CA18675 is acknowledged. We also thank Dr. J. S. Baran (G. D. Searle & Co.) for supplying the 17,17-(ethylenedioxy)estra-1,3,5(10)-triene-3,11β-diol (SC 16093), Dr. E. Mazzola of the Food and Drug Administration for the use of the NMR spectrometer and useful discussions, and Dr. E. A. Caress of George Washington University for obtaining and interpreting the mass spectra of various compounds. Finally we thank Dr. George Kalbalka for a sample of **4a** and many helpful discussions.

Registry No. **1a**, 57-63-6; **1b**, 72-33-3; **1d**, 34816-55-2; **2a**, 91176-86-2; **2b**, 81844-94-2; **2c**, 91085-37-9; **2d**, 91085-38-0; **2e**, 91085-39-1; **3a**, 91085-40-4; **3b**, 78479-31-9; **3c**, 91085-41-5; **3d**, 91085-42-6; **3e**, 91085-43-7; **4a**, 91085-44-8; **4b**, 82123-96-4; **4c**, 91085-45-9; **4d**, 90857-55-9; **5**, 2553-34-6; catecholborane, 274-07-7.

Synthesis and β-Adrenergic Blocking Activity of New Aliphatic and Alicyclic Oxime Ethers†

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We describe the synthesis and pharmacological properties of two new series of aliphatic and alicyclic β-adrenergic blockers, most of them containing a cyclopropyl ring. They belong either to 2-hydroxy-3-(*tert*-butylamino)propyl ether A or 2-hydroxy-3-*tert*-(butylamino)propyl ketoxime ether B derivatives. The *O*-[2-hydroxy-3-(*tert*-butylamino)propyl] dicyclopropyl ketoxime **5** exhibited a β-adrenergic antagonist activity comparable to that of propranolol. It was found that ketoxime ethers B generally showed higher potency than the corresponding ethers A. We confirm that the presence of an aromatic nucleus is not crucial for the β-adrenergic activity. Structure–activity relationships among these series are discussed.

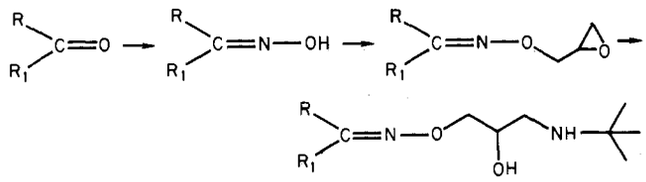
In a previous paper,[1] we have shown that some aliphatic oxime ethers could exhibit interesting β-adrenergic blocking activities. This result encouraged us to pursue our efforts to increase the activity of these molecules and to clarify structure–activity relationships within this series. In this paper we report the synthesis and the pharmacology of these new β-blockers, most of which contain a cyclopropyl ring.

Chemistry. Scheme I shows the classical synthetic route starting with the appropriate ketone oximes for the preparation of compounds **1–10** (Table I). Compounds **11–18** (Table II) were similarly prepared from the sodium salt of the corresponding alcohol (Scheme II).

Most of the ketones used in this work are commercially available or can be obtained by known procedures. Several attempts to prepare ketone **19** were unsuccessful. Thus, the action of MeMgI on crotonyl chloride led to a complex mixture of 1,1-dimethylbutadiene, methyl crotyl ketone, dimethylcrotylcarbinol, methyldicrotylcarbinol, and the desired allyl methyl ketone as evidenced by NMR, MS, and GLC. Similarly, the action of 3-butenyltrimethylsilane on MeCOCl, using $TiCl_4$ as a catalyst,[2] afforded a mixture of β-chloro ketone, 3-butenyl ketone, and cyclopropylacetone from which the last compound could not be isolated satisfactorily. Finally, the ketone **19** was obtained by using the procedure described in Scheme III. The reaction of crotonyl chloride with EtOH in the presence of $N(Et)_3$ gave the rearranged ethyl vinylacetate;[3] this ester was submitted to a Simmons–Smith reaction by using diiodomethane and Zn/Cu couple.[4] The direct action of MeLi (2 equiv) on cyclopropylacetic acid gave a poor yield of I (ca. 10%). Similar findings were mentioned in the literature[5] for lower aliphatic acids. As an alternative, the corresponding acid chloride was reacted with dimethylcadmium[6] to give the cyclopropylacetone with an overall yield of approximately 36%.

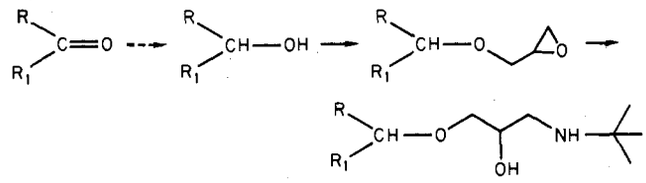
$NaBH_3CN$ reduction of the oxime ether **3** gave **8**.

Scheme I



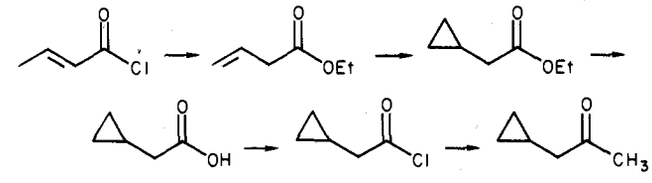
A

Scheme II



B

Scheme III



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† A part of this work was presented at the 2nd Camerino Symposium, Italy, Sept 1983. This work forms part of a thesis for the doctorat ès sciences to be submitted by M. Bouzoubaa to the University Louis Pasteur, Strasbourg.

‡ Department of Medicinal Chemistry.

§ Department of Pharmacology.

‖ Laboratories P.O.S.

(1) Leclerc, G.; Bieth, N.; Schwartz, J. *J. Med. Chem.* **1980**, *23*, 620.
(2) Sakurai, H.; Imai, T.; Hassim, A. *Tetrahedron Lett.* **1977**, *46*, 4045.
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(4) Bigley, D. B.; Fetter, C. L. *J. Chem. Soc.* **1979**, 2, 122.
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(6) Cason, J.; Prout, J. S. "Organic Syntheses"; Wiley: New York, 1967; Collect. Vol. III, p 601.

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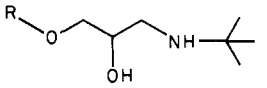
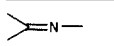
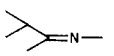
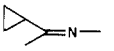
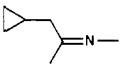
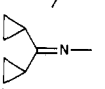
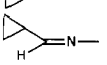
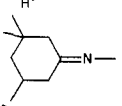
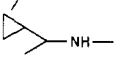
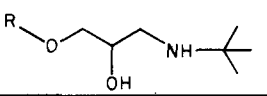
Table I. Physical Properties and β-Blocking Activity of Aliphatic and Alicyclic Oxime Ethers

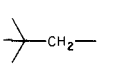
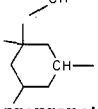


no.	R	% yield	mp, °C	crystn solv	formula	pK_a	P^f	pA_2 ± SE (n)[a] atria	pA_2 ± SE (n)[a] trachea	broncho-selectivity[d]
1		16	131	EtOAc/ $(Et)_2O$	$C_{10}H_{22}N_2O_2$· HCl	9.42	0.02	6.51 ± 0.05[e] (7)	7.65 ± 0.32[e] (12)	13.8
2		34	112	EtOAc/ MeOH	$C_{12}H_{26}N_2O_2$· oxoalate	9.27	0.19	7.32 ± 0.26 (8)	6.65 ± 0.15 (10)	0.2
3		27	128	EtOAc/ MeOH	$C_{12}H_{24}N_2O_2$· oxalate	9.45	0.18	7.98 ± 0.15 (6)	7.90 ± 0.54[c] (10)	0.8
4			108	EtOAc/ $(i\text{-}Pr)_2O$	$C_{13}H_{26}N_2O_2$· oxalate	9.57	0.28	7.08 ± 0.25 (8)	7.32 ± 0.18 (8)	1.7
5		15	159	EtOAc	$C_{14}H_{26}N_2O_2$· $^1/_2$fumarate	9.64	0.85	8.30 ± 0.30 (6)	8.67 ± 0.24[e] (7)	2.3
6		6	195	i-PrOH/ MeOH	$C_{11}H_{22}N_2O_2$· $^1/_2$fumarate	9.64	0.02	8.01 ± 0.17 (7)	7.09 ± 0.38[e] (12)	0.1
7		20	88	C_6H_6/ MeOH	$C_{16}H_{32}N_2O_2$· oxalate	9.41	4.96	5.88 ± 0.16 (4)	7.78 ± 0.51[e] (9)	79.4
8		59	192	EtOAc/ MeOH	$C_{12}H_{26}N_2O_2$· 2maleate	9.10 10.20	0.13	4.90 ± 0.14 (5)	5.30 ± 0.08[e] (9)	2.5
9	oxazolidine of **3**	85	oil		$C_{13}H_{24}N_2O_2$·					
10	pivalate of **3**	50	118	EtOAc	$C_{17}H_{32}N_2O_3$· fumarate	8.65	8.30	6.92 ± 0.16 (5)	8.05 ± 0.18 (5)	13.5
	propanolol					9.50	26.00	8.62 ± 0.17 (13)	8.47 ± 0.22 (9)	0.7

[a] pA_2 ± standard error with the number of experimental values in parentheses. [b] pAH = −log of the molar concentration of antagonist that inhibits 50% of the maximal effect of the agonist. [c] Graphical estimation. [d] Antilog of the difference between the tracheal and atrial pA_2 values. [e] Schild plot slopes differ significantly from 1. [f] P values ± 0.05.

Table II. Physical and β-Blocking Activities of Aliphatic and Alicyclic Ethers



no.	R	% yield	mp, °C	crystn solv	formula	pK_a	P^f	pA_2 ± SE (n)[a] atria	pA_2 ± SE (n)[a] trachea	broncho-selectivity[d]
11		45	145	EtOAc	$C_{11}H_{25}NO_2$· maleate	9.73	0.26	6.31 ± 0.08 (6)	7.49 ± 0.36[c] (12)	15.1
12		70	146	EtOAc	$C_{10}H_{23}NO_2$· maleate	9.90	0.02	4.87 ± 0.08 (5)	6.37 ± 0.22[e] (8)	31.5
13		14	134	EtOAc/ MeOH	$C_{12}H_{27}NO_2$· HCl	9.68	0.51	6.74 ± 0.23 (7)	7.64 ± 0.17[e] (8)	7.9
14		15	149	EtOAc	$C_{12}H_{25}NO_2$· $^1/_2$fumarate	9.67	0.23	4.43 ± 0.32[c] (3)	4.96 ± 0.09 (4)	3.4
15		7	125	EtOAc	$C_{11}H_{23}NO_2$· maleate	9.73	0.05	7.09 ± 0.12 (6)	6.23 ± 0.06 (6)	0.15
16		9	112	EtOAc	$C_{14}H_{27}NO_2$· fumarate	9.63	0.63	4.51 ± 0.30[c] (2)	4.51 ± 0.16[c]	1.0
17		21	116	EOAc	$C_{12}H_{25}NO_2$· oxalate	9.76	0.09	5.47 ± 0.13 (4)	6.01 ± 0.19[e] (6)	3.5
18		26	138	EtOAc	$C_{16}H_{33}NO_2$· fumarate	9.94	8.59	5.82[b] (4)	7.01 ± 0.14[e] (7)	47.9
	propranolol					9.50	26.00	8.62 ± 0.17 (13)	8.47 ± 0.22 (9)	0.7

[a] pA_2 ± standard error with the number of experimental values in parentheses. [b] pAH = −log of the molar concentration of antagonist that inhibits 50% of the maximal effect on the agonist. [c] Graphical estimation. [d] Antilog of the difference between the tracheal and atrial pA_2 values. [e] Schild plot slopes differ significantly from 1. [f] P values ± 0.05.

Discussion and Structure-Activity Relationships

In our previous paper,[1] although we had a limited series of compounds, we proposed that the aromatic nucleus of β-blockers did not seem to be essential, contrary to the generally held views.[7-12]

The findings reported in Tables I and II, based on structures lacking an aromatic nucleus, confirm our pre-

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vious observations and allow certain conclusions to be made regarding the importance of an aromatic ring on the β-adrenergic activity.

In this series, it appears that oxime derivatives are generally much more potent than their corresponding ether analogues. The most active compound **5**, with a $pA_2 = 8.7$ on isolated guinea pig trachea, is as active as propranolol. Specifically, compounds **1**, **3**, and **6** are respectively ca. 20, 80, and 7 times more active on the isolated guinea pig atria and trachea than the ether analogues **12**, **17**, and **15**. The dicyclopropyl oxime derivative **5** is ca. 6000 times more active on atria and 10 000 times more active on trachea than the corresponding ether **16**. The fact that compounds **1**, **11**, and **12** described in our previous paper were nearly equipotent had led us to conclude that the nitrogen atom of the oxime function was not crucial for the β-adrenergic activity. The results obtained here seem to indicate that this oxime linkage is probably more important than might have been expected. Thus, $NaBH_3CN$ reduction of the >C=N- bond of **3** gives compound **8** that has only $^1/_{40}$th the activity of **3** on atria and $^1/_{1000}$th the activity of **3** on trachea. Interestingly, we observed that the presence of a cyclopropyl ring had a positive influence on the β-adrenergic activity: on trachea the monocyclopropyl derivative **3** is ca. 20 times more active than **2**, and in turn, the dicyclopropyl derivative **5** is ca. 5 times more active than **3**. The role of the cyclopropyl ring is unclear but cannot be accounted for only by lipophilicity, since **2**, which has nearly the same partition coefficient ($P \sim 0.18$) value as **3** (same number of carbon atoms), is ca. 20 times less active. However, the biological activity of compounds **3** and **5** may be due to the electron density of the cyclopropyl rings and the conjugation with the ketoxime function, whereas the lack of such features in compounds **8**, **16**, and **17** may be the cause of their poor activity. Increasing the size of the substituents on the oxime function, and consequently the lipophilicity of the molecule, led to a compound such as **7**. The fact that this compound is less active than **3** or **5** indicates that the atrium β_1-adrenergic receptor maintains some steric requirements in the oxime area that are best satisfied in **3** or **5**. Variations in this area are allowed to a certain extent since the cyclopropyl aldehyde derivative **6** is as active as **3** on atria. However, moving the cyclopropyl ring away from the oxime linkage by one carbon atom led to **4** which has only $^1/_{10}$th the activity of **3** on atria. The rather low partition coefficient of **3** when compared to those of classical aromatic β-blockers (P = 26 for propranolol) led us to prepare some lipophilic derivatives of **3**. Thus, the pivaloyl ester **10** ($pA_2 \sim 8$) is ca. 50 times more lipophilic than the parent compound **3**. We have noted that **10** was partly hydrolyzed (ca. 25%) under the experimental conditions used[13] (pH 7.4, 1 h, 37 °C); thus the pA_2 observed could be due to the regeneration of the starting drug **3**. Similarly, LL 21-945, the pivaloyl ester of 4-[3-(*tert*-butylamino)-2-hydroxypropoxy]-9-fluorenone hydrogen maleate[14] was found to be only 10 times less active than the parent compound. The hydrochloride oxazolidine derivative **9** is too unstable in aqueous solution to be examined. It is hydrolyzed in 15 min under the experimental conditions used. Similar observations were mentioned for the oxazolidine derivative of bunolol.[15] pK_A values given in Tables I and II vary between 8.4 and 9.9 and therefore cannot explain the wide range (ca. 10^4) in biological activities observed in this series.

Interestingly, our results seem to be in partial agreement with the hypothesis[16] that cardiac receptors are associated with a more hydrophilic environment than tracheal or vascular receptors. Indeed, the more lipophilic compounds **7**, **10**, and **18** are more active on trachea than on atria respectively by 80, 13, and 50 times. Conversely, hydrophilic compounds **6**, **15**, and to a lesser extent **2** are more active on atria than on trachea. However, some notable exceptions are found since the very hydrophilic compound **1** is ca. 14 times more active on trachea than on atria.

In the anesthetized dog, **3** showed the classical hemodynamic profile of a β-adrenergic blocking agent; it reduced cardiac frequency and cardiac output and increased peripheral resistances. Contrary to propranolol, **3** slightly increased arterial blood pressure in agreement with its relative β_2-activity.[17] Compound **3** showed a better tolerance than **5** in rabbit ocular instillations. Further, in the model of Bartsch and Knopf,[18] no anesthesia of the rabbit cornea was observed with **3**. Both these properties may be related to the lack of an aromatic nucleus. For these reasons, compound **3** has been chosen for clinical trial under the name of Falintolol.[19]

Experimental Section

Melting points were obtained on a calibrated Kofler hot stage apparatus and are uncorrected. Infrared spectra were measured in $CHCl_3$ with a Beckman IR 33 spectrophotometer. NMR spectra were recorded on a Perkin-Elmer R 12 A spectrometer with Me_4Si in a capillary as an external reference. Compounds 1–18 were analyzed for C, H, and N and gave results within 0.4% of the theoretical values.

Pharmacological Tests of β-Adrenergic Blocking Activity. β_1- and β_2-adrenolytic activities were determined on the atria and trachea of guinea pigs. The antagonisms of isoproterenol-induced positive chronotropism on isolated spontaneously beating right atria and isoproterenol-induced relaxation of trachea were measured according to Horii et al.[20] and Levy and Wilkenfeld,[21] respectively. The preparations were suspended in Krebs–Henseleit solution, aerated with 95% O_2 and 5% CO_2, at temperatures and resting tensions of 32 °C and 0.5 g for atria and 37 °C and 1 g for trachea. The physiological solution was composed as follows (in mM): NaCl, 120, KCl 4.80, $MgSO_4 \cdot 7H_2O$ 1.20, $CaCl_2 \cdot 2H_2O$ 2.53, KH_2PO_4 1.20, $NaHCO_3$ 25, glucose 10. Tracheal chain preparations were allowed to gain tone spontaneously. Ascorbic acid (1.13×10^{-5} M) was present during the elaboration of each isoprenaline dose–response curve (3×10^{-10} to 3×10^{-8} M). Preincubation time with the antagonists was 30 min. The β-antagonistic activities were expressed in terms of pA_2 values for competitive antagonists according to Arunlakshana et al.[22] When the antagonism was not competitive, it was expressed as pAH (-log of the molar concentration of antagonist that inhibits 50% of the maximal effect of the agonist) according to Ariens and Van Rossum.[23] β_2/β_1 bronchoselectivity is the antilog of the difference

(9) Biel, J. H.; Lum, B, K. B. *Prog. Drug. Res.* **1966**, *10*, 46.
(10) Brittain, R. T.; Jack, D.; Ritchie, A. C. *Adv. Drug. Res.* **1970**, *5*, 197.
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(16) Basil, B.; Clark, J. R.; Koffee, E. C. J.; Jordan, R.; Lorele, S. A. H.; Pain, D. L.; Wooldridge, K. R. M. *J. Med. Chem.* **1976**, *19*, 339.
(17) Unpublished results.
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(20) Horii, D.; Kawada, T.; Takeda, K.; Imai, S. *Arzneim.-Forsch.* **1974**, *24*, 1275.
(21) Levy, B.; Wilkenfeld, B. E. *Eur. J. Pharmacol.* **1970**, *11*, 67.
(22) Arunlakshana, O.; Schild, H. O. *Br. J. Pharmacol.* **1959**, *14*, 48.

between the tracheal and atrial pA_2 values for each antagonist.

Partition Coefficient. Reagents. a pH 5.70 buffer was prepared by mixing 100 mL of 0.1 M citric acid with 140 mL of 0.2 M anhydrous Na_2HPO_4. The bromocresol green solution was prepared by dissolving 30 mg of bromocresol green in 100 mL of the pH 5.70 buffer and filtering.

Measurements. Exactly 0.1 molar equiv of compounds was dissolved in 8.5 mL of phosphate buffer, pH 7.4, presaturated with 1-octanol for 12 h. The solution was shaken with 8.5 mL of 1-octanol (presaturated with buffer) at 350 strokes/min at 20 °C for 4 h, after which time the layers were centrifuged for 2 min at 3000 rpm; the organic phase was discarded, and the concentration of drug remaining in the aqueous phase was determined by spectrophotometric analysis. Bromocresol green solution was added to the aqueous phase and the dye complex formed was extracted with $CHCl_3$ and the absorbance measured at 410 nm as described[24] previously. The partition coefficient was then calculated from the formula $P = (D_i - D_f)/D_f$, where D_i = optical density of aqueous solution before extraction and D_f = optical density of aqueous solution after extraction. The experiments were carried out twice and are accurate to ±0.05.

Dissociation Constants. The pK_a values of compounds were determined by potentiometric titration. The salts (about 20-mg samples accurately weighted) were dissolved in 35 mL of distilled water and 5 mL of 0.1 N aqueous KNO_3 at 20 ± 1 °C and neutralized by 0.05 N NaOH by using a Mettler DL 40 automatic memotitrator.

Preparation of Oxime Ether Derivatives 1–7. This preparation is illustrated by the synthesis of *O*-[2-hydroxy-3-(*tert*-butylamino)propyl]cyclopropyl methyl ketone oxime (**3**).

Cyclopropyl methyl ketone oxime was synthesized according to ref 25. NaH (50 mmol) was added slowly to 50 mmol of cyclopropyl methyl ketone oxime in 100 mL of dry THF. The solution was stirred magnetically until no hydrogen was evolved. This solution was then added dropwise to a solution of 3.9 mL (50 mmol) of epibromohydrin in 10 mL of dry THF and stirred for 48 h during which a precipitation of NaBr occurred. The NaBr was filtered and the THF was evaporated. The crude epoxide was dissolved in 20 mL of dry ethanol containing 10 mL of *t*-$BuNH_2$ and stirred magnetically at room temperature for 24 h. The solvents were removed at a reduced pressure, and the only residue was dissolved in dilute HCl (10%). Neutral and acidic materials were extracted twice with Et_2O.

The aqueous layer was made alkaline with K_2CO_3 and extracted twice with EtOAc. The organic phase was dried over $MgSO_4$ and the solvent evaporated. Oxalic acid (6.3 g) was dissolved in a minimum of EtOAc and was added to the crude base. The salt formed was induced to crystallize by scratching; two recrystallizations from EtOAc–MeOH (90:10) gave 4.3 g of **3**: yield 27%; mp 128 °C. ^{1}H NMR ($CDCl_3$) δ 4.00 (m, 2 H), 3.80 (m, 1 H), 2.70 (m, 2 H), 1.95 and 1.45 (2 s, 3 H), 1.50 (m, 1 H), 0.75 and 0.65 (2 m, 4 H). Anal. ($C_{14}H_{26}N_2O_6$) C, H, N.

Preparation of the Ether Derivatives 11–18. These compounds were prepared according to ref 1.

Preparation of Compounds 8–10. *O*-[2-Hydroxy-3-(*tert*-butylamino)propyl]-*N*-(cyclopropylethyl)hydroxylamine (**8**) was prepared according to ref 1: yield 59%; mp 192 ± 1 °C. ^{1}H NMR (C_6D_6) δ 4.15 (m, 2 H), 4.05 (m, 1 H), 3.60 and 3.00 (1, 3 H), 2.80 (m, 2 H), 2.30 (m, 1 H), 1.45 (m, 1 H), 1.30 (d, 3 H), 1.05 (s, 9 H), 0.50 (m, H). Anal. ($C_{20}H_{34}N_2O_{10}$) C, H, N.

Cyclopropyl methyl ketone *O*-[(3-*tert*-butyl-5-oxazolidinyl)-methyl]oxime (**9**) was prepared according to ref 15: yield 85%; bp ~133 °C (0.3 mmHg); ^{1}H NMR (C_6D_6) δ 4.95 (m, 3 H), 4.45 (m, 2 H), 1.70 and 1.43 (2 s, 3 H), 1.60 (m, 1 H), 0.65 (m, 4 H).

Cyclopropyl methyl ketone *O*-[2-(pivaloyloxy)-3-(*tert*-butylamino)propyl]oxime (**10**) was prepared according to ref 26: yield 50%; mp 118 ± 1 °C; ^{1}H NMR (CCL_4) δ 4.85 (m, 1 H), 4.00 (m, 2 H), 2.10 (m, 2 H), 1.55 and 1.40 (2 s, 3 H), 1.10 (s, 9 H), 1.00 (s, 9 H), 0.60 (m, 4 H). Anal. ($C_{21}H_{36}NO_{27}$) C, H, N.

Preparation of Cyclopropylacetone (19). Cyclopropylacetic acid[4] (0.0110 mol) was converted to cyclopropylacetyl chloride with $SOCl_2$. Cyclopropylacetyl chloride (4.0 g, 0.035 mol) was treated with 0.5 equiv (0.017 mol) of Me_2Cd by adapting the procedure of Cason and Prout.[6] The compound obtained, yield 2 g (68%), had the following characteristics: bp 128 °C; ^{1}H NMR (CCl_4) δ 2.25 (d, 2 H), 2.15 (s, 3 H), 1.10 (m, 1 H), 0.60 and 0.30 (2 m, 4 H).

Registry No. 1, 90941-11-0; 1·HCl, 73313-16-3; 1 (epoxide), 24161-04-4; **2**, 90941-12-1; **2**·oxalate, 90941-29-0; **2** (epoxide), 90941-22-3; **3**, 88134-91-2; **3**·oxalate, 88134-93-4; **3** (epoxide), 88135-05-1; **4**, 90941-13-2; **4**·oxalate, 90941-30-3; **4** (epoxide), 90941-23-4; **5**, 88134-94-5; **5**·$^1/_2$fumarate, 88134-95-6; **5** (epoxide), 90941-24-5; **6**, 90941-14-3; **6**·$^1/_2$fumarate, 90941-31-4; **6** (epoxide), 90941-25-6; **7**, 88135-00-6; **7**·oxalate, 88135-01-7; **7** (epoxide), 88135-06-2; **8**, 90941-15-4; **8**·2maleate, 90941-32-5; **9**, 90941-16-5; **10**, 90941-17-6; **10**·fumarate, 90941-33-6; 11, 73313-27-6; 11·maleate, 73313-28-7; 11 (epoxide), 3814-55-9; **12**, 73313-31-2; **12**·maleate, 73313-32-3; **12** (epoxide), 4016-14-2; **13**, 90941-18-7; **13**·HCl, 90941-34-7; **13** (epoxide), 78906-14-6; **14**, 80762-89-6; **14**·$^1/_2$fumarate, 90941-35-8; **14** (epoxide), 3066-51-1; **15**, 88134-96-7; **15**·maleate, 88134-97-8; **15** (epoxide), 88135-04-0; **16**, 88134-98-9; **16**·fumarate, 88134-99-0; **16** (epoxide), 90941-26-7; **17**, 90941-19-8; **17**·oxalate, 90941-36-9; **17** (epoxide), 90941-27-8; **18**, 90941-20-1; **18**·fumarate, 90941-37-0; **18** (epoxide), 90941-28-9; **19**, 4160-75-2; **19** (oxime), 90941-21-2; $(CH_3)_2CO$, 67-64-1; $CH_3COCH(CH_3)_2$, 563-80-4; $(CH_3)_2C{=}NOH$, 127-06-0; $CH_3C{=}NOH(CH(CH_3)_2)$, 600-20-4; $(CH_3)_2CHCH_2OH$, 78-83-1; $(CH_3)_2CHOH$, 67-63-0; $(CH_3)_3CCH_2OH$, 75-84-3; $CH_2{=}CHC(CH_3)_2OH$, 115-18-4; $(CH_3)_3CNH_2$, 75-64-9; (*E*)-$CH_3CH{=}CHCOCl$, 625-35-4; $CH_2{=}CHCH_2COOEt$, 1617-18-1; cyclopropyl methyl ketone, 765-43-5; dicyclopropyl ketone, 1121-37-5; cyclopropanecarboxaldehyde, 1489-69-6; 3,3,5-trimethylcyclohexanone, 873-94-9; cyclopropyl methyl ketone oxime, 51761-72-9; dicyclopropyl ketone oxime, 1453-52-7; cyclopropanecarboxaldehyde oxime, 66291-30-3; 3,3,5-trimethylcyclohexanone oxime, 37694-11-4; cyclopropanemethanol, 2516-33-8; α-cyclopropylcyclopropanemethanol, 14300-33-5; α-methylcyclopropanemethanol, 765-42-4; 3,3,5-trimethylcyclohexanol, 116-02-9; ethyl cyclopropylacetate, 53432-87-4; cyclopropylacetic acid, 5239-82-7; cyclopropylacetyl chloride, 54322-65-5.

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