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

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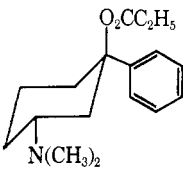
The syntheses of *trans*-3-dimethylamino-1-phenyl-1-propionoxycyclohexane (**1**) and 4(e)-dimethylamino-2(e)-phenyl-2(a)-propionoxy-*trans*-decalin (**2**) are described. 3-Dimethylaminocyclohexanone (**4**) was treated with C_6H_5Li to give *trans*-3-dimethylamino-1-phenylcyclohexanol (**5**). Conversion of **5** to **1** was through treatment with propionic anhydride in C_5H_5N. Compound **2** was prepared by a similar sequence from 4-dimethylamino-*trans*-2-decalone. Unsuccessful attempts to synthesize the *cis* analog of **1** and 9(a)-dimethylamino-2(e)-phenyl-2(a)-propionoxy-*trans*-decalin are briefly discussed. The relative analgetic activities show that **1** has an ED_{50} of 63 mg/kg and **2** is inactive at 100 mg/kg; this is compared to morphine having an ED_{50} of 1.2 mg/kg in this test.

An examination of published investigations into the stereochemical aspects of analgetics reveals that a great deal of the work has dealt with heterocyclic molecules related to the 4-phenylpiperidine analgetics such as meperidine and the prodines. With few exceptions, studies on compounds related to meperidines have incorporated a 1,4 cyclic relationship wherein the N is in a ring and the phenyl and polar functions, an ester or ketone, are substituted on the "central" C separated from N by two atoms. The proposal by Beckett and Casy for the analgetic active site was derived from morphine and other quasi-rigid models containing a two-carbon chain which lies out of the plane of the amine and phenyl ring. The receptor surface, of necessity, required a cavity to accommodate this chain.[2]

In an effort to assess the requirement for an out-of-plane chain, *trans*-3-dimethylamino-1-phenyl-1-propionoxycyclohexane (**1**) and 4(e)-dimethylamino-2(e)-phenyl-2(a)-propionoxy-*trans*-decalin (**2**) were synthesized as potential analgetics.[3]



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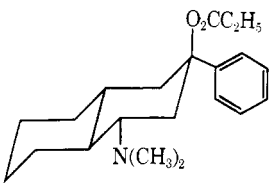

2

Compounds **1** and **2** contain the minimum structural features for analgetic activity with one exception: there is no "out-of-plane two-carbon chain." A comparison of the relative activity of **1** and **2** should also yield information on the preferred conformation for maximum potency. Compound **1**, being a flexible system, can accommodate the receptor and should be more active than **2**. However, if the activity of the rigid model **2** approaches that of **1**, then it can be reasoned that the action of **1** is exerted in the most stable conformation as represented in structure **2**.

The synthesis of 3-dimethylaminocyclohexanone (**4**) (Scheme I) was accomplished by the conjugate addition of Me_2NH to 2-cyclohexen-1-one (**3**) utilizing conditions described for the addition of primary and secondary amines to methyl vinyl ketone.[4]

Treatment of **4** with C_6H_5Li according to the method of Ziering and Lee[5] afforded *trans*-3-dimethylamino-1-phenylcyclohexanol (**5**). The corresponding *cis* amino alcohol **6** could not be detected by glpc, column chromatography, or examination by tlc. Reaction with C_6H_5MgBr also gave only **5**. The structure of **5** was assigned on the basis of its ir spectra taken at various concentrations in CS_2. These spectra showed only a single non-H-bonded OH band at 3604 cm^{-1} which did not disappear upon dilution to very low concentrations.[6] The absence of intramolecular H bonding indicates therefore that OH and Me_2N groups in **5** are *trans*. Esterification of **5** was carried out smoothly in refluxing pyridine–propionic anhydride[7] to give **1** in 60% yield.

The synthesis of the *cis* isomer **6** was attempted by several routes. C_6H_5Li addition to the monoketal of 1,3-cyclohexanedione (**7**)[8] gave 7-phenyl-1,4-dioxaspiro-[4.5]-7-decanol (**8**). Treatment with dilute HCl afforded the best yield (~20%) of the ketone **9**, the majority of the product being the elimination reaction to give the conjugated ketone.

Treatment of **9** with $NaBH_4$ afforded *cis*- and *trans*-3-hydroxy-1-phenylcyclohexanol (**10** and **11**) in a 1:1 ratio. The two isomers were separated by column chromatography and their structures were assigned on the basis of the order of their elution from the column and nmr data. Ir studies were not employed because of the low solubility of the compounds in nonpolar solvents. Isomer **10** (mp 136–137°) was the first compound eluted from the column; the nmr spectrum shows the 3 proton deshielded to δ 4.18 by the 3-OH and the observed half-band width of **11** Hz is that expected for an equatorial proton.[9] Isomer **11** (mp 137.5–138°) was eluted from the column with more polar solvents indicating stronger binding to the silica gel matrix.

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(2) (a) A. H. Beckett and A. F. Casy, *Progr. Med. Chem.*, **4**, 171 (1965); (b) C. A. Winter in "Analgetics," G. DeStevens, Ed., Academic Press, New York, N. Y., 1965.

(3) *cis–trans* nomenclature refers to the relative orientation of the polar functions; *cis* or *trans* 1-OCOEt/3-NMe_2.

(4) N. C. Ross and R. Levine, *J. Org. Chem.*, **29**, 2346 (1964).

(5) A. Ziering and J. Lee, *ibid.*, **12**, 911 (1947).

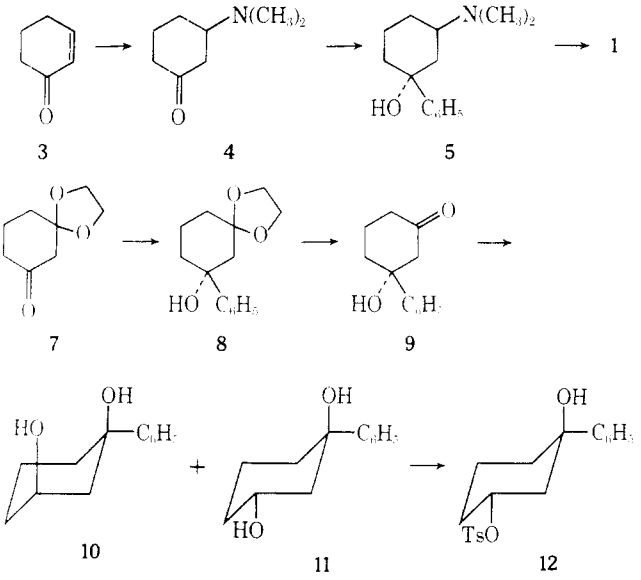
(6) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Englewood Cliffs, N. J., 1965, p 36.

(7) A. H. Beckett, A. F. Casy, G. Kirk, and J. Walker, *J. Pharm. Pharmacol.*, **9**, 939 (1957).

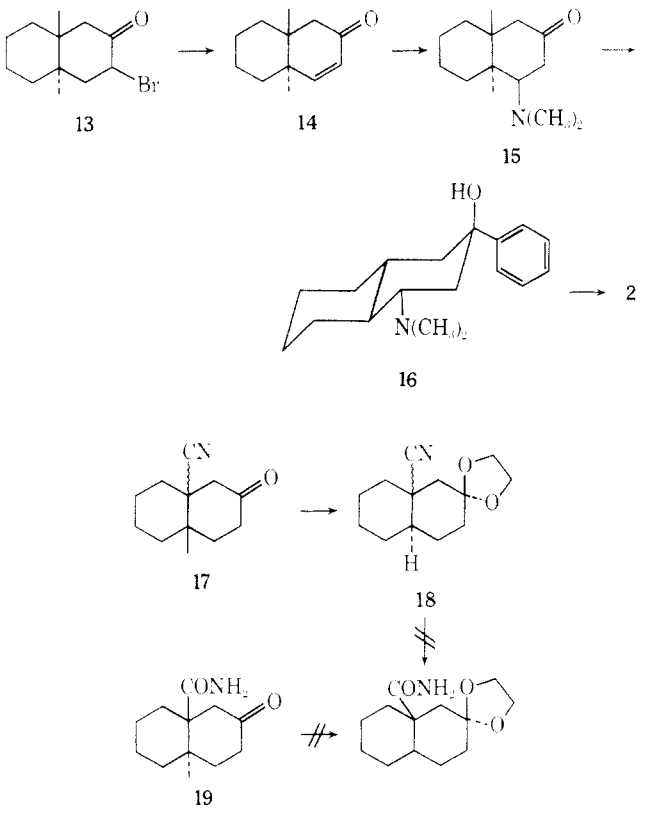
(8) M. P. Mertes, *J. Org. Chem.*, **26**, 5236 (1961).

(9) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964: (a) p 79; (b) p 47.

SCHEME I



SCHEME II



The nmr spectrum of isomer **11** exhibits a deshielded 3-proton band at δ 3.84 with 22-Hz half-band width, corresponding to an axial proton.[9] Thus, **10** is assigned the structure in which the 1- and 3-OH groups are *cis*-diaxial and the isomer **11** is assigned the structure in which the 1- and 3-OH are *trans* with the 3-OH group existing primarily in the equatorial conformation. Although both **10** and **11** are flexible cyclohexyl ring systems, it is to be expected that a 1,3-diaxial arrangement of the OH groups in *cis* isomer **10** would be stabilized by intramolecular H bonding while a 1,3 axial-equatorial orientation of the OH groups in **11** should be favored over the alternate conformation which would precipitate severe 1,3-diaxial interactions between the C_6H_5 and 3-OH. These conclusions are reinforced by comparison of the chemical shifts of the 3 proton in **10** and **11** which are δ 4.18 and 3.84, respectively.[9b]

The next step in the sequence proposed for the synthesis of **6** called for selective formation of *trans*-3-*p*-toluenesulfonate ester **12**. Ester **12** was prepared in pyridine and it proved to be stable in solution but decomposed upon exposure to air. Attempted displacement of the sulfonate ester **12** with Me_2NH at temperatures below 70° afforded only unchanged **12** while reaction at higher temperatures produced tars. NaN_3 displacement of the sulfonate group of **12** under conditions described by Bose and coworkers[10] occurred fairly smoothly. However, LAH reduction of the corresponding 3-azide afforded only unreacted azide or tars depending upon the conditions under which the reaction was carried out.

Other unsuccessful approaches to the preparation of **6** involved the attempted displacement of the methiodide salt of **5** by such N nucleophiles as Me_2NH and NaN_3.

A pathway for the synthesis of **2** was proposed which called for the conjugate addition of Me_2NH to *trans*-Δ^3-2-decalone **14**. The requisite olefinic ketone **14** was obtained by bromination[11] of *trans*-2-decalone in AcOH to form bromo ketone **13** which was dehydrohalogenated to **14** with Li_2CO_3 and LiBr in DMF[12] (Scheme II). Addition of Me_2NH to **14** produced the amino ketone **15** was which treated directly with C_6H_5Li to give a single isomer, 4(e)-dimethylamino-2(e)-phenyl-2(a)-hydroxy-*trans*-decalin (**16**). The ir spectra of dilute solutions of **16** in tetrachloroethylene exhibited a single OH absorption band at 3610 cm^{-1} which did not diminish upon dilution. The absence of any absorption bands characteristic of intramolecular H bonding indicates that the 2-OH and the 4-NMe_2 groups of **16** cannot be in a 2,4-diaxial configuration. When **16** was subjected to acid catalyzed solvolysis, the only amino alcohol recovered was unchanged **16**. Thus the C_6H_5 group was not epimerized and it is assigned the stable equatorial configuration. Since **16** has an axial OH group at C-2 which does not H bond with the 4-dimethylamino moiety, the dimethylamino is assigned the equatorial configuration.

A variety of esterification methods were employed in an effort to convert **16** to its propionate ester **2**, but reactions requiring the application of heat in the presence of acid or base decomposed **16**, while room-temperature reactions afforded unchanged starting material. The synthesis of 4(e)-dimethylamino-2(e)-phenyl-2(a)-propionoxy-*trans*-decalin (**2**) was accomplished by treating the PhLi adduct of **15** directly with propionic anhydride in the manner described by Casy and coworkers.[13]

Several schemes were employed in an attempt to prepare a *trans*-decalin analog containing an axial dimethylamino substituent at the 9 position. Introduction of N at the 9 position was sought by attempted conju-

(10) A. K. Bose, J. F. Kistner, and L. Farber, *J. Org. Chem.*, **27**, 2925 (1962).

(11) (a) M. P. Mertes, A. A. Ramsey, P. E. Hanna, and D. Miller, in preparation; (b) C. W. Shoppe and T. E. Bellas, *J. Chem. Soc.*, 3366 (1963).

(12) E. J. Corey and A. G. Hartman, *J. Amer. Chem. Soc.*, **87**, 5736 (1965).

(13) A. F. Casy, M. A. Iorio, and P. Pocha, *J. Chem. Soc., C*, 942 (1967).

gate additions of NH_3, Me_2NH, and NaN_3 to $\Delta^{1,9}$-2-decalone which was prepared according to the method of Stork and coworkers.[14] None of these Michael-type reactions proved to be a satisfactory method of obtaining a useful intermediate.

An alternate route to the 9-axial amino-*trans*-decalin system was through Hoffman rearrangement of a 9-carboxamide moiety. For this purpose, the Michael addition of KCN to $\Delta^{1,9}$-2-decalone was performed according to the methods of Nagata and coworkers[15] to afford a mixture of 9-cyano-*cis*-and-*trans*-2-decalones (**17**). The mixture of cyanodecalones was allowed to react with ethylene glycol to form the corresponding mixture of ethylene ketals. The isomers were separated by fractional crystallization to yield the desired 9(a)-cyano-*trans*-2-decalone ethylene ketal (**18**).[15] However, all efforts to hydrolyze **18** to the corresponding carboxamide in refluxing $NaOH–H_2O_2$ mixtures afforded only unchanged **18**.

The synthesis of 9-carboxamide-*trans*-2-decalone (**19**) was accomplished by the procedure of Meyer and Schnautz[16] which involves addition of KCN to the olefin in a $MeOH–H_2O$ medium. The resulting mixture of 9-carboxamide-*cis*- and -*trans*-2-decalones was separated by fractional crystallization to afford **19**. When **19** was treated with ethylene glycol in order to prepare the ethylene ketal, the only product which could be isolated was the 2-(β-hydroxy)ethoxy-γ-lactam **20**, characterized by the ir spectrum which exhibits a lactam carbonyl band at 1692 cm^{-1} and does not contain the "amide II band" in the 1587-cm^{-1} region which is characteristically present in the spectra of primary amides. The formation of **20** is not surprising in view of the findings of Meyer and Schnautz[16] who reported that **19** exists in solution almost exclusively as the hydroxylactam. Nagata and coworkers[17] reported formation of similar ethylene glycol derivatives when the synthesis of the ethylene ketals of some 3-keto steroids containing a 5-carboxamide substituent was attempted.

Protection of the carbonyl group of **19** by formation of the dimethyl ketal was also unsuccessful. The ethylene dithioketal of **19** which had been previously reported[16] was prepared, but treatment of this compound under Hoffman conditions (Br_2 and $NaOCH_3$) did not afford any identifiable products. Hoffman rearrangement of the unprotected keto amide **19** was also unfruitful.

Biological Results.—The analgetic activity of **1** and **2** was examined by the mouse hot plate method using subcutaneous administration.[18] Compound **1** had an ED_{50} of 63.6 mg/kg (55.1–73.4 mg/kg) with an onset of 4 min, peak of 26 min, and duration of 135 min. Compound **2**, the analogous 2,4-*trans*-decalin was inactive up to 100 mg/kg. Compound **1** has marginal activity compared to morphine and codeine (ED_{50} = 1.2 and 7.5 mg/kg). The failure to observe any significant activity in the rigid analog **2** would suggest that **1**, being a flexible system, is exerting its action in a conformation other than the preferred as shown. However, the relevance of these conclusions to analgetic activity is subject to question since **1** has only marginal activity and the hot plate test does not necessarily reflect analgetic properties.

Experimental Section[19]

3-Dimethylaminocyclohexanone (**4**).—A solution of 20.0 g (0.21 mole) of 2-cyclohexen-1-one in 75 ml of Et_2O was added dropwise with stirring to an Et_2O solution of anhydrous Me_2NH (34.0 g, 0.75 mole) in an ice bath. The solution was stirred for 2 hr at 0–5°. Et_2O and excess Me_2NH were evaporated under N_2 to afford **4** as a brown oil which was utilized in the next reaction without further purification. The picrate of **4** was prepared in and recrystallized from EtOH, mp 128.0–128.5° (lit.[20] 102–103°, 131–132°). *Anal.* ($C_{14}H_{18}N_4O_8$)C, H, N.

trans-**3-Dimethylamino-1-phenylcyclohexanol** (**5**).—A solution of crude 3-dimethylaminocyclohexanone (**4**) (0.21 mole) in 50 ml of dry Et_2O was added dropwise with stirring to 0.30 mole of freshly prepared C_6H_5Li in an ice bath. After addition was complete, the mixture was stirred overnight at 25°. The reaction mixture was cooled and 100 ml of H_2O was added dropwise with stirring. The Et_2O and H_2O layers were filtered to afford 22 g of crude **5**, mp 129–132°. An additional portion of **5** was obtained by extraction of the aqueous layer with $CHCl_3$. The combined organic portions were extracted with 200 ml of 5% HCl. The HCl extract was made basic with 5% Na_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried ($MgSO_4$), and evaporated to afford a dark liquid which was dissolved in acetone and filtered with Norit. Addition of Et_2O to the filtrate resulted in precipitation of 5.02 g of **5**; total yield was 60% from 2-cyclohexen-1-one. The product was recrystallized from Et_2O and from MeAc C_6H_{12}, mp 136–137°. A sample was purified for elemental analysis by sublimation [100° (0.15 mm)], mp 136–137°. *Anal.* ($C_{14}H_{21}NO$), C, H, N.

trans-**3-Dimethylamino-1-phenyl-1-propionoxycyclohexane** (**1**).—A solution of 3.0 g (0.013 mole) of **5** in 20 ml of anhydrous C_5H_5N and 20 ml of $(EtCO)_2O$ was stirred at 120° for 12 hr. The reaction mixture was cooled to 25°, poured into an iced solution of dilute NH_4OH, and extracted with Et_2O. The Et_2O extracts were washed with H_2O, dried ($MgSO_4$), and evaporated *in vacuo* to afford a dark liquid which was chromatographed on alumina. The column was eluted with $C_6H_{14}–C_6H_6$ and C_6H_6–EtOAc mixtures to yield 2.16 g (60%) of **1**. The methiodide of **1** was prepared in Et_2O and recrystallized from EtOAc–MeOH, mp 207.5–208.5°. *Anal.* ($C_{18}H_{28}INO_2$) C, H, N.

3-Hydroxy-3-phenylcyclohexanone (**9**).—An Et_2O solution of 1,4-dioxaspiro[4.5]-7-decanone[8] (**7**) (11.0 g, 0.07 mole) was added dropwise with stirring to an Et_2O suspension of freshly prepared C_6H_5Li (0.15 mole) cooled in an ice bath. After addition the reaction mixture was stirred at 25° for 3 hr. The reaction flask was again cooled and the mixture was decomposed by dropwise addition of H_2O. The Et_2O layer was separated and dried ($MgSO_4$). Removal of the solvent afforded crude **8** as a brown liquid.[8]

The alcohol **8** was dissolved in 50 ml of Et_2O and stirred for 4 hr at 25° with 150 ml of 5% HCl. The layers were separated and the aqueous layer was extracted with several portions of Et_2O. The Et_2O extracts were combined and dried ($MgSO_4$), and solvent was removed *in vacuo*. Trituration of the liquid residue with a small volume of Skellysolve B and Et_2O afforded

(14) G. Stork, A. Brizzolaru, J. Smuskovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

(15) W. Nagata, I. Kikkawa, and M. Fujimoto, *Chem. Pharm. Bull.* (Tokyo), **11**, 226 (1963).

(16) W. L. Meyer and N. G. Schnautz, *J. Org. Chem.*, **27**, 2011 (1962).

(17) W. Nagata, S. Hirad, H. Itazaki, and K. Takeda, *ibid.*, **26**, 2413 (1961).

(18) 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 and E. L. May, *J. Med. Chem.* **8**, 563 (1965); (b) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953).

(19) All melting points were taken on the Thomas–Hoover capillary melting point apparatus and are corrected. Analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., by Weiler and Strauss Microanalytical Laboratory, Oxford, England, by Bernhardt Microanalytical Laboratories, Mühlheim, Germany, and on an F & M Model 185, University of Kansas. Ir spectra were recorded on Beckman IR-8 and IR-10 spectrophotometers, nmr spectra on Varian A-60 and A-60A analytical spectrometers with Me_4Si as internal standard. Uv spectra were recorded on the Beckman DU spectrophotometer. Unless noted in the Experimental Section the nmr and ir spectra were as expected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements are within ±0.4% of theoretical.

(20) (a) M. Mousseron, R. Jacquier, A. Fontaine, and R. Zagdoun, *Bull. Soc. Chim. Fr.*, 1246 (1954); (b) U. Bruckhardt, C. A. Grob, and H. R. Kiefer, *Helv. Chim. Acta*, **50**, 231 (1967).

2.82 g (20% from **7**) of **9**, which was recrystallized from Et_2O and from MeAc–cyclohexane (mp 155–156°). *Anal.* ($C_{12}H_{14}O_2$) C, H.

cis- **and** *trans*-**3-Hydroxy-3-phenylcyclohexanol (10 and 11).**—A solution of $NaBH_4$ (0.30 g, 0.013 mole) in 50 ml of 95% EtOH was added in small portions to an EtOH solution of **9** (3.0 g, 0.016 mole) cooled in an ice bath. After stirring for 1 hr, several milliliters of glacial AcOH were added to destroy excess $NaBH_4$. The mixture was evaporated to 50 ml under N_2, diluted with H_2O, made basic with Na_2CO_3, and extracted with $CHCl_3$. The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to yield 2.84 g (95%) of the mixed isomers as a white solid. The two isomers were separated by column chromatography on silica gel; elution with C_6H_6 and C_6H_6–Et_2O afforded 1.39 g (45%) of the *cis* isomer **10** followed by 1.44 g (46%) of *trans* isomer **11**.

Isomer **10**, recrystallized from MeAc–C_6H_{12}, melted at 136.5–137°: nmr ($CDCl_3$) 1.16–2.50 (8 H, C_6H_{11}), 3.33–4.00 (2 H, O*H*), 4.00–4.36 (1 H, *H*COH, $W_{1/2}$ = 11 Hz), 7.06–7.68 (5 H, aromatic). *Anal.* ($C_{12}H_{16}O_2$) C, H.

Isomer **11** recrystallized from MeAc–C_6H_{12} melted at 137.5–138°: nmr (C_2D_6SO) 0.92–2.20 (8 H, C_6H_{11}), 3.50–4.18 (1 H, *H*COH, $W_{1/2}$ = 22 Hz), 4.18–4.90 (2 H, O*H*), 6.98–7.68 (5 H, aromatic). *Anal.* ($C_{12}H_{16}O_2$) C, H.

trans-**3-Hydroxy-3-phenylcyclohexyl** *p*-**Toluenesulfonate (12).**—Compound **11** (0.5 g, 0.0026 mole) was dissolved in 25 ml of dry C_5H_5N and cooled to 0°. *p*-Toluenesulfonyl chloride (0.57 g, 0.003 mole) was added and the solution was kept at 0° for 24 hr. After the solution was poured into 100 ml of ice–H_2O and acidified with HCl, 0.49 g of **12** was obtained by filtration. Recrystallization from MeAc–C_6H_{12} gave white crystals, mp 100–101°. The material decomposed rapidly on standing giving a dark green solid. Characterization of the white solid by ir and nmr spectroscopy gave the expected results.

3-Bromo-*trans*-**3-decalone (13).**[11]—A solution of Br_2 (65.5 g, 0.41 mole) in 100 ml of glacial AcOH was added with stirring to *trans*-2-decalone (60.0 g, 0.39 mole) in 900 ml of glacial AcOH. The reaction mixture was stirred for 45 min at 25° and partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ extracts were combined, washed repeatedly with H_2O, dilute Na_2CO_3, and again with H_2O. The solution was dried ($MgSO_4$) and evaporated under vacuum giving 92.3 g (100%) of **13** as a brown oil which was utilized in the next reaction without further purification.

trans-**Δ³-2-Decalone (14).**[12]—A solution of bromo ketone **13** (45.1 g, 0.19 mole) in 50 ml of dry DMF was added to a stirred suspension of anhydrous LiBr (26.0 g, 0.30 mole) and Li_2CO_3 (34.5 g, 0.46 mole) in 200 ml of dry DMF at 120° under N_2. The mixture was stirred at 120–125° for 2 hr, cooled, poured into 700 ml of 25% AcOH, and extracted with several portions of $CHCl_3$. The combined extracts were washed with H_2O, dried ($MgSO_4$), and evaporated *in vacuo* to give a brown liquid which was distilled under N_2 to afford **14** (16.9 g, 58%, bp 66–71° (0.2 mm) as a relatively pure liquid. The product was further purified by preparative tlc on silica gel (hexane–Et_2O, 1:1) nmr ($CDCl_3$) 0.75–2.90 (12 H), 5.93 (1 H, doublet, J = 10 Hz with fine splitting, CH=C*H*C=O), 6.72 (1 H, doublet, J = 10 Hz, C*H*=CHC=O); uv λ_{max}^{EtOH} 228.5 mμ (ε 9170).

The semicarbazone of **14** 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(e)-Dimethylamino-2(e)-phenyl-2(a)-hydroxy-*trans*-**decalin (16).**—To a stirred solution of Me_2NH (225 ml) in 100 ml of Et_2O was added a solution of **14** (10.0 g, 0.066 mole) in 50 ml of Et_2O at 0–5°. After addition, the reaction was stirred for 6 hr at 0°. Excess Me_2NH and Et_2O were evaporated under N_2 giving crude 4(e)-dimethylamino-*trans*-2-decalone (**15**) as a brown oil.

A solution of **15** (0.066 mole) in 50 ml of anhydrous Et_2O was added dropwise to a cold, stirred suspension of C_6H_5Li (0.26 mole) in 50 ml of Et_2O. After addition, the mixture was stirred overnight at 25°. The reaction flask was cooled and 50 ml of H_2O was added dropwise. The Et_2O layer was separated, dried ($MgSO_4$), and evaporated under vacuum to afford 18 g of viscous liquid which was chromatographed on neutral alumina (activity grade II). Nonpolar components were eluted with Skellysolve B–C_6H_6. Elution with C_6H_6–EtOAc afforded 7.76 g (43% from **14**) of **16** as a brown glass.

The methiodide of **16** was prepared in C_6H_6 and recrystallized from MeOH–EtOAc, mp 165–166°. *Anal.* ($C_{19}H_{30}INO$) C, H, N.

4(e)-Dimethylamino-2(e)-phenyl-2(a)-propionoxy-*trans*-**decalin (2).**—An Et_2O solution of **15** (0.04 mole) was added dropwise with stirring to a cooled suspension of freshly prepared C_6H_5Li (0.08 mole) in 50 ml of Et_2O. The ice bath was removed after addition and the mixture was stirred for 2 hr at 25°. The reaction was again cooled and $(Et_2CO)_2O$ (26.0 g, 0.20 mole) in 50 ml of Et_2O was added. After stirring 6 hr at 25°, the reaction was cooled and treated with 10% Na_2CO_3 solution. The Et_2O layer was separated and 10% NaOH was added to the H_2O layer which was further extracted with CH_2Cl_2. Organic extracts were combined, washed with H_2O, dried (Na_2SO_4), and evaporated *in vacuo*. The dark liquid residue was chromatographed on a column of neutral alumina (activity grade II). Nonpolar components were eluted with Skellysolve B–C_6H_6. Elution with C_6H_6–EtOAc afforded 1.45 g (20% from **15**) of **2** as a thick oil. *Anal.* ($C_{21}H_{31}NO_2$) C, H, N.

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Insect Chemosterilants. VIII. Boron Compounds[1a]

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Benzeneboronic acid and seven of its homologs containing electron-withdrawing substituents were moderately effective chemosterilants of house flies, *Musca domestica* L. The sterilizing activity of 39 cyclic condensation products of benzeneboronic acids with *o*-aminophenol, pyrocatechol, or other aromatic compounds was often higher than that of the parent boronic acid.

The reproductive capacity of insects can be reduced or eliminated by various types of chemical compounds.[2] Chemosterilants containing boron have been described only recently[3,4] and the full scope of their activity has not been explored. Because species specificity is a distinguishing feature of most chemosterilants that are not alkylating agents, structure–activity correlations cannot be applied generally to other than the test species. This paper describes the sterilizing activity of certain boron compounds in house flies, *Musca domestica* L., but some of these compounds were also tested in

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(4) J. A. Settepani, M. M. Crystal, and A. B. Bořkovec, *J. Econ. Entomol.*, **62**, 375 (1969).