(m, 2, cyclopropane). Anal. ($C_{25}H_{23}NO_3S$) C, H, N.

***N*-(2-Aminoethyl)-1,1a,6,10b-tetrahydrodibenzo[*a*,*e*]cyclopropa[*c*]cyclohepten-6-imine (16).** A solution of 4.8 g (0.0125 mol) of *N*-[2-(toxyloxy)ethyl]-1,1a,6,10b-tetrahydrodibenzo[*a*,*e*]cyclopropa[*c*]cyclohepten-6-imine, 20 mL of dry hexamethylphosphoramide,[6] and 25 mL of ammonia was sealed in a Carius tube and kept at 25 °C for 5 days. The solution was poured into 150 mL of water and twice extracted with 75 mL of ether. The organic layer was twice extracted with 50 mL of cold 10% hydrochloric acid. The aqueous solution was washed with 75 mL of ether and then made basic by the addition to a cold solution of sodium hydroxide. The oil was extracted with ether and dried over potassium carbonate, and the solvent was evaporated. The residue was flash distilled at 170 °C (bath) (0.1 μm) to give 2.5 g (83% yield) of **16**: NMR τ 2.4–3.1 (m, 8, aromatic H), 6.1–6.7 (m, 2, $=NCH_2$), 6.8–7.3 (m, 2, CH_2N), 7.4–7.8 (m, 2, cyclopropane), 8.1–8.7 [m + s, 4; the s (2 H) is exchangeable with D_2O; NH_2 and cyclopropane]. Anal. ($C_{18}H_{18}N_2$) C, H, N.

***N*-(2-Hydroxyethyl)-5*H*-dibenzo[*a*,*d*]cycloheptene-5-imine (4).** Using method C, **4** was obtained in 53% yield: mp 117–119 °C after crystallization from benzene (lit.[8] mp 113–114 °C); NMR τ 1.8–3.0 (m, 10, aromatic + H-10 and H-11), 5.7–7.6 (m, 5, CH_2CH_2OH). This compound was indentical, by infrared and NMR spectroscopy, with the product obtained according to ref 8. Anal. ($C_{17}H_{15}NO$) C, H, N.

2′-Methylspiro[5*H*-dibenzo[*a*,*d*]cycloheptene-5,2′-oxazolidine] (5b). A mixture of 5.00 g (0.019 mol) of 5,5-dichlorodibenzo[*a*,*d*]cycloheptene (**3**) and 40 mL of 2-(methylamino)ethanol was heated to 50 °C for a short period and then stirred at room temperature overnight. Ether and water were added, and the crude product obtained from the ether layer was crystallized from cyclohexane to give 1.94 g (38%) of **5b**, mp 110.5–111.5 °C. An analytical sample had mp 111–112 °C: NMR τ 2.0–2.3 (m, 2, aromatic H), 2.5–2.8 (m, 6, aromatic H), 2.9 (s, 2, H-10 and H-11), 6.0 (t, J = 6.5 Hz, 2, CH_2O), 7.3 (t, J = 6.5 Hz, 2, CH_2N), 8.2 (s, 3, Me). Anal. ($C_{18}H_{17}NO$) C, H, N.

Pharmacology. Antitetrabenazine (TBZ) Test. This test was used to detect potential antidepressant activity. Groups of 10 Carworth CF_1S female mice, 18–21 g each, were fasted 1.5 h and were intubated with test compounds at oral doses of 0, 5, 25, and 125 mg/kg or 0, 1, 3, 9, 27, and 81 mg/kg in 0.20 mL of 1% Methocel. The mice were challenged 30 min later with tetrabenazine (as the methanesulfonate), 32 mg/kg intraperitoneally (dissolved in 0.20 mL of 0.05 M KCl at pH 2.0). One hour after the test was administered (30 min after tetrabenazine), the mice were examined for signs of exploratory activity and ptosis (eyelid closure). Antagonism of exploratory loss was recorded when a mouse, lifted by the tail from a group of 10 in a testing box and placed on a stainless-steel testing box lid (12.5 × 2 in. with 0.33 in. mesh), either turned its head horizontally 30° in both directions or moved to the edge of the screen within 10 s after being placed on the screen. Antagonism of ptosis was recorded when exactly 2 s after placing the mouse facing the observer lid closure was less than 50% in both eyes.

General Pharmacology Screen. Female white mice, 16–20 g each, were fasted 17–24 h and then dosed orally with test drug or standard drug at 0, 4, 12, 36, 108 or 324 mg/kg. Mice were observed at 0.5, 2, 5, and 24 h after drug administration for the number of survivors and for signs of ataxia, pupillary dilation, excitement, and protection from electroshock.

Ataxia. The mouse or rat was placed upright on the bench top facing away from the observer. Motor incoordination manifested by abnormal gait or lack of precision during purposive movements constituted ataxia. Mice which did not walk or run spontaneously were prodded gently.

Pupillary Diameter. The mouse was held by the tail and neck nape with one hand while its head was steadied by gently holding its muzzle with the other hand. Pupillary diameter was measured with a dissecting microscope (B and L) (20× magnification) with an eyepiece fitted with a 10-mm micrometer disk divided into 0.1-mm divisions. The head of the mouse was placed about 8 cm below the microscope objective. A Nichloas microscope lamp (B and L) was focused on the eye of the mouse and pupillary diameter was determined rapidly (2–5 s).

Electroshock Convulsions. At 2 and 5 h after dosing, each mouse was held by the tail and neck nape and was positioned with the corneas of the eye touching saline-saturated corneal wick electrodes. A supramaximal (about 50 mA) alternating current (from a Model B Medcraft ECT unit, set for 70 V) was passed for 0.2 s through the corneal electrodes. A decrease of the typical maximal convulsive seizure produced by this stimulus (i.e., absence of the hindlimb extensor component) constituted electroshock protection.

Excitement and Irritability. Increased spontaneous motor activity, running and jumping, prior to handling was recorded as excitement.

An ED_{50}, the calculated dose at which 50% of the test animals would have responded, was calculated by the method of Thompson[11] for each of the described parameters for the test compounds and the standard drugs.

(11) W. R. Thompson, *Bacteriol. Rev.*, 11, 115 (1947).
(12) J. Bernstein and K. Lossee, U.S. Patent 3 052 721 (1962); A. M. Monro, R. M. Quinton, and T. I. Wrigley, *J. Med. Chem.*, 6, 255 (1963).

4-Aryl-4-aminocyclohexanones and Their Derivatives, a Novel Class of Analgesics. 3. *m*-Hydroxyphenyl Derivatives

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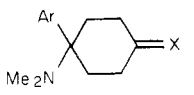
Derivatives of 4-aryl-4-(dimethylamino)cyclohexan-1-ones substituted by *m*-hydroxy groups were obtained by using as a key reaction the displacement of cyanide from the α-aminonitrile of 1,4-cyclohexanedione ketal, with the THP ether of *m*-hydroxyphenylmagnesium bromide. A number of the products show narcotic antagonist activity. Amino alcohols obtained on reaction of the free ketones with phenethyl Grignard reagents are potent analgetics, though devoid of antagonist activity. Systematic variation of the substituent on nitrogen revealed nonclassical structure–activity relationships; the dimethylamino group gives the most potent antagonist.

We have reported earlier on the synthesis and opioid analgesic activity of derivatives of 4-aryl-4-aminocyclohexanone (**1**).[2,3] The nature of the synthesis used in the earlier work made it awkward to carry a phenol through the scheme. Since it is well known that a *m*-hydroxy group has a profound influence on molecules with analgesic activity, we sought a relatively short route to these analogues.



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(1) Adria Laboratories, Columbus, Ohio.
(2) D. Lednicer, P. F. VonVoigtlander, and D. E. Emmert, *J. Med. Chem.*, **23**, 424 (1980).
(3) D. Lednicer, P. F. VonVoigtlander, and D. E. Emmert, *J. Med. Chem.*, in press.

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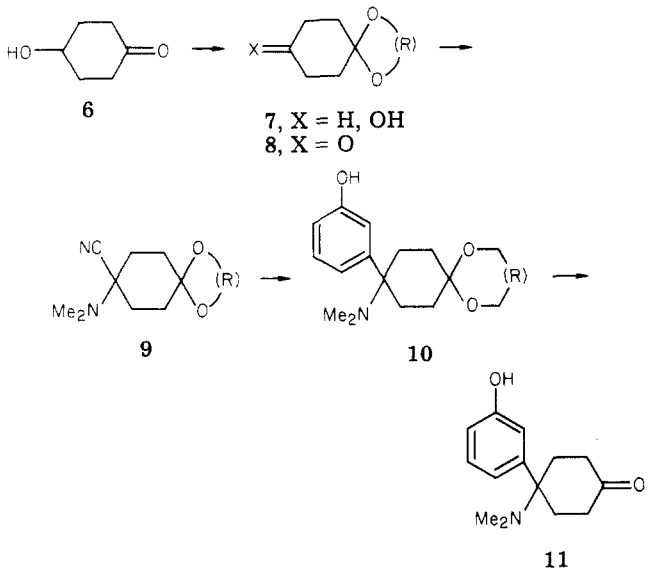
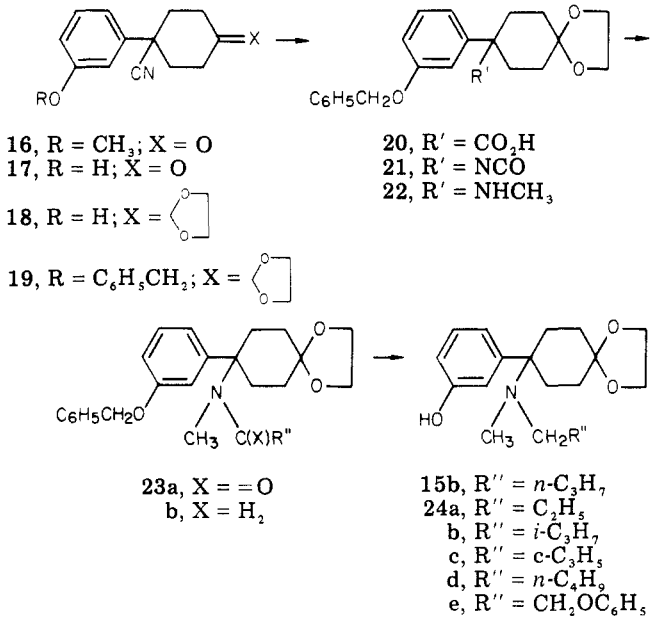
Scheme I[a]



6 7, X = H, OH; 8, X = O 9 10 11

[a] a, R = $(CH_2)_3$; b, R = $CH_2C[(CH_3)_2]CH_2$; c, R = $CH_2CH(CH_2CH{=}CH_2)CH_2$; d, R = $CH_2CH(C_6H_5)CH_2$.

Scheme II



16, R = CH_3; X = O
17, R = H; X = O
18, R = H; X =
19, R = $C_6H_5CH_2$; X =

20, R′ = CO_2H
21, R′ = NCO
22, R′ = $NHCH_3$

23a, X = =O
b, X = H_2

15b, R″ = n-C_3H_7
24a, R″ = C_2H_5
b, R″ = i-C_3H_7
c, R″ = c-C_3H_5
d, R″ = n-C_4H_9
e, R″ = $CH_2OC_6H_5$

The functional array present at the 4 position of these molecules suggested that they might be accessible by a relatively obscure reaction—displacement of the cyano group from α-aminonitriles by aryl Grignard reagents.[4,5] Preparation of the requisite starting material, the monoketal of cyclohexanone-1,4-dione, began by a modification of the literature procedure;[6] in our hands the oxidation of 4-hydroxycyclohexanone was most conveniently carried out by the 3,5-dimethylpyrrazole modification of the Collins oxidation. Reaction of the product (2) with Me_2NH·HCl and KCN in aqueous Me_2NH afforded crystalline aminonitrile 3 in excellent yield. Exposure of this intermediate to phenylmagnesium bromide gave the ketal 4 identical in all respects with that prepared by the earlier stepwise synthesis.

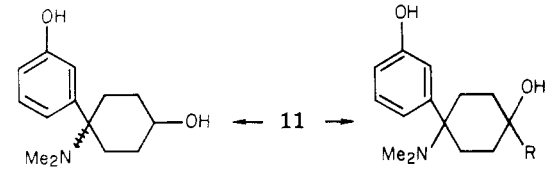
2, X = O
3, X = CN, NMe_2

4, Ar = C_6H_5
5, Ar = m-HOC_6H_5

The observation that the product (5) of 1 with the Grignard reagent from the THP ether of m-bromophenol showed narcotic antagonist activity prompted further examination of this series.

Chemistry. The large role which the ketal plays on the potency in the earlier series[2] led us first to examine the effect on biological activity of modification of this function. Thus, a series of different ketals was prepared from 4-hydroxycyclohexanone (Scheme I). These were then, in turn, oxidized, converted to the α-aminonitrile, and treated with the Grignard reagent from m-bromophenol tetrahydropyranyl ether.

Hydrolysis of 5 afforded the ketone 11. The ketone was

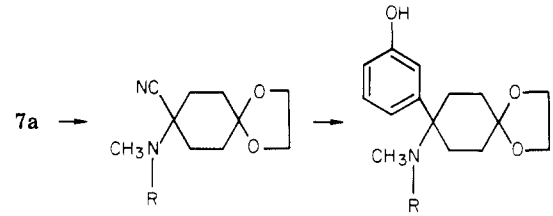


12 13

R = CH_3, $CH_2C_6H_5$, $CH_2CH_2C_6H_5$, $CH_2CH_2(p\text{-}ClC_6H_4)$

then reduced (12) and also condensed with a series of organometallic reagents to ascertain whether the previously observed increase in potency conferred by this transformation applied to the m-hydroxy series as well (13). Stereochemical assignment of the isomeric amino alcohols rests on polarity on silica gel, in analogy to the earlier work.

Initial approaches toward the preparation of analogues in which the substitution on nitrogen was varied consisted of the substitution of other amines for Me_2NH in the α-aminonitrile forming reaction. Thus, allylmethylamine afforded a crystalline product (14a), which gave the desired



14a, R = $CH_2CH{=}CH_2$
b, R = $(CH_2)_3CH_3$

15a, R = $CH_2CH{=}CH_2$
b, R = $(CH_2)_3CH_3$

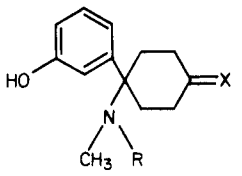
aminophenol in fair yield on Grignard displacement. The same sequence using butylmethylamine afforded the aminonitrile as an oil, which could not be crystallized; displacement gave the desired product 15b in only trace yields (2%).

The interesting biological activity exhibited by 15b made it desirable to develop a synthetic scheme that would give a better yield of not only that compound but also some intermediate, which would allow a systematic investigation of the effect of substitution on nitrogen on the pharmacology. Following various attempts to modify the aminonitrile displacement, we were led to modify the scheme based on the Curtius rearrangement described in our earlier reports (Scheme II).

In brief, cyano ketone 16 is demethylated (BBr_3) and the phenol protected as the benzyl ether (19). The product is then taken on to acid 20 by the set of transformations described earlier; modified Curtius rearrangement (21),

(4) C. R. Hauser and D. Lednicer, J. Org. Chem., 24, 46 (1954).
(5) D. Lednicer and J. C. Babcock, J. Org. Chem., 27, 2541 (1962).
(6) D. Lednicer and P. F. VonVoigtlander, J. Med. Chem., 22, 1157 (1979).

Table I. Analgesic, Sedative, and Narcotic Antagonist Activities



compd	X	R	ED_{50},[a] mg/kg[b] flick	pinch	screen	writh	antag
5	OCH_2CH_2O	CH_3	>100	>100	>100	2.8	13
10a	$OCH_2CH_2CH_2O$	CH_3	>100	>100	>100	40	32
10b	$OCH_2C(CH_3)_2CH_2O$	CH_3	>100	>100	>100	>100	>100
10c	$OCH_2CH(CHCH{=}CH_2)CH_2O$	CH_3	>100	>100	>100	>100	>100
10d	$OCH_2CH(C_6H_5)CH_2O$	CH_3	>100	>100	>100	>100	>100
11	O	CH_3	45	45	>200	18	40
12	OH, H (trans)	CH_3	>100	>100	>100	>100	18
13a	OH, CH_3 (trans)	CH_3	>200	>200	>200	50	>100
13b	OH, CH_3 (cis)	CH_3	>100	>100	>100	40	>100
13c	OH, $CH_2C_6H_5$ (trans)	CH_3	0.18	0.18	71	0.16	>100
13d	OH, $CH_2C_6H_5$ (cis)	CH_3	>100	>100	>100	71	>100
13e	OH, $CH_2CH_2C_6H_5$ (trans)	CH_3	0.005	0.006	0.8	0.005	>100
13f	OH, $CH_2CH_2C_6H_5$ (cis)	CH_3	>100	>100	>100	63	>100
13g	OH, $CH_2CH_2(p\text{-}ClC_6H_5)$ (trans)	CH_3	10	10	>100	4.0	>100
13h	OH, $CH_2CH_2(p\text{-}ClC_6H_5)$ (cis)	CH_3	>100	>100	>100	>100	>100
15a	OCH_2CH_2O	$CH_2CH{=}CH_2$	>200	>200	>200	>200	141
15b	OCH_2CH_2O	$(CH_2)_3CH_3$	4.0	4.0	>100	7.0	>100
24a	OCH_2CH_2O	$(CH_2)_2CH_3$	>100	>100	>100	>100	79
24b	OCH_2CH_2O	$CH_2CH(CH_3)_2$	>25	>25	>25	>25	>25
24c	OCH_2CH_2O	CH_2-c-C_3H_5	>100	>100	>100	>100	>100
24d	OCH_2CH_2O	$(CH_2)_4CH_3$	3	3	>25	2	>25
24e	OCH_2CH_2O	$CH_2CH_2OC_6H_5$	>100	>100	>100	>100	>100
morphine sulfate			1.5	1.6	>100	0.6	>100
naloxone hydrochloride			>100	>100	>100	>100	1.5
pentazocine lactate			7	6	>50	4	>50

[a] See Experimental section and footnote *b* for description of methods. [b] The upper and lower 95% confidence intervals[7] were not more than 2 and 0.5 times the ED_{50}, respectively.

followed by reduction, gives the key intermediate **22**. Acylation of the secondary amine readily gave the noncrystalline amide **23a** under standard conditions; reduction ($LiAlH_4$) gave the oily amines. Finally, hydrogenolysis of **23b** led to the desired aminophenols. This sequence with butyryl chloride gave a sample of **15b** identical in all respects with that prepared by the α-aminonitrile displacement reaction.

Results

The analgesic (tail flick, tail pinch, and HCl writhing), sedative (inclined screen), and morphine antagonist activities of these *m*-hydroxy compounds are summarized in Table I. In contrast to the previously reported 4-aryl-4-aminocyclohexanone derivatives,[2,3] some of the *m*-hydroxy analogues display significant narcotic antagonist activity. In this regard, the ethylene ketal compound is the most potent antagonist. The more complex ketals and the ketone analogue are less potent or inactive at the highest doses treated. The active antagonists also have some limited activity on some of the analgesic tests (most consistently on HCl writhing). This suggests that they are not pure narcotic antagonists but rather are analgesics of the narcotic antagonist type. A different spectrum of activity emerges with the geminally substituted alcohols. Lengthening this substitution and adding an aromatic ring system to it in the trans configuration greatly enhances agonist (analgesic) activity at the expense of narcotic antagonist activity. This enhanced analgesic potency is analogous to that previously reported with analogues lacking the *m*-hydroxy function.[3]

Endogenous opioids, as well as a large number of synthetic analgesics, possess a phenolic hydroxyl group. It is of note that high-potency compounds in the series at hand do not require this function.[3] Rather, inclusion of a *m*-hydroxy seems to be a minimum requirement for derivatives in this new series which present narcotic antagonist activity.

The role of allylic or pseudoallylic substitution on nitrogen in several series of narcotic antagonists is well known. However, these groups (allyl, cyclopropylmethyl) actually *decrease* antagonist potency in the present series. Thus, within the ethylene ketal series antagonism reaches a maximum with methyl (**5**); lengthening the chain (**24a,b**) decreases this activity. That this is due to some factor other than lipophilicity can be deduced by comparison of a straight-chain compound (**15b**) with the closely related branched analogue (**24b**); this seemingly small change leads to loss of analgesic activity.

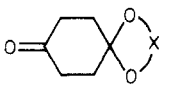
A recent report[7] summarized the analgesic, narcotic antagonist, and in vitro [^{3}H]naloxone binding activity of selected members of the 4-aryl-4-aminocyclohexanone series. The ability of these compounds to compete for [^{3}H]naloxone binding sites further substantiates the opioid nature of their analgesic properties. In addition, these studies demonstrated a minimal effect of Na^+ upon the binding affinity of the *m*-hydroxyphenyl derivatives. This latter observation is consistent with the present report of narcotic antagonist activity with these same analogues.

Experimental Section

Melting points are uncorrected and are reported as observed on a Thomas-Hoover capillary melting point apparatus. NMR spectra were obtained in $CDCl_3$ on a Varian A60D or T60 spec-

(7) P. F. VonVoigtlander, D. Lednicer, R. A. Lewis, and D. D. Gay, "Endogenous and Exogenous Opiate Agonists and Antagonists", E. L. Way, Ed., Pergamon, New York, 1980.

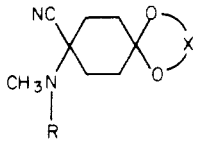
Table II. Cyclohexane-1,4-dione Ketals



X	recrystn solv	mp, °C	yield, %	formula	anal.
$CH_2CH_2CH_2$	PE	47-49	66[a]	$C_9H_{14}O_3$	C, H
$CH_2C[(CH_3)_2]CH_2$	PE	46-48.5	81	$C_{11}H_{18}O_3$	C, H
$CH_2CH(CH_2CH=CH_2)CH_2$		b	90[a]	$C_{12}H_{18}O_3$	
$CH_2CH(C_6H_5)CHCH_2$	EtOAc	133-135	88	$C_{15}H_{18}O_3$	C, H

[a] Based on hydroxycyclohexanone. [b] Material melts below room temperature.

Table III. 1-(*N*,*N*-Dialkylamino)-1-cyano-4-(dioxaspiroalkane)cyclohexanes



no.	X	R	recrystn solv	yield, %	mp, °C	formula	anal.
3	CH_2CH_2	CH_3	SSB[a]	78	79-81	$C_{11}H_{18}N_2O_2$	C, H, N
14a	CH_2CH_2	$CH_2CH=CH_3$	petr ether	90	47-50	$C_{13}H_{20}N_2O_2$	C, H, N
14b	CH_2CH_2	$(CH_2)_3CH_3$	CH_2Cl_2-EtOAc[b]	66	114-120	$C_{14}H_{25}ClN_2O_2 \cdot 1.5H_2O$	C, H, N
9c	$CH_2CH(CH_2CH=CH_2)CH_2$	CH_3	petr ether	63	71-75	$C_{15}H_{24}N_2O_2$	C, H, N
9b	$CH_2C[(CH_3)_2]CH_2$	CH_3	SSB	87	89-93	$C_{14}H_{24}N_2O_2$	C, H, N
9a	$CH_2CH_2CH_2$	CH_3	SSB	92	92-94.5	$C_{12}H_{20}N_2O_2$	C, H, N
9d	$CH_2CH(C_6H_5)CH_2$	CH_3	CH_2Cl_2-SSB	84	140-142.5	$C_{18}H_{24}N_2O_2$	C, H, N

[a] Skellysolve B. [b] Purified and characterized as the HCl salt.

trometer. Mass spectra were determined on an Atlas MAT CH4 instrument. The authors are indebted to the Department of Physical and Analytical Chemistry Research at The Upjohn Co. for elemental analyses. Where symbols for the elements occur, these indicate that analytical results for those elements were within 0.4% of theory.

4-Hydroxycyclohexan-1-one Ketals (7). In a typical experiment, a mixture of 0.042 mol of 4-hydroxycyclohexanone, 0.04 mol of the appropriate glycol, and 0.20 g of *p*-toluenesulfonic acid in 100 mL of benzene was heated at reflux under a Dean–Stark trap until collection of water ceased (4.6 h). The mixture was then allowed to cool, washed with saturated aqueous sodium bicarbonate, and taken to dryness. The product, if crystalline, was recrystallized. Those acetals which failed to crystallize were used in the next step without further purification. **7b** (R = $CH_2C(CH_3)_2CH_2$): mp 84–86 °C (Skellysolve B, SSB); 90% yield. Anal. ($C_{11}H_{20}O_3$) C, H. **7d** [R = $CH_2CH(C_6H_5)CH_2$]: mp 109–115 °C (Et_2O); 54% yield. Anal. ($C_{15}H_{20}O_3$) C, H.

Cyclohexane-1,4-dione Ketals (8; Table II). To a well-stirred suspension of 14.7 g of rigorously dried CrO_3 in 250 mL of dry CH_2Cl_2 there was added 14.2 g of 3,5-dimethylpyrazole. A solution of 0.023 mol of the hydroxy ketal in 60 mL of dry CH_2Cl_2 was then added to the dark solution at a rate so as not to exceed gentle reflux. Following an additional 10 min of stirring, the total reaction mixture was poured onto a column of 350 mL of silica gel in CH_2Cl_2. When all the reaction mixture had percolated onto the silica, the column was eluted with 50% EtOAc in SSB. The crystalline fractions were then combined and recrystallized.

1-(*N*,*N*-Dialkylamino)-1-cyano-4-(dioxaspiroalkane)-cyclohexanes (Table III). A. Dimethylamino Analogues. Dimethylamine was passed into a mixture of 25 mL of H_2O and 3 mL of MeOH until no further gas was absorbed. There was then added, in turn, 3.0 g of KCN, 450 g of dimethylamine hydrochloride, and 0.019 mol of the appropriate ketone ketal. Following 48 h of stirring at room temperature, the mixture was extracted with $CHCl_3$. The organic layer was taken to dryness and the residue recrystallized.

B. Higher Dialkylamines. To a solution of 0.07 mol of the dialkylamine and 3 mL of MeOH in 20 mL of 2.5 N hydrochloric acid there was added 3.0 g of KCN and 3 g of the ketone ketal. The reaction was then run and worked up as above.

4-Phenyl-4-(dimethylamino)cyclohexanone Ethylene Ketal Hydrochloride (4). To a solution of 10 mL of 3 M C_6H_5MgBr in C_6H_6 in 20 mL of THF there was added 0.91 g of aminonitrile **3** in 20 mL of THF. Following 18 h of standing at room temperature, the mixture was cooled in ice and treated with 20 mL of saturated aqueous NH_4Cl and C_6H_6. The organic layer was separated, washed with H_2O and brine, and taken to dryness. The residue was chromatographed on 100 mL of silica gel (elution with 0.25% NH_4OH, 5% MeOH in CH_2Cl_2). There was obtained 0.25 g of the amine, whose NMR is identical with that of material prepared earlier by the alternate route. The product was converted to the HCl salt, and this recrystallized from CH_2Cl_2–EtOAc to give 0.70 g (10%) of crystals: mp 237–239 °C; mmp authentic material 240–242 °C.

Table IV. 4-(*m*-Hydroxyphenyl)-4-(dialkylamino)-cyclohexanone Ketals

no.	recrystn solv	mp, °C	yield, %	formula	anal.
5	EtOAc-C_6H_{12}	175-177	17	$C_{16}H_{23}NO_3$	C, H, N
15a	MeOH-H_2O	88-90	13	$C_{18}H_{25}NO_3 \cdot {}^2/_3H_2O$	C, H, N
15b	CH_2Cl_2-Me_2CO	205-207	4.4	$C_{19}H_{30}ClNO_3$	C, H, N
10a	EtOAc-C_6H_{12}	147-150	8.3	$C_{17}H_{25}NO_3$	C, H, N
10b	EtOAc	208-209.5	31	$C_{19}H_{29}NO_3$	H, N; C[b]
10c	Et_2O	153-154.5	30	$C_{20}H_{29}NO_3$	C, H, N
10d	EtOAc	147-149	19	$C_{23}H_{29}NO_3$	C, H, N

[a] Characterized as the HCl salt. [b] C: calcd, 71.44; found, 70.76.

4-(*m*-Hydroxyphenyl)-4-(dialkylamino)cyclohexanone Ketals 10 and 15 (Table IV). A solution of 9.50 g (0.055 mol) of *m*-bromophenol, 9.50 g of dihydropyran, and 0.46 g of *p*-toluenesulfonic acid in 100 mL of Et_2O was allowed to stand at room temperature for 4 h. About 20 mL of benzene was then added. The solution was washed with 25 mL each of 1 N NaOH, water, and brine and taken to dryness.

The Grignard reagent was then prepared from the THP ether obtained above and 1.33 g of magnesium in 110 mL of THF. A solution of 0.15 mol of the appropriate α-aminonitrile in 50 mL of THF was then added to the organometallic reagent. Following 24 h of heating at reflux, the mixture was cooled in ice and treated with 25 mL of saturated aqueous NH_4Cl and a small amount of

Table V. 1-Alkyl-4-(*m*-hydroxyphenyl)-4-(dimethylamino)cyclohexan-1-ols

no.	isomer	chromat solv[c]	recrystn solv	mp, °C	yield, %	formula	anal.
13a	t[a]	20[d]	MeOH-EtOAc	220-222	21	$C_{15}H_{23}NO_2 \cdot {}^1/_3H_2O$	H, N; C[e]
13b	c[b]	20[d]	Me_2CO-SSB	187-188	18	$C_{15}H_{23}NO_2 \cdot {}^1/_3H_2O$	C, H, N
13e	t	5[f]	MeOH-EtOAc	197-198.5	19	$C_{22}H_{29}NO_2 \cdot {}^1/_3H_2O$	C, H, N
13f	c	20[d]	MeOH-EtOAc	221-223	31	$C_{22}H_{29}NO_2$	C, H, N
13c	t	5[f]	Me_2CO-SSB	206-207	23	$C_{21}H_{27}NO_2$	C, H, N
13d	c	20[g]	MeOH-EtOAc	158-160[h]	23	$C_{21}H_{28}ClNO_2 \cdot H_2O$	C, H, N
13g	t	7.5[d]	MeOH-EtOAc	209-210	17	$C_{22}H_{28}ClNO_2$	H, N; C[i]
13h	c	10[g]	MeOH-EtOAc	127-130	28	$C_{22}H_{28}ClNO_2 \cdot H_2O$	C, H, N

[a] Amine and hydroxyl trans. [b] Amine and hydroxyl cis. [c] Percent MeOH in CH_2Cl_2. [d] Solvent contains 2% NH_4OH. [e] C: calcd, 70.55; found, 70.93. MS, *m/e* 249. [f] Solvent contains 0.5% NH_4OH. [g] Solvent contains 1% NH_4OH. [h] Hydrochloride salt. [i] C: calcd, 70.70; found, 70.24.

benzene. The organic layer was separated, washed with water and benzene, and taken to dryness. The residual gum was dissolved in ether and treated with just sufficient 1.5 N ethereal HCl to precipitate the basic materials. The precipitate was dissolved in 40 mL of H_2O; after 5 min the solution was brought to pH 8 with solid $NaHCO_3$. The reaction mixture was then extracted thoroughly with $CHCl_3$, and the extracts were combined and taken to dryness. The residual gum was chromatographed on silica gel (elution with 0.5% NH_4OH, 7.5% MeOH in CH_2Cl_2).

4-(Dimethylamino)-4-(*m*-hydroxyphenyl)cyclohexan-1-one (11). A solution of 1.92 g (7 mmol) of the ketal 5 in 30 mL of MeOH and 15 mL of 2.5 N HCl was allowed to stand at room temperature for 48 h. The bulk of the solvent was removed under vacuum, and the residue was brought to pH 8 with solid $NaHCO_3$. The mixture was extracted thoroughly with $CHCl_3$, and the extracts were taken to dryness. The residue was recrystallized from Me_2CO–SSB to give 0.48 g of ketone: mp 127–130 °C; mass spectrum, *m/e* (relative intensity) 233 (M^+). Anal. $C_{14}H_{19}NO_2$; C, H, N.

4-(Dimethylamino)-4-(*m*-hydroxyphenyl)cyclohexan-1-ol (12). To a solution of 1.38 g (6 mmol) of the amino ketone in 20 mL of 95% ethanol there was added 0.50 g of $NaBH_4$. Following 6 h of stirring at room temperature, the bulk of the solvent was removed under vacuum. The residue was suspended in water and the mixture brought to pH 8 with CO_2. This mixture was then extracted thoroughly with $CHCl_3$. The residue which remained when the extracts were taken to dryness was recrystallized from MeOH–EtOAc. There was obtained 0.70 g (50%) of product, mp 205–207 °C. Anal. ($C_{14}H_{21}NO_2$) H, N; C: calcd, 71.45; found, 70.95.

4-(*m*-Hydroxyphenyl)-4-(dimethylamino)-1-alkylcyclohexan-1-ols (13; Table V). In a typical experiment, the Grignard reagent was prepared from 60 mmol of the appropriate halide in 100 mL of THF. To this there was added at room temperature 1.37 g (6 mmol) of ketone 11 in 20 mL of THF. Following 3 days of standing at room temperature, the mixture was treated with 25 mL of saturated aqueous NH_4Cl and C_6H_6. The organic layer was separated, washed with H_2O and brine, and taken to dryness. The residue was then chromatographed on silica gel. The appropriate fractions were combined and recrystallized.

4-Cyano-4-(*m*-hydroxyphenyl)cyclohexanone (17). To an ice-cooled solution of 2.26 g (0.01 mol) of 4-cyano-4-(*m*-methoxyphenyl)cyclohexanone in 40 mL of CH_2Cl_2 there was added all at once 2.92 mL (7.69 g, 0.03 mol) of BBr_3. At the end of a 4-h stirring the mixture was treated cautiously with 30 mL of H_2O. The mixture was then diluted with $CHCl_3$. The organic layer was separated, washed with H_2O and saturated $NaHCO_3$, and taken to dryness. There was obtained 2.0 g (93%) of the phenol, mp 125–126 °C. The analytical sample (Me_2CO–SSB) melted at 129–130.5 °C. Anal. ($C_{13}H_{13}NO_2$) C, H, Cl.

4-Cyano-4-(*m*-hydroxyphenyl)cyclohexanone Ethylene Ketal (18). A mixture of 8.80 g (0.041 mol) of the ketone, 2.5 mL of ethylene glycol, and 0.26 g of *p*-TSA in 170 mL of C_6H_6 was heated at reflux under a Dean–Stark trap for 4 h. The mixture was allowed to cool, washed successively with saturated $NaHCO_3$ and brine, and taken to dryness. The residual solid was recrystallized from CH_2Cl_2–SSB to give 9.85 g (93%) of product, mp 109–110.5 °C. Anal. ($C_{15}H_{17}NO_3$) C, H, N.

4-Cyano-4-[*m*-(benzyloxy)phenyl]cyclohexanone Ethylene Ketal (19). Sodium hydride (1.84 g of 50% dispersion in mineral oil) was added to a solution of 9.85 g (0.038 mol) of the phenol in 40 mL of DMF and 80 mL of C_6H_5. Following 15 min of stirring at room temperature and 1 h at reflux, there was added 6.35 g of α-bromotoluene. The mixture was then stirred at reflux for an additional 4 h, allowed to cool, and washed thoroughly with H_2O followed by brine. The solid which remained when the organic layer was taken to dryness was recrystallized from Et_2O–petroleum ether to give 11.70 g (88%) of product, mp 67–69 °C. Anal. ($C_{22}H_{23}NO_3$) C, H, N.

1-[*m*-(Benzyloxy)phenyl]-4-oxocyclohexane-1-carboxylic Acid Ethylene Ketal (20). A mixture of 7.0 g (0.02 mol) of the nitrile and 1.20 g of NaOH in 50 mL of ethylene glycol was heated at reflux for 18 h. The solution was allowed to cool, poured into ice–H_2O, and covered with Et_2O. The mixture was cautiously acidified with constant swirling by means of 5 mL of concentrated HCl. The organic layer was separated, washed with brine, and taken to dryness. There was obtained 7.22 g (98%) of acid, mp 108–110.5 °C, sufficiently pure for use in the subsequent step. The analytical sample (Et_2O) melted at 118.5–120.5 °C. Anal. ($C_{22}H_{24}O_5$) C, H.

4-[*m*-(Benzyloxy)phenyl]-4-isocyanatocyclohexan-1-one Ethylene Ketal (21). A solution of 18.32 g (0.050 mol) of the acid, 7.4 mL (5.4 g, 0.053 mol) of Et_3N, and 14.02 g (0.051 mol) of $(C_6H_5O)_2PON_3$ in 135 mL of anisole was heated in an oil bath at 90 °C for 1 h. The solvent was then removed under vacuum. The oily residue was placed on a chromatographic column containing 710 mL of silica gel. The column was eluted as quickly as practicable with 2% EtOAc in CH_2Cl_2. Those fractions shown by TLC to contain product were combined and taken to dryness to give 15.0 g (82%) of the isocyanate, as a waxy solid. Material from one run was recrystallized several times from Et_2O–petroleum ether to afford a sample, mp 49.5–53 °C. Anal. ($C_{22}H_{23}NO_4$) C, H, N.

4-[*m*-(Benzyloxy)phenyl]-4-(methylamino)cyclohexan-1-one Ethylene Ketal (22). To a well-stirred suspension of 2.32 g (0.061 mol) of $LiAlH_4$ in 30 mL of THF there was added 14.76 g (0.040 mol) of the isocyanate in 240 mL of THF. The mixture was stirred at room temperature for 30 min, at reflux for 5 h, and then cooled in an ice bath. There was added, in turn, 2.3 mL of H_2O, 2.3 mL of 15% NaOH, and 6.9 mL of H_2O. The precipitated inorganic gel was collected on a filter, and the filtrate was taken to dryness. The residual solid was recrystallized from Et_2O–petroleum ether to yield 10.09 g (71%) of amine, mp 63.5–66.5 °C. The analytical sample from an earlier run melted at 64–66 °C. Anal. ($C_{22}H_{27}NO_3$) C, H, N.

4-(*N*-Alkyl-*N*-methylamino)-4-(*m*-hydroxyphenyl)cyclohexan-1-one Ethylene Ketals (24; Table VI). In a typical experiment, an ice-cooled solution of 1.77 g (5 mmol) of the amine and 0.7 mL of Et_3N in 15 mL of THF was treated with 1.1 equiv of the appropriate acid chloride in 10 mL of THF. Following 7 h of standing in the cold, the bulk of the solvent was removed under vacuum. The residue was partitioned between H_2O and Et_2O. The organic layer was washed with H_2O, $NaHCO_3$, and brine and taken to dryness.

A solution of the crude amide in 30 mL of THF was added to 0.27 g of $LiAlH_4$ in 10 mL of THF. Following 7 h of heating at reflux, the mixture was cooled in ice and treated, in turn, with 0.23 mL of H_2O, 0.25 mL of 15% NaOH, and 0.69 mL of H_2O. The inorganic gel was collected on a filter, and the filtrate was taken to dryness.

A mixture of the product obtained above, 2.5 mL of 2 N HCl in Et_2O, and 1.0 g of 10% Pd/C in 150 mL of EtOAc was shaken

Table VI. 4-(*N*-Alkyl-*N*-methylamino)-4-(*m*-hydroxyphenyl)cyclohexan-1-one Ethylene Ketals

no.	chromat solv	mp, °C	yield, %	recrystn solv	formula
24d	MeOH-CH_2Cl_2(7.5:1)	*b*	72		$C_{20}H_{32}ClNO_3 \cdot 0.5H_2O$
24b	MeOH-$CHCl_3$[a](7.5:1)	203-204	31	$CHCl_3$-CH_3CN	$C_{19}H_{30}ClNO_3$
24e	MeOH-$CHCl_3$[a](3.5:1)	*b*,*c*	10		$C_{23}H_{30}ClNO_3$
24c	MeOH:$CHCl_3$[b](5:1)	214-215	50	CH_2Cl_2-CH_3CN	$C_{19}H_{28}ClNO_3$
24a		204-207	49	$CHCl_3$-EtOAc	$C_{18}H_{28}ClNO_3$

[a] Chromatographed on high-performance LC column. [b] Amorphous. [c] No satisfactory analysis could be obtained: M_r calcd 367; MS, *m/e* 367 (M^+).

under H_2 for 24 h. The catalyst was then collected on a filter and washed exhaustively with $CHCl_3$. The filtrate was taken to dryness. If crystalline, the residue was recrystallized. Alternately this was converted to the free base and chromatographed. The appropriate fractions were then combined, reconverted to the HCl salt, and recrystallized.

4-(*N*-Butyl-*N*-methylamino)-4-(*m*-hydroxyphenyl)cyclohexan-1-one Ethylene Ketal (15b). Using the above three-step procedure and $CH_3(CH_2)_2COCl$ as the acid chloride, there was obtained **15b** (51%), mp 209–211 °C, identical in all respects (IR, NMR, and TLC) with a sample prepared by the aminonitrile method. Anal. ($C_{19}H_{30}ClNO_3$) C, H, N.

Biology. Methods. The biological testing consisted of a battery of standard assays.[6] Briefly, CF-1 female mice were dosed subcutaneously with a suspension (or solution) of the test compound in 0.25% aqueous methylcellulose and 15 min later subjected to a series of procedures to detect analgesia, sedation, and narcotic antagonism. The tail-flick, tail-pinch and HCl writhing procedures were used to detect analgesia, whereas the inclined screen test was used to measure sedation. After the completion of the tests (about 45 min postinjection), 6.3 mg/kg morphine sulfate was given subcutaneously and 15 min later the mice were retested on the tail-flick procedure to determine if the compound might have narcotic antagonist properties. Blockade of morphine-induced elevation of tail-flick latency was scored as antagonism. Six mice were tested at each dose in this battery of assays. When multiple doses were examined, the ED_{50} values were calculated by the method of Spearman and Karber.[8]

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Notes

Cognition-Activating Properties of 3-(Aryloxy)pyridines

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A series of 3-(aryloxy)pyridines was found to possess activity in enhancing retention for passive avoidance learning in mice. This test was used to select compounds with potential therapeutic properties for the treatment of cognitive disorders. Reference drugs that gave positive results in this procedure included *d*-amphetamine, magnesium pemoline, methyl phenidate, picrotoxin, phenytoin, and ethosuximide. All active compounds gave inverted U-shaped dose–response curves. The most active compounds of the 3-(aryloxy)pyridines included 3-phenoxypyridine (**1**), 3-(2-fluorophenoxy)pyridine (**2**), 3-(4-fluorophenoxy)pyridine (**4**), 3,3′-oxybis(pyridine) (**23**), and 3,3′-oxybis(pyridine) 1-oxide (**24**). 3-Phenoxypyridine (**1**) was clearly superior to all of the analogues tested in terms of the level of retention, grammometric potency, and the breadth of its inverted U-shaped dose–response curve. It was given the designation of CI-844 and after a detailed study of its pharmacological profile was submitted for preclinical toxicology.

Cognitive dysfunctions occur in persons of all ages as a result of many conditions including diseases, accidents and injuries, developmental defects, and normal aging. An agent that would act favorably on learning/memory mechanisms would have vast sociopolitical, cultural, and economic implications.[1]

One major area where such an agent would be most beneficial is the treatment of the estimated 5–10% of school-age children who suffer from some type of learning disability such as minimal brain dysfunction (or attentional deficit disorder).[2,3] A second important area of application for a cognition-enhancing drug is at the other end of the developmental continuum: the cognitive disorders and intellectual impairments that regularly occur in the elderly. This area is partly the result of the remarkable progress that has been made in health care in the 20th century, resulting in the large increase in the number of people who live to old age. Age-related cognitive impairments are found both in normal senescence and in patients with senile organic brain syndrome.[4,5]

Treatments for learning disabilities in the young have mainly employed amphetamine-like stimulants to produce a calming effect and increase attention.[6-8] Drugs which

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