these groups possess closely similar values of σ_m and σ_p. Extending the similarity to other strong electron-withdrawing groups, π should again be independent of the mode of substitution.

A consideration of eq 20 suggests that the dynamic process of forming a hydrophobic bond may be associated with a covariant behavior of the polarizability and desolvation characteristics of a drug or drug substituent. On the other hand, under static, or equilibrium, conditions such covariant behavior may no longer predominate and a drug–receptor interaction may then be considered as either polarizability or desolvation controlled. Under the latter conditions, eq 20 would reduce to

$$\pi = pP_E \quad (21)$$

and

$$\pi = m\sigma \pm m'\sigma^2 \quad (22)$$

In general the σ^2 term may be deleted from eq 22 since for all but strongly electron-withdrawing substituents this term is negligible. The correlations observed between π and σ[11,27] and the linear relationships found between chloramphenicol activity and P_E[28] and between sulfonamide activity and σ[29] may be interpreted on the basis of eq 21 and 22. It must be stressed, however, that interactions with pharmacologically inert substances may also be described in similar terms.

Conclusions.—The possibilities for further study and the interpretations of available data suggested by the present approach are by no means exhausted in the discussion. It is clear, however, that appropriate modifications of current chemical theories are themselves the general frame of reference on which physicochemical approaches to the study of drug action should be based.

Acknowledgment.—This work was supported under National Institutes of Health Grant 9199-01 from the Institute of Allergy and Infectious Diseases.

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Notes

o,o'-Disubstituted Phenylcyclopropylamines[1a]

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Received September 20, 1968

A number of 2-arylcyclopropylamines exhibit potent inhibitory activities on monoamine oxidases[2] from various tissues.[3] Likewise, 2-phenoxycyclopropylamine[4] and several of its derivatives,[5] as well as 2-cyclohexyloxycyclopropylamine,[6] share these properties *in vitro* and *in vivo*. The *o*-toloxy homolog, *o*-$CH_3C_6H_4OC_3H_4NH_2$,[5b] is almost as potent as the parent phenoxy compound, whereas *ortho* substitution of 2-phenylcyclopropylamine decreases the activity.[4] The number of conformations of phenoxycyclopropane compounds is limited and must be restricted further by *ortho* substituents. Even in *o,o'*-disubstituted anisoles[7,8] and sterically hindered 2-aryloxyethylaminoguanidines[9] the oxygen atom does not appear to be conjugated with the aromatic ring, making it impossible for the groups at the ether oxygen to lie in the plane of the phenyl group. The decrease in conjugative effects, the enhanced basicity of the ether oxygen, and the bulk of the *ortho* substituents should lead to alterations in biological profile, and may lead to a block of metabolic reactions attacking the cyclopropoxy side chain. A study of *o,o'*-disubstituted phenoxycyclopropylamines has therefore been made in our laboratories.

The *o,o'*-disubstituted analogs (R = CH_3, Cl) were synthesized according to the outline in Chart I. The addition of carbethoxycarbene to vinyl ethers furnished mixtures of *cis* and *trans* esters, the *trans* isomer prevailing.[5b]

2-(2,6-Xylyloxy)cyclopropylamine was also quaternized to a cyclopropylog (**6**) of xylocholine.[10]

Effects on the Central Nervous System of Mice. Gross Observation.—Compounds **1–3** produced significant behavioral changes while **4–6** were inactive at 400 mg/kg. Compounds **1–3** showed stimulatory effects consisting of increased motor activity, clonic and

(1) (a) This investigation was supported by a generous grant, No. GM-12781, from the Institute of General Medicine, National Institutes of Health, Department of Health, Education and Welfare. (b) Presented as part of a Ph.D. dissertation, University of Virginia, 1967.

(2) For a review, see C. L. Zirkle and C. Kaiser in "Psychopharmacological Agents," Vol. I, M. Gordon, Ed., Academic Press, New York, N. Y., 1964, Chapter 12.

(3) A. Burger and S. Nara, *J. Med. Chem.*, **8**, 859 (1965).

(4) C. L. Zirkle, C. Kaiser, D. H. Tedeschi, R. E. Tedeschi, and A. Burger, *ibid.*, **5**, 1265 (1962).

(5) (a) J. Finkelstein, E. Chiang, and J. Lee, *ibid.*, **8**, 432 (1965); (b) *ibid.*, **9**, 440 (1966).

(6) J. Finkelstein, E. Chiang, F. M. Vane, and J. Lee, *ibid.*, **9**, 319 (1966).

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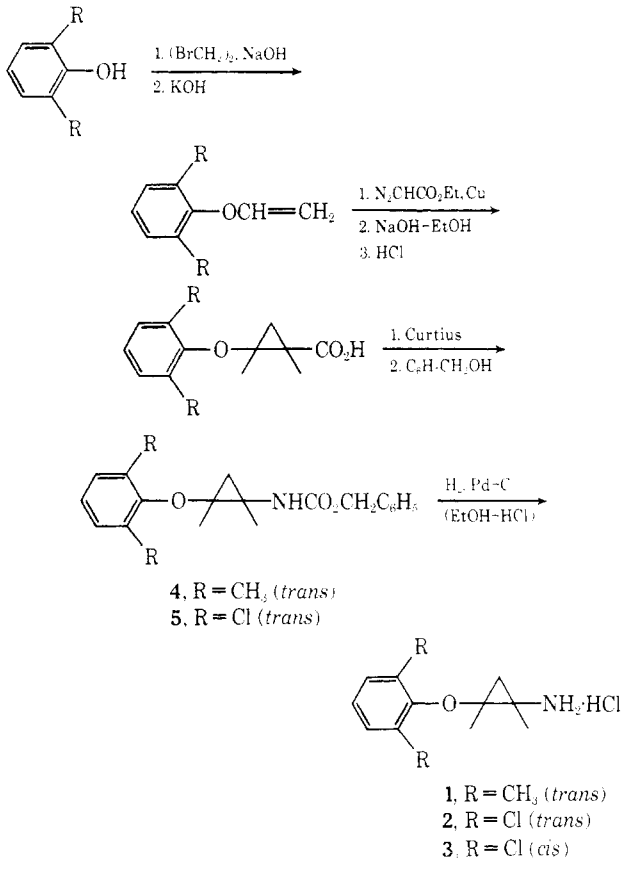
(8) T. J. Frolen and L. Goodman, *J. Am. Chem. Soc.*, **83**, 3405 (1961).

(9) J. Augstein, S. M. Green, A. M. Monro, T. J. Wrigley, A. R. Katritzky, and J. J. T. Tiddy, *J. Med. Chem.*, **10**, 391 (1967).

(10) F. C. Copp, *Advan. Drug Res.*, **1**, 163 (1964).

CHART I



tonic convulsions, tremors, exophthalmos, salivation, and piloerection at 100 mg/kg. Compounds **1** and **3** did not cause death until 100 mg/kg was administered, whereas **2** did not produce death at this dose.

Spontaneous Activity.—The time-course effect of **1–3** on spontaneous activity indicated that the compounds are depressants with the greatest effect generally occurring approximately 15 min after drug administration. However, this interpretation might be suspect since it is possible that the compounds are stimulating to the point where the animals undergo disorienting tremors and thus do not move laterally to interrupt the photocell beams. Doses of 12.5, 25, and 50 mg/kg of **1** produced decreases of 49.6, 85.9, and 92.2%; **2**, 27.9, 25.6, and 33.9%; and **3**, 50.3, 62.8, and 84.5% of activity. All three test compounds greatly potentiated hexobarbital sleeping times: mice treated with **2** and **3** all slept in excess of 4 hr, whereas the control animals, treated only with hexobarbital, slept an average of 33.9 min; animals treated with **1** all slept in excess of 3 hr; however, the control animals slept an average of 33.5 min. This was an unexpected finding in view of the stimulatory effects noted in the gross observation studies.

Reserpine Inhibition.—Table I shows the behavioral effects of **1–3** in comparison with imipramine (non-MAO inhibitor), amphetamine, and α-ethyltryptamine acetate (MAO inhibitor), both before and after reserpine administration. Imipramine administered before reserpine prevented ptosis in all four animals tested but there were no other behavioral changes. Amphetamine also prevented ptosis but also produced salivation, general increase in activity, exophthalmos, piloerection, and stereotypy behavior. Ethyltryptamine produced the same effect as amphetamine but without the stereotypy behavior. Test compounds **1–3**, in doses of 25 and 50 mg/kg, produced the same effect as ethyltryptamine.

TABLE I

BEHAVIORAL EFFECTS IN MICE

Drug (dose, mg/kg ip)	Before reserpine (45 min)	After reserpine (4 hr)
Imipramine (50)	Prevents ptosis for 45 min	Ptosis, ataxia, with no behavioral effects
Amphetamine (10)	Salivation, piloerection, ↑ act., stereotypy, exophthalmos	Reverses ptosis, ↑ act. after 15 min
α-Ethyltryptamine (25)	Salivation, piloerection, ↑ act., exophthalmos	Reverses ptosis, 5 min, ↑ act.
1–3	Same as α-ethyltryptamine	Reverse ptosis, ↑ act. in 30 min
Reserpine	Ptosis, ↓ act.	Ptosis even when stim, no act. when stim

When administered after reserpine, imipramine, in doses of 25 and 50 mg/kg, did not reverse depression nor counteract reserpine-induced ptosis. Amphetamine in doses of 5 and 10 mg/kg reversed ptosis approximately 20–45 min after injection, increased activity, and produced the stereotypy circling behavior. Ethyltryptamine reversed ptosis within 5 min and also increased activity. Compounds **1–3** also reversed ptosis and increased activity in all four animals tested. Animals treated with reserpine alone showed profound ptosis and depressed activity. In this test, then, the test compounds mimicked both amphetamine and ethyltryptamine.

Experimental Section

Melting points are corrected, and boiling points are uncorrected. Elemental analyses by Galbraith Laboratories, Knoxville, Tenn. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Ir spectra were determined on a Perkin-Elmer spectrophotometer Model 337 in KBr (solids) or neat (liquids), pmr spectra on a Varian Model A-60 (TMS internal standard). Where D_2O was used, the standard was sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DDS). Solvents were removed on a Rinco rotary evaporator at a water aspirator. Pmr spectra are on file with one of the authors (J. F. Siuda).

Chemistry. β-Bromoethyl 2,6-Xylyl Ether.—Although this ether had been mentioned previously (ref 10, p 172) it had not been described in detail. To a solution of 2,6-xylenol (2 moles) in 1 l. of 95% EtOH was added 82 g (2.1 moles) of NaOH in H_2O (250 ml) and then 1,2-dibromoethane (800 g). After refluxing for 6 hr, the now neutral solution was treated with NaOH (41 g) and dibromoethane (400 g), refluxing was continued, and this treatment was repeated at intervals for 48–60 hr until the solution no longer turned acidic. EtOH was removed, the residue was extracted three times with Et_2O, and the extract was washed ($NaOH–H_2O$, NH_4Cl, H_2O), dried ($MgSO_4$), and fractionated through a 15-cm Vigreux column; yield 61–71%, bp 90–91° (1.2 mm), ir and nmr spectra as expected. *Anal.* ($C_{10}H_{13}BrO$) C, H, Br.

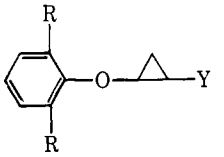
β-Bromoethyl 2,6-dichlorophenyl ether was prepared in an analogous manner; yield 78%, bp 140° (1 mm), pmr spectrum as expected. *Anal.* ($C_8H_7BrCl_2O$) C, H.

Vinyl 2,6-xylyl ether was prepared from the β-bromoethyl ether and powdered KOH; bp 78–80° (19 mm),[11] yield 44%,

(11) M. F. Shostakovskii, A. V. Kalabina, and J. G. Perova [*Izv. Fiz.-Khim. Nauchn.-Issled. Inst. pri Irkutskom Gos. Univ.*, **5**, 111 (1961); *Chem. Abstr.*, **58**, 8946c (1963)] reported bp 74–75° (9 mm).

TABLE II

2-(2,6-DISUBSTITUTED PHENOXY)CYCLOPROPANE DERIVATIVES



R	Y	Yield, %[a]	Mp[b] or bp (mm),[c] °C	Formula	Analyses
Cl	CO_2Et[d]	34	118–125 (0.7)	$C_{12}H_{12}Cl_2O_3$	C, H
Me	CO_2Et[d]	55	112–116 (1.4)		
Cl	*cis*-CO_2H	10.7	112.5–114.5[f]	$C_{10}H_8Cl_2O_3$	C, H
Cl	*trans*-CO_2H	76.7	107–108.5[g]	$C_{10}H_8Cl_2O_3$	C, H
Me	CO_2H[d]	82	65–68[g]		
Cl	*cis*-$NHCO_2CH_2C_6H_5$	73	80.5–82.5[g]	$C_{17}H_{15}Cl_2NO_3$	C, H, N
Cl	*trans*-$NHCO_2CH_2C_6H_5$ (**5**)	81	81–82[g]	$C_{17}H_{15}Cl_2NO_3$	C, H, N
Me	$NHCO_2CH_2C_6H_5$[e] (**4**)	80	88.5–90[g]	$C_{19}H_{21}NO_3$	C, H
Cl	*cis*-$NH_3^+Cl^-$ (**3**)	81	170–171 dec[h]	$C_9H_{10}Cl_3NO$	C, H, N
Cl	*trans*-$NH_3^+Cl^-$ (**2**)	79	180.5–181.5 dec[h]	$C_9H_{10}Cl_3NO$	C, H, N
Me	$NH_3^+Cl^-$[e] (**1**)	81	201.5–203.5 dec[h]	$C_{11}H_{16}ClNO$	C, H, N
Me	$N^+(CH_3)_3 \cdot I^-$ (**6**)		171–173 dec[h]	$C_{14}H_{22}ION$	H, N; C[i]

[a] Crude product. [b] Corrected. [c] Uncorrected. [d] Mixture of isomers. [e] Probably *trans*. [f] From C_6H_6. [g] From Et_2O–petroleum ether (bp 30–60°). [h] From absolute EtOH–EtOAc. [i] C: calcd, 48.42; found, 47.71.

pmr spectrum as expected. **2,6-Dichlorophenyl vinyl ether**[12] was obtained from the corresponding β-bromoethyl ether with absolute ethanolic NaOEt, bp 106–109° (12 mm), yield 49%, pmr spectrum as expected.

The physical and analytical data for the following compounds are given in Table II.

Ethyl 2-(2,6-Disubstituted phenoxy)cyclopropanecarboxylates.—A mixture of 0.5 mole of the vinyl ether and 1.2 moles of ethyl diazoacetate was added dropwise to 0.5 mole of the stirred vinyl ether and *ca.* 2.5 g of copper bronze at 130° at such a rate that vigorous N_2 evolution was maintained. The temperature rose to 150–155°; addition was complete after *ca.* 1 hr, and heating and stirring at 150° was continued for 0.5 hr. After cooling and filtering, the brown residue was distilled. The crude dichloro ester had bp 83–155° (4 mm); the crude xylyl ester, 95–122° (0.2 mm). Redistillation gave the esters as *cis–trans* mixtures.

2-(2,6-Disubstituted phenoxy)cyclopropanecarboxylic Acids.—*cis–trans* mixtures were obtained by refluxing the ethyl esters (1 mole) in EtOH (600 ml) with 30% aqueous NaOH (1 mole) for 1 hr, removing EtOH, and extracting continuously (36–48 hr) the carboxylic acids from the acidified residue with ether. The geometric isomers of 2-(2,6-xylyloxy)cyclopropanecarboxylic acid could not be separated. For the separation of the mixture of 2-(2,6-dichlorophenoxy)cyclopropanecarboxylic acids, the crude mixture was dried at 0.1 mm, yield 92.5 g, mp 77–105°. It was dissolved in a minimum of hot EtOAc and allowed to crystallize overnight. The filtered material was washed with hexane and consisted of 54.1 g of the *trans* acid, mp 107–109.5°. Recrystallization of the material in the mother liquor from EtOAc gave another 5.3 g (total 59.4 g) of pure *trans* acid.

The combined mother liquors contained 30 g of a solid which could not be crystallized fractionally any further. The best separation was achieved by dissolving 30 g of this mixture in a minimum of Me_2CO and chromatographing through 450 g of 60–100 mesh Florisil. The column (121 × 3 cm) was eluted with hexane (500 ml) until most Me_2CO was removed, then AcOH–hexane (1:99%) was used, and 80-ml fractions were collected. The first 49 fractions (4240 ml) contained no solid; fractions 50–70 gave 10.6 g of the *trans* acid. Elution with AcOH–hexane (2:98%), until evaporation furnished no more solid, yielded 9.9 g (10.7%) of *cis* acid. The total yield of *trans* acid was therefore 71.0 g (76.7%).

Benzyl N-[2-(2,6-Disubstituted phenoxy)cyclopropyl]carbamates.—The 2-(2,6-disubstituted phenoxy)cyclopropanecarboxylic acids (0.1 mole) were converted to the corresponding azides by a modified Curtius procedure,[13] the oily azides being dried ($MgSO_4$) and dissolved in toluene. The toluene solution was refluxed gently with dry benzyl alcohol (62 ml) for 6–12 hr, the solvent and excess $PhCH_2OH$ were removed (60°, 0.1 mm), and the residual amber oil was crystallized from Et_2O–petroleum ether (bp 30–60°).

2-(2,6-Disubstituted phenoxy)cyclopropylamines.—A solution of one of the above urethans (10 mmoles) in absolute EtOH (35 ml) containing 1 ml of concentrated HCl was hydrogenolyzed over 10% Pd–C. After about 5 hr the catalyst was filtered off, the solution was evaporated to dryness, and the solid residue was washed well (Et_2O). The amine hydrochlorides were colorless solids which were recrystallized from EtOH–EtOAc.

In the case of the 2,6-dichlorophenoxy derivative, the same amine hydrochloride (mixture melting point, ir spectral comparison) was obtained by the method just described, and by refluxing *trans*-1-(2,6-dichlorophenoxy)-2-isocyanocyclopropane[14] with 15% HCl for 15 hr.

Pharmacologic Methodology. Gross Observation.—A gross observation rating scale which reflects qualitative drug effects on gross behavior was employed for evaluating the compounds. The scale was divided into four major drug actions: (1) stimulation, (2) depression, (3) autonomic activity, and (4) reflexes and tone. Each of these actions is, in turn, subdivided into component characteristic responses (increased motor activity, body tremors, etc.). Each trial consisted of the simultaneous observation of a drug-treated and nontreated control animal. Items on the scale were checked 15, 30, 60, 90, 120, and 240 min after drug administration, so that the time course of the drug effect might be ascertained. The test compounds were administered intraperitoneally to mice (four animals per dose level) in doses ranging from 12 to 400 mg/kg.

Spontaneous Activity.—This test was performed simultaneously on four photocell activity cages (Metro Industries, Inc., New York, N. Y.) for 1 hr, utilizing five mice per photocell unit. The mice were placed in the unit immediately after intraperitoneal administration of the compounds. The doses (12.5, 25, and 50 mg/kg) were selected on the basis of the gross observation study and were randomized in a factorial design among the four activity cages in order to negate the difference in sensitivity among the test units.

Hexobarbital Sleeping Times.—Groups of mice (ten animals each) received either 25 or 50 mg/kg of each compound followed by the intraperitoneal administration of 100 mg/kg of hexobarbital sodium 30–45 min later. The control group received hexobarbital sodium only. Sleeping times for the animals of all groups were recorded as the interval between loss and return of the righting reflex. The criteria for the loss and return of the reflex were the inability and ability, respectively, of the animal to right himself within 30 sec in three successive trials when placed

(12) V. L. Tweedie and B. G. Barron, *J. Org. Chem.*, **25**, 2023 (1960).

(13) J. Weinstock, *ibid.*, **26**, 3511 (1961).

(14) This was obtained by gently refluxing the toluene solution of the corresponding azide for several hours.

on its back. Trials were terminated arbitrarily 3–4 hr after the loss of righting reflex if the animals continued to sleep.

Reserpine Inhibition.—Three groups of male albino mice (four animals each) were administered **1** (25 mg/kg), **2** (50 mg/kg), and **3** (50 mg/kg) intraperitoneally followed by 2.5 mg/kg sc of reserpine 45 min later. The animals were then checked for ptosis and other behavioral effects 45 min after reserpine. A fourth group received reserpine only (2.5 mg/kg). Similar tests were performed using imipramine (50 mg/kg), amphetamine (10 mg/kg), and α-ethyltryptamine (25 mg/kg) as the control compounds.

Three additional groups of mice (four animals each) were treated with reserpine (2.5 mg/kg sc), followed by the intraperitoneal administration of either **1**, **2**, or **3** (same doses as above) 4 hr later. Albino mice were used on the same test design using imipramine (25 and 50 mg/kg ip), amphetamine (5 and 10 mg/kg ip), and α-ethyltryptamine (25 mg/kg).

Studies on the Cholinergic Receptor. III.[1,2] Parasympatholytic Properties of *cis*- and *trans*-4-Dimethylaminomethyl-2-phenyl-1,3-dioxolane Methiodide

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2-Phenyl-4-dimethylaminomethyl-1,3-dioxolane methiodide (III) is a parasympatholytic agent[3] of undefined geometry.[4] Because the *cis* arrangement of the 2 and 4 substituents is known to be of importance[1,5] in the potent parasympathomimetic agent, 2-methyl-4-dimethylaminomethyl-1,3-dioxolane methiodide (V), it appeared to be of interest to prepare the *cis* and *trans* isomers of III and determine their parasympatholytic properties.

We now report that III, as prepared by the method of Fourneau and Chantaloux,[6] is a 1:1 mixture of the *cis* and *trans* isomers, thus further substantiating our previous observations[1,5] that molecular complex formation appears to be common among quaternary and other derivatives of 1,3-dioxolane. Samples of the *cis* and *trans* isomers of III, each enriched to the extent of about 80%, have been prepared by partial separation of the isomers at the intermediate 2-phenyl-4-chloromethyl-1,3-dioxolane stage. The assignment of structure was by nmr spectroscopy[1,7] and has been discussed in detail in the previous paper of this series. The parasympatholytic properties of IIIa and IIIb were determined using the rat jejunum preparation previously described.[8] IIIa and IIIb were found to be equipotent as antagonists of *cis*-2-methyl-4-dimethylaminomethyl-1,3-dioxolane methiodide (Figure 1).

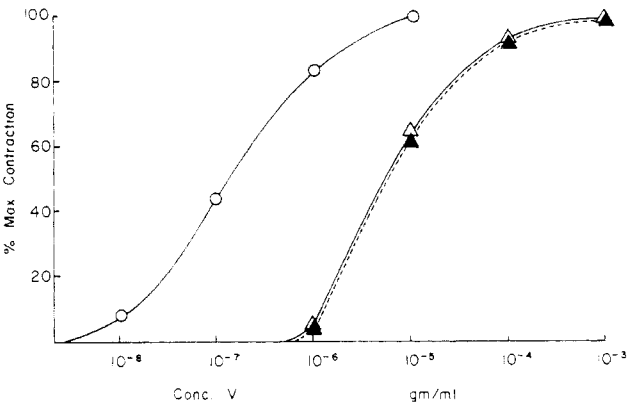
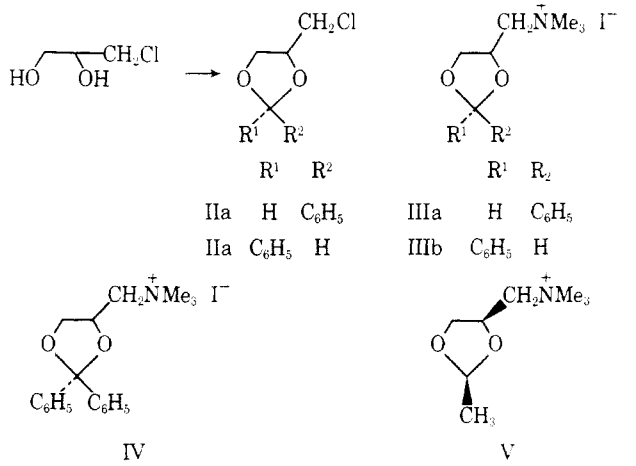


Figure 1.—Dose-response curves for *cis*-2-methyl-4-dimethylaminomethyl-1,3-dioxolane methiodide (V) in the absence (○) and in the presence of IIIa (△) and IIIb (▲), both 5×10^{-7} g/ml.



This lack of stereospecificity is of some interest and suggests that a large nonpolar binding surface exists at the receptor surface capable of binding equally well the phenyl groups of IIIa and IIIb. In accordance with this, introduction of a second phenyl group (IV) produces a marked increase in parasympatholytic activity.[3] However, the relationship between this binding site and that occupied by the methyl group of the agonist compound remains undetermined. Conceivably, the methyl group occupies a unique portion of the large nonpolar area as suggested in the model of the cholinergic receptor advanced by Belleau.[9,10] Alternatively, the two binding sites may be completely distinct as would be the case if the agonist and antagonist molecules bind to different areas of the receptor surface.

Experimental Section

Melting points were determined on a Thomas–Koffler hot stage and are corrected. The nmr spectra, in CD_3CN solution, methiodides, or neat material (TMS), were recorded on a Varian A-60 spectrometer. Glpc analyses, on 10% Carbowax columns, were carried out using an F & M Scientific instrument (Model

(1) Part II: D. R. Garrison, M. May, H. F. Ridley, and D. J. Triggle, *J. Med. Chem.*, **12**, 130 (1969).

(2) This work was supported by grants from the National Institutes of Health (GM 11603) and NASA (NGR-33-015-016).

(3) J. M. van Rossum and E. J. Ariëns, *Arch. Int. Pharmacodyn. Ther.*, **118**, 418 (1959).

(4) D. J. Triggle, "Chemical Aspects of the Autonomic Nervous System," Academic Press, London, 1965, p 112.

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(6) E. Fourneau and S. Chantaloux, *Bull. Soc. Chim. France*, **12**, 845 (1945).

(7) N. Baggett, K. W. Buck, A. B. Foster, R. Jeffries, B. H. Rees, and J. M. Webber, *J. Chem. Soc.*, 3382 (1965).

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(9) B. Belleau, *Advan. Drug. Res.*, **2**, 89 (1965).

(10) B. Belleau, *Ann. N. Y. Acad. Sci.*, **144**, 705 (1967).