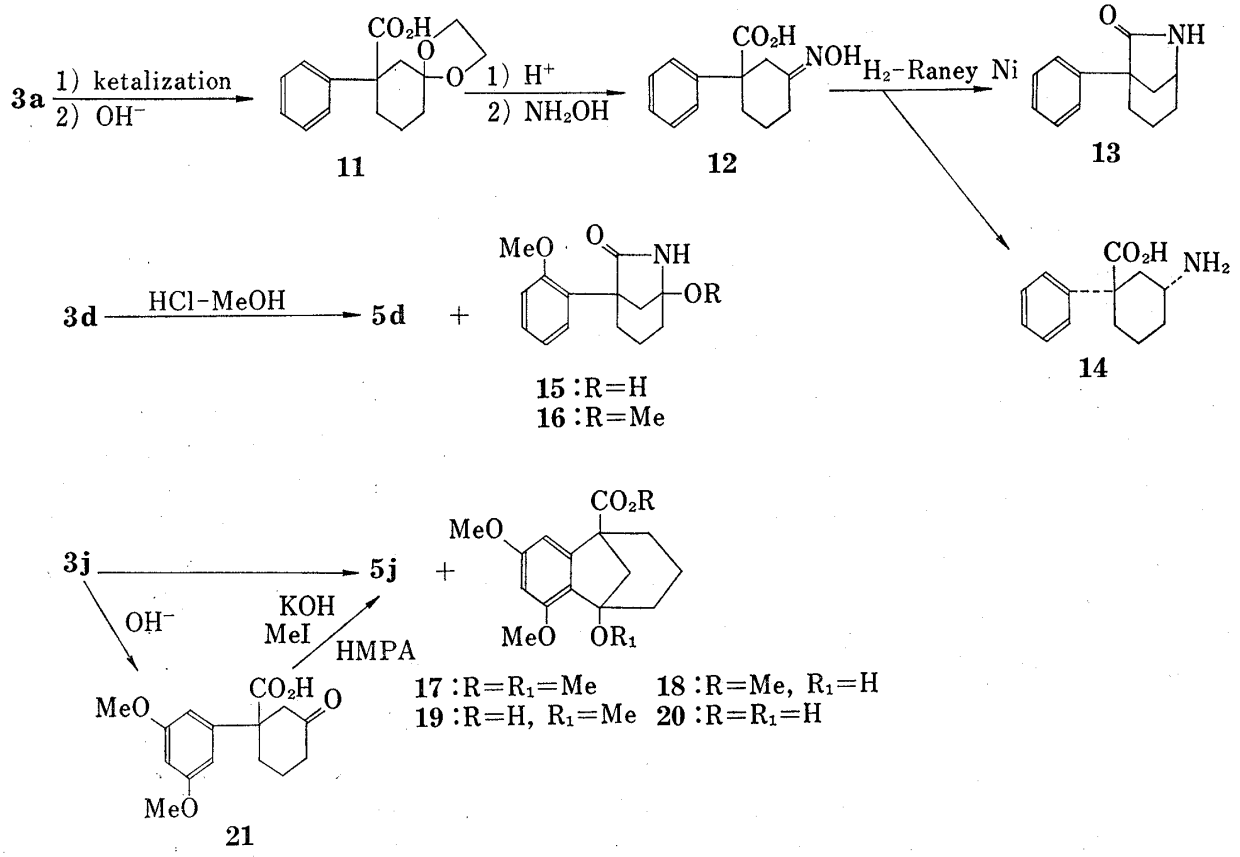


Chart 2

Methyllithium (MeLi) treatment of the lactams (**8d, f, h, j**) followed by reduction with sodium borohydride ($NaBH_4$) gave, in each instance, a single epimer of the corresponding 7-methyl derivatives (**10d, f, h, j**), respectively (Chart 1). By analogy with the previous case,[1] *endo* configuration was assigned to the 7-methyl group of these compounds. O-Demethylation of **10d, f, h, j** gave the corresponding phenols (**10e, g, i, k**), respectively.

In view of the pronounced analgetic activity found in the 6,7-dimethyl derivatives in this series,[1] synthesis of the corresponding N-substituted derivatives (**31**) was carried out (Chart 3). For this purpose, the keto ester (**5b**) was hydrogenated over PtO_2 in the presence of benzylamine

9) P. Pfäffli and H. Hauth, *Helv. Chim. Acta*, **56**, 347 (1973).
10) P.E. Pfeffer, T.A. Foglia, P.A. Barr, I. Schmeltz and L.S. Silbert, *Tetrahedron Letters*, **1972**, 4063.

to give a mixture of the *cis* and *trans* benzylamino ester (**22a, b**). The mixture did not give the lactam (**23**) by heating presumably because of the weak basicity of the benzylamino group. However, prolonged heating of the mixture with sodium methoxide (to enhance the nucleophilicity of the nitrogen) in benzene–methanol gave a good yield (84%) of **23**, a small amount of the *trans* amino ester (**22b**) being also isolated (11%). The N-benzyl lactam (**23**) also resulted from the lactam (**24**)[1] *via* N-benzylation in a quantitative yield. Treatment of **23** with MeLi followed by $NaBH_4$ reduction afforded the 7 *endo*-methyl derivative (**25**) in 81% yield.

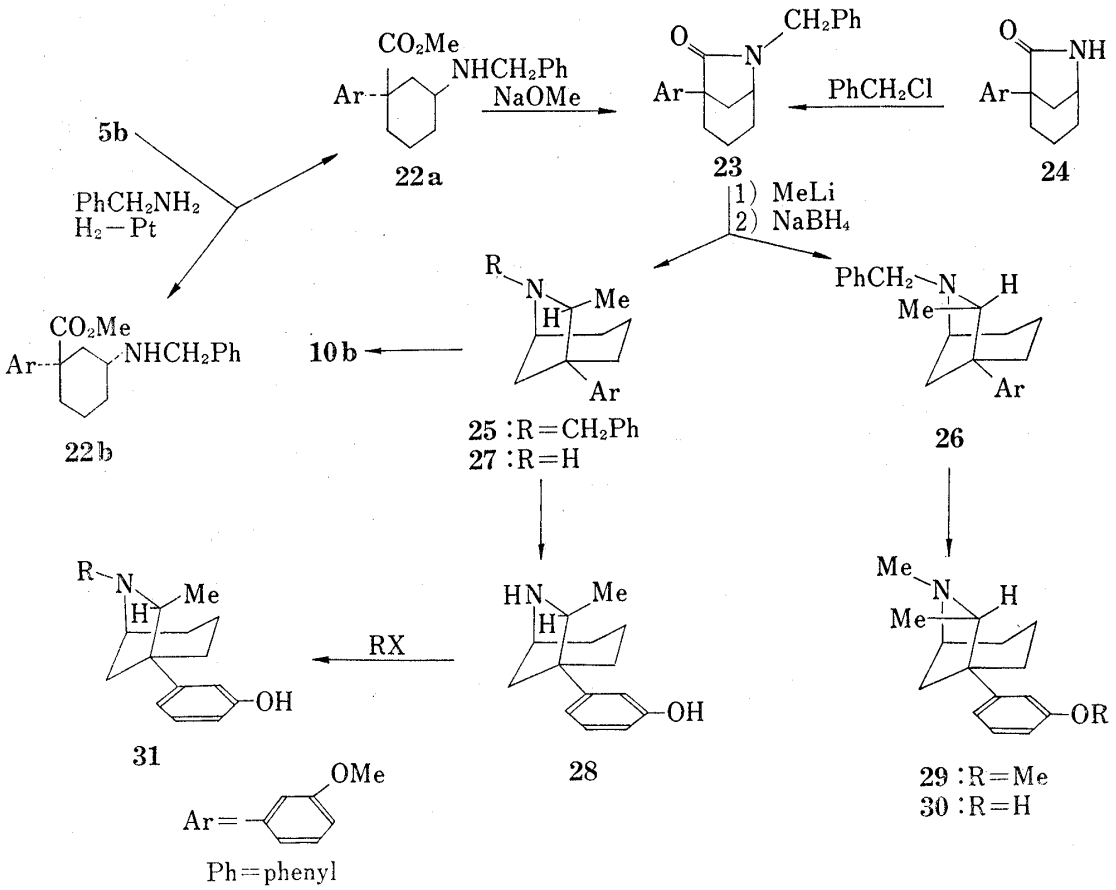


Chart 3

In this instance, a very small amount of the 7 *exo*-methyl isomer (**26**) was also isolated in 2.7% yield. Hydrogenolysis of **25** over colloidal Palladium in acetic acid gave the secondary amine (**27**). N-Formylation of **27** followed by lithium aluminum hydride (LAH) reduction yielded the known[1] 6,7 *endo*-dimethyl derivative (**10b**), the stereochemistry of **27** (and hence that of **25**) being thus established. Similary, the 7 *exo*-methyl isomer (**26**) was ultimately converted to the phenolic 6,7 *exo*-dimethyl derivative (**30**) in view of the pharmacological interest. O-Demethylation of **27** gave the phenol (**28**) from which the N-substituted derivatives (**31**) listed in Table I were prepared by the usual method.

Introduction of methyl substituent on C_7 in this series greatly enhanced the analgetic activity of the parent compound.[1] To examine the effect of similar substitution on C_8, synthesis of 6,8-dimethyl and 6,7,8-trimethyl derivatives was performed (Chart 4). Introduction of methyl group on C_2 of the α,β-unsaturated ketone (**2b**) was carried out according to the procedure described by Stork, *et al.*[11] giving the 2-methyl enone (**33**) in 23% yield. Much

11) G. Stork and J. Benaim, *J. Am. Chem. Soc.*, **93**, 5938 (1971).

more satisfactory was the conversion of 3-ethoxy-2-methyl-2-cyclohexen-1-one (**32**)[12] to **33** by the Grignard reaction with *m*-methoxyphenylmagnesium bromide (71% yield). Hydrocyanation of **33** in the usual manner for 21 hr gave the cyano ketone (**34**) in 74% yield.

As was expected, **34** was found to be a mixture (*ca.* 4: 1) of the C_2 diastereoisomers, the two secondary methyl signals being observed at 0.97 and 1.10 ppm in its nuclear magnetic resonance (NMR) spectrum, respectively. From this mixture, the major product with methyl signal at 0.97 ppm could be separated in a crystalline form and was assigned to the *trans* (CN/Me) structure.[13] In view of susceptibility to epimerization, however, the mixture of diastereoisomers (**34**) was used for the next step without separation.[14] Conversion of the cyano group in **34** to the ester function by heating with methanolic hydrogen chloride proved to be refractory apparently because of the steric crowding caused by the 2-methyl group. Alkaline hydrolysis of the crude cyano ketone (**34**) gave the keto acid (**35**) in 74% yield. In the NMR spectrum, the two methyl signals were observed at 0.84 and 1.03 ppm, respectively. Esterification of **35** was conveniently effected with methyliodide and potassium hydroxide in alcoholic HMPA[10] to give the keto ester (**36**) as a mixture of diastereoisomers with two doublets at 0.79 and 1.11 ppm (*ca.* 3: 2, respectively) in 72% yield. Reductive amination of this mixture in the presence of aqueous methylamine over PtO_2 followed by thermal cyclization gave a mixture of the isomeric lactams in 93% yield. Finally, the mixture was separated

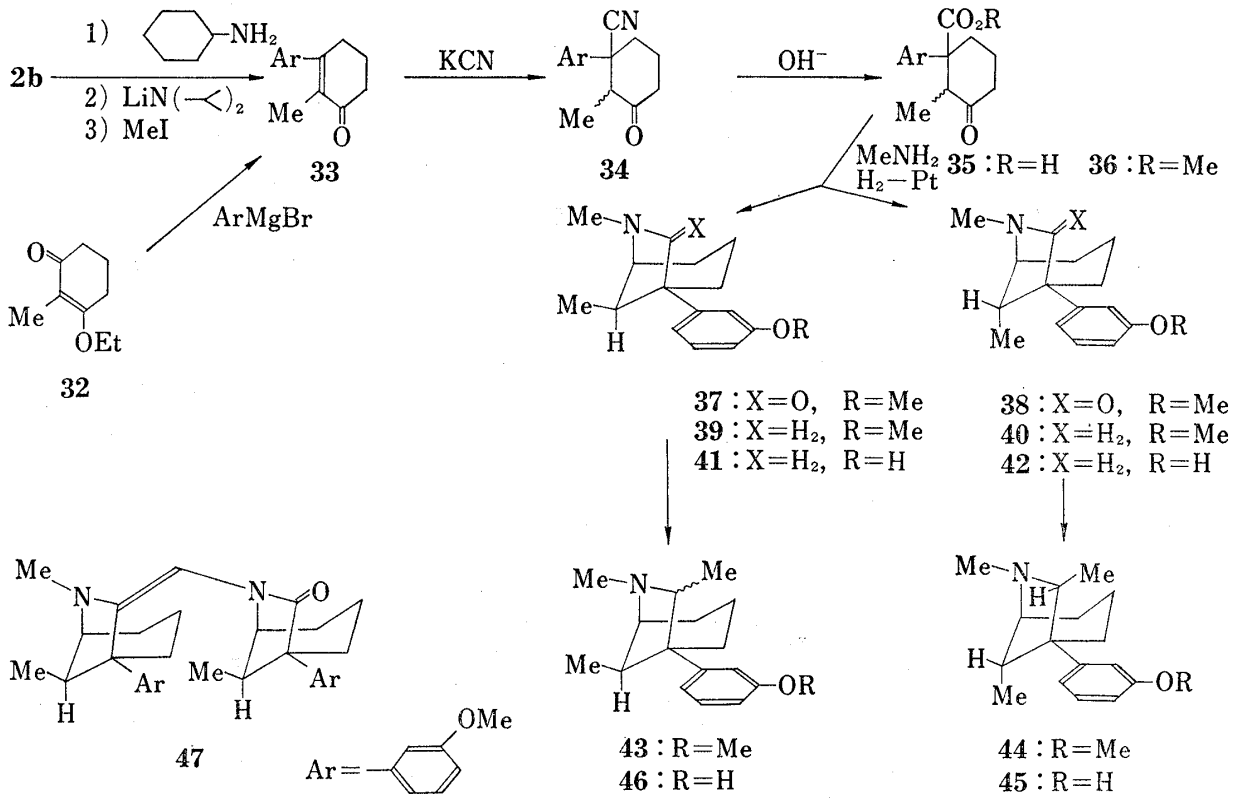


Chart 4

12) E.G. Meek, J.H. Turnbull and W. Wilson, *J. Chem. Soc.*, **1973**, 811.

13) When the phenyl group located equatorially, the methyl group of the *cis* (CN/Me) isomer would have equatorial conformation and was expected to be shifted downward by the deshielding effect of the adjacent carbonyl group. Hence the isomer with methyl signal at higher field was assigned to the *trans* (CN/Me) structure.

14) This proved to be true, when it was found that the separated single isomer of the keto ester (**36**) afforded the two C_8 epimeric lactams (**37** and **38**) on reductive amination. Thus, the separation of the stereoisomers at earlier stage than the lactams (**37** and **38**) proved to be meaningless. See Experimental Section.

by chromatography on silica gel to afford the 8 *exo*-methyl lactam (**37**) and the 8 *endo* isomer (**38**) in yields of 53.8 and 33.2%, respectively. Stereochemistry of these isomers was determined by NMR spectral data. Thus, the *exo* isomer (**37**) showed the secondary methyl signal at 0.73 ppm compared with 0.90 ppm for the *endo* isomer (**38**). This diamagnetic shift of 0.17 ppm was apparently ascribed to the anisotropic effect of the lactam carbonyl group.[15] LAH reduction of the 8 *endo*-methyl lactam (**38**) in the usual manner gave the amine (**40**) without difficulty. On the other hand, similar reduction of the *exo* isomer (**37**) proceeded rather slowly. However, the 6,8 *exo*-dimethyl amine (**39**) was obtained in 98% yield after prolonged heating (30 hr). **39** and **40** had the almost identical chemical shifts (0.87 and 0.89 ppm, respectively) for their C_8-methyl signals, since the effect of C_7 carbonyl anisotropy has been removed. Introduction of methyl group on C_7 of **38** in the usual manner resulted in formation of the single epimer of the 6,7,8-trimethyl derivative (**44**) in a quantitative yield. Considering that the presence of the *endo* methyl group on C_8 would not alter the stereochemistry of addition of hydrogen to the intermediate 7-methylene group, one is led to assign 7 *endo*-methyl structure to **44** by analogy with **10b**.[1]

As was expected, the 8 *exo*-methyl lactam (**37**) reacted with MeLi only with difficulty. Thus, on prolonged treatment with a large excess of MeLi followed by reduction with $NaBH_4$, **37** produced a very small amount (5.4%) of the 6,7,8-trimethyl derivative (**43**) and the dimeric product (**47**) with a recovery of the starting material (57%). Because one cannot easily predict the stereochemistry of the hydride approach in this case and the only one product is in hand for spectral analysis, the stereochemistry of **43** remains unknown. The structure of the dimeric product, mp 201—203°, obtained in 20% yield in this reaction was tentatively assigned to **47** by the elemental analysis and spectral evidence given in the Experimental Section. Formation of **47** may be explained by the attack of anion of the N-methyl group to the lactam carbonyl of another molecule.

Table I. N-Substituted 3-Hydroxyphenyl-7*endo*-methyl-6-azabicyclo-[3,2,1]octane Derivatives (**31**)

R	Salt	Crystn.[a] solvent	mp(°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
C_2H_5	HCl	A	228—231	$C_{16}H_{24}ONCl$	68.20 (68.05)	8.52 (8.59)	4.97 (4.95)
C_3H_7	HCl	B	244—248	$C_{17}H_{26}ONCl$	69.04 (68.80)	8.80 (8.80)	4.74 (4.71)
C_4H_9	HCl	A	217.5—219	$C_{18}H_{28}ONCl$	69.77 (69.84)	9.11 (9.01)	4.52 (4.57)
C_5H_{11}	HCl	A-C	151—154	$C_{19}H_{30}ONCl$	70.48 (70.53)	9.27 (9.30)	4.33 (4.26)
C_6H_{13}	HCl	B	164—165	$C_{20}H_{32}ONCl$	71.09 (70.99)	9.55 (9.51)	4.14 (4.09)
$CH_2C{\equiv}CH$	HCl	B-D	235—238	$C_{17}H_{22}ONCl$	69.97 (69.70)	7.60 (7.58)	4.80 (4.68)
$CH_2CH{=}CH_2$	HCl	B-D	181—185	$C_{17}H_{24}ONCl$	69.54 (69.36)	8.17 (8.23)	4.77 (4.71)
$CH_2CH{=}C(CH_3)_2$	HBr	B-D	178—180	$C_{19}H_{28}ONBr \cdot 1/2\ H_2O$	60.79 (60.75)	7.78 (7.64)	3.73 (3.91)
CH_2- 	HCl	B-D	216—219	$C_{18}H_{26}ONCl$	70.23 (69.80)	8.51 (8.54)	4.55 (4.43)
CH_2CH_2Ph	HCl	C	231—233	$C_{22}H_{28}ONCl$	73.83 (73.54)	7.88 (7.97)	3.91 (3.87)

[a] A; iso-PrOH; B, EtOH; C, acetone; D, ether
Ph=phenyl

15) T.H. Siddall, III and W.E. Stewart, *J. Mol. Spectrosc.*, **24**, 290 (1967).

The compounds prepared in the present study were tested[16] for their analgetic activities by the mouse writhing method.[17] The N-substituted 7 *endo*-methyl derivatives (**31**) exhibited more potent activities than the corresponding 7-unsubstituted derivatives. Introduction of methyl group on C_8 resulted in a marked fall in the activity. The comprehensive structure-activity relationships of the compounds will be reported in a later communication.

Experimental

All melting points were determined with a Yanagimoto capillary melting point apparatus (Model MP-1) and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi IR-215 spectrophotometer. NMR spectra were determined on a Model JEOL ME-60 instrument in $CDCl_3$ (containing tetramethylsilane at δ 0.00 as an internal standard), unless otherwise specified. Coupling constants (J) are given in Hz and the following abbreviations are used; s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. Mass spectra were measured on a Hitachi RMS-4 mass spectrometer. Ultraviolet (UV) spectra were recorded on a Hitachi 323 spectrophotometer. Gas chromatography (GC) were obtained on a Shimadzu GC-4BPF instrument using a 3% OV-17 column. The organic solutions were dried over Na_2SO_4 and all evaporations were carried out *in vacuo*.

3-Aryl-2-cyclohexen-1-ones (**2**)——In a typical procedure, to a stirred solution of *m*-methoxyphenylmagnesium bromide (prepared from 150 g of *m*-bromoanisole, 19.5 g of magnesium and trace of iodine) in THF (178 ml) was added a solution of 98 g of **1** in THF (70 ml) at 10—21°. The mixture was stirred at room temperature for 1 hr and decomposed by addition of 10% H_2SO_4 (350 ml) under cooling. THF was removed and the residue was diluted with H_2O and extracted with benzene. Evaporation of the extracts gave, after washing with 10% NaOH and H_2O and drying, an oil which was distilled to give 138.7 g (98%) of 3-(3-methoxyphenyl)-2-cyclohexen-1-one (**2b**), bp 168—170° (2 mmHg). IR ν_{max}^{liquid} cm^{-1}: 1660 (C=C–C=O). NMR: 3.74 (3H, s, OCH_3), 6.25 (1H, broad s, C=CH). Mass Spectrum *m/e*: 202 (M^+), 174 (base peak). *Anal.* Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 76.98; H, 6.82.

The following enones (**2**) were prepared in the same manner as that described above by use of the appropriate arylmagnesium bromides in comparable yields.

3-(2-Methoxyphenyl)-2-cyclohexen-1-one (**2d**), bp 136—139° (3 mmHg). *Anal.* Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.19; H, 7.01. 3-(4-Methoxyphenyl)-2-cyclohexen-1-one (**2f**), mp 81—83°. Lit.[18] mp 84—85°. 3-(3,4-Dimethoxyphenyl)-2-cyclohexen-1-one (**2h**), mp 119—120°. Plates from benzene–iso-propyl ether. *Anal.* Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.31; H, 7.01. 3-(3,5-Dimethoxyphenyl)-2-cyclohexen-1-one (**2j**), bp 165° (0.7 mmHg). *Anal.* Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.11; H, 6.82.

3-Aryl-3-cyanocyclohexan-1-ones (**3**)——In a typical procedure, a mixture of **2b** (6.06 g), KCN (4.02 g), trimethylamine hydrochloride (4.33 g), H_2O (21 ml), and DMF (120 ml) was heated at 93—94° for 6 hr and evaporated. The residue was diluted with H_2O and extracted with benzene. The extracts were washed with H_2O, 10% HCl and H_2O, successively. Evaporation of the dried extracts left an oil which was distilled to give 5.26 g (77%) of 3-cyano-3-(3-methoxyphenyl)cyclohexan-1-one (**3b**), bp 175° (0.8 mmHg). IR ν_{max}^{liquid} cm^{-1}: 1710 (C=O), 2240 (C≡N). The distillate was crystallized as prisms from iso-propyl ether, mp 48—48.5°. *Anal.* Calcd. for $C_{14}H_{15}O_2N$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.21; H, 6.36; N, 5.99.

The following cyano ketones (**3**) were prepared in the same manner as that described above.

3-Cyano-3-phenylcyclohexan-1-one (**3a**), bp 147—149° (0.4 mmHg). *Anal.* Calcd. for $C_{13}H_{13}ON$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.11; H, 6.29; N, 6.91. 3-Cyano-3-(2-methoxyphenyl)cyclohexan-1-one (**3d**), mp 100—102° (from iso-propyl ether).[19] *Anal.* Calcd. for $C_{14}H_{15}O_2N$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.56; H, 6.67; N, 6.17. 3-Cyano-3-(4-methoxyphenyl)cyclohexan-1-one (**3f**), mp 119—123° (from MeOH). *Anal.* Calcd. for $C_{14}H_{15}O_2N$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.01; H, 6.67; N, 5.89. 3-Cyano-3-(3,4-dimethoxyphenyl)cyclohexan-1-one (**3h**), mp 139—140° (from benzene). *Anal.* Calcd. for $C_{15}H_{17}O_3N$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.19; H, 6.64; N, 5.77. 3-Cyano-(3,5-dimethoxyphenyl)-cyclohexan-1-one (**3j**), mp 103—104° (from EtOH). *Anal.* Calcd. for $C_{15}H_{17}O_3N$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.63; H, 6.66; N, 5.53.

Reaction of 2b with KCN in the Presence of Ammonium Chloride——A mixture of **2b** (36 g), KCN (23.9 g), NH_4Cl (14.25 g), H_2O (200 ml) and DMF (250 ml) was heated at 100° for 4.5 hr, evaporated, and extracted with benzene. Washing of the benzene extracts with 10% HCl caused precipitation of a crystalline solid which was collected and washed with H_2O to give 8.2 g (18%) of **4**·HCl, mp 185—189°. Recrystallization

16) The tests were conducted by Drs, G. Hayashi and S. Nurimoto and their associates at the Safety Research Laboratory of this company.
17) S. Nurimoto, S. Suzuki, G. Hayashi and M. Takeda, *Japan J. Pharmacol.*, **24**, 461 (1974).
18) S.N. Ege and P. Yates, *Can. J. Chem.*, **45**, 2933 (1967).
19) The reaction was carried out at 100° for 18 hr.

from MeOH gave needles, mp 187—189°. IR (free base) ν_{max}^{liquid} cm^{-1}: 2230 (C≡N), 3300, 3480 (NH_2). Mass Spectrum *m/e*: 255 (M^+), 123 (base peak). *Anal.* Calcd. for $C_{15}H_{18}ON_3Cl$: C, 61.74; H, 6.22; N, 14.40. Found: C, 62.10; H, 6.35; N, 14.72. The benzene extracts, after washing with H_2O, evaporation, and distillation, gave 21.6 g (53%) of **3b**, bp 170—173° (0.7 mmHg).

Reaction of 2a with Acetone Cyanohydrine——A mixture of **2a**[5] (1.7 g), acetone cyanohydrine (1.11 g), Na_2CO_3 (0.075 g), H_2O (1.2 ml) and MeOH (3 ml) was refluxed for 9 hr, diluted with H_2O, and extracted with $CHCl_3$. Evaporation of the dried $CHCl_3$ gave an oil, which was chromatographed over silica gel (50 g). The first part of elution with $CHCl_3$ gave **2a** (0.255 g, 15%). The second part of elution with $CHCl_3$ gave **3a** (0.5 g, 24%). Elution with $CHCl_3$–MeOH (98: 2) gave 0.1 g of crystals, mp 213—215°. Mass Spectrum *m/e*: 399 (M^+). The structure of this dimeric product was not elucidated. Further elution with $CHCl_3$–MeOH (98: 2) gave 0.43 g (20%) of 1-phenyl-3-oxocyclohexanecarboxamide, mp 125—128°. Recrystallization from AcOEt gave needles, mp 128—131°. IR ν_{max}^{Nujol} cm^{-1}: 1675 (NH_2CO), 1705 (C=O), 3200, 3250, 3380 (NH_2). Mass Spectrum *m/e*: 217 (M^+), 174. *Anal.* Calcd. for $C_{13}H_{15}O_2N$: C, 71.86; H, 6.95; N, 6.44. Found: C, 71.79; H, 7.05; N, 6.51.

Reaction of 2a with KCN in Acetic Acid and Aqueous Ethanol——To a stirred solution of **2a** (13 g), 95% EtOH (460 ml) and AcOH (13.8 g) was added a solution of KCN (30 g) in H_2O (84 ml). The mixture was stirred at 35° for 80 hr, diluted with H_2O (500 ml), and extracted with $CHCl_3$. Evaporation of the $CHCl_3$ extracts gave, after washing with H_2O and drying, an oil which was distilled to give 9.1 g (61%) of **3a**, bp 147—149° (0.4 mmHg).

Prolongation of the reaction time resulted in a marked fall of the yield of **3a** with a formation of the dimeric product, mp 233—234°. The structure of the latter was not elucidated.

Methyl 1-Aryl-3-oxocyclohexanecarboxylates (5)——In a typical procedure, a solution of **3b** (9.5 g) in MeOH (95 ml) was saturated with dry HCl and the mixture was refluxed for 4 hr. MeOH was removed and the residue was diluted with H_2O, and extracted with benzene. The extracts were washed with H_2O, dil. $NaHCO_3$, and H_2O, successively. Evaporation of the dried extracts gave an oil, which was distilled to give 9.55 g (88%) of methyl 1-(3-methoxyphenyl)-3-oxocyclohexanecarboxylate (**5b**), bp 176—178° (2 mmHg). IR ν_{max}^{liquid} cm^{-1}: 1710 (C=O), 1730 (CO_2Me). NMR: 2.87 (2H, d, $J_{gem}=9$, C_2-H), 3.65 (3H, s, CO_2CH_3), 3.8 (3H, s, $ArOCH_3$). Mass Spectrum *m/e*: 262 (M^+), 203 (base peak). *Anal.* Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92; Found: C, 68.37; H, 6.67.

The following keto esters (**5**) were obtained in the same manner as that described above in comparable yields.

Methyl 1-phenyl-3-oxocyclohexanecarboxylate (**5a**), mp 83—84°. Prisms from iso-propyl ether–hexane. *Anal.* Calcd. for $C_{14}H_{16}O_3$: C, 72.38; H, 6.94. Found: C, 72.49; H, 7.03. Methyl 1-(4-methoxyphenyl)-3-oxocyclohexanecarboxylate (**5f**), mp 77—78°. Needles from iso-propyl ether. *Anal.* Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.79; H, 6.99. Methyl 1-(3,4-dimethoxyphenyl)-3-oxocyclohexanecarboxylate (**5h**), mp 108—110° (from MeOH). *Anal.* Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.35; H, 6.91.

Methanolysis of 3d——Methanolysis of **3d** (11 g) in MeOH (110 ml) was carried out by the procedure described above. The crude product was crystallized from benzene to give 3.55 g of **15**, mp 176—180°. Recrystallization from AcOEt gave prisms, mp 180—181.5°. IR ν_{max}^{Nujol} cm^{-1}: 1670 (NHCO), 3170 (OH), 3360 (NH). *Anal.* Calcd. for $C_{14}H_{17}O_3N$: C, 67.99; H, 6.93; N, 5.66. Found: C, 68.08; H, 6.97; N, 5.62. The mother liquor from **15** (benzene) was concentrated and the residue was recrystallized from benzene to give 3.35 g of **16**, mp 144—144.5°. IR ν_{max}^{Nujol} cm^{-1}: 1705 (C=O), 3410 (NH). Mass Spectrum *m/e*: 261 (M^+). NMR: 3.36 (3H, s, C_5-OCH_3), 3.83 (3H, s, $ArOCH_3$), 6.0 (1H, broad s, NH), 7.35 (2H, s, solvated C_6H_6), 6.8—7.5 (4H, m, aromatic protons). *Anal.* Calcd. for $C_{15}H_{19}O_3N \cdot 1/3C_6H_6$: C, 71.05; H, 7.37; N, 4.87. Found: C, 71.15; H, 7.38; N, 4.73. Mother liquors from **15** and **16** (all combined) were evaporated and the residue was chromatographed over silica gel (60 g). The first part of the eluate with C_6H_6–AcOEt (9: 1) gave, after recrystallization from iso-propyl ether, 1.2 g (9.5%) of **5d**, mp 85—87°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (C=O), 1725 (CO_2Me). *Anal.* Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.74; H, 6.97. The second part of the eluate gave an additional amount (0.9 g, total yield 33.9%) of **16**. An additional amount (0.15 g, total yield 31.2%) of **15** was obtained by further elution with C_6H_6–AcOEt (9: 1).

When the methanolysis of **3d** was carried out by heating for 70 hr (additional hydrogen chloride was introduced after 35 hr), the keto ester (**5d**) was obtained in 64.7% yield.

Methanolysis of 3j——A solution of **3j** (10.6 g) in MeOH (100 ml) was saturated with dry HCl and the mixture was refluxed for 12 hr. The mixture was evaporated, diluted with H_2O, and extracted with benzene. Evaporation of the dried extracts gave, after distillation, 7 g of oil, bp 170—187° (0.8 mmHg). This oil was chromatographed over silica gel (250 g) and eluted with benzene–AcOEt (3: 1). The first part of the eluate gave 0.7 g (5.9%) of **5j**, mp 103—104°. Prisms from EtOH. IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O), 1725 (CO_2Me). NMR: 1.5—3.1 (8H, m, -CH_2-), 3.65 (3H, s, CO_2CH_3), 3.77 (6H, s, $ArOCH_3$), 6.3—6.5 (3H, m, aromatic protons). *Anal.* Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.72; H, 6.96. Further elution with C_6H_6–AcOEt (3: 1) gave 2.5 g (20%) of 1-carbomethoxy-3,4,6-trimethoxy-1,3-propano-indan (**17**) as an oil. IR ν_{max}^{liquid} cm^{-1}: 1725 (CO_2Me). NMR: 1.3—2.1 (8H, m, -CH_2-), 3.36 (3H, s, C_3-OCH_3), 3.82 (6H, s, $ArOCH_3$), 3.85 (3H, s, CO_2Me), 6.45 (1H, d, $J=2$, aromatic proton), 6.48 (1H, d, $J=2$, aromatic proton). Mass Spectrum

m/e: 306 (M^+), 264 ($M^+-C_3H_6$), 247 (M^+-CO_2Me, base peak). Hydrolysis of **17** with potassium hydroxide in aqueous MeOH at room temperature gave the corresponding acid (**19**) in a quantitative yield. Needles from benzene, mp 186—187°. IR ν_{max}^{Nujol} cm^{-1}: 1730 (CO_2H). NMR: 1.4—2.1 (8H, m, $-CH_2-$), 3.38 (3H, s, C_3-OCH_3), 3.84 (6H, s, $ArOCH_3$), 6.44 (1H, d, $J=2.5$, aromatic proton), 6.60 (1H, d, $J=2.5$, aromatic proton), 9.5 (1H, broad s, CO_2H). *Anal.* Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.93; H, 6.94. Further elution with C_6H_6–AcOEt (3: 1) gave 2.1 g (17.6%) of 1-carbomethoxy-4,6-dimethoxy-3-hydroxy-1,3-propano-indan (**18**) as an oil. IR ν_{max}^{liquid} cm^{-1}: 1725 (CO_2Me), 3420 (OH). NMR: 1.43—2.77 (8H, m, $-CH_2-$), 3.65 (1H, broad s, OH, disappeared on addition of D_2O), 3.81 (6H, s, ArOMe), 3.84 (3H, s, CO_2Me), 6.40 (1H, d, $J=2$, aromatic proton). 6.51 (1H, d, $J=2$, aromatic proton). Hydrolysis of **18** with KOH afforded the corresponding acid (**20**). Prisms from AcOEt, mp 175—176°. IR ν_{max}^{Nujol} cm^{-1}: 1720 (CO_2H), 3420 (OH). NMR: 1.4—2.8 (8H, m, $-CH_2-$), 3.80 (3H, s, $ArOCH_3$), 3.83 (3H, s, $ArOCH_3$), 6.42 (1H, d, $J=2.5$, aromatic proton), 6.61 (1H, d, $J=2.5$, aromatic proton). 7.20 (2H, broad s, CO_2H and OH). Mass Spectrum *m/e*: 278 (M^+), 236 ($M^+-C_3H_6$, base peak). *Anal.* Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52; O, 28.75. Found: C, 64.61; H, 6.59; O, 28.92.

Methyl 1-(3,5-Dimethoxyphenyl)-3-oxocyclohexanecarboxylate (5j)——A mixture of **3j** (14.6 g), KOH (14.6 g), ethylene glycol (146 ml) and H_2O (146 ml) was refluxed for 24 hr, diluted with H_2O (1500 ml) and washed with ether. The aqueous layer was made acidic with dil. HCl and extracted with $CHCl_3$. Evaporation of the $CHCl_3$ gave, after washing with H_2O and drying, 15.6 g of the crude carboxylic acid (**21**) as an oil. To a stirred solution of this oil and powdered NaOH (2.47 g) in EtOH (75 ml) and HMPA (75 ml) was added methyliodide (15.95 g). The mixture was heated at 55° for 1 hr, diluted with H_2O (1200 ml), acidified with HCl, and extracted with benzene. Evaporation of the extracts gave, after washing with H_2O and drying, a residue which was recrystallized from EtOH giving 12.45 g (75.7% from **3j**) of **5j**, mp 103—104°.

1-Aryl-6-methyl-6-azabicyclo[3,2,1]octan-7-ones (8)——In a typical procedure, a mixture of **5b** (95.2 g), PtO_2 (0.68 g), 40% aqueous methylamine (56.5 ml) and MeOH (450 ml) was shaken in H_2 atmosphere at room temperature for 8 hr. The catalyst was removed and the filtrate was concentrated. The oily residue, after heating at 110—130° under reduced pressure (5 mmHg) for 2 hr, was dissolved in benzene and washed with 10% HCl and H_2O. Evaporation of the dried extracts gave, after recrystallization from iso-propyl ether, 64.5 g (72.3%) of 1-(3-methoxyphenyl)-6-methyl-6-azabicyclo[3,2,1]octan-7-one (**8b**), mp 68—70°. This proved to be identical with an authentic sample[1] (IR, mp and thin-layer chromatography (TLC)). The HCl layer was basified with NH_4OH and extracted with benzene. Evaporation of the dried extracts gave an oil which was converted to the hydrochloride and recrystallized from iso-PrOH giving 19.3 g (17%) of *trans* methyl 1-(3-methoxyphenyl)-3-methylaminocyclohexanecarboxylate (**7b**)·HCl, mp 178.5—180°. IR ν_{max}^{Nujol} cm^{-1}: 1720 (CO_2Me). *Anal.* Calcd. for $C_{16}H_{24}O_3NCl$: C, 61.20; H, 7.77; N, 4.46. Found: C, 61.04; H, 7.83; N, 4.39.

The following lactams (**8**) were obtained by the method described above in comparable yields.

1-(2-Methoxyphenyl)-6-methyl-6-azabicyclo[3,2,1]octan-7-one (**8d**), mp 116—117°.[20] Prisms from iso-propyl ether. *Anal.* Calcd. for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.36; H, 7.81; N, 5.57. 1-(4-Methoxyphenyl)-6-methyl-6-azabicyclo[3,2,1]octan-7-one (**8f**), mp 88—91°. Prisms from iso-propyl ether. *Anal.* Calcd. for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.11; H, 7.76; N, 5.51. 1-(3,4-Dimethoxyphenyl)-6-methyl-6-azabicyclo[3,2,1]octan-7-one (**8h**), bp 190° (bath temperature, 1 mmHg). *Anal.* Calcd. for $C_{16}H_{21}O_3N$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.58; H, 7.51; N, 5.13. 1-(3,5-Dimethoxyphenyl)-6-methyl-6-azabicyclo[3,2,1]octan-7-one (**8j**), bp 195° (bath temperature, 1 mmHg). *Anal.* Calcd. for $C_{16}H_{21}O_3N$: C, 69.79; H, 7.69; N, 5.09. Found: C, 70.01; H, 7.82; N, 5.03.

1-Aryl-6,7*endo*-dimethyl-6-azabicyclo[3,2,1]octanes (10, R=OMe)——In a typical procedure, to a ethereal solution of MeLi (prepared from 0.31 g of Li, 3.2 g of MeI and 30 ml of ether) was added a solution of **8d** (1.84 g) in benzene (50 ml) at 0°. The mixture was stirred at room temperature overnight and decomposed by addition of H_2O under cooling. The organic layer was washed with H_2O, dried and evaporated to give 1.4 g of 1-(2-methoxyphenyl)-6-methyl-7-methylene-6-azabicyclo[3,2,1]octane (**9d**). Plates from MeOH, mp 86—87°. IR ν_{max}^{MeOH} cm^{-1}: 1632 (C=C-N). Mass Spectrum *m/e*: 243 (M^+). *Anal.* Calcd. for $C_{16}H_{21}ON$: C, 78.97; H, 8.70; N, 5.77. Found: C, 78.67; H, 8.68; N, 5.78. A mixture of this enamine (1.3 g), $NaBH_4$ (0.5 g) and EtOH (70 ml) was stirred at room temperature overnight. The mixture was evaporated, diluted with H_2O, and extracted with $CHCl_3$. Evaporation of the dried $CHCl_3$ gave, after recrystallization from hexane, 1.3 g (76% from **8d**) of 6,7*endo*-dimethyl-1-(2-methoxyphenyl)-6-azabicyclo[3,2,1]octane (**10d**), mp 70—72° as prisms. *Anal.* Calcd. for $C_{16}H_{23}ON$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.39; H, 9.51; N, 5.63. The hydrochloride was recrystallized from iso-PrOH–ether and had mp 235—237°.

The following 6,7*endo*-dimethyl derivatives (**10**, R=OMe) were obtained by the same procedure described above in comparable yields.

6,7*endo*-Dimethyl-1-(4-methoxyphenyl)-6-azabicyclo[3,2,1]octane (**10f**) hydrochloride, mp 242—244°. Needles from PrOH–ether. *Anal.* Calcd. for $C_{16}H_{24}ONCl$: C, 68.20; H, 8.53; N, 4.96. Found: C, 67.88; H, 8.38; N, 4.87. 1-(3,4-Dimethoxyphenyl)-6,7*endo*-dimethyl-6-azabicyclo[3,2,1]octane (**10h**) hydrochloride, mp 248—251°. *Anal.* Calcd. for $C_{17}H_{26}O_2NCl$: C, 65.48; H, 8.40; N, 4.49. Found: C, 65.36; H, 8.34; N, 4.43.

20) Hydrogenation was carried out at 50° with an initial pressure of 2 kg/cm² for 6 hr.

1-(3,5-Dimethoxyphenyl)-6,7*endo*-dimethyl-6-azabicyclo[3,2,1]octane (**10j**) hydrochloride, mp 218—219°. Prisms from iso-PrOH. *Anal.* Calcd. for $C_{17}H_{26}O_2NCl$: C, 65.48; H, 8.40; N, 4.49. Found: C, 65.48; H, 8.44; N, 4.31.

6,7*endo*-Dimethyl-1-(hydroxyphenyl)-6-azabicyclo[3,2,1]octanes (10, R=OH)——In a typical procedure, **10f**·HCl (2.87 g) and 47% HBr (30 ml) were refluxed for 2 hr and evaporated. The crystalline residue was filtered and washed with acetone. Recrystallization from EtOH gave 2.67 g (84%) of 6,7*endo*-dimethyl-1-(4-hydroxyphenyl)-6-azabicyclo[3,2,1]octane (**10g**) hydrobromide, mp 262—265°. *Anal.* Calcd. for $C_{15}H_{22}ONBr$: C, 57.69; H, 7.10; N, 4.49. Found: C, 57.64; H, 7.14; N, 4.41.

The following hydroxyphenyl derivatives (**10**, R=OH) were obtained by the method described above.

6,7*endo*-Dimethyl-1-(2-hydroxyphenyl)-6-azabicyclo[3,2,1]octane (**10e**) hydrobromide, mp 256—258°. Prisms from EtOH. *Anal.* Calcd. for $C_{15}H_{22}ONBr$: C, 57.69; H, 7.10; N, 4.49. Found: C, 57.92; H, 7.26; N, 4.66. 1-(3,4-Dihydroxyphenyl)-6,7*endo*-dimethyl-6-azabicyclo[3,2,1]octane (**10i**) hydrobromide, mp 265—269°. Plates from EtOH. *Anal.* Calcd. for $C_{15}H_{22}O_2NBr$: C, 54.89; H, 6.76; N, 4.27. Found: C, 54.68; H, 6.83; N, 4.15. 1-(3,5-Dihydroxyphenyl)-6,7*endo*-dimethyl-6-azabicyclo[3,2,1]octane (**10k**) hydrobromide, mp 253—254° (decomp.). Prisms from EtOH. *Anal.* Calcd. for $C_{15}H_{22}O_2NBr$: C, 54.89; H, 6.76; N, 4.27. Found: C, 54.91; H, 6.77; N, 4.30.

1-Phenyl-3-oxocyclohexanecarboxylic Acid Ethylene Ketal (11)——A mixture of **3a** (1.36 g), benzenesulfonic acid (0.05 g), ethylene glycol (1 ml), and toluene (20 ml) was refluxed for 10 hr with continuous removal of H_2O. The mixture was poured into aqueous K_2CO_3 solution and extracted with ether. Evaporation of the dried extracts gave an oil, which was chromatographed over silica gel (25 g). Elution with $CHCl_3$ gave, after recrystallization from iso-propyl ether, 0.94 g (57%) of 3-cyano-3-phenylcyclohexan-1-one ethylene ketal, mp 103—104°. IR ν_{max}^{Nujol} cm^{-1}: 2230 (C≡N), 1175, 1095, 1020 (ketal). *Anal.* Calcd. for $C_{15}H_{17}O_2N$: C, 74.04; H, 7.04; N, 5.76. Found: C, 74.39; H, 7.20; N, 5.76. A mixture of this ketal nitrile (1.5 g), KOH (1.5 g), H_2O (30 ml) and ethylene glycol (30 ml) was refluxed for 48 hr. The mixture was diluted with H_2O (40 ml), acidified with AcOH, extracted with $CHCl_3$, and washed with H_2O. Evaporation of the dried $CHCl_3$ gave, after recrystallization from AcOEt–hexane, 1.22 g (74.4%) of **11**, mp 125—127° as prisms. IR ν_{max}^{Nujol} cm^{-1}: 1695 (CO_2H). *Anal.* Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.65; H, 7.20.

Catalytic Hydrogenation of 3-Hydroxyimino-1-phenylcyclohexanecarboxylic Acid (12)——A mixture of **11** (1.45 g) and AcOH (15 ml) was refluxed for 24 hr and evaporated. The residue was taken in ether and extracted with 5% $NaHCO_3$. The aqueous layer was acidified with HCl and extracted with ether. Evaporation of the dried extracts gave 1.1 g of 1-phenyl-3-oxocyclohexanecarboxylic acid as an oil. A mixture of this oil, hydroxylamine hydrochloride (0.43 g), $NaOAc \cdot 3H_2O$ (0.9 g), H_2O (3 ml), and EtOH (11 ml) was refluxed for 1 hr. The mixture was evaporated, diluted with H_2O, and extracted with ether. Evaporation of the dried ether gave 1.3 g of crude 3-hxdroxyimino-1-phenylcyclohexanecarboxylic acid (**12**) as an oil. A mixture of this acid (**12**), Raney Nickel (W-7, 1.5 ml), NaOH (0.22 g), conc. NH_4OH (2.5 ml), and EtOH (25 ml) was hydrogenated in an autoclave with an initial pressure of 75 kg/cm^2. The mixture was heated at 100° for 3 hr and filtered from the catalyst. The filtrate was acidified with AcOH and evaporated. The residue was digested with EtOH and filtered to give mixture of the amino acids, mp 243—247°. This in xylene (50 ml) was refluxed for 72 hr and evaporated. The residue was digested with ether and filtered to give 0.235 g of *trans* 3-amino-1-phenylcyclohexanecarboxylic acid (**14**), mp 261—264°. The hydrochloride was recrystallized from EtOH–ether and had mp 170—172°. *Anal.* Calcd. for $C_{13}H_{18}O_2NCl \cdot H_2O$: C, 57.05; H, 7.37; N, 5.12. Found: C, 57.45; H, 7.28; N, 5.15.

The ethereal filtrate from **14** was evaporated and the residue was recrystallized from AcOEt–hexane giving 0.235 g of 1-phenyl-6-azabicyclo[3,2,1]octan-7-one (**13**), mp 138—139°. This proved to be identical with an authentic sample[1] (mp and IR).

6-Benzyl-1-(3-methoxyphenyl)-6-azabicyclo[3,2,1]octan-7-one (23)——A) From **5b**: A mixture of **5b** (30 g), benzylamine (13.46 g), PtO_2 (0.5 g), and MeOH (300 ml) was shaken in H_2 atmosphere at room temperature for 6 hr and filtered. The filtrate was acidified with dry HCl and evaporated. The residue was washed with ether, digested with EtOH, and filtered to give 32.2 g of the mixture of *cis* and *trans* methyl 3-benzylamino-1-(3-methoxyphenyl)cyclohexanecarboxylate hydrochloride, mp 205—208°. Recrystallization of a portion of this mixture from MeOH–ether gave the hydrochloride of the *cis* amino ester (**22a**), mp 211—212°. IR ν_{max}^{Nujol} cm^{-1}: 1728 (C=O). NMR (free base): 1.43 (1H, s, NH, disappeared on addition of D_2O), 3.54 (3H, s, CO_2CH_3), 3.76 (3H, s, $ArOCH_3$), 3.81 (2H, s, $NCH_2C_6H_5$), 7.31 (5H, s, C_6H_5). Mass Spectrum *m/e*: 353 (M^+). *Anal.* Calcd. for $C_{22}H_{28}O_3NCl$: C, 67.76; H, 7.24; N, 3.59. Found: C, 67.52; H, 7.08; N, 3.57. A mixture of the free amino ester (regenerated from 32 g of the above mixture of the *cis* and *trans* hydrochloride), methanolic solution of NaOMe (prepared from 1.92 g of Na and 640 ml of MeOH), and benzene (640 ml) was refluxed for 42 hr and evaporated. The residue was diluted with H_2O and extracted with benzene. Evaporation of the extracts gave, after washing with 10% HCl and H_2O and drying, an oil. The oil was washed with ether and filtered giving 3.52 g (7.9% from **5b**) of the *trans* amino ester (**22b**)·HCl, mp 198—201°. Recrystallization from MeOH–ether gave needles, mp 204—206°. IR ν_{max}^{Nujol} cm^{-1}: 1720 (CO_2CH_3). NMR (free base): 1.64 (1H, s, NH, disappeared on addition of D_2O), 3.58 (3H, s, CO_2CH_3), 3.87 (3H, s, $ArOCH_3$), 7.32 (5H, s, C_6H_5). *Anal.* Calcd. for $C_{22}H_{28}O_3NCl$: C, 67.76; H, 7.24; N, 3.59. Found: C, 67.49; H, 7.31; N, 3.61. The ethereal filtrate from **22b**·HCl was evaporated giving 22.15 g (60.3% from **5b**) of **23** as an oil, bp 195° (bath tempera-

ture, 0.05 mmHg). IR ν_{max}^{Nujol} cm^{-1}: 1690 (C=O). *Anal.* Calcd. for $C_{21}H_{23}O_2N$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.21; H, 7.19; N, 4.29.

Heating of a mixture of **22a,b** at 100° under reduced pressure for 1 hr resulted in a quantitative recovery of the material.

B) From **24**: A mixture of 0.42 g of NaH (69% oil dispersion: washed with hexane), 30 ml of dioxane, and 2.31 g of **24**[1] was heated at 60—62° for 1 hr. Benzyl chloride (1.52 g) was then added and heating was continued at 100° for 3 hr. The mixture was decomposed by addition of H_2O, evaporated, diluted with H_2O, and extracted with ether. Evaporation of the dried extracts gave 3.17 g (quantitative) of **23**, identical with the sample previously obtained from **5b** (IR and TLC).

6-Benzyl-1-(3-methoxyphenyl)-7*endo*-methyl-6-azabicyclo[3,2,1]octane (25) Picrate——To an ethereal solution of MeLi (prepared from 2.8 g MeI, 0.262 g of Li and 15 ml of ether) was added a solution of **23** (1.5 g) in benzene (30 ml). The mixture was stirred at room temperature overnight and worked up in the usual manner giving 1.5 g of oil. To a solution of this oil in EtOH (60 ml) was added $NaBH_4$ (0.36 g) and the mixture was stirred at room temperature overnight. The usual work-up gave 1.3 g of an oil. GC analysis showed two isomers (95:5). The mixture was chromatographed over silica gel (100 g). The first part of elution with $CHCl_3$–MeOH (95: 5) gave, after conversion to the picrate, 1.84 g (81%) of **25**·picrate, mp 180—184°. Analytical sample was recrystallized from MeOH and had mp 184—186°. NMR (free base): 1.13 (3H, d, J=6, C-CH_3), 2.86 (1H, q, J=6, C_7-H), 3.72 (3H, s, OCH_3). *Anal.* Calcd. for $C_{28}H_{30}O_8N_4$: C, 61.08; H, 5.49; N, 10.18. Found: C, 61.27; H, 5.62; N, 10.25. The second part of the eluate gave, after conversion to the picrate, 0.56 g (2.7%) of 6-benzyl-1-(3-methoxyphenyl)-7*exo*-methyl-6-azabicyclo[3,2,1]octane (**26**) picrate, mp 210—212° (from MeOH). *Anal.* Calcd. for $C_{28}H_{30}O_8N_4$: C, 61.08; H, 5.49; N, 10.18. Found: C, 61.18; H, 5.61; N, 10.21.

1-(3-Methoxyphenyl)-7*endo*-methyl-6-azabicyclo[3,2,1]octane (27) Hydrochloride——A mixture of **25** (7.21 g), colloidal palladium (2.2 g) and AcOH (165 ml) was shaken in H_2 atmosphere for 1.5 hr. The catalyst was removed and the filtrate was concentrated. Conversion of the residue to the hydrochloride and recrystallization from acetone–EtOH–ether gave 5.35 g (89.2%) of **27**·HCl, mp 174—176°. *Anal.* Calcd. for $C_{15}H_{22}ONCl$: C, 67.27; H, 8.28; N, 5.23. Found: C, 67.19; H, 8.29; N, 5.15.

Conversion of 27 to 10b——A mixture of **27** (regenerated from 0.3 g of the hydrochloride) and ethyl formate (10 ml) was refluxed for 4 hr and evaporated. To a solution of the residue in THF (15 mdel) was add LAH (0.215 g) and the mixture was refluxed for 2 hr. The usual work-up gave an oil which was converted to 0.29 g (80%) of the hydrobromide, mp 177—179° (from EtOH–ether). This proved to be identical with an authentic sample[1] of **10b**·HBr (TLC, mp and IR).

1-(3-Hydroxyphenyl)-7*endo*-methyl-6-azabicyclo[3,2,1]octane (28) Hydrobromide——A mixture of **27**·HCl (5.22 g) and 47% HBr (52 ml) was refluxed for 1 hr. After cooling, the precipitate was collected and recrystallized from MeOH–ether to give 5.48 g (94.3%) of **28**·HBr. mp 282—284°. *Anal.* Calcd. for $C_{14}H_{20}ONBr$: C, 56.38; H, 6.76; N, 4.69. Found: C, 56.31; H, 6.76; N, 4.66. The free base was recrystallized from EtOH and had mp 217—218.5°. *Anal.* Calcd. for $C_{14}H_{19}ON$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.46; H, 8.74; N, 6.34.

6,7*exo*-Dimethyl-1-(3-hydroxyphenyl)-6-azabicyclo[3,2,1]octane (30) Hydrobromide——This compound was obtained from **26** *via* hydrogenolysis, formylation, LAH reduction and O-demethylation in the same manner as that described above in 58% overall yield. Prisms from EtOH, mp 228—231°. *Anal.* Calcd. for $C_{15}H_{22}ONBr$: C, 57.69; H, 7.10; N, 4.49. Found: C, 57.59; H, 7.15; N, 4.43.

The NMR data for the intermediate methoxy derivative (**29**) were as follows: free base; 1.19 (3H, d, J=6.5, C_7-CH_3), 2.50 (3H, s, NCH_3), 2.65 (1H, q, J=6.5, C_7-H), 2.99 (1H, m, C_5-H), 3.81 (3H, s, OCH_3). Hydrochloride (mp 192—194°); 1.62 (3H, d, J=6.5, C_7-CH_3), 2.95 (3H, d, J=4.5, $\overset{+}{N}CH_3$), 3.77 (3H, s, OCH_3).

N-Substituted 1-(3-Hydroxyphenyl)-7*endo*-methyl-6-azabicyclo[3,2,1]octane Derivatives (31)——In a typical procedure, a mixture of **28** (0.35 g), amyl bromide (0.3 g), $NaHCO_3$ (0.3 g) and DMF (5 ml) was heated at 100° for 2 hr. The mixture was diluted with H_2O and extracted with ether. Evaporation of ether gave, after washing with H_2O and drying, an oil which was converted to 0.5 g (97%) of the hydrochloride of 6-amyl-1-(3-hydroxyphenyl)-7*endo*-methyl-6-azabicyclo[3,2,1]octane (**31**) (R=C_5H_{11}), mp 148.5—152°. Recrystallization from iso-PrOH–acetone gave prisms, mp 151—154°.

The N-substituted derivatives (**31**) prepared in a similar manner are listed in Table I.

3-(3-Methoxyphenyl)-2-methyl-2-cyclohexen-1-one (33)——A) From **32**: To a solution of *m*-methoxyphenylmagnesium bromide (prepared from 19.9 g of *m*-bromoanisole and 2.6 g of magnesium) in THF (60 ml) was added a solution of 3-ethoxy-2-methyl-2-cyclohexen-1-one (**32**)[12] (12.6 g) in THF (10 ml) at 5° and the mixture was stirred at room temperature for 2 hr. The usual work-up and distillation gave 12.6 g (71.2%) of **33**, bp 135—138° (3 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1660 (C=C–C=O). NMR: 1.72 (3H, t, J=1.5, C-CH_3), 3.82 (3H, s, OCH_3). *Anal.* Calcd. for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.40; H, 7.54.

B) From **2b**: A mixture of **2b** (4 g), cyclohexylamine (4.4 g), *p*-toluenesulfonic acid (0.05 g) and toluene (80 ml) was refluxed for 24 hr with continuous removal of H_2O. The mixture was concentrated and distilled to give 3.1 g of the N-cyclohexylimine, bp 165—170° (3 mmHg). To a solution of lithium diisopropylamide (prepared from 0.21 g of Li, 1.68 g of butyl bromide, and 1.11 g of diisopropylamine) in ether (15 ml) and THF (10 ml) was added a solution of the above imine (3.1 g) in THF (30 ml) and the mixture was refluxed for 6 hr. To this was added CH_3I (2 ml) and heating was continued overnight under reflux. The mixture was filtered

from inorganic material and the filtrate was concentrated to give a brown oil. A mixture of this oil, $AcONa \cdot 3H_2O$ (4 g), AcOH (8 ml) and H_2O (8 ml) was refluxed for 4 hr, diluted with H_2O, and extracted with benzene. The extracts were washed with 10% HCl, H_2O, 5% $NaHCO_3$, and H_2O, successively. Evaporation of the dried extracts gave 2.5 g of a brown oil which was chromatographed over silica gel (100 g). Elution with $CHCl_3$ gave 1 g (23%) of **33** as an oil. This proved to be identical with the sample obtained from **32** (TLC, GC, NMR and IR).

3-Cyano-3-(3-methoxyphenyl)-2-methylcyclohexan-1-one (34)——A mixture of **33** (4.32 g), KCN (2.68 g), trimethylamine hydrochloride (2.87 g), H_2O (14 ml), and DMF (80 ml) was heated at 100° under stirring for 21 hr. The mixture was filtered from inorganic material and the filtrate was evaporated. The residue was diluted with H_2O and extracted with C_6H_6. The extracts were washed with 10% HCl, H_2O, 5% $NaHCO_3$, and H_2O, successively. Evaporation of the dried extracts gave, after distillation, 3.6 g (74%) of **34**, bp 165—167° (3 mmHg) as a mixture of C_2-diastereoisomers. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (C=O), 2240 (C≡N). NMR: 0.97 (*ca.* 2.4H, d, J=6.5, C_2-CH_3), 1.10 (*ca.* 0.6H, d, J=6.5, C_2-CH_3), 3.83 (3H, s, OCH_3). The mixture slowly crystallized on standing. Recrystallization from iso-propyl ether gave prisms, mp 70.5—72°. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O), 2240 (C≡N). Mass Spectrum *m/e*: 243 (M^+). NMR: 0.97 (3H, s, J=6.5, C_2-CH_3), 2.93 (1H, q, J=6.5, C_2-H), 3.83 (3H, s, OCH_3). From these NMR data, this was assigned to the *trans* (CN/Me) structure. *Anal.* Calcd. for $C_{15}H_{17}O_2N$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.85; H, 7.06; N, 5.83.

6,8*exo*-Dimethyl-1-(3-methoxyphenyl)-6-azabicyclo[3,2,1]octan-7-one (37) and Its 8*endo*-Methyl Isomer (38)——A mixture of **34** (30 g, mixture of diastereoisomers), KOH (30 g), ethylene glycol (600 ml), and H_2O (600 ml) was refluxed for 27 hr, diluted with H_2O, and washed with $CHCl_3$. The aqueous layer was acidified with AcOH, extracted with $CHCl_3$, and washed with H_2O. Evaporation of the dried $CHCl_3$ gave 24 g (74%) of 1-(3-methoxyphenyl)-2-methyl-3-oxocyclohexanecarboxylic acid (**35**) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (CO_2-H, C=O). NMR: 0.84 (*ca.* 1.8H, d, J=7, C_2-CH_3), 1.03 (*ca.* 1.2H, d, J=7, C_2-CH_3). To a solution of **35** (22 g), NaOH (3.9 g), EtOH (80 ml), and HMPA (80 ml) was added CH_3I (23.9 g) and the mixture was heated at 50° for 1 hr. The usual work-up and distillation gave 16.7 g (72%) of the diastereoisomeric mixture of the methyl ester (**36**), bp 160—165° (3 mmHg). NMR: 0.79 (*ca.* 1.8H, d, J=7, C_2-CH_3), 1.11 (*ca.* 1.2H, d, J=7, C_2-CH_3). 3.61 (*ca.* 1.2H, s, CO_2CH_3), 3.65 (*ca.* 1.8H, s, CO_2CH_3), 3.73 (3H, s, OCH_3).

A portion of this mixture was subjected to thick layer chromatography giving the pure *cis* and *trans* isomers, respectively. The *cis*[21] (CO_2CH_3/CH_3) isomer obtained from the upper fraction as an oil had following spectral data. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1710 (C=O). NMR: 1.11 (3H, d, J=7, C_2-CH_3), 3.0 (1H, q, J=7, C_2-H), 3.61 (3H, s, CO_2CH_3), 3.73 (3H, s, $ArOCH_3$). The *trans*[21] (CO_2CH_3/CH_3) isomer obtained from the lower fraction as an oil had the following spectral data. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1723 (C=O). NMR: 0.79 (3H, d, J=7, C_2-CH_3), 3.24 (1H, q, J=7, C_2-H), 3.65 (3H, s, CO_2CH_3), 3.73 (3H, s, $ArOCH_3$).

A mixture of 10.3 g of the above keto ester (**36**, mixture of isomers), 40% aqueous methylamine (10 ml), PtO_2 (0.5 g) and MeOH (150 ml) was hydrogenated in a Paar apparatus with an initial pressure of 2 kg/cm^2. The mixture was heated at 50° for 45 hr, filtered from the catalyst, and evaporated. The residue in toluene (50 ml) was refluxed for 3 hr, diluted with benzene (100 ml) and filtered. The filtrate was washed with 10% HCl, H_2O, 5% $NaHCO_3$, and H_2O, successively. Evaporation of the dried solvent gave 9 g of brown oil. GC analysis showed two isomers (3: 2). The mixture was chromatographed over silica gel (420 g) and eluted with AcOEt–hexane (1: 4). The first part of the eluate gave 5.2 g (53.8%) of the 6,8*exo*-dimethyl lactam (**37**) as an oil, bp 170° (bath temperature, 2 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1675 (lactam). NMR: 0.73 (3H, d, J=7, C_{8exo}-CH_3), 2.85 (3H, s, NCH_3), 3.75 (3H, s, OCH_3). *Anal.* Calcd. for $C_{16}H_{21}ON$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.71; H, 8.14; N, 5.33. From the second part of the eluate, 3.2 g (33.2%) of the 6,8*endo*-dimethyl lactam (**38**) was obtained as an oil, bp 145° (bath temperature, 2 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1675 (lactam). NMR: 0.90 (3H, d, J=7, C_{8endo}-CH_3), 2.90 (3H, s, NCH_3), 3.73 (3H, s, OCH_3). *Anal.* Calcd. for $C_{16}H_{21}ON$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.93; H, 8.19; N, 5.40.

Similar reductive amination of the *trans* (CO_2CH_3/CH_3) ester (**36**) at 50° for 8 hr followed by thermal cyclization resulted in the formation of the lactams (**37** and **38**) and the ester (*cis* **36**) with a recovery of *trans* **36** in ratio of about 2: 1: 1: 1 (by GC analysis).

6,8*exo*-Dimethyl-1-(3-methoxyphenyl)-6-azabicyclo[3,2,1]octane (39) Hydrobromide——A mixture of **37** (2.6 g), LAH (1.9 g) and THF (120 ml) was refluxed for 30 hr. The usual work-up and conversion of the crude base to the hydrobromide gave, after recrystallization from EtOH–ether, 3.2 g (98%) of **39**·HBr, mp 212—214°. *Anal.* Calcd. for $C_{16}H_{24}ONBr$: C, 58.90; H, 7.41; N, 4.29. Found: C, 58.59; H, 7.43; N, 4.23. NMR: 1.08 (3H, d, J=7, C_{8exo}-CH_3), 3.16 (3H, d, J_{NH}=4, $\overset{+}{N}CH_3$), 3.85 (3H, s, OCH_3). free base: 0.87 (3H, d, J=7, C_{8exo}-CH_3), 2.60 (3H, s, NCH_3), 3.79 (3H, s, OCH_3).

6,8*endo*-Dimethyl-1-(3-methoxyphenyl)-6-azabicyclo[3,2,1]octane (40) Hydrobromide——A mixture of **38** (2.6 g), LAH (1.9 g) and THF (120 ml) was refluxed for 5 hr. 2.8 g (85.9%) of **40**·HBr, mp 204—206.5° was obtained by the usual procedure. Needles from EtOH. *Anal.* Calcd. for $C_{16}H_{24}ONBr$: C, 58.90; H, 7.41; N, 4.29. Found: C, 58.81; H, 7.55; N, 4.32. NMR: 0.90 and 1.04 (3H, d, J=7, C_{8endo}-CH_3), 2.96 and

21) Stereochemical assignment was based on the chemical shifts values of C_2-CH_3 and C_2-H of the two isomers.[14]

3.06 (3H, d, J=6, $\overset{+}{N}CH_3$), 3.84 and 3.85 (3H, s, OCH_3). These twin peaks of roughly equal intensity were not integrated into single peaks on heating (up to 110°) or addition of trifluoroacetic acid and were probably due to the presence of two protonated species of the amino group.[22] The regenerated free base had the following NMR data. 0.89 (3H, d, J=7, C_{8endo}-CH_3), 2.54 (3H, s, NCH_3), 3.79 (3H, s, OCH_3).

6,8*exo*-Dimethyl-1-(3-hydroxyphenyl)-6-azabicyclo[3,2,1]octane (41)——A mixture of **39**·HBr (1 g) and 47% HBr (10 ml) was refluxed for 2 hr. The mixture was evaporated, basified with NH_4OH and extracted with $CHCl_3$. Evaporation of the dried $CHCl_3$ gave, after recrystallization from acetone, 0.63 g (88.8%) of **41**, mp 170—172° as prisms. *Anal.* Calcd. for $C_{15}H_{21}ON$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.74; H, 9.15; N, 6.08.

6,8*endo*-Dimethyl-1-(3-hydroxyphenyl)-6-azabicyclo[3,2,1]octane (42)——The procedure was made as described above. Yield was 92% from **40**. Prisms from acetone, mp 178—181° (turbid melt at 80°). IR ν_{max}^{Nujol} cm^{-1}: 1715 (solvated acetone. *Anal.* Calcd. for $C_{15}H_{21}ON \cdot 1/2$ acetone: C, 75.84; H, 9.15; N, 5.53. Found: C, 75.73; H, 9.27; N, 5.38. NMR: 0.84 (3H, d, J=7, C_{8endo}-CH_3), 2.17 (3H, s, solvated Me_2CO), 2.52 (3H, s, NCH_3).

1-(3-Methoxyphenyl)-6,7*endo*,8*endo*-trimethyl-6-azabicyclo[3,2,1]octane (44) Hydrobromide——To a ethereal solution of MeLi (prepared from 0.49 g of Li, 5 g of MeI, and 55 ml of ether) was added a solution of **38** (3.1 g) in benzene (75 ml) and the mixture was stirred at 20° for 45 hr. The usual work-up gave the oily enamine, which was reduced with $NaBH_4$ (1 g) in EtOH (150 ml) at room temperature overnight. Work-up in the usual manner gave 3 g (quantitative) of **44** as an oil. NMR: 0.82 (3H, d, J=7, C_{8endo}-CH_3), 1.00 (3H, d, J=7, C_{7endo}-CH_3), 2.52 (3H, s, NCH_3), 3.78 (3H, s, OCH_3). The hydrobromide was recrystallized from EtOH and had mp 256—258°. NMR: 0.97 (3H, d, J=7, C_{8endo}-CH_3), 1.53 (3H, d, J=7, C_{7endo}-CH_3), 3.03 (3H, s, $\overset{+}{N}CH_3$), 3.83 (3H, s, OCH_3). *Anal.* Calcd. for $C_{17}H_{26}ONBr$: C, 60.00; H, 7.70; N, 4.12. Found: C, 59.83; H, 7.83; N, 4.14.

MeLi Treatment of 37 and Subsequent Reduction with $NaBH_4$——To an ethereal solution of MeLi (prepared from 0.66 g of Li, 6.8 g of MeI and 50 ml of ether) was added a solution of **37** (4.2 g) in benzene (100 ml). The mixture was stirred at room temperature for 5 hr and then refluxed for 3 hr. The usual work-up gave an oil (4.2 g). To a solution of this oil in EtOH (200 ml) was added $NaBH_4$ (1.5 g) and the mixture was stirred at room temperature for 24 hr. The mixture was concentrated, diluted with H_2O and extracted with AcOEt. The AcOEt was extracted with 10% HCl. The acidic layer was basified with NH_4OH and extracted with AcOEt. Evaporation of the dried extracts gave 1.8 g of oil which was crystallized from iso-propyl ether giving 0.7 g (17.3%) of the dimeric compound (**47**), mp 195—198°. Recrystallization from MeOH gave needles, mp 201—203°. IR ν_{max}^{Nujol} cm^{-1}: 1665 (lactam). UV λ_{max}^{MeOH} mμ: 217 (ε, 21000), 273.5 (13000), 280.5 (12000). NMR: −0.25 (3H, d, J=6.5, C_8-CH_3), 0.68 (3H, d, J=6.5, C_8-CH_3), 2.78 (3H, s, NCH_3), 3.80 (6H, s, $ArOCH_3$), 5.22 (1H, s, CH=C). Mass Spectrum *m/e*: 500 (M^+). *Anal.* Calcd. for $C_{32}H_{40}O_3N_2$: C, 76.76; H, 8.05; N, 5.60. Found: C, 76.82; H, 8.10; N, 5.65.

Evaporation of the mother liquor (iso-propyl ether) gave 1 g of oil which was chromatographed over silica gel (70 g). Elution with AcOEt–hexane (1 : 3) gave an additional amount of **47** (0.1 g, total yield 20%). Elution with MeOH gave 0.9 g of oil. This was dissolved in ether, filtered from insoluble material, and acidified with methanolic HBr giving 0.3 g (5.4%) of the hydrobromide of 1-(3-methoxyphenyl)-6,7,8*exo*-trimethyl-6-azabicyclo[3,2,1]octane (**43**). Recrystallization from EtOH–ether gave needles, mp 248—250°. NMR: 0.88 (3H, d, J=7, C-CH_3), 1.90 (3H, d, J=7.5, C-CH_3), 3.19 (3H, d, J_{NH}=4.5, $\overset{+}{N}CH_3$), 3.84 (3H, s, OCH_3). *Anal.* Calcd. for $C_{17}H_{26}ONBr$: C, 60.00; H, 7.70; N, 4.12. Found: C, 59.92; H, 7.94; N, 4.18. The regenerated free base had the following NMR data. 0.63 (3H, d, J=7.5, C-CH_3), 1.33 (3H, d, J=6.5, C-CH_3), 2.66 (3H, s, NCH_3), 3.81 (3H, s, OCH_3).

From the neutral fraction (AcOEt), 2.5 g (57%) of the starting material was recovered.

1-(3-Hydroxyphenyl)-6,7*endo*, 8*endo*-trimethyl-6-azabicyclo[3,2,1]octane (45) Hydrobromide——This compound was obtained by O-demethylation of **44** in 97% yield. Prisms from EtOH, mp 250—253°. *Anal.* Calcd. for $C_{16}H_{24}ONBr$: C, 58.90; H, 7.41; N, 4.29. Found: C, 58.69; H, 7.47; N, 4.29.

1-(3-Hydroxyphenyl)-6,7,8*exo*-trimethyl-6-azabicyclo[3,2,1]octane (46) Hydrobromide——O-Demethylation of **43** gave **46**·HBr in 76% yield. Prisms from EtOH, mp 240—243° (decomp.). *Anal.* Calcd. for $C_{16}H_{24}ONBr$: C, 58.90; H, 7.41; N, 4.29. Found: C, 58.46; H, 7.55; N, 4.31.

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