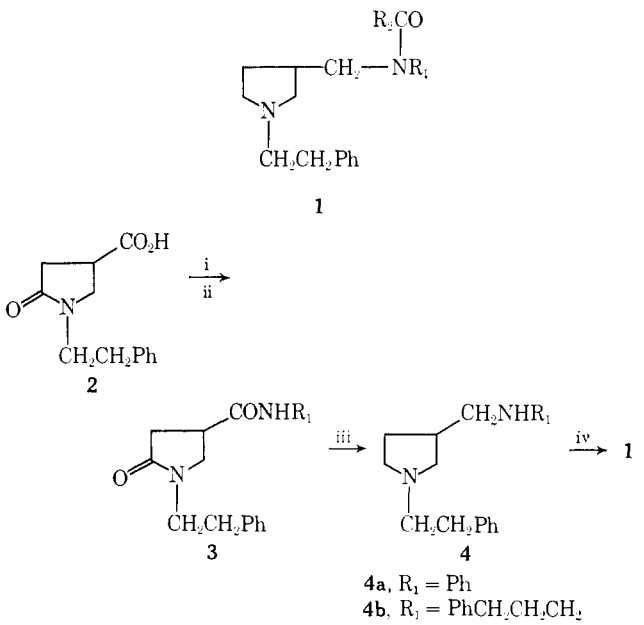
SCHEME I



Reagents: i = $SOCl_2$, ii = R_2NH_2, iii = LAH, iv = R_2COCl

ethyl-5-oxo-3-pyrrolidinylcarboxylic acid (126 g, 0.5 mole) in $CHCl_3$ (200 ml) was added to freshly distd $SOCl_2$ (250 g, 2.1 mole). The reaction mixture was heated under reflux for 2 hr. The solvent and unreacted $SOCl_2$ were evapd under reduced pressure and the residual oil used without further purification.

Preparation of Amides. Method A.—Amines and *N*-phenethyl-5-oxo-3-pyrrolidinylcarbonyl chloride in equimolar quantities were allowed to react in an excess of 2% NaOH. A solid sepd on cooling, this was collected, washed (H_2O), and recrystd.

Method B.—Amines (2.0 moles) and *N*-phenethyl-5-oxopyrrolidinylcarbonyl chloride (1.0 mole) were allowed to react in dry $CHCl_3$ at −60°. A solid, which sepd on storage, was collected and washed ($CHCl_3$) and the washings were added to the filtrate. The combined washings were dried (Na_2SO_4) and evapd. The residual oils solidified on cooling and were recrystd. For details see Table II.

***N*-Phenethyl-3-pyrrolidinylmethylamines (4).**—LAH (4.7 g, 0.15 mole) was suspended in dry dioxane (150 ml) in a Soxhlet apparatus. *N*-Phenethyl-5-oxo-3-pyrrolidinylcarboxamides (0.1 mole) were packed into the thimble and extracted. The products were worked up in the usual way and purified as such or characterized as acyl derivatives.

***N*-Phenethyl-3-pyrrolidinylmethylaniline (4a)** was redistilled under reduced pressure, the fraction boiling at 190° (1.5 mm) was collected: yield 14.75 g (52%). *Anal.* ($C_{19}H_{24}N_2$) C,H,N.

***N*-Phenethyl-3-pyrrolidinylphenethylamine·2HBr (4b)** was recrystd from EtOH–Et_2O: mp 255–256°; yield 31.95 g (68%) *Anal.* ($C_{21}H_{30}Br_2N_2$) C,H,N.

***N*-(Substituted phenyl)-*N'*-(1-phenethyl-3-pyrrolidinyl)acetamides (1). Method A.**—*N*-Phenethyl-3-pyrrolidinylmethylamines (0.1 mole) in dry $CHCl_3$ (100 ml) were added to anhyd $NaHCO_3$ (0.15 mole). The suspension was cooled to 0° and the appropriate acid chloride (0.2 mole) added. The reaction mixture was heated under reflux for 5 hr and filtered hot. The filtrate was dried (Na_2SO_4) and evapd. The residual oils were distd under reduced pressure.

Method B.—*N*-Phenethyl-3-pyrrolidinylmethylamines (0.1 mole) in dry $CHCl_3$ (100 ml) were treated with the appropriate acid chloride (0.3 mole) and the reaction mixture was heated under reflux for 2 hr. Excess acid chloride and solvent was distd off under reduced pressure. The residue was basified by addn of 36% KOH and the base extd with Et_2O (4 × 25 ml). The products were isolated as in method A. Compound **4** was insol in Et_2O.

Acknowledgments.—The pharmacological testing was carried out by Messrs. Allen & Hanburys Ltd., Ware, England. One of us (M.S.) wishes to thank this company for a postgraduate scholarship.

2,2′-Dialkoxybenzhydrylamides and 2,2′-Dialkylbenzhydryl Esters of N,N-Disubstituted α-Amino Acids. Synthesis and Pharmacological Evaluation

ARMANDO NOVELLI, VICENTE FERRARI, OSCAR ALONSO, AND JORGE R. BARRIO*

Departamento de Química Orgánica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Buenos Aires, Argentina

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Isomers of lidocaine which do not have two Me groups ortho to the anesthesiophore group differ markedly in anesthetic properties.[1] Obviously the considerable steric hindrance plays an important role in this pharmacological activity. Moreover, the replacement of a functional NH by O can lead to isosteric compounds of similar properties.[2,3]

The title compounds were chosen for study because they contain a key structural feature of lidocaine: steric hindrance; moreover, we were interested in studying what effect replacement of NHCO by OCO in this type of molecules would have on the activity profile.

The synthesis of the intermediate halo esters was achieved under mildly basic conditions. Attempts to prepare them by boiling di-*o*-tolylcarbinol and $ClCO-CH_2Cl$ were unsuccessful, di-*o*-tolylchloromethane[4] was obtained.

An attempt was made to correlate local anesthetic potency with the bond order of the CO linkage as measured by the CO stretching frequency. A previous correlation of this type has been reported.[5,6] Examination of Table I shows there is no correlation between the CO absorption frequency and the local anesthetic potency. Direct comparison of esters and amides perhaps should not be made, particularly with the hindered amides reported here, since amides in general are representatives of a lower absorption frequency.

Biological Results.—Compounds **1–28** were tested for their local anesthetic activity and the results of the observations are summarized in Table I. Potency and duration of local anesthetic activity were assessed by the Bülbring and Wajda technique.[7] Aliquots of 0.25% solns of **1–20** in distd H_2O were injected intradermally in guinea pigs. Compounds **21–28**, because of instability in H_2O, were injected at a dose level of 0.25% in propyleneglycol. Local anesthesia was indicated by the absence of a flinching response when the treated site was pricked at 5, 10, 15, 30, 60, 120, and 180 min after injection. Lidocaine was used for comparison throughout the experiments.

It is apparent from these primary results that **3** is somewhat more active than lidocaine itself. However, the injection site was inflamed and edematous. Twenty-four hours after the experiment the animals

* To whom correspondence should be addressed.

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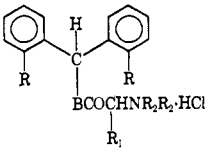
TABLE I



Compd	R	R_1	NR_2R_2	B	Yield, %	Mp, °C	Formula[c]	Carbonyl absorption frequency, cm^{-1}	Surface local anesthetic activity[a]
1	OMe	H	$-N(CH_3)_2$	NH	91	205–206	$C_{19}H_{25}ClN_2O_3$	1666	0.80
2	OMe	H	$-N(C_2H_5)_2$	NH	88	200–201	$C_{21}H_{29}ClN_2O_3$[b]	1672	0.96
3	OMe	H	$-N(CH_2)_3CH_2$	NH	85	145–146	$C_{21}H_{27}ClN_2O_3$	1658	1.30
4	OMe	H	$-N(CH_2)_4CH_2$	NH	80	203–204	$C_{22}H_{29}ClN_2O_3$	1656	0.90
5	OMe	H	$-N(CH_2)_2OCH_2CH_2$	NH	82	207–208	$C_{21}H_{27}ClN_2O_4$	1658	0.70
6	OMe	Me	$-N(CH_3)_2$	NH	78	246–247	$C_{20}H_{27}ClN_2O_3$	1661	<0.10
7	OMe	Me	$-N(C_2H_5)_2$	NH	81	229–230	$C_{22}H_{31}ClN_2O_3$[d]	1672	0.50
8	OMe	Me	$-N(CH_2)_3CH_2$	NH	79	208–209	$C_{22}H_{29}ClN_2O_3$	1669	0.50
9	OMe	Me	$-N(CH_2)_4CH_2$	NH	80	220–221	$C_{23}H_{31}ClN_2O_3$	1661	0.80
10	OMe	Me	$-N(CH_2)_2OCH_2CH_2$	NH	76	209–210	$C_{22}H_{29}ClN_2O_4$	1669	0.80
11	OEt	H	$-N(CH_3)_2$	NH	79	199–200	$C_{21}H_{29}ClN_2O_3$	1666	0.96
12	OEt	H	$-N(C_2H_5)_2$	NH	76	191–192	$C_{23}H_{33}ClN_2O_3$	1669	0.96
13	OEt	H	$-N(CH_2)_3CH_2$	NH	78	193–194	$C_{23}H_{31}ClN_2O_3$	1658	0.80
14	OEt	H	$-N(CH_2)_4CH_2$	NH	79	194–195	$C_{24}H_{33}ClN_2O_3$	1667	0.40
15	OEt	H	$-N(CH_2)_2OCH_2CH_2$	NH	74	203–204	$C_{23}H_{31}ClN_2O_4$	1656	0.80
16	OEt	Me	$-N(CH_3)_2$	NH	81	237–238	$C_{22}H_{31}ClN_2O_3$	1667	<0.10
17	OEt	Me	$-N(C_2H_5)_2$	NH	78	234–235	$C_{24}H_{33}ClN_2O_3$	1669	<0.10
18	OEt	Me	$-N(CH_2)_3CH_2$	NH	76	220–221	$C_{24}H_{33}ClN_2O_3$	1672	<0.10
19	OEt	Me	$-N(CH_2)_4CH_2$	NH	77	246–247	$C_{25}H_{35}ClN_2O_3$	1669	<0.10
20	OEt	Me	$-N(CH_2)_2OCH_2CH_2$	NH	75	216–217	$C_{24}H_{33}ClN_2O_4$	1675	0.10
21	Me	H	$-N(C_2H_5)_2$	O	59	198–200	$C_{21}H_{28}ClNO_2$	1764	0.98
22	Me	H	$-N(CH_2)_3CH_2$	O	44	195–196	$C_{21}H_{26}ClNO_2$[e]	1751	1.04
23	Me	H	$-N(CH_2)_4CH_2$	O	63	177–179	$C_{22}H_{28}ClNO_2$[f]	1748	0.72
24	Me	H	$-N(CH_2)_2OCH_2CH_2$	O	52	173–175	$C_{21}H_{26}ClNO_3$	1748	0.39
25	Me	Me	$-N(C_2H_5)_2$	O	28	147–148	$C_{22}H_{30}ClNO_2$	1730	1.02
26	Me	Me	$-N(CH_2)_3CH_2$	O	68	161–162	$C_{22}H_{28}ClNO_2$[g]	1742	0.86
27	Me	Me	$-N(CH_2)_4CH_2$	O	66	168–169	$C_{23}H_{30}ClNO_2$	1730	1.02
28	Me	Me	$-N(CH_2)_2OCH_2CH_2$	O	58	135–136	$C_{22}H_{28}ClNO_3$	1739	1.10

[a] Values refer to lidocaine, assigned a relative anesthetic potency of 1. [b] C: calcd, 62.55; found, 63.00. [c] All compounds were analyzed for C, H, Cl, N. [d] C: calcd, 64.94; found, 64.50. [e] H: calcd, 7.23; found, 7.75. [f] C: calcd, 70.68; found, 69.90. [g] H: calcd, 7.49; found, 8.20.

were killed. Subsequent histological examination of the areas showed acute inflammatory response with proliferation of polynuclear cells. However, 7 days after the injection, tissue irritation had disappeared.

Experimental Section[8]

2,2'-Dialkoxy-*N*-formylbenzhydrylamines.—$(NH_4)_2CO_3$ (22 g) and HCOOH (22 ml) were mixed, heated cautiously, and then slowly distd until the temp was about 160°. To the hot mixture 10 g of the appropriate 2,2'-dialkoxybenzhydrylamine[9] was added and the temp raised to 180–185° for 10 hr. After cooling the mixture was poured into 40 ml of H_2O and the product was collected, washed, dried, and recrystd (EtOH).

2,2'-Dimethoxy-*N*-formylbenzhydrylamine (29) was obtained in 98% yield (10.8 g), mp 180–181°. *Anal.* ($C_{16}H_{17}NO_3$) C, H, N.

(8) All melting points were taken in Fischer-John apparatus and are uncorrected. Ir spectra were measured on a Perkin-Elmer Model 137 E Infracord. Microanalyses were performed at this laboratory. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

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2,2'-Diethoxy-*N*-formylbenzhydrylamine (**30**) was obtained in 93% yield (10.2 g), mp 170–171°. *Anal.* ($C_{18}H_{21}NO_3$) C, H, N.

2,2'-Dialkoxybenzhydrylamines.—A suspension of 10 g of the appropriate *N*-formyl derivative in 50 ml of HCl 5% was refluxed until a clear soln was obtd. After cooling the amine·HCl crystd.

2,2'-Dimethoxybenzhydrylamine·HCl (**31**) was obtained in 76% yield (7.8 g), mp 246–247°. *Anal.* ($C_{15}H_{18}ClNO_2$) C, H, Cl, N.

2,2'-Diethoxybenzhydrylamine·HCl (**32**) was obtained in 85% yield (9.8 g), mp 239–240°. *Anal.* ($C_{17}H_{22}ClNO_2$) C, H, Cl, N.

2,2'-Dialkoxybenzhydrylamides.—A soln of 0.01 mole of $ClCOCH_2Cl$ or $BrCOCHBrCH_3$ in 10 ml of C_6H_6 was added over a period of 0.5 hr to a cold, stirred soln of 0.02 mole of the appropriate free benzhydrylamine in 10 ml of C_6H_6. The mixture was kept at 20–25° for 12 hr and then filtered. The filtrate was treated with an excess of the appropriate amine and the mixture was refluxed for 15 hr. After cooling, C_6H_6 extract was filtered, washed twice with H_2O, and dried ($MgSO_4$), the solvent was evaporated, and the hydrochloride was prepared (EtOH–ether).

2,2'-Dialkylbenzhydryl Esters.—A soln of 0.01 mole of $ClCOCH_2Cl$ or $BrCOCHBrCH_3$ in 10 ml of C_6H_6 was added over a period of 0.5 hr to a cold, stirred soln of 2.12 g (0.01 mole) of di-*o*-tolylcarbinol[10] and 0.89 ml (0.011 mole) of pyridine in 30 ml of C_6H_6. The mixture was stirred an addn 0.5 hr. It was filtered, the filtrate treated with an excess of the appropriate amine, and the mixture kept at 40–45° for 3 days. After cooling, it was treated as described in the above procedure.

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Molecular Orbital Conformation of Phenyl Choline Ether

LEMONT B. KIER*

Columbus Laboratories, Battelle Memorial Institute, Columbus, Ohio

AND JACK M. GEORGE

College of Medicine, The Ohio State University, Columbus, Ohio

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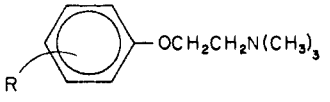
Over the past decade a considerable amount of theoretical interest has been shown in the structural considerations of the nicotinic activity of a variety of molecules. Fukui studied a series of phenyl choline ethers, (I), using simple Hückel MO calculations.[1]



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The study revealed that the substituent groups influence frontier electron density at the O and the superdelocalizability at the ortho positions, and that these indices correlated with nicotinic activity. The suggestion was made that the O atom and the ortho position on the ring might be spatially related to the onium group in the phenyl choline ethers in the same manner as the ether and CO oxygen atoms in the potent nicotinic agent, ACh (Figure 1). Thus an ortho ring position would play a role at the receptor comparable to the carbonyl O atom.

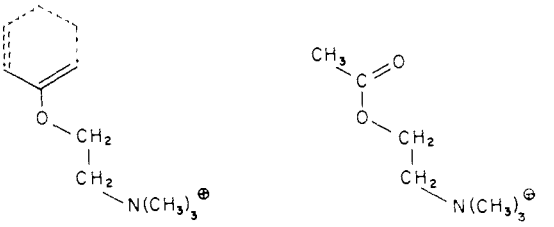
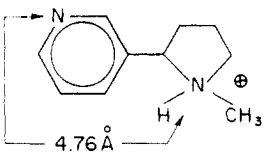


Figure 1.—Spatial relationship between phenyl choline ether and acetylcholine postulated by Fukui[1] and predicted from this study.

We have reported extended Hückel MO calculations on both ACh[2] and nicotine[3] in which we concluded that both nicotine and ACh can assume preferred conformations in which the pyridine N and carbonyl O atoms, respectively, are of similar distance from the onium groups in each molecule (Figure 2). The role



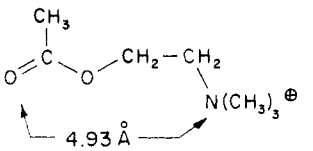


Figure 2.—Spatial relationship between nicotine and acetylcholine in their predicted preferred conformations.[3]

of the ether O in the nicotinic activity of ACh is not evident from this comparison, since there is no atom in nicotine that appears equivalent to the ether O at a receptor. The receptor equivalence of the pyridine N and the carbonyl O is certainly suggested from these studies.

In a recent study by Crow, *et al.*, a series of ring-substituted phenyl choline ethers was considered using simple Hückel theory.[4] The relationships between calculated reactivity indices and nicotinic activity revealed correlations only with the energy of the highest occupied MO and the superdelocalizability at the ring ortho positions. These findings agree with those of Fukui[1] except for the lack of a correlation between an oxygen reactivy index and activity. The suggestion arising from these results was that the aromatic ring interacts with the receptor, probably at one of the ortho positions, to form a charge-transfer complex.

A basic problem still remains with the phenyl choline ethers if the ortho ring position is to be seriously considered as mimicking the carbonyl O of ACh at the

* To whom correspondence should be addressed.

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