suspension of 6 g (0.15 mole) of commercial $NaNH_2$. The mixture was refluxed for 7 hr and allowed to cool overnight. After addition of water, the organic layer was separated and extracted with dilute HCl. The acid solution was made basic with NH_4OH and extracted with $CHCl_3$. After removal of the chloroform, the residue soon crystallized. The product was recrystallized from ethyl acetate; mp 90–91°.

Anal. Calcd for $C_{22}H_{25}ClN_2S$: C, 68.12; H, 6.55. Found: C, 67.87; H, 6.31.

N-Cyanomethylisoquinuclidine (Xa).—A mixture of 16.6 g (0.15 mole) of isoquinuclidine, 11.3 g (0.15 mole) of chloroacetonitrile, 41.4 g of anhydrous K_2CO_3, and 500 ml of toluene was refluxed with stirring for 20 hr. The inorganic salt was filtered off, and the filtrate was extracted with dilute HCl. The acid extracts were neutralized with NH_4OH and extracted ($CHCl_3$). The product was distilled; yield 12 g (53%), bp 90–92° (2 mm), $n^{24}D$ 1.4955.

Anal. Calcd for $C_9H_{14}N_2$: C, 71.95; H, 9.39; N, 18.65. Found: C, 72.20; H, 9.52; N, 18.83.

N-(2-Cyanoethyl)isoquinuclidine (Xb).—From 20 g (0.18 mole) of isoquinuclidine, 22.5 g (0.15 mole) of 3-bromopropionitrile, and 41.4 g of K_2CO_3 in 500 ml of toluene, by the above procedure, was obtained 21.5 g (87.5%) of product having bp 95–105° (1 mm), $n^{25}D$ 1.4953.

Anal. Calcd for $C_{10}H_{16}N_2$: C, 73.12; H, 9.82. Found: C, 72.97; H, 9.69.

The **hydrochloride** after recrystallization from ethanol–ether had mp 240–242° dec.

Anal. Calcd for $C_{10}H_{16}N_2 \cdot HCl$: C, 59.84; H, 8.54; N, 13.96. Found: C, 59.77; H, 8.32; N, 14.00.

N-(2-Aminoethyl)isoquinuclidine (XIa).—A solution of 10 g (0.067 mole) of Xa in 50 ml of anhydrous ether was added dropwise with stirring to a refluxing solution of 3 g of $LiAlH_4$ in 600 ml of ether. The mixture was stirred under reflux for 20 hr. After the usual decomposition, the product was isolated as a colorless oil; yield 85 g (82%), bp 90–92° (6 mm), $n^{24}D$ 1.5005.

Anal. Calcd for $C_9H_{18}N_2$: C, 70.07; H, 11.76. Found: C, 70.55; H, 11.88.

The **dihydrochloride** had mp 201–203°.

Anal. Calcd for $C_9H_{18}N_2 \cdot 2HCl$: C, 47.58; H, 8.87. Found: C, 48.09; H, 8.85.

N-(3-Aminopropyl)isoquinuclidine (XIb).—From 20 g of Xb and 6 g of $LiAlH_4$ in ether was obtained 15.5 g (77%) of an oil, bp 86–90° (1 mm), $n^{25}D$ 1.4980.

Anal. Calcd for $C_{10}H_{20}N_2$: C, 71.37; H, 11.98. Found: C, 71.71; H, 12.06.

N-(2-Guanidinoethyl)isoquinuclidine Sulfate (IXa).—A mixture of 7.5 g (0.049 mole) of XIIa and 12.2 g of S-methylisothiourea sulfate in 50 ml of ethanol was heated under reflux with stirring for 6 hr. The white solid was filtered and washed with cold ethanol. The product (9 g, 63%) was purified by dissolving it in water and adding ethanol until turbid; mp 300–303°, lit.[6] mp 310–315°.

Anal. Calcd for $C_{10}H_{20}N_4 \cdot H_2SO_4$: C, 40.80; H, 7.53; N, 19.03. Found: C, 40.30; H, 7.62; N, 19.13.

N-(3-Guanidinopropyl)isoquinuclidine Sulfate (IXb).—By a similar procedure this compound was obtained in 52% yield, mp 310–312°.

Anal. Calcd for $C_{11}H_{22}N_4 \cdot H_2SO_4$: C, 42.84; H, 7.84; N, 18.17. Found: C, 42.52; H, 8.27; N, 18.37.

Analgetic Activity of Some δ-Amino Ketones And Their Derivatives

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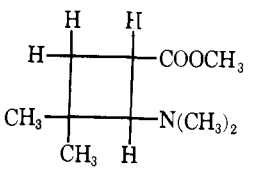
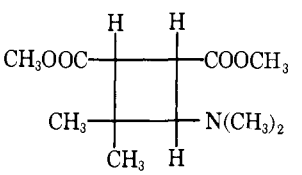
The β-aminocyclobutane, methyl 2-dimethylamino-3,3-dimethylcyclobutanecarboxylate (I), exhibits aspirin-like analgetic activity. Treatment of I with Grignard reagents offers a convenient route to substituted δ-amino ketones. Some of these δ-amino ketones have proved to be more potent analgetics than the parent cyclobutane, I. The completely aliphatic compound, 1,5-dicyclohexyl-2,2-dimethyl-1-dimethylamino-5-pentanone citrate (**10**), is presumed to be a morphine-like analgetic because of its antagonism by nalorphine hydrochloride. Manipulation of the carbonyl group of 1,5-diphenyl-2,2-dimethyl-1-dimethylamino-5-pentanone (1) by reduction or addition has indicated that the degree of analgesia is diminished.

A series of substituted β-aminocyclobutanes, which were received from Tennessee Eastman Co., displayed some analgetic activity in our pharmacological screening program. Both methyl 2-dimethylamino-3,3-dimethylcyclobutanecarboxylate (I)[1] and dimethyl 3,3-dimethyl-4-dimethylaminocyclobutane-1,2-dicarboxylate (II) showed slight analgetic activity as determined by the tail-flick method in the rat.[2] Compound I appears to be nonnarcotic since it is not antagonized by nalorphine hydrochloride. This is the first instance of analgetic activity reported for structures containing a nonaromatic cyclobutane ring.[3] Clinical studies indicate that the degree of analgesia produced by the citrate salt of I is equivalent to that of aspirin. This salt also elicits side effects similar to aspirin.



I



II

Accordingly, we decided to make modifications of I with the hope of improving its analgetic potency. While attempting to convert the ester portion of I into a tertiary alcohol with phenylmagnesium bromide, an unexpected ring-cleavage reaction occurred. The chemistry of this ring opening of I with Grignard reagents has recently been reported.[4] Cleavage of the cyclobutane ring results in the formation of two types of δ-amino ketones. The amount of each type of product depends on the nature of the Grignard reagent. (see Scheme I).

Some of the δ-amino ketones have shown greater analgetic activity than their parent ring compound, I. One of the most interesting observations of this study is that the analgetic activity of a wholly ali-

(1) K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelly, *J. Org. Chem.*, **26**, 625 (1961).

(2) F. E. D'Amour and D. L. Smith, *J. Pharmacol. Exptl. Therap.*, **72**, 74 (1948).

(3) 1-Aminomethylbenzocyclobutene is reported to have a potency equivalent to morphine with a more rapid onset of action and much shorter duration: J. A. Skorcz and J. E. Robertson, *J. Med. Chem.*, **8**, 255 (1965).

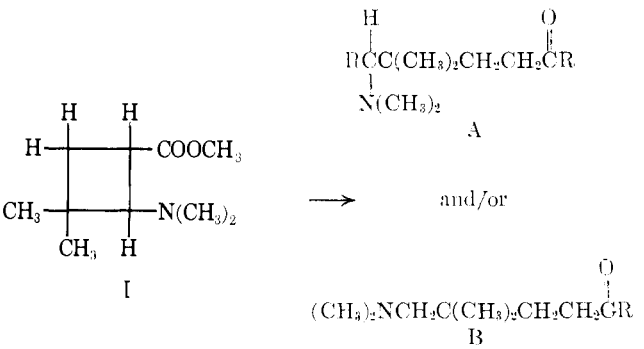
(4) L. Weintraub, A. Wilson, D. L. Goldhamer, and D. P. Hollis, *J. Am. Chem. Soc.*, **86**, 4880 (1964).

TABLE I

No.	B	R′	Mp or bp (mm), °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
				$RCHC(CH_3)_2CH_2CH_2CR'$ (O; $N(CH_3)_2$)						
1	C_6H_5	C_6H_5	42–44	$C_{21}H_{27}NO$	81.51	8.80	4.53	81.37	8.87	4.64
2	o-$CH_3C_6H_4$	o-$CH_3C_6H_4$	182–184 (0.5)	$C_{23}H_{31}NO$	81.85	9.26	4.15	81.79	9.43	4.30
3	m-$CH_3C_6H_4$	m-$CH_3C_6H_4$	178–180 (0.1)	$C_{23}H_{31}NO$	81.85	9.26	4.15	82.00	9.30	4.22
4	p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	197 (0.3)	$C_{23}H_{31}NO$	81.85	9.26	4.15	81.64	9.24	4.05
5	o-$CH_3OC_6H_4$	o-$CH_3OC_6H_4$	72–73	$C_{23}H_{31}NO_3$	74.76	8.46	3.79	75.09	8.72	3.91
6	p-$CH_3O C_6H_4$	p-$CH_3OC_6H_4$	65–67	$C_{23}H_{31}NO_3$	74.76	8.46	3.79	74.57	8.46	3.74
7	CH_3	CH_3	97 (5.0)	$C_{13}H_{25}NO$	71.30	12.51	7.56	71.12	12.39	7.57
8	C_2H_5	C_2H_5	67 (0.1)	$C_{15}H_{29}NO$	73.18	12.76	6.57	73.40	12.90	6.79
9	C_5H_9	C_5H_5	149 (0.1)	$C_{19}H_{35}NO$	77.75	12.02	4.77	77.68	11.93	4.83
10	C_6H_{11}	C_6H_{11} (citrate salt)	99–100	$C_{27}H_{47}NO_8$	63.13	9.22	2.73	62.79	8.97	3.03
11	3-$CH_3C_6H_{10}$	3-$CH_3C_6H_{10}$	172 (0.5)	$C_{23}H_{43}NO$	79.02	12.40	4.01	78.41	12.33	4.15
12	H	C_5H_9	82–84 (0.1)	$C_{14}H_{27}NO$	74.61	12.08	6.22	74.59	11.73	5.96
13	H	C_6H_{11} (maleate salt)	116–117	$C_{19}H_{33}NO_5$	64.20	9.36	3.94	63.91	9.41	4.01
14	H	3-$CH_3C_6H_{10}$	116–120 (0.5)	$C_{16}H_{31}NO$	75.83	12.33	5.53	75.25	11.93	5.38
15	H	C_6H_5	107–108 (0.05)	$C_{15}H_{23}NO$	77.20	9.94	6.00	76.97	9.92	5.93
				$RCHC(CH_3)_2CH_2R'$ ($N(CH_3)_2$)						
16	C_6H_5	$(CH_2)_2C_6H_5$ (HCl salt)	118–119	$C_{21}H_{30}ClN$	75.99	9.11	4.22	75.57	8.80	4.18
17	C_6H_{11}	$(CH_2)_2C_6H_{11}$ (OH)	150–152 (0.2)	$C_{21}H_{41}N$	82.01	13.44	4.55	81.82	13.06	5.29
18	C_6H_5	$CH_2C(C_6H_5)_2$	231 (0.5)	$C_{27}H_{33}NO$	83.67	8.47	3.77	83.64	8.58	3.68

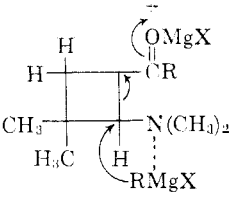
phatic compound, namely, 1,5-dicyclohexyl-2,2-dimethyl-1-dimethylamino-5-pentanone citrate (**10**) is antagonized by nalorphine hydrochloride and, therefore, appears to be a morphine-like analgetic.[5]

SCHEME I

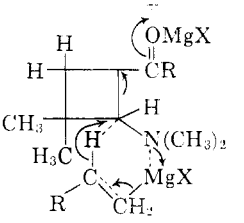


Chemistry.—Compounds **1** through **11** listed in Table I, were produced by the addition of 2 moles of Grignard reagent to I. The ring-opening mechanism of I is illustrated by transition state III. It combines nucleophilic attack of the Grignard reagent on the carbon bearing the amine group with assistance of electron withdrawal by the electrophilic halomagnesium–carbonyl complex to form product A.

Compounds **12–14** are formed by reductive cleavage of I as indicated by transition state IV. In this ring-opening reaction, hydride ion is the nucleophile which attacks the carbon bearing the amine group. This attack is similarly assisted through electron withdrawal by the electrophilic complex to form product B. These reduction products are formed concomitantly with the addition products of transition state III, when the Grignard reagent contains a β-hydrogen.[6]



III



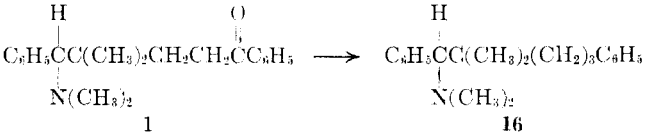
IV

Since reduction cannot take place with phenylmagnesium bromide, 5-phenyl-2,2-dimethyl-1-dimethylamino-5-pentanone (**15**) was synthesized through a different path. The synthesis of **15** was undertaken for the purpose of comparing its analgetic activity to that of **1**, which has a phenyl group replacing the hydrogen at the C-1 position.

$$C_6H_5MgBr + (CH_3)_2NCH_2C(CH_3)_2CH_2CH_2COOC_2H_5 \longrightarrow (CH_3)_2NCH_2C(CH_3)_2CH_2CH_2COC_6H_5$$

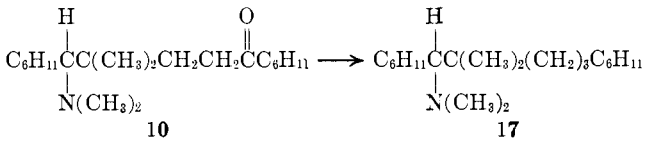
15

In order to ascertain whether the keto group is essential for inducing analgesia, **1** and **10** were reduced with hydrazine hydrate to give **16** and **17**, respectively.

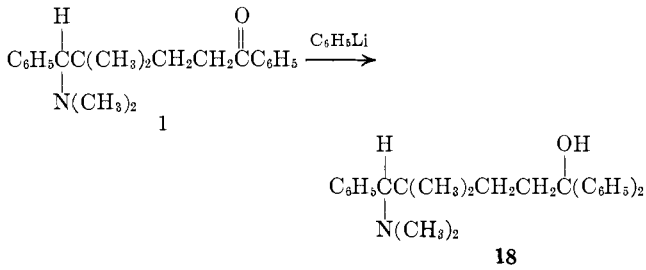


(5) A. Wilson and A. W. Pircio, *Nature*, **206**, 1151 (1965).

(6) The reaction appears to be sterically controlled. The greater the steric requirements of the Grignard reagent the greater is the formation of reduction product (type B), and therefore the competing reaction, giving addition product (type A), is diminished.



Even with excess phenylmagnesium bromide in ether or tetrahydrofuran there was no conversion of the ketone group of **1** to the tertiary alcohol. This transformation did take place when **1** was treated with the more powerful nucleophile, phenyllithium, to give 1,5,5-triphenyl-2,2-dimethyl-1-dimethylamino-5-pentanol (**18**).



Pharmacology.—Two methods were used to measure analgesia in animals. The first of these was the tail-flick method of D'Amour and Smith.[2] The intensity of the heat source was adjusted so that the average time for the untreated animal to flick its tail was about 4 sec. The pretreatment-response times of each animal were determined in duplicate, and again at 20-min intervals up to and including 60 min after the administration of the test material. An exposure time of 10 sec was never exceeded in order to prevent damage to tissue. Rats were used in groups of ten and the results are expressed in terms of the mean for the group. In routine screening for analgesia, activity was scored as the increase in response time above the control (in sec): ±, 0.5–0.9; +, 1.0–1.4; ++, 1.5–2.0; +++, greater than 2.0.

Compounds which showed interesting activity were studied more extensively. In these studies analgesia was expressed in terms of "minute-seconds" as described by Winter and Flataker.[7] This method of expressing analgetic potency utilizes both the intensity and duration of the analgesia.

The other method of determining analgetic activity was essentially that of Siegmund[8] as modified by Koster.[9] Mice were given the test material orally, 25 min prior to the injection of acetic acid. The total number of "writhing" responses commencing 5 min after the injection of the acetic acid were recorded for a 10-min period. The number of "writhing" responses were compared with those observed in control animals. The dose required to decrease the average number of writhing episodes by 50% was determined.

Nalorphine hydrochloride is known to antagonize a wide variety of known, clinically effective, potent analgetics of the narcotic type. The analgetic effectiveness of the test material was determined with and without nalorphine hydrochloride. Nalorphine hydrochloride was administered at the same time as the test material. The rat tail-flick method was employed and the drugs were administered intraperitoneally.

(7) C. A. Winter and L. Flataker, *J. Pharmacol. Exptl. Therap.*, **98**, 307 (1950).

(8) E. Siegmund, R. Cadmus, and G. Lu, *Proc. Soc. Exptl. Biol. Med.*, **95**, 729 (1957).

(9) R. Koster, M. Anderson, and E. de Beer, *Federation Proc.*, **18**, 412 (1959).

Results

In general it was observed that those compounds in Table I with R and R′ as alkyl, cycloalkyl, or aryl substituents were more active analgetics than those in which R is hydrogen. This fact is best illustrated by comparing compound **1** with **15**, and **10** with **13** in Table II. The influence of the carbonyl group on analgetic activity is evident by comparison of **1** and **10** to the reduced compounds, **16** and **17**, respectively, in Table II. The reduced compounds, less active than their precursors, still retain a definite activity of (+). Oral toxicity was greater in the aryl-substituted compounds (**1** and **16**) than the alkyl-substituted compounds (**10** and **17**).

TABLE II
ANALGETIC ACTIVITY AND ACUTE TOXICITY FOLLOWING ORAL ADMINISTRATION OF TEST COMPOUNDS

No.	LD_{50}, mg/kg (95% confidence limits)[a]	Analgetic activity: Dose, mg/kg	Analgetic activity: Rat tail-flick method[b]
1	408 (310–478)	50	+++
		25	++
2	125 (105–145)	20	−
3	1250 (1028–1410)	150	++
4	755 (691–873)	50	+
5	500 (385–665)	50	±
6	505 (390–688)	50	±
7	754 (702–811)	75	±
8	1010 (904–1122)	100	−
9	1515 (1309–1728)	100	−
10	750 (677–818)	100	+++
		50	++
11	>3000	200	+++
		100	+
12	750 (707–796)	75	−
13	620 (565–684)	60	−
14	2025 (1898–2137)	100	±
15	...	100	−
16	950 (880–1022)	100	+
		50	±
17	1518 (1410–1620)	100	+
18	1010 (900–1118)	100	−

[a] Values for the LD_{50} and confidence limits were calculated by the method of Litchfield and Wilcoxon.[11] [b] See text for the scoring method.

In more extensive analgetic testing the activities of compounds **1**, **10**, and **16** were compared to codeine phosphate and *d*-propoxyphene hydrochloride,[10] and the results appear in Table III. On intraperitoneal injection, **10** was comparable in activity to *d*-propoxyphene hydrochloride. Compound **10** exhibited somewhat less activity than codeine phosphate on oral administration.

Table IV summarizes the comparative analgetic activity of codeine phosphate, compounds **1**, **10**, and **16**, *d*-propoxyphene hydrochloride, and aspirin. The data in Table V demonstrate nalorphine hydrochloride antagonism toward the analgetic activity of **10**. It appears that the depression of analgetic activity of **10** is of the same order as codeine phosphate when administered concurrently with nalorphine hydrochloride.

(10) Darvon®.

TABLE III

ANALGETIC ACTIVITY IN RATS AS MEASURED BY THE TAIL-FLICK METHOD

Compd	Dose, mg/kg	No. of animals	Av total analgesia (min-sec)
Intraperitoneal Administration			
Codeine phosphate	2.5	10	50
	5.0	15	68
	10.0	15	100
	14.0	10	182
	20.0	15	229
10 (Dose based on amine)	2.5	10	28
	5.0	20	30
	10.0	15	95
	14.0	10	174
	20.0	20	193
1	2.5	20	39
	5.0	20	48
	10.0	20	68
	20.0	10	168
d-Propoxyphene·HCl	2.5	10	24
	5.0	10	37
	10.0	15	93
	14.0	15	132
	20.0	5	222
16 (Dose based on salt)	5.0	10	35
	10.0	20	39
	14.0	20	95
	20.0	20	161
Physiological saline	...	75	9
Oral Administration			
Codeine phosphate	10	50	39
	20	320	59
	45	15	77
	60	10	117
10	25	15	38
	50	25	74
	75	10	83
	100	10	149
1	25	25	23
	50	10	69
	75	10	89
	100	10	167
Distilled H_2O	...	415	4

TABLE IV

INHIBITION OF ACETIC ACID INDUCED WRITHING IN MICE

Compd	Route of administration	No. of animals	Protective dose[a] ED_{50}, mg/kg
Codeine phosphate	Ip	30	10.0 (6.9–12.8)[b]
	Oral	15	30.3 (20.8–41.1)
10	Ip	15	5.4 (4.0–7.3)
	Oral	15	75.0 (55.2–105.6)
1	Ip	30	17.2 (11.7–25.4)
	Oral	15	50.5 (31.6–74.4)
d-propoxyphene·HCl	Oral	15	50.9 (35.4–68.7)
Aspirin	Oral	30	91.1 (59.7–135.4)
16	Oral	30	94.2 (60.8–129.9)

[a] The dose required to decrease the average incidence of writhing episodes by 50%. [b] The figures in parentheses are the 95% confidence limits.[11]

The acute toxicity was determined in mice. The test drug, dissolved or suspended in distilled water, was given by gastric intubation to female albino mice (21 ± 3 g). The animals were observed for acute, lethal effects for a period of 7 days after administration of the test drug. The LD_{50} values were estimated by the method of Litchfield and Wilcoxon[11] from the number of animals surviving 7 or more days (see Table II).

TABLE V

ANTAGONISM OF NALORPHINE HYDROCHLORIDE TO THE ANALGETIC ACTIVITY OF CODEINE AND 10[a]

	Av total analgesia (min-sec)			
Dose, mg/kg	Codeine phosphate	Codeine phosphate + nalorphine·HCl	10	10 + nalorphine·HCl
14	206	65	200	70
8.5	...	...	62	36

[a] All drugs were administered intraperitoneally. Nalorphine hydrochloride at the dose given (1 mg/kg) did not produce significant analgesia.

Experimental Section

Methyl 2-dimethylamino-3,3-dimethylcyclobutanecarboxylate (1) obtained from Tennessee Eastman Co. was distilled (bp 66–67° at 2.5 mm) before use. All alkyl and aryl halides were highest purity grades obtained from Eastman and Matheson. Rods of magnesium of minimum (99.80%) purity from Fisher Scientific Co. were cut on the lathe to furnish fresh magnesium turnings for preparation of Grignard reagents. All melting and boiling points are uncorrected. Melting points were taken by the capillary method in a modified Hershberg apparatus. Infrared spectra were recorded on a Beckman IR-7 spectrophotometer. Nmr spectra were determined in $CDCl_3$ with a Varian A-60 spectrometer (TMS as zero reference). The following experimental procedures illustrate the general methods used to synthesize the compounds listed in Table I and are specific for the most important compounds described.

1,5-Diphenyl-2,2-dimethyl-1-dimethylamino-5-pentanone (1).—To 0.24 mole of phenyl Grignard reagent in 50–75 ml of anhydrous ether, prepared in the usual manner, was added, dropwise, 18.5 g (0.1 mole) of I in 35 ml of anhydrous ether at a rate which maintained gentle reflux. After addition, the mixture was refluxed for 2 hr. The mixture was cooled and poured into cold NH_4Cl solution, and the aqueous phase extracted with ether. The ether extracts were extracted with 1 *N* HCl. The acid solution was made alkaline with solid $NaHCO_3$ and brought to pH 10 with 5 *N* NaOH. This mixture was extracted with ether and dried (Na_2SO_4), and the ether was evaporated. The residual oil was distilled at 178–179° (0.5 mm). The pale yellow liquid solidified upon standing: mp 42–44°; yield 80%; ν_{max}^{smear} 3085 w, 3060 w, 3020 w, 2820 m, 2780 m, 1685 s, 1598 m, 1493 m, 1387 m, 1365 m, 757 s, 742 s, 705 s cm^{-1}; nmr (ppm), singlet (3H) at 0.9 and singlet (3H) at 1.1 (nonequivalent *gem*-dimethyl), multiplet (2H) at 1.8 and multiplet (2H) at 2.8 ($-CH_2CH_2C-$), singlet (6H) at 2.2 ($C_6H_5CHN(CH_3)_2$) and singlet (1H) at 3.2 ($C_6H_5CHN(CH_3)_2$), multiplet (10H) at 7.0–7.8 (aromatic). The above experiment generalizes the preparations of compounds **1**–**8** in Table I.

1-Cyclohexyl-2,2-dimethyl-1-dimethylamino-5-pentanone Maleate (13) and 1,5-Dicyclohexyl-2,2-dimethyl-1-dimethylamino-5-pentanone Citrate (10).—From the treatment of 0.5 mole of I with 1.1 moles of cyclohexylmagnesium bromide, 131 g of crude oil was obtained. Distillation of this oil gave 10.2 g of I; 7 g of reduction product (type B), 1-cyclohexyl-2,2-dimethyl-1-dimethylamino-5-pentanone-5 (a), bp 108° (0.8 mm); and 90 g of addition product (type A), 1,5-dicyclohexyl-2,2-dimethyl-1-dimethylaminopentanone-5 (b). (a) ν_{max}^{smear} 2820 w, 2765 m, 1710 s, 1385 w, 1365 w, 1045 m, 845 w cm^{-1}; nmr (ppm), singlet (6H) at 0.9 (*gem*-dimethyl), multiplet (15H) at 1.0–2.0 ($C_6H_{11}COCH_2CH_2-$), singlet (2H) at 2.1 ($-CH_2N(CH_3)_2$), singlet (6H) at 2.33 ($N(CH_3)_2$).

Anal. Calcd for $C_{15}H_{29}NO$: C, 75.25; H, 12.21; N, 5.85. Found: C, 75.88; H, 12.57; N, 5.41.

(b) ν_{max}^{smear} 2780 m, 1710 s, 1385 w, 1365 m, 1010 m, 894 m cm^{-1}.

(11) J. F. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949).

Anal. Calcd for $C_{21}H_{39}NO$: C, 78.44; H, 12.23; N, 4.36. Found: C, 77.88; H, 12.15; N, 4.35.

Reduction product a was converted into a maleate salt (**13**) and addition product b was converted into a monocitrate salt (**10**). Analyses of both salts are recorded in Table I.

The above synthesis generalizes the concomitant formation of addition and reduction products when the Grignard reagent contains a β-hydrogen atom. This applies to compounds **9**–**14** in Table I.

5-Phenyl-2,2-dimethyl-1-dimethylamino-5-pentanone (15).—Phenylmagnesium bromide (0.05 mole) was prepared by treating 1.28 g of magnesium with 8.24 g of bromobenzene in 25 ml of anhydrous ether. Ethyl 4,4-dimethyl-5-dimethylaminovalerate[4] (3 g, 0.015 mole) in 15 ml of ether was added dropwise to the phenyl Grignard reagent. The mixture was then refluxed for 4 hr, cooled, poured into NH_4Cl solution (large excess), and extracted with ether. HCl was used to extract this ether layer. The combined aqueous–acidic solution was made basic and extracted with ether. The ethereal solution was dried (Na_2SO_4) and filtered, and the ether was evaporated. A preliminary distillation indicated the presence of a small amount of starting ester in the ketone fractions. The mixture was hydrolyzed with acid, made alkaline, then extracted with ether (1-g recovery). The residue was distilled at 107–108° (0.05 mm); yield 0.5 g; ν_{max}^{smear} 3060 w, 2820 m, 2775 m, 1689 s, 1600 m, 1387 w, 1365 m, 1045 s, 847 m, 743 m, 695 s cm^{-1}.

1,5-Diphenyl-2,2-dimethyl-1-dimethylaminopentane Hydrochloride (16).—A mixture of 8.6 g of 1, 8.6 g of KOH pellets, and 20 ml of 85% hydrazine hydrate in 80 ml of diethylene glycol was refluxed for 30 min (Dean–Stark trap), while 2 ml of water was collected and removed.[12] The mixture was cooled, and an additional 50 ml each of hydrazine hydrate and diethylene glycol were added. After an additional 2-hr reflux, 50 ml of distillate was removed. The mixture was refluxed 2 hr more, and another 20 ml of distillate was removed. The reaction mixture, a homogeneous solution at this point, was cooled and poured into water. The mixture was extracted with ether, and the ether layer was extracted with 2 *N* HCl. The acid extract was made basic with solid $NaHCO_3$ and brought to pH 10 with 5 *N* NaOH. The mixture was extracted with ether, dried (Na_2SO_4), and filtered, and the ether was evaporated *in vacuo*. The residue of 6.8 g was distilled to give 6 g of 1,5-diphenyl-2,2-dimethyl-1-dimethylaminopentane: bp 153–154° (0.3 mm); ν_{max}^{smear} 3084 m, 3060 m, 3021 s, 2820 s, 2780 s, 1605 s, 1583 s, 1495 s, 1385 w, 1364 w, 1018 s, 752 s, 702 s cm^{-1}. The amine was converted into its HCl salt (**16**), mp 118–119°. This procedure serves as a model for preparation of **17**.

1,5,5-Triphenyl-2,2-dimethyl-1-dimethylamino-5-pentanol (18).—A number of attempts were made to prepare **18** by treatment of 1 with phenylmagnesium bromide both in ether and tetrahydrofuran. There were never any OH-stretching bands observed in the infrared spectra, and only starting material (1) could be recovered. Phenyllithium (0.22 mole) was prepared from 0.44 g-atom of lithium and 0.22 mole of bromobenzene in 200 ml of ether. A solution of 62.0 g (0.2 mole) of 1 in 170 ml of anhydrous ether was added dropwise over 45 min to the organolithium reagent. Anhydrous benzene (370 ml) was added to the mixture, and ether was allowed to evaporate through the condenser upon heating. The mixture was refluxed for 8 hr after removing the ether and poured onto ice and 40 ml of concentrated HCl. A tan precipitate appeared (hydrochloride salt, only slightly water soluble). This salt (83.5 g) was dissolved in 700 ml of boiling water and the cooled solution was adjusted to pH 10 with 5 *N* NaOH. This resulted in the separation of a viscous oil which was extracted with ether and dried (Na_2SO_4). After evaporation of the ether the glassy mass was distilled, bp 231° (0.5 mm), to give 51 g (66%) of the alcohol (**18**); $\nu_{max}^{CCl_4}$ 3600 w (sharp), 3080 m, 3060 m, 3020 m, 2820 m, 2780 m, 1600 m, 1582 w, 1505 w, 1390 m, 1365 m, 705 s cm^{-1}.

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(12) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

Substituted 2,3-Dihydro-1,5-benzothiazepin-4(5H)-one and Related Compounds. II. A New Class of Antidepressants[1]

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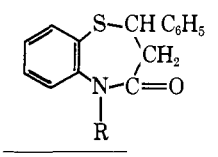
The syntheses of 2-aryl-2,3-dihydro-1,5-benzothiazepin-4(5H)-ones, 2,3,4,5-tetrahydro-2-phenyl-1,5-benzothiazepine, 2-phenyl-1,5-benzothiazepin-4(5H)-one, 2,3-dihydro-2-phenyl-1,5-benzoxazepin-4(5H)-one, 1,3,4,5-tetrahydro-4-phenyl-2H-1-benzazepin-2-one, and 4-phenyl-1H-1,4-benzodiazepine-2,5(3H,4H)-dione and their alkylation with basically substituted alkyl halides are described. Of the thirty-three basically substituted derivatives reported, four were found to be effective in calming rats with lesions in the septal area of the brain.

We have recently reported[2] the preparation of a number of substituted 2,3-dihydro-1,5-benzothiazepin-4(5H)-ones. Three of these compounds, Ia,[3] b, and c, were active in calming rats with lesions in the septal area of the brain. These compounds were unique in that they caused no ataxia at their effective dose; in contrast, the effective dose of chlordiazepoxide is accompanied by considerable ataxia.[4] Although Ib was about twice as active as Ia and Ic in the septal rat by the intraperitoneal route, Ia was selected for further study because of its more predictable adsorption by the oral route. Subsequent studies in the cat showed that Ia depressed only the amygdala of the cat's brain, whereas chlordiazepoxide depressed the amygdala, hippocampus, and septal areas.[4] In the initial clinical study, Ia caused moderate to marked



HCl

Ia, R = $(CH_2)_2N(CH_3)_2$[3]
b, R = $(CH_2)_2N(C_2H_5)_2$
c, R = $(CH_2)_3N(CH_3)_2$

(1) Presented in part before the Division of Medicinal Chemistry, 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1964.

(2) J. Krapcho, E. R. Spitzmiller, and C. F. Turk, *J. Med. Chem.*, **6**, 544 (1963).

(3) Thiazesim is the approved generic name for 5-(2-dimethylaminoethyl)-2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5H)-one.

(4) Z. P. Horovitz, A. R. Furgiuele, L. J. Brannick, J. C. Burke, and B. N. Craver, *Nature*, **200**, 369 (1963).