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Investigation of the *gem*-Dialkyl Effect in Medicinal Agents†

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The preparation of four series of compounds (cholinergic agonists, postganglionic cholinergic antagonists, antihistamines, and local anesthetics), all containing *gem*-dialkyl groups in the alkanolamine portion, is described, and their biological activities are reported. It is concluded that the *gem*-dialkyl effect is not important in the compounds tested.

In earlier studies of the *gem*-dialkyl effect ketals formed from ethylene glycol and cyclohexanone, cyclopentanone, and 2-methylcyclopentanone were shown to be more stable to acid hydrolysis than the corresponding ketals from 1,3-propanediol,[1] whereas ketals involving 2,2-dialkyl-1,3-propanediols and the same ketones proved considerably more stable than those from 1,3-propanediol. Furthermore, the larger the *gem*-alkyl groups the greater the stability of the ketal. Ketals formed from 2,2-diisopropyl-1,3-propanediol are all more stable than the corresponding ketals involving ethylene glycol. In the androstanedione series, the ratio of the equilibrium constant for ketalization at the 3 position with 1,3-propanediols to that at the 17 position was greater the larger the alkyl groups at the 2 position in the propanediols.[2,3]

With this background in mind, interest in the *gem*-dialkyl effect in medicinal agents was aroused since this effect could vary slightly the distance between the functional groups in various classes of drugs. For example, consider many cholinergic drugs (both agonists and antagonists), many antihistamines, and certain local anesthetics as functional derivatives of amino alcohols of the general formula I.

$$R_2N(CH_2)_nOX$$

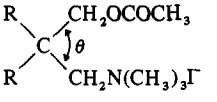
I

R = small alkyl groups; X = groups leading to ether or ester functions; n = 2 or 3

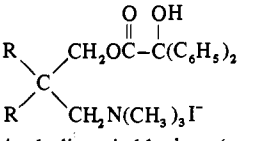
In most cases, the compounds studied have been dialkylaminoethanol derivatives (n = 2), and the literature abounds with papers dealing with spatial relationships of the two polar end groups.[4]

Inspection of 1,3 systems reveals that the geometrical relationships of end groups in 1,3-disubstituted propanes is quite different from these relationships in 1,2-disubstituted ethanes. Furthermore, the relative positions of the end groups in the 1,3-propane system to each other and to bioreceptors are capable of systematic small variations by changing the size of groups in the 2 position (*gem*-dialkyl effect) because the *gem*-dialkyl groups change the angle, θ (shown only in **A**).

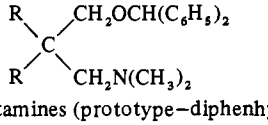
With this in mind, the four types of compounds shown below (types **A–D**) were prepared and tested pharmacologically in order to find out what variations in activity would result from such changes.



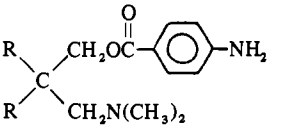
A. Potential cholinergic agonists or antagonists (prototype–acetylcholine)



B. Potential ganglionic cholinergic blockers (prototype–oxyphenonium)



C. Potential antihistamines (prototype–diphenhydramine)



D. Potential local anesthetics

In addition to having the R‡ groups methyl and ethyl, various size cycloalkyl rings were to be used, *e.g.*, R, R =

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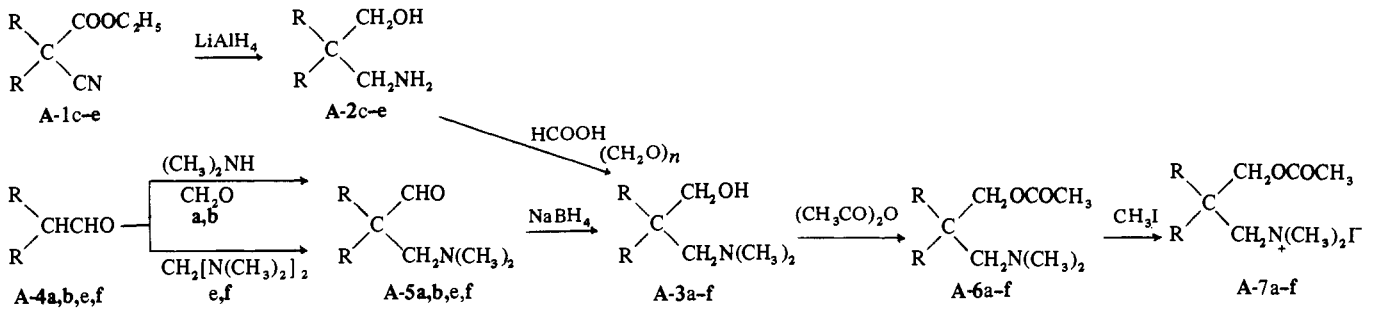
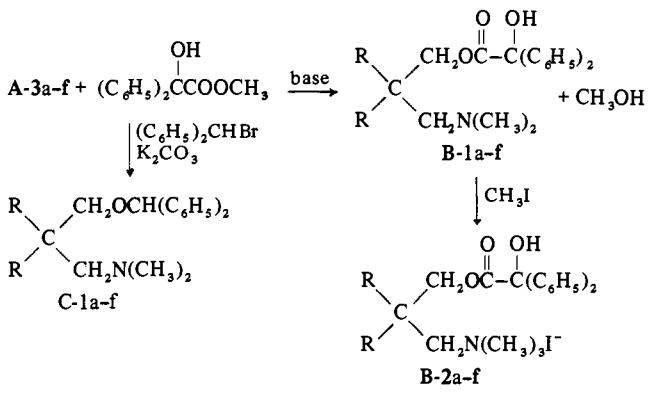
‡The R groups in all compounds have the following structures: a, CH_3; b, C_2H_5; c, $(CH_2)_2$ (cyclopropyl ring); d, $(CH_2)_3$ (cyclobutyl); e, $(CH_2)_4$ (cyclopentyl); and f, $(CH_2)_5$ (cyclohexyl).

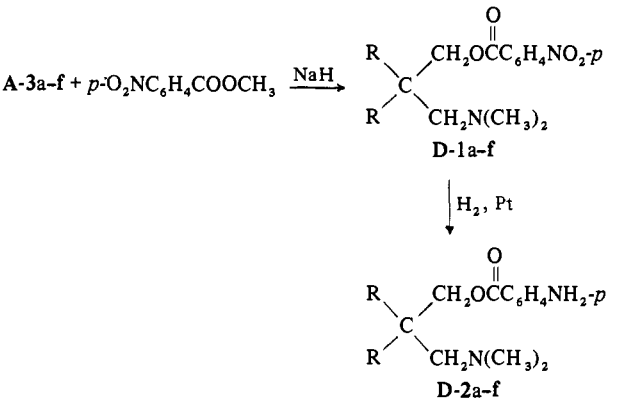
Scheme I. Compounds of Type A



Scheme II. Compounds of Type B and C



Scheme III. Compounds of Type D



$(CH_2)_n$, where n = 2, 3, 4, and 5. This feature would allow the angle between the two R groups to be varied more widely than if only alkyl groups were used. The syntheses were carried out as shown in Schemes I-III.

Experimental Section§

Compounds of Type A. 1-Aminomethyl-1-hydroxymethylcyclopropane (A-2c). A soln of 0.1 mole of A-1c, bp 89-91° (15 mm), prepared in 46% yield as described,[5] in 250 ml of dry ether was added to a soln of 0.2 mole of LAH in 250 ml of ether so as to maintain gentle reflux and then refluxed for 1 hr more. After the addition of water and 50% NaOH, the product was isolated as usual. Distn afforded A-2c, bp 67-68° (1.5 mm), in 65% yield. Analysis was carried out on the oxalate, mp 204-205°. *Anal.* ($C_{12}H_{24}N_2O_6$) C, H, N.

In a similar way A-1d,[6] bp 93-95° (15 mm), 59% yield, and A-1e,[6] bp 94-96° (1.5 mm), 73% yield, were reduced to A-2d,[7] bp 83-85° (4 mm), 77% yield, and A-2e,[7] bp 104-106° (1.5 mm), 70% yield, respectively.

2-Methyl-2-dimethylaminomethylpropanol (A-5a). A well-stirred mixt of 85 g (1.18 moles) of isobutyraldehyde, 80 g of $(CH_3)_2NH_2Cl$, 45 g of $(CH_2O)_n$, and 40 ml of ethanol was refluxed for 90 min. An additional 45 g of $(CH_2O)_n$ was added and refluxing continued for 2 hr. The mixt was cooled, dild with 200 ml of ether, and extd three times with 10% HCl. The HCl extracts were reextd with ether, then made alkaline with 50% NaOH and extd with ether. After the usual treatment, the product was distd to give an 85% yield of A-5a,[8] bp 148-150°. In a similar way, 2-ethyl-2-dimethylaminomethylbutanal,[9] A-5b, bp 65-66° (1.5 mm), was prepd in 76% yield, 1-dimethylaminoethylcyclohexanecarboxaldehyde[8] (A-5f), bp 84-86° (1.5 mm), in 77% yield, and 1-dimethylaminomethylcyclopentanecarboxaldehyde (A-5e), bp 77-79° (1.5 mm) [*Anal.* ($C_9H_{17}NO$) C, H], in 85% yield from the corresponding aldehydes.

2-Methyl-2-dimethylaminomethyl-1-propanol (A-3a). An aqueous soln of 0.1 mole of $NaBH_4$ was added dropwise with stirring to a soln of 0.2 mole of A-5a in MeOH during 2 hr. After 2 hr more, the MeOH was evapd and the mixt made acid with concd HCl. After being extd with ether, the aqueous portion was made alkaline with 50% NaOH, and the product extd into ether. After the usual work-up distn afforded A-3a,[10] bp 58-60° (1.5 mm), in 78% yield. In a similar way, 2-ethyl-2-dimethylaminomethyl-1-butanol (A-3b), bp 80-81° (1.5 mm) [*Anal.* ($C_9H_{21}NO$) C, H, N], 86% yield; 1-hydroxymethyl-1-dimethylaminomethylcyclopentane (A-3e), bp 89-91° (1.5 mm) [*Anal.* ($C_9H_{19}NO$) C, H, N], 89% yield; and 1-hydroxymethyl-1-dimethylaminomethylcyclohexane (A-3f), bp 101-103° (1.5 mm), 86% yield were prepared from their A-5 precursors.

1-Hydroxymethyl-1-dimethylaminomethylcyclopropane (A-3c). To 0.5 mole of 97-100% HCOOH was added with cooling 0.1 mole of A-2c and then 2.2 moles of 36% formalin. The stirred mixture was slowly heated to 90-100° for 12 hr, then cooled and acidified with concd HCl.# Most of the remaining HCOOH and formalin was removed under reduced pressure, and the residue was made alkaline with 50% NaOH. After the usual work-up distn afforded 67% of A-3c, bp 59-61° (1.5 mm). *Anal.* ($C_7H_{15}NO$) C, H, N. In a similar way 1-hydroxymethyl-1-dimethylaminomethylcyclobutane (A-3d), bp 73-74° (1.5 mm) [*Anal.* ($C_8H_{17}NO$) C, H, N], 56% yield, and A-3e (see above), 65% yield, were prepared from A-2d and A-2e.

Formation of Acetates A-6a-f. These acetates were prepd by heating at reflux for 12 hr a soln of 0.1 mole of amino alcohol, A-5a-f, and 5 ml of pyridine in 50 ml of Ac_2O. The HOAc and remaining Ac_2O were removed on a rotary evaporator. An ether soln of the product was extracted with 10% HCl. The acid extracts were washed with ether and made alkaline with 50% NaOH. After the usual work-up, the products were distd (see Table I).

§ All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analyses by Micro-Analysis, Inc., Wilmington, Del., and by Galbraith Laboratories, Knoxville, Tenn. All nmr spectra were recorded on a Varian A-60 instrument in CCl_4 with $(CH_3)_4Si$ as internal standard. Vpc analyses of liquid compounds were carried out on a F and M 609 flame ionization gas chromatograph using a 2-ft stainless steel column packed with 10% silicone rubber SE-30 on 60-80S 609. The term "worked up in the usual way" means that an ether-benzene solution of the products was washed with dilute alkali and/or dilute hydrochloric acid, with saturated salt solution, and was then filtered through a cone of $MgSO_4$. The solvents were then removed by distillation or on a rotary evaporator. The residue was then vacuum distilled or crystallized (or both). The yields reported represent materials which gave a single peak by vpc analysis. Compounds which analyzed within ±0.4% of the theoretical are designated in the usual way.

#Essentially the Eschweiler-Clarke procedure, see ref 11.

Table I. Dimethylamino Acetates,[a] A-6a-f, and Methiodides, A-7a-f[b]

No.	Compd	Bp (mm), °C	Yield,[c] %	Mp, °C[d]
A-6a	2-Methyl-2-dimethylaminomethyl-1-propanol acetate[e]	85-86 (15)	70	140-141
A-6b	2-Ethyl-2-dimethylaminomethyl-1-butanol acetate	88-89 (1.5)	80	153-154
A-6c	1-Acetoxymethyl-1-dimethylaminomethylcyclopropane	69-71 (1.5)	72	165-166
A-6d	1-Acetoxymethyl-1-dimethylaminomethylcyclobutane	80-81 (1.5)	69	238-239
A-6e	1-Acetoxymethyl-1-dimethylaminomethylcyclopentane	92-94 (1.5)	72	175-176
A-6f	1-Acetoxymethyl-1-dimethylaminomethylcyclohexane	129-130 (13)	79	115-116

[a]The acetates, homogeneous by vpc, were not analyzed but converted quantitatively into the corresponding methiodides, A-7a-f. [b]The methiodides were recrystallized from alcohol-benzene mixtures. [c]The yield reported is that of a narrow range distillate. [d]The mp of the methiodides, A-7a-f. [e]Known, see Blankart.[14]

Table II. Dimethylamino Benzilates, B-1a-f, and Methiodides, B-2a-f

No.	Compd	Yield, %	Mp, °C	Mp,[a] °C
B-1a	3-Dimethylamino-2,2-dimethylpropyl benzilate	89	66-67	136-137
B-1b	3-Dimethylamino-2,2-diethylpropyl benzilate	78	58-59	133-134
B-1c	1-Hydroxymethyl-1-dimethylaminomethylcyclopropane benzilate	94	79-80	155-156
B-1d	1-Benzilatoxymethyl-1-dimethylaminomethylcyclobutane	88	76-77	179-180
B-1e	1-Benzilatoxymethyl-1-dimethylaminomethylcyclopentane	87	62-63	187-188
B-1f	1-Benzilatoxymethyl-1-dimethylaminomethylcyclohexane	75	77-78	181-182

[a]The mp of the methiodides, B-2a-f. All methiodides were recrystallized from alcohol-benzene mixtures.

Table III. Benzhydryl Ethers, C-1a-f

No.	Compd	Bp, °C	Yield, %
C-1a	3-Dimethylamino-2,2-dimethylpropyl benzhydryl ether	119-120	65
C-1b	3-Dimethylamino-2,2-diethylpropyl benzhydryl ether	135-136	65
C-1c	1-Benzhydryloxymethyl-1-dimethylaminomethylcyclopropane	129-131	61
C-1d	1-Benzhydryloxymethyl-1-dimethylaminomethylcyclobutane	136-137	51
C-1e	1-Benzhydryloxymethyl-1-dimethylaminomethylcyclopentane	144-146	54
C-1f	1-Benzhydryloxymethyl-1-dimethylaminomethylcyclohexane	149-151	63

Table IV. *p*-Nitrobenzoates, D-1a-f, and *p*-Aminobenzoates, D-2a-f

No.	Compd	Mp, °C	Yield,[a] %
D-1a	*p*-Nitrobenzoate of A-3a	37-38	67
D-2a	*p*-Aminobenzoate of A-3a	80-81	*a*
D-1b	*p*-Nitrobenzoate of A-3b	60.5-61.5	63
D-2b	*p*-Aminobenzoate of A-3b	77-78	*a*
D-1c	*p*-Nitrobenzoate of A-3c	29-30	58
D-2c	*p*-Aminobenzoate of A-3c	94-95	*a*
D-1d	*p*-Nitrobenzoate of A-3d	53-54	62
D-2d	*p*-Aminobenzoate of A-3d	107-108	*a*
D-1e	*p*-Nitrobenzoate of A-3e	61-62	63
D-2e	*p*-Aminobenzoate of A-3e	81-82	*a*
D-1f	*p*-Nitrobenzoate of A-3f	81-82	71
D-2f	*p*-Aminobenzoate of A-3f	127-128	*a*

[a]Yield almost quantitative.

Formation of Methiodides A-7-f. These were prepd by treatment with CH_3I and were recrystd from suitable solvents.

Compounds of Types B, C, and D. Preparation of Benziliates, B-1a-f. A stirred mixture of 0.05 mole of the amino alcohols, A-3a-f, 0.1 mole of methyl benzilate, 0.2 g of Na, and 100 ml of PhH was refluxed for 6 hr in a reaction flask fitted with a short column topped by a total reflux-partial takeoff head. Methanol-rich fractions were taken off as MeOH was formed by ester interchange. When the temperature reached the bp of benzene, the mixture was cooled, dild with 150 ml of ether, and extd with three 50-ml portions of 10% HCl. The combined aqueous extracts were extracted with ether and made alkaline with 50% NaOH with cooling. After the usual work-up, the products were vacuum distd. As all benzilates solidified the mps of the recrystd benzilates are given in Table II.

Preparation of Methiodides B-2a-f. The above esters, B-1a-f, were treated with CH_3I to give the methiodides listed in Table II in quant yield. All methiodides were recrystd from suitable solvents.

Preparation of Benzhydryl Ethers C-1a-f. To a mixture of 0.1 mole of the amino alcohols, A-3a-f, and 13.8 g of K_2CO_3 at 125° was added dropwise with stirring 24.7 g (0.1 mole) of hot benzhydryl bromide. The mixt was held at 125-130° for 6 hr, cooled, and dild with ether. The ether soln was washed with three 50-ml portions of water and then with one 100-ml and two 50-ml portions of 10% HCl. The combined HCl extracts were washed with ether and made alkaline with 50% NaOH. The product was extd into ether and worked up in the usual way to yield crude products which were distd at 0.1 mm to yield the benzhydryl ethers listed in Table III. All were liquids.

Preparation of *p*-Nitrobenzoates D-1a-f. Solns of 0.1 mole of the amino alcohols, A-3a-f, in 100 ml of dry PhH were treated with 2.5 g of NaH until the evoln of H_2 ceased. A soln of 0.2 mole of methyl *p*-nitrobenzoate in 100 ml of PhH was added, and the stirred mixt was refluxed for 9 hr, allowing the CH_3OH to distill. The PhH soln was then washed with three 50-ml portions of 10% HCl. The combined extracts were washed with ether, make alkaline with 50% NaOH, and worked up as usual with ether-PhH. The solvent-free

Table V. Biological Results

Cholinergic agonists			Cholinergic antagonists		Antihistamines		Local anesthetics[a]		
Compounds	α	pD_2	Compounds	pA_2	Compounds	pA_2	Compounds	TAC_5	Cocaine anesthetic ratio
Acetylcholine	1.0	6.7	Atropine	8.8	Papaverine	4.8	Cocaine	0.31	1.0
A-7a	0.56	3.4	B-2a	9.5	C-1a	4.5	D-2a	0.61	0.51
A-7b	0.39	3.4	B-2b	7.2	C-1b	5.6	D-2b	0.60	0.52
A-7c	0.87	3.9	B-2c	7.9	C-1c	5.2	D-2c	0.70	0.44
A-7d	0.62	3.8	B-2d	7.2	C-1d	5.5	D-2d	0.76	0.41
A-7e	0.56	2.9	B-2e	7.1	C-1e	5.1	D-2e	0.39	0.79
A-7f	0.77	2.9	B-2f	6.9	C-1f	4.7	D-2f	0.43	0.72

[a]All compounds were irritating to the eye.

residues were crystd from isopropyl alcohol or hexane to yield the *p*-nitrobenzoates, **D-1a-f**, listed in Table IV.

Preparation of *p*-Aminobenzoates D-2a-f. Solns containing 0.05 mole of the *p*-nitrobenzoates, **D-1a-f**, in 100 ml of EtOH were hydrogenated over 0.2 g of platinum oxide catalyst at room temperature at 15 psi for 30 min. After filtration of the catalyst, the solvent was removed and the residue recrystd from PhH-hexane or CCl_4 to yield the *p*-aminobenzoates listed in Table IV in over 95% yield.

Biological Results. The biological activities of the compounds prepared in this study are summarized in Table V. Cholinergic agonist, cholinergic antagonist, and antihistamine activities were determined using the cumulative dose-response technique of van Rossum.[12]

Compounds **A-7a-f** were tested for cholinergic agonist activity on rat jejunum using acetylcholine as the reference agonist.

Compounds **B-2a-f** were tested for postganglionic cholinergic blocking activity on rat jejunum using furtrethonium as the reference agonist and atropine as the reference antagonist.

Compounds **C-1a-f** were tested for antihistamine activity on guinea pig ileum using histamine as the reference agonist and papaverine as the reference antagonist.

Compounds **D-2a-f** were tested for corneal anesthetic activity in rabbits. Each compound was tested at 3 different concentrations, both eyes of a single rabbit being used for each concentration. *The concentration which produced anesthesia of 5-min duration was obtained from a dose-response curve of anesthesia against log concentration.* This concentration is the "threshold anesthetic concentration" or TAC_5.[13] The cocaine anesthetic ratio is the TAC_5 of cocaine divided by the TAC_5 of the compound being tested.

While many of the compounds tested (particularly the antagonists) exhibited activities comparable to the reference drugs, we were unable to detect progressive changes in activity which could be related to the nature of the *gem*-dialkyl substituents. Apparently, small differences in the distance between the oxygen and nitrogen functions attributable to the *gem*-dialkyl effect are not important in the systems under scrutiny.

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Utilization of Operational Schemes for Analog Synthesis in Drug Design†

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Some proposals are presented for the stepwise selection for synthesis of new analogs of an active lead compound which are designed to maximize the chances of synthesizing the most potent compounds in the series as early as possible. The schemes are based on a fundamental assumption of the Hansch method that a particular substituent may modify activity relative to the parent compound by virtue of resulting changes in hydrophobic, electronic, and steric effects. Some examples of how this approach might have fared if it had been applied to a number of existing series have been analyzed.

A very common problem in drug design is to find the optimum substitution on a benzene ring or on the benzenoid portion of a fused ring system in an active lead compound for maximization of drug potency. Since there are many possible substituents and several different ring positions, the number of possible compounds to consider containing up to say two substituents is very large. Thus, it would be highly advantageous to determine at an early stage which of these compounds might really be worth synthesizing.

Historically, approaches to this problem have been rather haphazard, depending for the most part on the particular experience and intuition of the medicinal chemist involved and the relative availability of the starting materials required for synthesis. With the advent[1] and subsequent development[2] of the Hansch method for structure-activity correlations a more rational approach to this problem became possible. Thus, a limited group of substituents which will give good discrimination between π, σ, and E_s can be selected[3] and an initial group of 6-12 compounds synthesized. After performing a regression analysis and assuming a worthwhile correlation is obtained, it should be possible to determine which parameters are influencing activity and to what relative degree. Knowing this, and having available a comprehensive list of possible substituents and their respective parameters, those compounds can be selected for synthesis with the highest indicated potency values commensurate with synthetic accessibility.

Since the regression analysis has been carried out with a minimum number of observations, the reliability of the correlation will not be high, but nevertheless the analysis will identify those compounds with the highest probability of enhanced potency based on the available data. When data on the second group of compounds become available, they can be combined with the first group so that the correlations can be continuously refined as new data become available.

This procedure is suitable when the compounds are relatively easy to synthesize and a considerable time lag is encountered in obtaining activity data. However, it is less satisfactory under circumstances where synthesis is more difficult and test results are more readily forthcoming. In the latter case it would be desirable to proceed with every compound synthesized in the most probable direction toward greater potency. This maximizes the chances of

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