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Synthesis of γ-Dimethylaminomethyl-α-phenylcycloalkyl Propionates as Potential Analgetics[1]

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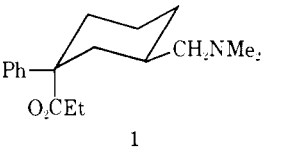
An assessment of the requirement for a 2-C chain separating the central quaternary C from the amino group in compounds possessing analgetic activity was undertaken by the synthesis of *cis*-3-dimethylaminomethyl-1-phenyl-1-propionoxycyclohexane (**1**), *trans*-3-dimethylaminomethyl-1-phenyl-1-propionoxycyclohexane (**2**), 9(a)-dimethylaminomethyl-2(e)-phenyl-2(a)-propionoxy-*trans*-decalin (**3**), 4(a)-dimethylaminomethyl-2(e)-phenyl-2(a)-propionoxy-*trans*-decalin (**4**), 4(e)-dimethylaminomethyl-2(e)-phenyl-2(a)-propionoxy-*trans*-decalin (**5**), and 4(e)-dimethylaminomethyl-2(a)-phenyl-2(e)-propionoxy-*trans*-decalin (**6**). Conversion of the ethyl ketal of 3-nitromethylcyclohexanone **8b** into the primary amine **9**, reductive methylation to give **10**, and deketalization produced 3-dimethylaminomethylcyclohexanone (**11**). Addition of PhLi afforded both *cis*- and *trans*-3-dimethylaminomethyl-1-phenylcyclohexanol (**12** and **13**), which were esterified with propionic anhydride to produce *cis*- and *trans*-3-dimethylaminomethyl-1-phenyl-1-propionoxycyclohexane (**1** and **2**). Compound **3** was prepared by reduction of 9(a)-cyano-*trans*-2-decalone ethylene ketal (**15**) to the amine **16**, methylation, and deketalization to form 9(a)-dimethylaminomethyl-*trans*-2-decalone (**18**). PhLi addition to the ketone afforded only 9(a)-dimethylaminomethyl-2(e)-phenyl-2(a)-hydroxy-*trans*-decalin (**19**). Esterification with propionic anhydride afforded **3**. The series **4**–**6** was prepared by Michael addition of CN^- to *trans*-Δ^3-2-octalone (**21**) followed by conversion into the ketal **23**. LAH reduction of the nitrile **23**, methylation of the resulting primary amine, and deketalization followed by reaction with PhLi gave **4**. Epimerization of 4(a)-cyano-*trans*-2-decalone ethylene ketal (**23**) to 4(e)-cyano compound **28** was accomplished with strong base. Reduction to the primary amine, methylation, conversion into the ketone 4(e)-dimethylaminomethyl-*trans*-2-decalone (**30**), and treatment with PhLi produced the isomeric alcohols 4(e)-dimethylaminomethyl-2(e)-phenyl-2(a)-hydroxy-*trans*-decalin (**31**) and 4(e)-dimethylaminomethyl-2(a)-phenyl-2(e)-hydroxy-*trans*-decalin (**32**). These were esterified to yield **5** and **6**. The analgetic activity by the mouse–hotplate method showed **1**, **4**, and **5** to have an ED_{50} ranging from 48 to 70 mg/kg with highest activity in **1** which was one-fifth as potent as codeine. Compounds **2**, **3**, and **6** were inactive at 100 mg/kg.

The classical structure–activity relationships for analgetics show few exceptions to the 2-C chain that separates the amine function and the central quaternary carbon.[2] In view of the recent concepts of multiple analgetic receptors or at least different modes of binding to a single receptor[3] the "2-C" requirement is of interest. In an effort to examine this relationship, compounds have been designed that fulfill all of the classical requirements except the 2-C chain.

For this purpose *cis*-3-dimethylaminomethyl-1-phenyl-1-propionoxycyclohexane (**1**),[4] *trans*-3-dimethylaminomethyl-1-phenyl-1-propionoxycyclohexane (**2**), 9(a)-dimethylaminomethyl-2(e)-phenyl-2(a)-propionoxy-*trans*-decalin (**3**), 4(a)-dimethylaminomethyl-2(e)-phenyl-2(a)-propionoxy-*trans*-decalin (**4**), 4-(e)-dimethylaminomethyl-2(e)-phenyl-2(a)-propionoxy-*trans*-decalin (**5**), and 4(e)-dimethylaminomethyl-2(a)-phenyl-2(e)-propionoxy-*trans*-decalin (**6**) were synthesized for appraisal of their analgetic potency.



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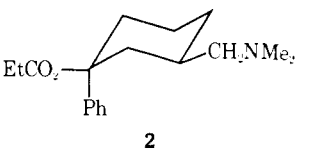

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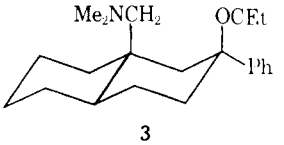

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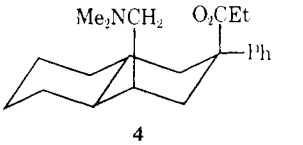

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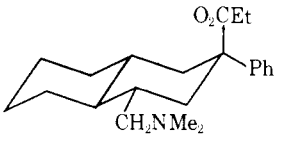

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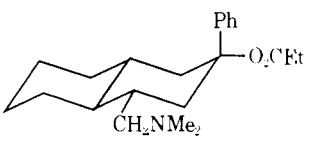

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(1) This work was supported by Grant GM-1341, Division of General Medical Sciences, and by Grant CA-10739 from the National Cancer Institutes, National Institutes of Health. Taken in part from the dissertations presented by A. A. Ramsey and P. E. Hanna to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree. D. D. Miller was supported by the National Science Foundation as an undergraduate research participant. For a related paper see M. P. Mertes, P. E. Hanna, and A. A. Ramsey, *J. Med. Chem.*, **13**, 125 (1970).

(2) (a) A. H. Beckett and A. F. Casy, *J. Pharm. Pharmacol.*, **6**, (1954); (b) A. H. Beckett and A. F. Casy, *Progr. Med. Chem.*, **4**, 171 (1965).

(3) (a) P. S. Portoghese, *J. Med. Chem.*, **8**, 609 (1965); (b) P. S. Portoghese, *J. Pharm. Sci.*, **55**, 865 (1966).

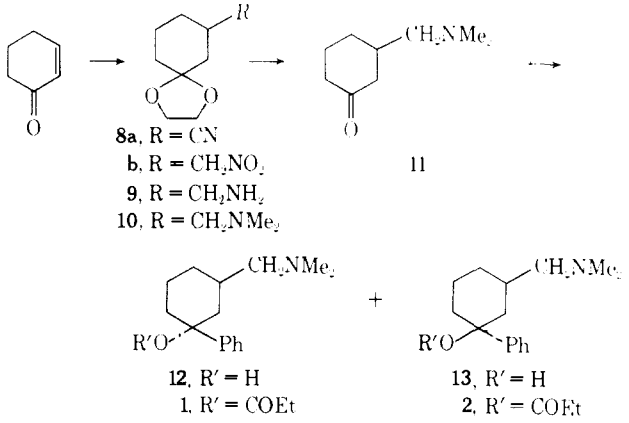
(4) *cis*–*trans* nomenclature in this work refers to the relative orientation of the phenyl and the dimethylaminomethyl groups.

Each of these compounds displays a 3-C separation between the central C and the tertiary amino-group.

The synthesis of **1** and **2** (Scheme I) was attempted initially *via* the cyano ketone **7**, prepared by CN^- addition to 2-cyclohexenone catalyzed by NH_4Cl[5] or from acetone cyanohydrin;[6] HCN and Et_2Al failed to give **7**.[5] After conversion of **7** into the ketal **8a**, Ra Ni reduction to the amine **9** followed by methylation with CH_2O–$NaBH_4$ produced 3-dimethylaminomethylcyclohexanone ethylene ketal (**10**).[7]

Because of poor yields in the formation of **7** and **8** an alternate procedure *via* $MeNO_2$ addition to 2-cyclohexenone was employed.[5] 3-Nitromethylcyclohexanone[8] was converted into the ketal **8b** which was reduced to give the amine **9** in high yield.

SCHEME I



Reductive methylation[7] to **10** followed by acid hydrolysis of the ketal gave **11**. The addition of PhLi[9] gave the *cis* (**12**) and *trans* (**13**) isomers[4] in a 1:1 ratio. After separation on neutral alumina the ir spectra of the *cis* isomer **12** showed the unbonded OH at 3618 cm^{-1} and an intermolecular bonded OH at 3430 cm^{-1} which disappeared on dilution. The ir spectra of the *trans* isomer **13** showed the free and bonded OH at 3620 and 3380 cm^{-1}; the 3380 cm^{-1} band did not disappear on dilution indicating intramolecular H bonding to the amino group.[10]

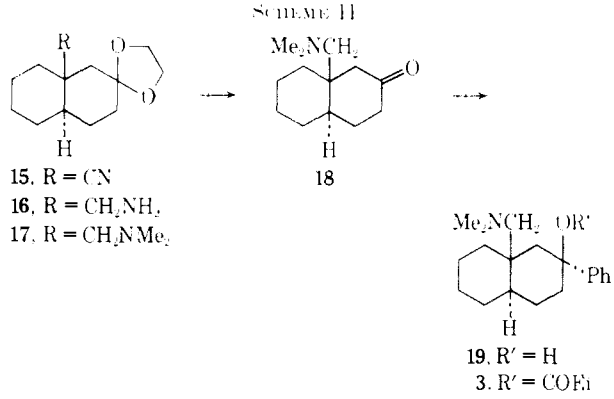
Esterification of **12** was accomplished with $(EtCO)_2O$ in C_5H_5N[11] and with EtCOCl and C_5H_5N in toluene at 25° to give **1**. Esterification of **13** to give **2**, however, was accomplished with $(EtCO)_2O$ in C_5H_5N and required refluxing.

The synthesis of **3** (Scheme II) utilized CN^- addition to $\Delta^{1,9}$-2-octalone[12] giving a mixture of *cis*- and *trans*-9-cyano-2-decalone (**14**).[13] After formation of the ketal the *trans* isomer **15** was purified by recrystallization.[13] Reduction of **15** by LAH to the amine **16** was followed by reductive methylation to give **17**. After deketalization, PhLi addition to the ketone **18** gave only one isomer, the amino alcohol **19**. Ir dilution studies showed an intramolecular bonded OH at 3480 cm^{-1} that did not shift on dilution.[10] Thus the aminomethyl and OH groups of **19** are *cis* diaxial.

In an attempt to alter the stereochemistry of the addition of C_6H_5Li to a rigid ketone, a series of reactions were undertaken to determine the effect of Lewis acids on the stereochemistry of this addition. Lewis acids, it was reasoned, would complex with ketone and should, as the complex, alter the stereochemistry of the addition. The reaction of 4-*t*-butylcyclohexanone with PhLi in the presence of $AlCl_3$, BF_3, or no Lewis acid, by normal addition or inverse addition all produced 4-*t*-butyl-1-phenylcyclohexanol in approximately a 58:42, *cis*:*trans* ratio. It was concluded from this data that Lewis acids do not appreciably affect the stereochemistry of PhLi addition to ketones.

Esterification of **19** to give **3** was accomplished with relative ease using propionic anhydride in C_5H_5N. Attempts to prepare the MeI salt for analysis were unsuccessful presumably due to severe steric hindrance.

SCHEME II



For the synthesis of the 4-substituted *trans*-2-decalol series (**4**, **5**, and **6**), (Schemes III and IV), the most direct approach seemed to be a Michael addition of CN^- to *trans*-Δ^3-2-octalone (**21**). It was readily synthesized from *trans*-2-decalone by bromination in HOAc, yielding the bromo ketone **20** followed by dehydrohalogenation. Li_2CO_3 and LiBr in DMF[14] proved superior to either $CaCO_3$ in refluxing $ACNMe_2$,[15] or refluxing *s*-collidine. Catalytic hydrogenation of **21** produced *trans*-2-decalone supporting the stereochemical assignment.

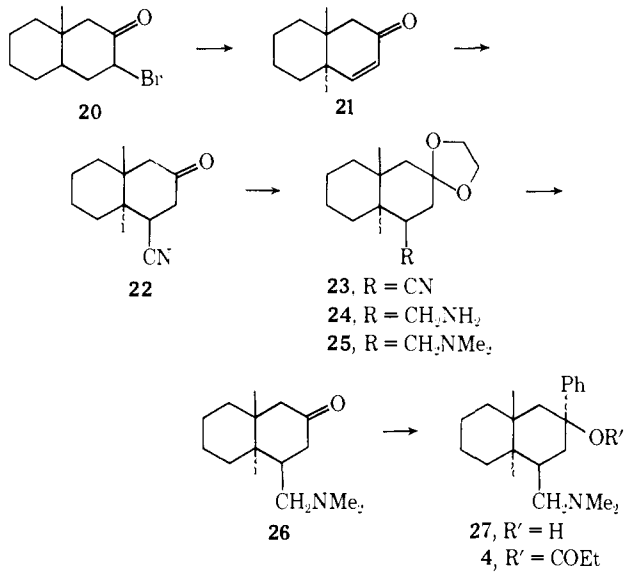
The conjugate addition of CN^- from acetone cyanohydrin[6] produced cyano ketone **22** which was treated directly with ethylene glycol and *p*-toluenesulfonic acid in C_6H_6 to produce 4(a)-cyano-*trans*-2-decalone ethylene ketal (**23**).

The CN function of **23** was shown to be axial by nmr; the proton at position 4 is deshielded by the nitrile to 2.90 ppm, out of the CH_2 envelope. The half-band width of 10.5 Hz is that expected for an equatorial proton at position 4. The cyano ketal **23** was reduced to primary amine **24** with LAH followed by methylation with CH_2O $NaBH_4$ to yield 4(a)-dimethylaminomethyl-*trans*-2-decalone ethylene ketal (**25**).

The amino ketone **26** was obtained by hydrolysis of amino ketal **25** in aq HCl. Addition of ketone **26** to PhLi produced 4(a)-dimethylaminomethyl-2(e)-

(5) W. Nagata, I. Kikkawa, and M. Fujimoto, *Chem. Pharm. Bull.*, **11**, 225 (1963).
(6) N. Nazarov and S. I. Zav'yalov, *Zh. Obshch. Khim.*, **24**, 166 (1954); *J. Gen. Chem. U.S.S.R.*, **24**, 475 (1954).
(7) H. Minato and T. Nagasaki, *J. Chem. Soc. C*, 1866 (1966).
(8) A. McCoubrey, *ibid.*, 2931 (1951).
(9) A. Ziering and J. Lee, *J. Org. Chem.*, **12**, 911 (1947).
(10) M. Tichy, *Advan. Org. Chem.*, **5**, 115 (1965).
(11) A. H. Beckett, A. F. Casy, G. Kirk, and J. Walker, *J. Pharm. Pharmacol.*, **9**, 939 (1957).
(12) G. Stork and H. Landesman, *J. Amer. Chem. Soc.*, **78**, 5128 (1956).
(13) W. Nagata and I. Kikkawa, *Chem. Pharm. Bull.*, **11**, 289 (1963).
(14) E. J. Corey and A. G. Hortman, *J. Amer. Chem. Soc.*, **87**, 5736 (1965).
(15) G. F. H. Green and A. G. Long, *J. Chem. Soc.*, 2532 (1961).

Scheme III

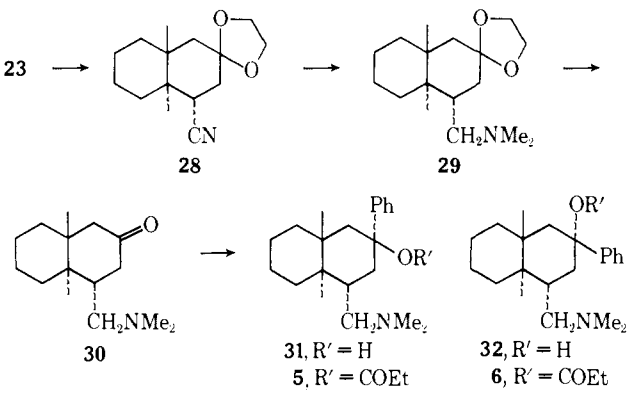


phenyl-2(a)-hydroxy-*trans*-decalin (**27**) as the only isomer formed. The ir spectra of very dilute solutions of **27** showed broad bonded OH absorption which did not disappear upon further dilution. This demonstrates the existence of strong intramolecular H bonding due to the *cis*-diaxial orientation of the 2-OH and 4-dimethylaminomethyl groups.

Esterification of **27** was readily accomplished in $(EtCO)_2O$–C_5H_5N to afford **4** in 66% yield.

The 4-axial cyano ketal **23** also provided the departure point for the synthetic sequence leading to **5** and **6** (Scheme IV). Epimerization of **23** to 4(e)-cyano-

Scheme IV



2-decalone ethylene ketal (**28**) took place smoothly in the presence of NaH in refluxing toluene. The nmr spectrum of **28** shows that the 4 proton geminal to the CN group has moved upfield and is under the *trans*-decalin envelope. This observation is consistent with the general rule that axial ring protons absorb at higher field than do their equatorial counterparts.[16]

Reduction of **28** with LAH followed by methylation gave **29**. Hydrolysis of **29** in aq HCl resulted in smooth conversion into ketone **30**. Treatment of **30** with PhLi afforded 4(e)-dimethylaminomethyl-2(e)-phenyl-2(a)-hydroxy-*trans*-decalin (**31**) and 4(e)-dimethylaminomethyl-2(a)-phenyl-2(e)-hydroxy-*trans*-decalin (**32**) in a ratio of 2:1. The isomers were separated by column chromatography on Al_2O_3. Axial alcohol **31** was readily eluted from the column and was isolated as a viscous material which could not be crystallized. More polar solvent mixtures were required for the elution of the minor isomer **32** which was a crystalline solid.

In order to confirm the axial phenyl configuration, **32** was subjected to treatment with aq acid. Tlc and column chromatographic analysis of the resulting products gave an unknown material presumed to be the dehydration product and equatorial phenyl isomer **31**. None of the starting axial phenyl isomer **32** was detected in the reaction mixture. This epimerization of **32** to **31** verifies the assigned stereochemical configurations of the alcohols.

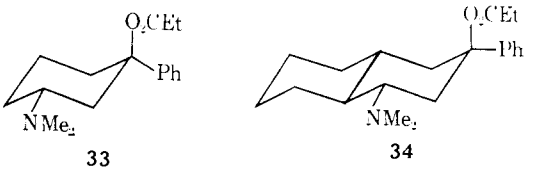
Esterification of **31** was achieved in refluxing $(EtCO)_2O$–C_5H_5N to afford **5** in 25% yield. In the same manner, **32** was converted into the propionate **6** in 70% yield. The greater ease of esterification of **32** over **31** probably reflects the enhanced reactivity of the less sterically hindered equatorial alcohol.

Biological Results.—The analgetic activity of these compounds was examined by the mouse–hotplate method using subcutaneous injection;[17] the results are shown in Table I. In the flexible cyclohexyl models **1** and **2** the isomer with the Ph and Me_2NCH_2 groups *cis*-diequatorial **1** was active while the isomer **2** with Ph axial and the ester and aminomethyl groups diequatorial (preferred conformation) was inactive. Compound **1**, a homolog of the Me_2N analog **33** (ED_{50} 63 mg/kg)[1], is almost twice as active as **33** when considered on a molar basis.

Table I
Analgesic Potency[a]

Compd	Equipotent molar ratios	ED_{50} mg/kg (range)	Onset	Peak	Duration (min)
Codeine	5.6	7.5			
Morphine	1.0	1.2			
1[b]	29	59.5 (50.1–70.6)	5	28	194
2[b]		Inactive to 100 mg			
3[b]		Inactive to 100 mg			
4[c]	32	48.5 (42.7–55.1)	7	39	176
5[c]	47	70.1 (59.0–83.3)	6	41	164
6[c]		Inactive to 100 mg			
33[c,d]	52	63.6 (55.1–73.4)	4	26	135

[a] See ref 17. [b] Tested as the cyclohexanesulfamic acid salt. [c] Tested as the free base. [d] See ref 1.



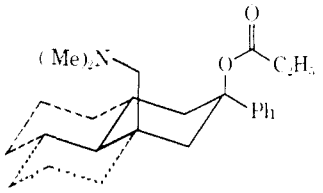
Activity in the decalin series shows the 2,4-phenyl axial decalin analog **6**, a rigid model of the cyclohexyl analog **2**, is also inactive. Both the 2,4-phenyl equa-

(16) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 79.

(17) The authors wish to thank Dr. E. L. May of the National Institutes of Health for testing these compounds. The methods used are described in the following references. (a) A. E. Jacobson, E. L. May, *J. Med. Chem.*, **8**, 563 (1965); (b) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, **107**, 385 (1953).

torial decalin analogs with the aminomethyl at 4 either axial (**4**) or equatorial (**5**) are active; highest activity in this series is found in the 4-axial isomer **4**. This contrasts with the inactivity of **34**.

The unexpected inactivity of the 2,9-decalin isomer **3** is difficult to rationalize since it is analogous to structure **4** having Ph equatorial with the aminomethyl and ester functions 1,3-diaxial. Thus, as shown in **35**, the



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4:————————
3:- - - - - - - - - -

dashed portion of the structure interacts with the receptor (**4**, ED_{50} = 48 mg/kg) while the dotted portion **3** prevents receptor interaction.

Another reason for the inactivity of **3** is that both **3** and **4** having 1,3-diaxial interaction, may prefer the twist boat form. Models representing these deformed structures show a much greater flexibility and range for the 4-dimethylaminomethyl group in **4** as compared with the rigidity of this group in **3**.

Experimental Section[18]

3-Cyanocyclohexanone (7). Method A. KCN–NH_4Cl in DMF.—A solution of 2.40 g (0.025 mole) of 2-cyclohexen-1-one in 60 ml of DMF was added to a solution of 3.30 g (0.050 mole) of KCN and 2.24 g (0.038 mole) of NH_4Cl in 60 ml of H_2O. This solution was stirred for 50 hr at room temperature under N_2, neutralized with HOAc, and evaporated *in vacuo*. The residue was partitioned between C_6H_6 and H_2O. The aq portion was reextracted with C_6H_6 and the combined C_6H_6 extracts were washed with H_2O, dried ($MgSO_4$), and evaporated to yield a green liquid which was chromatographed on Al_2O_3 (Woelm, Grade I). Elution with C_6H_6–Skelly B (bp 63–68°) mixtures produced 0.68 g (22%) of **7**.

Method B. Acetone Cyanohydrin and Na_2CO_3 in Aqueous MeOH.—A solution of 10.0 g (0.10 mole) of 2-cyclohexen-1-one and 11.1 g (0.13 mole) of acetone cyanohydrin in 30 ml of MeOH was added to a solution of 0.75 g of anhydrous Na_2CO_3 in 12 ml of H_2O. The resulting suspension was refluxed at 80° for 3 hr, cooled, and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with H_2O, dried ($MgSO_4$), and evaporated. The residue was chromatographed on Al_2O_3 (Woelm, Grade I); elution with Skelly B (bp 63–68°)–$CHCl_3$ mixtures afforded 6.12 g (50%) of relatively pure **7**.

The 2,4-dinitrophenylhydrazone of **7** was prepared in the normal manner and recrystallized from dioxane–H_2O, mp 211°. *Anal.* ($C_{15}H_{18}N_5O_4$) C, H; N, calcd 23.09, found 22.62.

3-Cyanocyclohexanone Ethylene Ketal (8a).—A solution of 3.22 g (0.03 mole) of 3-cyanocyclohexanone (**7**), 2.20 g (0.035 mole) of ethylene glycol, and 50 mg of *p*-toluenesulfonic acid in 30 ml of dry C_6H_6 was refluxed for 48 hr under a Dean–Stark water trap. The reaction mixture was cooled, concentrated, chromatographed on Al_2O_3 (Woelm, Grade I), and eluted with C_6H_6 to yield 1.00 g (20%) of **8a**.

(18) All melting points were taken on a calibrated Thomas-Hoover capillary melting point apparatus. Analyses were performed by Drs. G. Weiler and F. B. Strauss, Oxford, England, by Midwest Microlab, Inc., Indianapolis, Ind., and on an F & M Model 185, University of Kansas, Lawrence, Kan. Spectral data were obtained using Beckman IR-8, IR-10, Varian A-60, and A-60A spectrometers. The latter used Me_4Si as an internal standard except in D_2O where 3-trimethylpropanesulfonic acid sodium salt was employed. The nmr spectra were as expected. Where analyses are indicated only by symbols the elements are within 0.4% of the theoretical values.

3-Nitromethylcyclohexanone Ethylene Ketal (8b).—A solution of crude 3-nitromethylcyclohexanone[8] (0.23 mole), 17.40 g (0.28 mole) of ethylene glycol, and 0.50 g of *p*-toluenesulfonic acid in 150 ml of C_6H_6 was refluxed for 18 hr under a Dean–Stark water trap. A solution of 0.70 g of NaOH in dry MeOH was added to neutralize the acid, H_2O was then added, and the C_6H_6 layer was separated. The C_6H_6 extracts were combined, washed (H_2O), dried ($MgSO_4$), and evaporated leaving a brown oil. This oil was chromatographed on 100 g of Al_2O_3 (Woelm, Grade I) and eluted with C_6H_6 to yield 30.8 g (68%, from 2-cyclohexen-1-one) of **8b**.

3-Dimethylaminomethylcyclohexanone Ethylene Ketal (10). Method A from 8a.—A solution of 2.11 g (0.013 mole) of 3-cyanocyclohexanone ethylene ketal (**8a**) in 100 ml of EtOH and 20 ml of concentrated NH_4OH was hydrogenated over 3.0 g of W-2 Ra Ni at 1 atm for 12 hr. The catalyst was removed by filtration and the filtrate evaporated *in vacuo* to give **9** as a light green syrup. This syrup in 60 ml of MeOH was stirred with 3.6 ml (0.044 mole) of 37% CH_2O solution for 2 hr at room temperature. $NaBH_4$ (5.4 g, 0.14 mole) was added in small portions to this stirred solution over a 45-min period at 10–20° in an ice bath with stirring. The stirring was continued for 5 hr at room temperature. MeAc (36 ml) was added dropwise to this mixture in an ice bath to decompose the excess $NaBH_4$ and the solution was stirred overnight. The reaction mixture was poured into ice–H_2O and extracted with $CHCl_3$. These extracts were washed with H_2O, dried ($MgSO_4$), and evaporated to give a liquid which was distilled under reduced pressure to yield 1.08 g (42%) of **10**; bp 46° (0.15 mm).

Method B from 8b.—A solution of 17.06 g (0.085 mole) of 3-nitromethylcyclohexanone ethylene ketal (**8b**) in 150 ml of EtOH was hydrogenated over 1.5 g of 5% Pd-C for 3 hr at 1 atm. Filter-cel was added and the catalyst removed to leave 14.16 g (98%) of **9** as a light yellow oil; bp 57° (0.08 mm).

The picrate of **9** was prepared in Et_2O and recrystallized from EtOH, mp 200–201.5°. *Anal.* ($C_{21}H_{26}N_6O_{15}$) C, H, N.

CH_2O solution (37%, 7.8 ml, 0.096 mole) was added to a stirred solution of 4.50 g (0.026 mole) of **9** in 130 ml of dry MeOH and the solution was stirred for 1.5 hr at room temperature. $NaBH_4$ (11.7 g, 0.31 mole) was added in small portions to this mixture during 40 min at 10–20° in an ice bath with stirring and the stirring continued for an additional 2 hr at 20–25°. The excess $NaBH_4$ was decomposed by dropwise addition of 78 ml of MeAc to the reaction mixture with the temperature maintained below 25°. This solution was stirred overnight at room temperature and poured over ice. The resulting suspension was extracted with $CHCl_3$, the combined $CHCl_3$ extracts were washed with H_2O, dried (Na_2SO_4), and evaporated to yield **10** in quantitative yield; bp 46° (0.09 mm).

The MeI of **10** was prepared in C_6H_6 and recrystallized from EtOAc–MeOH, mp 183–184°. *Anal.* ($C_{12}H_{24}NO_2I$) C, H, N.

3-Dimethylaminomethylcyclohexanone (11).—A solution of 9.31 g (0.047 mole) of **10** in 300 ml of 0.5 *M* HCl was stirred at room temperature for 42 hr. The solution was cooled in an ice bath, made basic with 1 *M* NaOH, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with H_2O, dried ($MgSO_4$), and distilled to give 6.15 g (85%) of **11**; bp 32.5° (0.05 mm).

The picrate of **11** was prepared in EtOH and recrystallized from EtOAc–C_6H_{14}, mp 141–142°. *Anal.* ($C_{15}H_{20}N_4O_8$) C, H, N.

3-Dimethylaminomethyl-1-phenylcyclohexanol (12 and 13).—A solution of 5.81 g (0.037 mole) of 3-dimethylaminomethylcyclohexanone (**11**) in 150 ml of dry Et_2O was added dropwise with stirring to 80 ml (0.096 mole) of a 1.2 *M* solution of PhLi in Et_2O in an ice bath under N_2. After the addition was complete the ice bath was removed and the suspension stirred for 1 hr at room temperature. The reaction mixture was cooled again in ice and 250 ml of H_2O was added dropwise with stirring. The Et_2O layer was separated and the H_2O layer extracted with Et_2O. The combined Et_2O extracts were washed with H_2O, dried (Na_2SO_4), and evaporated to yield crude **12** and **13**. The two isomers were separated by column chromatography on Al_2O_3 (Merck 71707, 3% water). Elution with C_6H_6 afforded 2.33 g (27%) of **12** and elution with C_6H_6–Et_2O (1:1) afforded 2.11 g (25%) of **13**.

Isomer **12**, recrystallized from Skelly B, melted at 76–80°. The MeI of **12** was prepared in C_6H_6 and recrystallized from EtOAc–MeOH, mp 236–237.5°. *Anal.* ($C_{16}H_{26}INO$) C, H, N.

Isomer **13** was an oil which could not be recrystallized. The MeI of **13** was prepared in C_6H_6 and recrystallized from EtOH, mp 249.5–251°. *Anal.* ($C_{16}H_{26}INO$) C, H, N.

cis-**3-Dimethylaminomethyl-1-phenyl-1-propionoxycyclohexane** (**1**).—A solution of 1.02 g (0.0044 mole) of **12** in 8.5 ml of $(EtCO)_2O$ and 11 ml of C_5H_5N was stirred at 115° for 11 hr. The brown solution was poured into ice–H_2O containing 35 ml of NH_4OH solution and extracted with C_6H_6. The C_6H_6 extracts were washed with saturated aq NaCl, dried ($MgSO_4$), and evaporated at room temperature with a stream of N_2. The crude brown syrup was purified by preparative tlc on Al_2O_3 and developed with C_6H_{14}–Et_2O (5–1) to yield 0.374 g (30%) of **1**. The MeI of **1** was prepared in C_6H_6 and recrystallized from EtOH–EtOAc, mp 171.5–173°. *Anal.* ($C_{19}H_{30}INO_2$) C, H, N.

trans-**3-Dimethylaminomethyl-1-phenyl-1-propionoxycyclohexane** (**2**).—A solution of 0.52 g (0.0022 mole) of **13** in 11 ml of $(EtCO)_2O$ and 12 ml of C_5H_5N was stirred at 110° for 13 hr. The brown solution was poured into ice–H_2O containing NH_4OH and worked up as described for **1**. Column chromatography on alumina (Merck 71707, 3% H_2O) with C_6H_{14}–C_6H_6 mixtures yielded 0.40 g (62%) of **13**. The MeI of **13** was prepared in C_6H_6 and recrystallized from MeOH–EtOAc, mp 209.5–210.5°. *Anal.* ($C_{19}H_{30}NO_2I$) C, H, N.

9(a)-Aminomethyl-*trans*-**2-decalone Ethylene Ketal** (**16**).—A solution of 11.05 g (0.05 mole) of *trans*-9-cyano-2-decalone ethylene ketal (**15**) in 400 ml of dry Et_2O was added dropwise to a stirred solution of 18.0 g (0.50 mole) of LAH in 1.4 l of dry Et_2O under N_2 at room temperature. The stirred suspension was refluxed for 5 hr and cooled and the excess LAH was destroyed with EtOAc and H_2O. The white precipitate was removed by filtration; the Et_2O layer was dried ($MgSO_4$) and evaporated. The yellow residue was dissolved in CH_2Cl_2 and extracted with 5% tartaric acid. The acidic extract was made basic with 10% NaOH, extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated to yield 8.40 g (75%) of **16**; picrate mp 170–172° (lit.[13] 174–176°).

9(a)-Dimethylaminomethyl-*trans*-**2-decalone Ethylene Ketal** (**17**).—A solution of 8.10 g (0.036 mole) of **16** and 10.8 ml of 37% CH_2O solution in 180 ml of dry MeOH was stirred at room temperature for 2 hr. $NaBH_4$ (16.2 g, 0.43 mole) was added in portions while the temperature of the stirred solution was maintained at 30–35° for 90 min, then the solution was cooled again and MeAc (100 ml) was added dropwise to destroy the excess $NaBH_4$. The reaction mixture was poured over ice and extracted with CH_2Cl_2. This extract was dried ($MgSO_4$) and evaporated to yield 8.82 g (97%) of **17**. The MeI of **17** was prepared in C_6H_6 and recrystallized from EtOAc–MeOH, mp 218–220°. *Anal.* ($C_{16}H_{30}NO_2I$) C, H, N.

9(a)-Dimethylaminomethyl-*trans*-**2-decalone** (**18**).—A solution of 8.35 g (0.033 mole) of **17** in 150 ml of 0.5 *M* HCl was stirred at room temperature for 48 hr. This solution was made basic with 2.5 *M* NaOH while cooled in an ice bath and extracted with CH_2Cl_2. This extract was washed with saturated aq NaCl, dried ($MgSO_4$) and evaporated to yield 6.93 g of **18** in quantitative yield.

9(a)-Dimethylaminomethyl-2(e)-phenyl-2(a)-hydroxy-*trans*-**decalin** (**19**).—A solution of 0.51 g (0.0024 mole) of **18** in 10 ml of dry Et_2O was added dropwise with stirring to 10 ml of 1 *M* PhLi (0.01 mole) in dry Et_2O in an ice bath under N_2. After the addition was complete the ice bath was removed and the reaction stirred at room temperature for 1 hr. The reaction mixture was cooled again and 20 ml of H_2O was added dropwise with stirring. The Et_2O layer was separated and the H_2O layer extracted with Et_2O. The combined Et_2O extracts were dried ($MgSO_4$) and evaporated to yield a brown oil which was partitioned between 3% HCl and C_6H_6. The acidic portion was made basic and extracted with C_6H_6. This extract was dried ($MgSO_4$) and evaporated to yield 0.46 g (67%) of **19** as a solid which was recrystallized from Skelly B (bp 63–68°) mp 97–98.5°. *Anal.* ($C_{19}H_{29}NO$) C, H, N.

9(a)-Dimethylaminomethyl-2(e)-phenyl-2(a)-propionoxy-*trans*-**decalin** (**3**).—A solution of 0.47 g (0.0014 mole) of **19** was treated as described for the synthesis of **1** to give a brown syrup. This crude product was chromatographed on Al_2O_3 (Merck 71707) and eluted with C_6H_6–EtOAc mixtures to yield 0.32 g (68%) of **3**.

The picrate of **3** was prepared in EtOH and washed several times with Et_2O, mp 160.5–161.5°. *Anal.* ($C_{28}H_{36}N_4O_9$) C, H, N.

3-Bromo-*trans*-**2-decalone** (**20**).—A stirred solution of 30.5 g (0.2 mole) of *trans*-2-decalone in 450 ml of HOAc was treated with 1 drop of HOAc saturated with HBr followed by the dropwise addition of 33.8 g (0.22 mole) of Br_2 in 50 ml of HOAc at room temperature. The solution was stirred for 30 min and partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ portion was treated with Na_2CO_3 solution to neutralize the HOAc, washed with saturated aq NaCl, dried ($MgSO_4$), and evaporated leaving a tan oil which was utilized directly in the synthesis of **21**.

trans-Δ^1-**2-Octalone** (**21**).—A solution of **20** (0.2 mole) in 50 ml of DMF was added to a stirred suspension of 30 g (0.35 mole) of dry LiBr and 40 g (0.54 mole) of Li_2CO_3 in 450 ml of dry DMF at 120° under N_2. Stirring was continued at 120–125° for 75 min, the solution cooled, poured into dilute HOAc, and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with saturated aq NaCl, dried ($MgSO_4$), and evaporated. The resulting liquid was distilled [bp 62–66° (0.6 mm)] to yield 15.7 g (53%) of relatively pure **21**. This was further purified by preparative tlc on silica gel and developed with C_6H_{14}–Et_2O (1:1); uv, λ_{max}^{EtOH} 228.5, (ϵ 9170).

The semicarbazone was prepared in EtOH and recrystallized from EtOH–H_2O and EtOH–EtOAc, mp 204–207°. *Anal.* ($C_{11}H_{17}N_3O$) C, H, N.

4(a)-Cyano-*trans*-**2-decalone** (**22**).—A mixture of 10.0 g (0.067 mole) of **21**, 7.66 g (0.09 mole) of acetone cyanohydrin, and 10 ml of 10% Na_2CO_3 in 20 ml of THF and 200 ml of MeOH was stirred at reflux temperature for 3.5 hr. After evaporation of solvent, the residue was taken up in CH_2Cl_2, washed with dilute AcOH and H_2O, and dried ($MgSO_4$). Evaporation of CH_2Cl_2 *in vacuo* afforded 11.3 g of crude ketone **22** as a golden liquid.

4(a)-Cyano-*trans*-**2-decalone Ethylene Ketal** (**23**).—A solution of **22** (0.067 mole), ethylene glycol (6.2 g, 0.1 mole), and 0.4 g of *p*-toluenesulfonic acid was stirred and refluxed overnight in 50 ml of C_6H_6 in a flask fitted with a Dean–Stark water trap. The reaction mixture was cooled, treated with 10% Na_2CO_3, and diluted with H_2O. The layers were separated and the C_6H_6 portion was washed with H_2O and dried ($MgSO_4$). Evaporation of solvent afforded a dark liquid which was chromatographed on a column of Al_2O_3. Elution with C_6H_6 and C_6H_6–$CHCl_3$ afforded 6.5 g of a brown solid which was recrystallized from C_6H_6–Skellysolve B to give cyano ketal **23** (4.09 g, 27% from **21**); mp 96–97°; nmr ($CDCl_3$) δ 0.53–2.33 (14 H), 2.73–3.08 (1 H, $W_{1/2}$ = 10.5 Hz, CHCN), 3.93 (4 H, t, J = 3 Hz, OCH_2CH_2O). *Anal.* ($C_{13}H_{19}NO_2$) C, H, N.

4(a)-Aminomethyl-*trans*-**2-decalone Ethylene Ketal** (**24**).—A solution of 12.8 g (0.057 mole) of 4(a)-cyano-*trans*-2-decalone ethylene ketal (**23**) in 300 ml of anhydrous Et_2O was added dropwise to a stirred suspension of LAH (21.6 g, 0.57 mole) in 1500 ml of Et_2O according to the method used for **6** to give **24** (9.39 g, 72%) as a clear green oil; attempts to prepare the picrate of **24** were unsuccessful.

4(a)-Dimethylaminomethyl-*trans*-**2-decalone Ethylene Ketal** (**25**).—A solution of amino ketal **24** (9.27 g, 0.041 mole) and 13.3 ml (0.10 mole) of 37% CH_2O solution in 200 ml of MeOH was reduced with $NaBH_4$ (18.16 g, 0.48 mole) according to the procedure for **17** to give **25** (6.47 g, 63%) as a viscous oil. The MeI of **25** was prepared in Et_2O and recrystallized from EtOAc–MeOH. *Anal.* ($C_{16}H_{30}NOI$) C, H, N.

4(a)-Dimethylaminomethyl-*trans*-**2-decalone** (**26**).—A solution of 4(a)-dimethylaminomethyl-*trans*-2-decalone ethylene ketal (**25**) (3.03 g, 0.012 mole) in 100 ml of 2% HCl was stirred at room temperature for 46 hr followed by extraction with CH_2Cl_2. The CH_2Cl_2 extract was discarded. The acidic solution was cooled in an ice bath, made basic with 10% NaOH, and extracted with Et_2O. The combined Et_2O extracts were dried ($MgSO_4$) and evaporated to yield a yellow liquid which was chromatographed on neutral Al_2O_3 (activity grade II). Elution with C_6H_6–EtOAc afforded **26** (1.77 g, 70%).

4(a)-Dimethylaminomethyl-2(e)-phenyl-2(a)-hydroxy-*trans*-**decalin** (**27**).—An Et_2O solution of 4(a)-dimethylaminomethyl-*trans*-2-decalone (**26**) (2.43 g, 0.012 mole) was added with stirring to a suspension of PhLi in 20 ml of dry Et_2O in an ice bath. After addition, the reaction mixture was stirred for 6 hr at room temperature, cooled, and decomposed by the dropwise addition of 50 ml of H_2O. The Et_2O layer was separated, washed with H_2O, and dried ($MgSO_4$). Evaporation of solvent afforded a brown semisolid which was crystallized from EtOH–H_2O and dried over P_2O_5 to yield 2.16 g, 62%) of **27**, mp 88–89°. The MeI was prepared in Et_2O and recrystallized from EtOAc–MeOH, mp 260–260.5°. *Anal.* ($C_{20}H_{32}INO$) C, H, N.

4(a)-Dimethylaminomethyl-2(e)-phenyl-2(a)-propionoxy-*trans*-**decalin** (**4**).—A solution of **27** (1.63 g, 0.0056 mole) in 15 ml of C_5H_5N and 15 ml of $(EtCO)_2O$ was stirred at 115° for 14 hr. The reaction mixture was cooled, poured into ice–H_2O containing dilute NH_4OH, and extracted with Et_2O. After drying ($MgSO_4$), the Et_2O was evaporated giving a brown oil which was purified

by column chromatography on Al_2O_3. Elution with C_6H_6–EtOAc afforded ester **4** (1.30 g, 66%). The MeI was prepared in Et_2O and recrystallized from EtOAc–MeOH, mp 233°. *Anal.* ($C_{23}H_{36}NO_2I$) C, H, N.

4(e)-Cyano-*trans*-2-decalone Ethylene Ketal (28).—A solution of 4(a)-cyano-*trans*-2-decalone ethylene ketal (**23**) (4.12 g, 0.018 mole) was refluxed for 70 hr in 20 ml of PhMe with 0.5 g of a 50%, dispersion of NaH in mineral oil (previously washed with PhMe). The mixture was cooled, poured onto ice, and extracted with C_6H_6. The organic extracts were combined, washed with H_2O, and dried ($MgSO_4$). Evaporation of solvent afforded **28** as a tan oil (3.70 g, 89%). A sample of **28** was purified for elemental analysis by preparative tlc on Al_2O_3 (C_6H_6–Et_2O, 1:1). *Anal.* ($C_{13}H_{19}NO_2$) C, H, N.

4(e)-Dimethylaminomethyl-*trans*-2-decalone Ethylene Ketal (29).—A solution of 4(e)-cyano-*trans*-2-decalone ethylene ketal (**28**) (4.20 g, 0.019 mole) was reduced with excess LAH according to the directions for **16** to afford 2.90 g (0.013 mole, 68%) of the intermediate primary amine as a yellow oil.

Using the same method as shown for **17**, 0.496 g (0.002 mole) of the primary amine was converted into **29** (0.49 g, 86%). The MeI of **29** was prepared in C_6H_6 and recrystallized from EtOAc–MeOH, mp 210°. *Anal.* ($C_{16}H_{30}NO_2I$) C, H, N.

4(e)-Dimethylaminomethyl-*trans*-2-decalone (30).—As described in the synthesis of **26**, **29** (5.82 g, 0.023 mole) was converted into 3.58 g (0.017 mole, 75%) of **30**.

4(e)-Dimethylaminomethyl-2-hydroxy-2-phenyl-*trans*-decalin (31 and 32).—Compound **30** (2.33 g, 0.011 mole) was treated, as described for the synthesis of **27**, to give a liquid residue which was chromatographed on neutral Al_2O_3 (activity grade II). Elution with C_6H_6–EtOAc afforded **31** (1.26 g, 36%) followed by **32** (0.632 g, 18%).

The equatorial phenyl isomer **31** was a viscous material which could not be crystallized. The MeI of **31** was prepared in Et_2O and recrystallized from EtOAc–MeOH, mp 233°. *Anal.* ($C_{20}H_{32}NOI$) C, H, N.

The axial phenyl isomer **32** was recrystallized from EtOH–H_2O, mp 123–124°. *Anal.* ($C_{19}H_{29}NO$) C, H, N. Compound **32** (0.05 g) was dissolved in 5 ml of 10% HCl and stirred for 3 hr at 30°. The solution was cooled in an ice bath made basic with 10% NaOH, and extracted with Et_2O. The extracts were combined, dried ($MgSO_4$), and evaporated to afford 0.047 g of a mixture which was shown by tlc and column chromatography to consist of two components, a nonpolar compound of high R_f and the equatorial phenyl isomer **31**.

4(e)-Dimethylaminomethyl-2(e)-phenyl-2(a)-propionoxy-*trans*-decalin (5).—Using the method for the synthesis of **4**, compound **31** (1.15 g, 0.004 mole) gave a brown oil which was chromatographed on a column of Al_2O_3. Elution with C_6H_6 afforded 0.39 g (25%) of **5**. *Anal.* ($C_{22}H_{33}NO_2$) C, H, N.

4(e)-Dimethylaminomethyl-2(a)-phenyl-2(e)-propionoxy-*trans*-decalin (6).—A solution of 0.212 g (0.007 mole) of **32** treated as described for **4** gave a brown syrup which was purified by column chromatography on neutral Al_2O_3 (activity grade II). Elution with C_6H_6 and C_6H_6–EtOAc provided the equatorial ester **6** (0.177 g, 70%). *Anal.* ($C_{22}H_{33}NO$) C, H, N.

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Analgetics Based on the Pyrrolidine Ring. V

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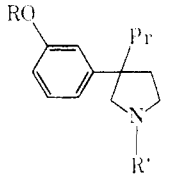
The synthesis of some new *m*-(3-propyl-3-pyrrolidinyl)phenols and the preliminary evaluation of their analgetic activities are described. A new optimum of activity has been found with *p*-R-phenethyl substitution on the pyrrolidine N. O-Methylation was much more deleterious than with the original *N*-Me optimum.

Previous papers[2,3] in this series have described an extensive number of pyrrolidines of diversified types. They can be represented by the general formula **1**. Further work on *m*-(1-methyl-3-propyl-3-pyrrolidinyl)-



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phenol (**1**, R = H; R′ = Me), now designated profadol, has shown that this compound is a potent analgetic with a particularly interesting spectrum of pharmacological activity.[4]

In the last paper in this series, some Me ethers of pyrrolidines with large N substituents were described. In particular, the (*p*-aminophenethyl)pyrrolidine [**1**, R = Me; R′ = $(CH_2)_2C_6H_4$-*p*-NH_2] showed definite analgetic activity. This paper describes experiments designed to investigate further the analgetic activity of pyrrolidine compounds in which the Me group has been replaced by a large substituent. Some additional work to examine the effect of substituents in the phenolic OH is also described.

Chemistry.—The synthesis of N-substituted pyrrolidines of type **1** by direct alkylation, or by N-acylation followed by reduction of the amide, is described in the Experimental Section. In the latter cases, where O-demethylation with BBr_3 was involved in the syn-

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