that PGE_1 is a unique compound that inhibits platelet aggregation induced by ADP, thrombin, and collagen; it is also active when administered intravenously, and it lyses formed platelet thrombi. The vast difference in antithrombotic activity between PGE_1 and closely related structures shows that minor modifications in the structure of prostaglandin can greatly alter the antithrombotic properties of the compound. This observation would suggest that it should be possible to modify the prostaglandin molecule further to yield an analog with potent antithrombotic properties, but with fewer side effects than PGE_1. Even if such an analog has only a short duration of activity, as in the case of PGE_1, it might be feasible to administer the compound clinically as a continuous intravenous infusion to inhibit platelet aggregation and other thromboembolic complications.

Acknowledgment.—The author thanks Mr. Daniel J. Wynalda for expert technical assistance, Dr. James R. Weeks for helping with the infusion experiments, and Drs. John E. Pike, E. G. Daniels, and F. H. Lincoln for the prostaglandins.

The Inhibition of Viral Neuraminidase by 1-Phenoxymethyl-3,4-dihydroisoquinolines. I. Steric Effects

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A series of 1-phenoxymethyl-3,4-dihydroisoquinolines were shown to be noncompetitive inhibitors of influenza virus neuraminidase. A structure–activity study revealed severe steric limitations on binding to a hypothetical receptor on the enzyme, the preferred conformation for binding being that where the phenyl and isoquinoline ring systems are approximately coplanar, and the oxygen and nitrogen atoms are cisoid. Corresponding isoquinolines and 1,2,3,4-tetrahydroisoquinolines are inactive. A novel dehydrogenation reaction has been discovered, which apparently proceeds *via* the N-oxide of the 3,4-dihydroisoquinoline.

The enzyme neuraminidase (N-acetylneuraminate glycohydrolase, EC 3.2.1.18) is present as a component of the surface protein in all strains of influenza and parainfluenza viruses, these viruses representing a large proportion of the common respiratory pathogens.[1]

Investigations[2-5] into the function of the enzyme in influenza virus replication have provided evidence that it assists in the release of virus from infected cells. Inhibition of the enzyme would be expected to slow down the rate of release, thus delaying the spread of virus within the host tissue. A search for inhibitors was therefore made as a rational approach to the chemotherapy of influenza, and this paper describes studies based on the discovery of inhibition by 1-phenoxymethyl-3,4-dihydroisoquinoline (**5**, R = H). Compounds within this series possessed considerable antiviral activity *in vitro*.[6] The compound (**5**, R = OCH_3) was subsequently tested in man and found to have a prophylactic effect against an influenza B infection.[7]

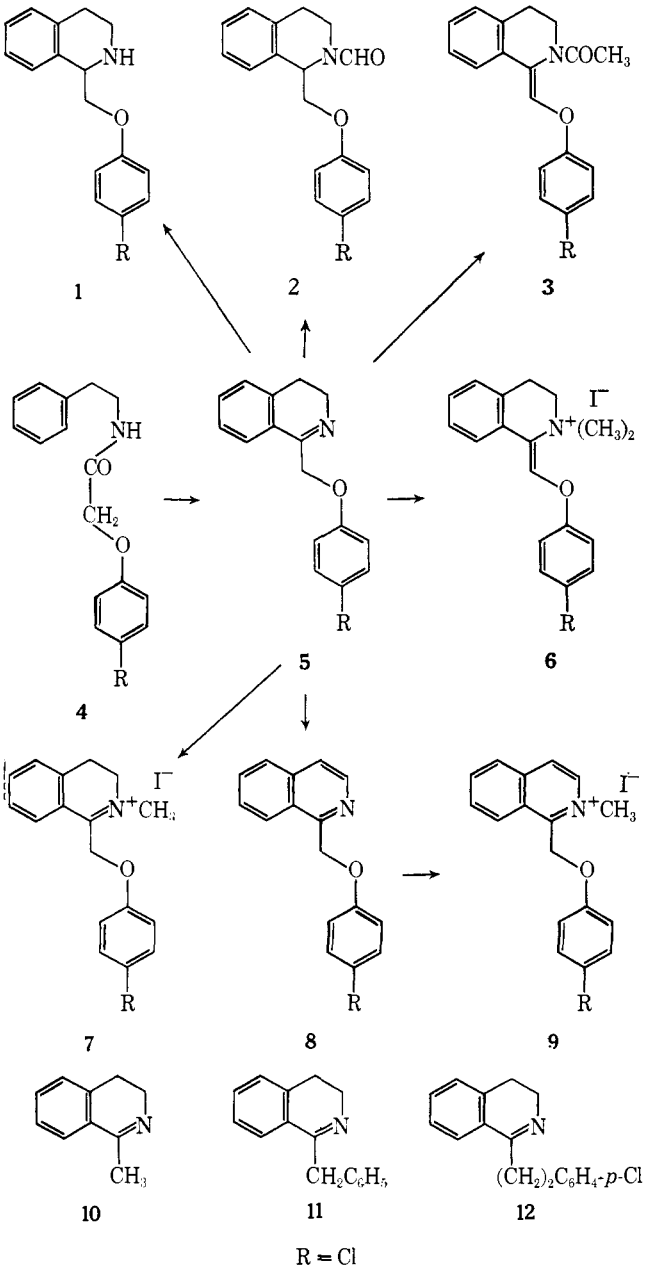
Structure–Activity Relationship.—It was soon established that simple *para* substitution in the phenyl ring to give compounds **5** (R = Cl, OCH_3) resulted in a significant but undramatic increase in enzyme-inhibitory activity. We therefore made a study of the effect of certain structural changes upon the binding of the chosen prototype (**5**, R = Cl) to a receptor on the enzyme, assuming that a comparison of levels of inhibition of the enzyme by compounds at equimolar concentrations provided a measure of their relative affinities for the receptor. It was hoped that in this way we could determine both steric and electronic limitations on binding, and eventually predict more active molecules. Chart I represents the most readily obtained related structures, and of these only the methiodide **7** was found to retain some activity. The N atom of the intermediate amide **4** and of the N-formyltetrahydroisoquinoline **2** is no longer basic, and so it was at first assumed that the nitrogen should be in a form capable of ionization, but the inactivity of the tetrahydroisoquinoline **1** (a strong base) and of the isoquinoline **8** was against this assumption, as was the fact that the inhibition of enzyme by **5** was found to be independent of pH, when this was varied from pH 5.5 to 7.5, the pK_a of **5** (R = Cl) being 6.57.[8] The inactivity of **1** and **8** is better explained on steric grounds, for an examination of molecular models[9] shows that the relative positions in space of the two aromatic nuclei, and of the N and O atoms, all possible binding sites, are different in compounds **5**, **1**, and **8**.

Compounds **10**, **11**, and **12** were prepared in order to confirm that the phenyl ring and oxygen atom were necessary for binding. All were inactive at the standard concentration of 2 mM, but slight inhibitory activity was found for **12** (in which CH_2 replaces O) at 5 mM. The function of the oxygen may be to furnish a stable constrained conformation which places the phenyl group at an aryl-binding site on the receptor.

Consideration of a model of **5** led us to the hypothesis

(1) J. E. Banatvala, *Proc. Roy. Soc. Med.*, **60**, 637 (1967).
(2) B. L. Padgett and D. L. Walker, *J. Bacteriol.*, **87**, 363 (1964).
(3) J. T. Seto and R. Rott, *Virology*, **30**, 731 (1966).
(4) R. G. Webster and W. G. Laver, *J. Immunol.*, **99**, 49 (1967).
(5) E. D. Kilbourne, W. G. Laver, J. L. Schulman, and R. G. Webster, *J. Virol.*, **2**, 281 (1968).
(6) K. W. Brammer, C. R. McDonald, and M. S. Tute, *Nature*, **219**, 515 (1968).
(7) A. S. Beare, M. L. Bynoe, and D. A. J. Tyrell, *Lancet*, i, 843 (1968).
(8) Measured by the uv method as in A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases, Laboratory Manual," John Wiley & Sons, Inc., New York, N. Y., 1962.
(9) Courtauld space-filling models.

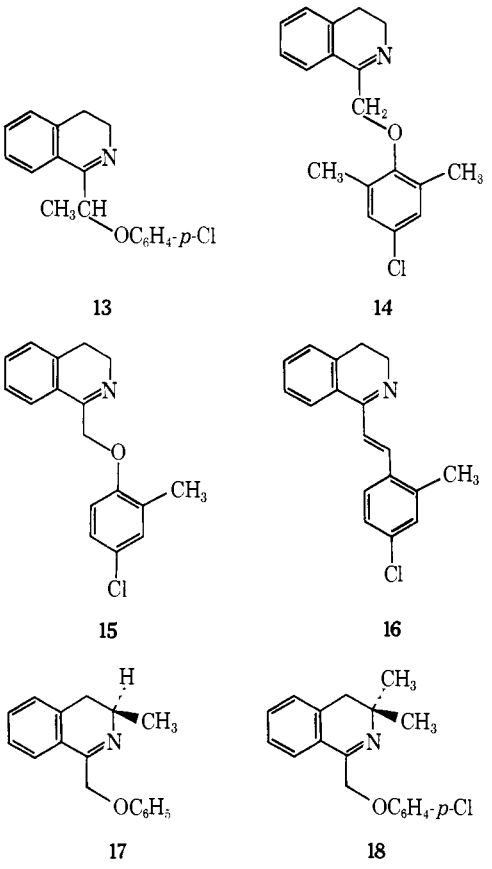
CHART I



that for maximum binding, not only should the two aromatic rings be in the positions determined by the cisoid arrangement of N and O atoms (transoid being unfavorable because of steric interaction between O and the H at position 8 of the isoquinoline), but also that the aromatic rings should be approximately coplanar. It was evident from the model that substitution of CH_3 on the CH_2 bridge, or substitution of both *ortho* positions to the ether link, would force the phenyl ring to rotate out of the plane of the isoquinoline ring in order to relieve steric compression. Compounds **13** and **14** (Chart II) were prepared and were much less active, supporting the hypothesis. Finally, comparison of **15** with *trans*-1-(4-chloro-2-methylstyryl)-3,4-dihydroisoquinoline[10] (**16**) revealed a similar degree of enzyme inhibition. Compound **16** is isosteric with the favored cisoid-coplanar conformation of **15** and apparently interacts with the same receptor on the

(10) We thank Dr. I. C. Appleby (Pfizer Ltd.) for a sample of this compound.

CHART II

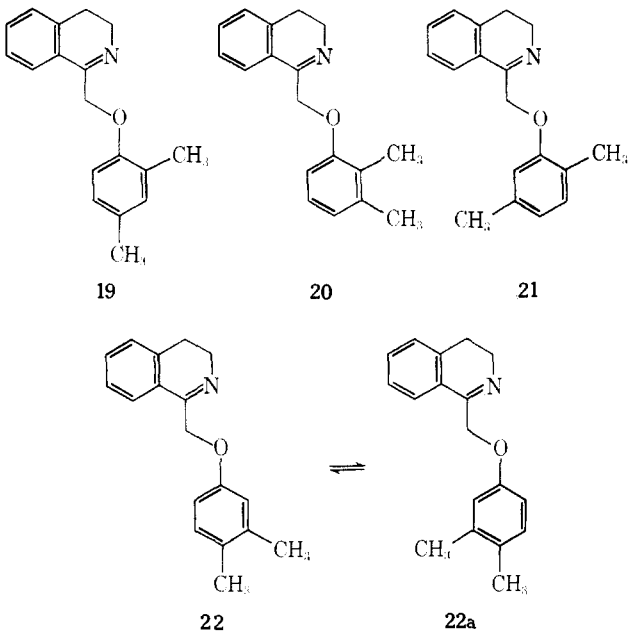


enzyme, as evidenced by a similar Lineweaver–Burk plot for both **16** and **5**. The comparable activities of **15** and **16** again emphasize the importance of steric rather than electronic effects, for although isosteric, the compounds are not isoelectric, the pK_a of **16** being 8.5.[8]

Steric limitations were further explored by the preparation of the 3-methyl and 3,3-dimethyl derivatives **17** and **18**. Disubstitution decreased the binding (**18** compared with **5**, R = Cl) presumably by hindering close approach of the molecule to the receptor, but monosubstitution (**17** compared with **5**, R = H) had virtually no effect. We suggest that one CH_3 affords no hindrance because the energy involved in changes between the various conformations of **17**, in which the CH_3 can be either above or below the plane of the ring, is small compared with the energy of binding to the receptor.

Another clue as to the steric limitations on the approach of the molecule to the receptor was obtained during a study of the effect of two substituents in the phenyl ring. The 2,4-, 2,3-, 2,5- and 3,4-dimethylphenoxy compounds **19**–**22** were compared (Chart III) and it was found that whereas **19** and **22** gave 49% inhibition, and **21** gave 58% inhibition, the 2,3-dimethylphenoxy compound **20** inhibited by only 14%. Now the presence of a CH_3 substituent *ortho* to the ether link prevents the molecule of **19**, **20**, or **21** from freely taking up the alternative favorable coplanar conformation obtained by rotation of the phenyl ring through 180°. Such rotation *is* possible with **22**, and the *m*-CH_3 can therefore assume the position indicated by **22a**. The reduction in binding of **20** is therefore attributed to steric hindrance provided by *m*-CH_3.

CHART III



None of our modifications of the prototype have led to any great increase in activity. We have shown here that this is principally because of steric effects; changes in activity due to hydrophobic and dipole effects are discussed in part II,[11a] where application of a modified Hansch[11b] Analysis with respect to these factors indicated that optimum activity has already been achieved.

Biochemistry.—A suspension of influenza A2/Singapore/1/57 virus in allantoic fluid was used as the source of viral neuraminidase without further purification. Purified collocalia mucoid[12] was used as substrate.

Standard neuraminidase inhibition assays were carried out in 0.05 *M* NaOAc buffer (pH 5.5) containing 2 m*M* $CaCl_2$ and 0.4 m*M* EDTA, normally in a final volume of 1 ml. The final enzyme concentration was a tenfold dilution of the original virus suspension and the substrate concentration was 10 mg of mucoid/ml. Enzyme activity was calculated from the amount of N-acetylneuraminic acid hydrolyzed from the mucoid during 20 min at 37°, as estimated by the Warren procedure.[13]

The inhibition of viral neuraminidase by **5** (R = Cl) at 2 m*M* was determined over the pH range 5.5–7.5. The results indicated that the level of inhibition did not vary significantly with pH (Table I), and thus the degree of ionization of the basic N atom of **5** (pK_a = 6.57) was not important in this interaction.

The inhibition of several dihydroisoquinoline derivatives was determined in the standard assay system varying the substrate concentration between 1 and 10 mg of mucoid/ml. (Experiments of this type established the K_m of influenza neuraminidase as approximately 3 mg/ml with respect to collocalia mucoid.) Analysis of the data in a double-reciprocal plot, according to the procedure of Lineweaver and Burk,[14] revealed that

TABLE I
INHIBITION OF NEURAMINIDASE BY COMPOUND 5 AT DIFFERENT pH VALUES[a]

pH	5.5	6.0	6.5	7.0	7.5
Inhib, %	52	51	48	49	49

[a] Standard assay conditions were used except that 0.05 *M* Tris (trishydroxymethylaminomethane) maleate at the indicated pH values replaced NaOAc as buffer solution.

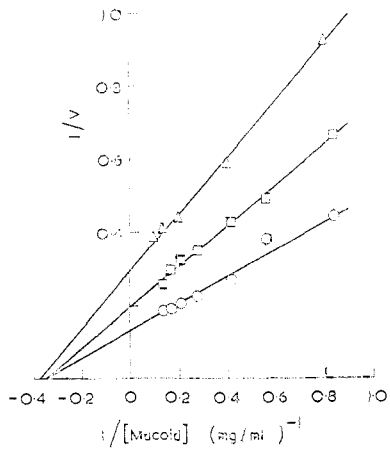


Figure 1.—Lineweaver–Burk plots of compounds **5** and **16**. The velocity, *V*, was measured by the procedure described for the standard neuraminidase assay and is expressed as micrograms of N-acetylneuraminic acid released per minute: ○, no inhibitor; □, **5** (1.5 m*M*); △, **16** (2.0 m*M*).

these compounds inhibit viral neuraminidase noncompetitively. The Lineweaver–Burk plots obtained with **5** (1.5 m*M*) and **16** (2 m*M*) are shown in Figure 1, and essentially similar results were obtained with four other analogs.

Chemistry.—Most of the 3,4-dihydroisoquinolines described in Table II were prepared by treating the appropriate phenethylamine with a substituted phenoxyacetic ester to give an amide, *e.g.*, **4**, which was then cyclized in a Bischler–Napieralski reaction using P_2O_5 in refluxing xylene.[15] The esters were obtained from a Williamson reaction between the phenol and methyl chloroacetate.[16] Ester and amide intermediates were characterized by ir spectra. The 1-methyl- and 1-benzyl-3,4-dihydroisoquinolines (**10**, **11**) were made according to published procedures.[15,17] The amide intermediate for the preparation of 3,3-dimethyl-1-(4-chlorophenoxymethyl)-3,4-dihydroisoquinoline (**18**) was obtained by the reaction of 4-chlorophenoxyacetonitrile[18] with 1,1-dimethyl-2-phenylethan-1-ol in the presence of H_2SO_4 (Ritter reaction).[19] Cyclization was accomplished in low yield, due to a competing cleavage of the amide giving 2,2-dimethylstyrene and 4-chlorophenoxyacetonitrile.

Of the compounds in Chart I, derived from the prototype **5**, only the isoquinoline **8** presented any difficulty. Attempted dehydrogenation of **5** using 10% Pd–C in refluxing xylene or decalin[20] resulted in the production of 4-chlorophenol and 1-methylisoquinoline by disproportionation. Dehydrogenation using chloranil in

(11) (a) M. S. Tute, *J. Med. Chem.*, **13**, 48 (1970); (b) C. Hansch, *Ann. Rept. Med. Chem.* 347 (1966).
(12) C. Howe, L. T. Lee, and H. M. Rose, *Arch. Biochem. Biophys.*, **95**, 512 (1961).
(13) L. Warren, *J. Biol. Chem.*, **234**, 1971 (1959).
(14) H. Lineweaver and D. Burk, *J. Am. Chem. Soc.*, **56**, 658 (1934).
(15) W. M. Whaley and W. H. Hartung, *J. Org. Chem.*, **14**, 650 (1949).
(16) J. Munch-Petersen, *Acta Chem. Scand.*, **5**, 519 (1951).
(17) H. R. Snyder and F. X. Werber, *J. Am. Chem. Soc.*, **72**, 2962 (1950).
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(20) F. D. Popp and W. E. McEwen, *ibid.*, **79**, 3773 (1957).

TABLE II

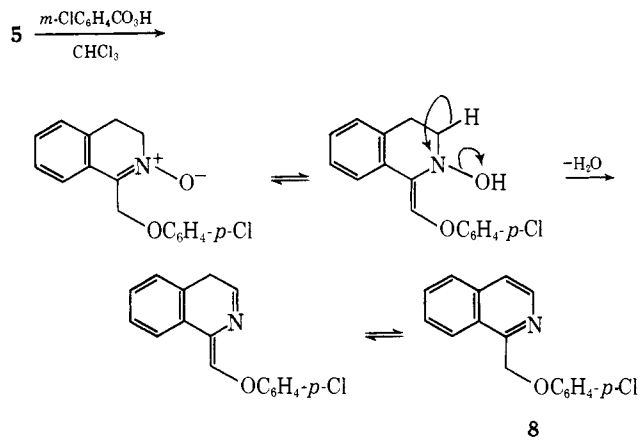
ENZYME INHIBITION, PHYSICAL CONSTANTS, AND ANALYSES

Compd	Neuraminidase inhib, %[a]	Recystn solvent[b]	Mp, °C	Yield, %[c]	Formula	Analyses
1	0	A	198–200	55	$C_{16}H_{16}ClNO \cdot HCl$	C, H, N, Cl
2	0	D	125–128	20	$C_{19}H_{16}ClNO_2$	C, H, N, Cl
3	0	C	168–169	80	$C_{18}H_{16}ClNO_2$	C, H, N, Cl
4	0	E	90–91	45	$C_{16}H_{16}ClNO_2$	C, H, H
5, R = H	34	C	210–212	33	$C_{16}H_{15}NO \cdot HCl$	C, H, N
5, R = Cl	46	B	203–207	85	$C_{16}H_{14}ClNO \cdot HCl$	C, H, N, Cl
5, R = OCH_3	38	B	180 dec	57	$C_{17}H_{17}NO_2 \cdot HCl$	C, H, N, Cl
6	0	A	158–160	50	$C_{18}H_{19}ClNO$	C, H, N
7	15	B	165–166	59	$C_{17}H_{17}ClNO$	C, H, N
8	0	A	183–184	22	$C_{16}H_{12}ClNO \cdot HCl$	C, H
9	0	A	172 dec	72	$C_{17}H_{15}ClNO$	C, H, N
10	0	B	194–195	59	$C_{10}H_{11}N \cdot HCl$	C, H, N, Cl
11	0[d]	A	229–230	30	$C_{16}H_{15}N \cdot HCl$	C, H, N
12	0	B	137–138	4	$C_{17}H_{16}ClN \cdot HCl$	C, H, N, Cl
13	14	B	85–86	31	$C_{17}H_{16}ClNO \cdot HCl \cdot H_2O$	C, H, N
14	23	B	202–204	45	$C_{18}H_{18}ClNO \cdot HCl$	C, H, N, Cl
15	44	A	208–209	33	$C_{17}H_{16}ClNO \cdot HCl$	C, H, N, Cl
16	48	F	229–231	21	$C_{18}H_{16}ClN \cdot HCl$	C, H, N
17	28	G	159–161	28	$C_{17}H_{17}NO \cdot HCl$	C, H, N, Cl
18	17	B	142–143	10	$C_{18}H_{18}ClNO \cdot HCl$	C, H, Cl
19	49	A	179–182	25	$C_{18}H_{19}NO \cdot HCl$	C, H, N, Cl
20	14	A	197 dec	14	$C_{18}H_{19}NO \cdot HCl$	C, H, N, Cl
21	58	A	189–191	12	$C_{18}H_{19}NO \cdot HCl$	C, H, N, Cl
22	49	A	211–213	22	$C_{18}H_{19}NO \cdot HCl \cdot H_2O$	C, H, N

[a] Inhibition by 2 m*M* compound at pH 5.5. [b] A, EtOH–Et_2O; B, MeOH–Et_2O; C, EtOH; D, petroleum ether (bp 100–120°); E, C_6H_6; F, 70% EtOH; G, Me_2CO. [c] In most cases, no attempt was made to improve yields. [d] 25% at 5 m*M*.

benzene or xylene[21] gave only an intractable tar. The desired isoquinoline was eventually prepared by the treatment of **5** with excess *m*-chloroperbenzoic acid, a procedure probably involving intermediacy of the N-oxide and elimination from this of the elements of H_2O[22] (Scheme I). As far as we are aware, this is a

SCHEME I



8

novel method for the dehydrogenation of an N heterocycle and may have more general applicability.

The 1,2,3,4-tetrahydroisoquinoline **1** was prepared from **5** using $NaBH_4$ in warm MeOH.[23] The N-formyl derivative **2** was prepared by reductive formylation of **5** using formic acid and formamide.[24] Acetylation of **5** with Ac_2O and NaOAc[23] gave 1-(4-chlorophenoxymethylene)-2-acetyl-1,2,3,4-tetrahydroisoquinoline (**3**).

(21) E. A. Braude, A. G. Brook, and R. P. Linstead, *J. Chem. Soc.*, 3569 (1954).

(22) Mechanism suggested by Professor A. R. Katritzky.

(23) I. Baxter and G. A. Swan, *J. Chem. Soc.*, 4014 (1965).

(24) I. Baxter, C. T. Allan, and G. A. Swan, *ibid.*, 3645 (1965).

Methylation of **5** with MeI in MeOH gave the methiodide **7**, and excess MeI with dry K_2CO_3 in acetone gave 1-(4-chlorophenoxymethylene)-2,2-dimethyl-1,2,3,4-tetrahydroisoquinolinium iodide (**6**). 1-(4-Chlorophenoxymethyl)-2-methyl-isoquinolinium iodide (**9**) was prepared from the isoquinoline **8** using the methylation procedure of Acheson.[25]

The synthesis of 1-(4-chlorophenethyl)-3,4-dihydroisoquinoline (**12**) involved a Willgerodt–Kindler reaction[26] on 4-chloropropiophenone to give 3-(4-chlorophenyl)propiothiomorpholide and then proceeded by hydrolysis to the acid, which when heated with phenethylamine in toluene with azeotropic removal of H_2O gave the corresponding amide, then cyclized to the 3,4-dihydroisoquinoline.

Experimental Section[27]

1-(4-Chlorophenoxymethyl)-2-methyl-3,4-dihydroisoquinolinium Iodide (7).—1-(4-Chlorophenoxymethyl)-3,4-dihydroisoquinoline (5.4 g) in MeOH (50 ml) was treated with excess MeI (10 ml) under reflux (1.5 hr). Concentration and addition of Et_2O precipitated the product, which was recrystallized from MeOH–Et_2O giving 4.4 g (54%) of yellow needles, mp 165–166° dec, λ_{max}^{MeOH} 287 mμ (ϵ_{max} 3400). *Anal.* ($C_{17}H_{17}ClINO$) C, H, N.

1-(4-Chlorophenoxymethylene)-2,2-dimethyl-1,2,3,4-tetrahydroisoquinolinium Iodide (6).—1-(4-Chlorophenoxymethyl)-3,4-dihydroisoquinoline (90 g) in dry Me_2CO (1000 ml) was treated with MeI (100 g) and dry K_2CO_3 (200 g). The mixture was

(25) R. M. Acheson and G. J. F. Bond, *ibid.*, 250 (1956).

(26) M. Carmack and M. A. Spielman, *Org. Reactions*, **3**, 83 (1956).

(27) Melting points are uncorrected (Electrothermal melting point apparatus). Ethereal extracts were dried over anhydrous $MgSO_4$. Evaporations were carried out on a Büchi-Rotavap evaporator. The ir spectra were recorded as Nujol mulls on an Infracord 137 spectrometer. Absorption bands were as expected. Phenols and amines used as starting materials were obtained from commercial suppliers. For those compounds prepared by general methods given in the footnotes, yields and recrystallization solvents are recorded in Table I. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

stirred and refluxed (3 hr), then filtered, and the filtrate was evaporated to obtain a crystalline residue. The bulk of the product was obtained by treating the cake of K_2CO_3 with hot H_2O, and filtering off the insoluble fraction. This was combined with the residue from Me_2CO evaporation, and recrystallized from MeOH giving 95 g (50%) of colorless crystals, mp 158–160° dec, λ_{max}^{MeOH} 269 mμ (ϵ_{max} 26,300). *Anal.* ($C_{18}H_{19}ClNO$) C, H, N.

1-(4-Chlorophenoxymethyl)isoquinoline (8).—1-(4-Chlorophenoxymethyl)-3,4-dihydroisoquinoline (10 g) in $CHCl_3$ (200 ml) was treated with *m*-chloroperbenzoic acid (13 g, 2.5 equiv).[28] The mixture was then heated to reflux (4 hr), cooled, washed (saturated $NaHCO_3$, H_2O), dried, and evaporated to a brown oil. The oil was taken up in a little C_6H_6 and chromatographed on neutral alumina (300 g, 2.5 × 40 cm column) eluting with 1:1 Et_2O–C_6H_5. Evaporation of the first 2000 ml of eluate gave a waxy substance (200 mg) which was discarded. The next 3000 ml yielded 2.2 g (22%) of the desired free base, mp 91–92°, converted to the hydrochloride by adding HCl in Et_2O to a solution in Et_2O. Recrystallization (EtOH–Et_2O) gave colorless crystals: mp 183°; $\lambda_{max}^{MeOH-1\% HCl}$ 230, 278, 335 mμ (ϵ_{max} 47,500, 4490, 5570). *Anal.* ($C_{16}H_{22}ClNO \cdot HCl$) C, H.

N-(1,1-Dimethyl-2-phenethyl)-4-chlorophenoxyacetamide.—4-Chlorophenoxyacetonitrile (33.5 g, 0.2 mole) was dissolved in AcOH with stirring. A mixture of concentrated H_2SO_4 (50 ml) and AcOH (25 ml) was added at room temperature, followed by 1,1-dimethyl-2-phenylethanol (34.0 g, 0.2 mole). The mixture was stirred and heated to 70° for 0.5 hr and then stoppered and left at room temperature for 2 hr. H_2O (250 ml) was added and the solution was neutralized with Na_2CO_3 and extracted with Et_2O, and the extract was dried and evaporated to yield an oil which solidified. Two recrystallizations from petroleum ether (bp 40–60°) gave 18.4 g (30%) of colorless crystals, mp 66–67°. *Anal.* ($C_{18}H_{20}ClNO$) C, H, N.

3-(4-Chlorophenyl)propiothiomorpholide.—4-Chloropropiophenone (20.0 g), sulfur (4.8 g), and morpholine (15.5 g) was stirred and refluxed for 17 hr. After cooling, the mixture was poured into warm EtOH (75 ml), whereupon brown crystals separated. Recrystallization from EtOH (charcoal) and then from EtOH–H_2O gave 12.0 g (37%) of yellow crystals, mp 98–100°. *Anal.* ($C_{13}H_{16}ClNOS$) C, H, N.

3-(4-Chlorophenyl)propionic Acid.—The thiomorpholide (9.0 g) was hydrolyzed by refluxing in a mixture of AcOH (20 ml), H_2O (45 ml), and concentrated H_2SO_4 (3 ml) for 5 hr. The crude product was precipitated by pouring into H_2O (180 ml), and the precipitate was digested with hot 5% NaOH (250 ml) for 4 hr. This gave a yellow solution and dark red oil. The yellow solution was decanted from the oil and acidified (HCl) to give a light yellow solid. Two recrystallizations from C_6H_6 gave 3.0 g (49%) of colorless plates, mp 115–116°. *Anal.* ($C_9H_9ClO_2$) C, H.

N-Phenethyl-3-(4-chlorophenyl)propionamide.—3-(4-Chlorophenyl)propionic acid (35.0 g) and phenylethylamine (23.0 g, 1 equiv) were refluxed in dry toluene (1500 ml) for 48 hr, with azeotropic removal of H_2O. Evaporation of the toluene left a brown residue, recrystallized (charcoal) from C_6H_6–petroleum ether (bp 100–120°) and then twice from petroleum ether (bp 100–120°) to give 30.0 g (55%) of colorless needles, mp 119–121°. *Anal.* ($C_{17}H_{18}ClNO$) C, H, N.

(28) The use of 1 equiv of *m*-chloroperbenzoic acid gave a yield of only 3.5%. Other components of the mixture have not yet been investigated.

Acknowledgment.—It is a pleasure to acknowledge the excellent technical assistance given by Mr. D. Cowley and Mrs. M. A. Price. We thank Mr. P. Wood for microanalyses and Professor A. R. Katritzky for advice and for checking the manuscript. We thank the directors of Pfizer Ltd. for permission to publish these results.

The Inhibition of Viral Neuraminidase by 1-Phenoxymethyl-3,4-dihydroisoquinolines. II. A Hansch Analysis

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Received May 5, 1969

A multiple regression analysis on a series of 1-(*para*- and *meta*-substituted phenoxymethyl)-3,4-dihydroisoquinolines, using the methods described by Hansch, relates various substituent constants to inhibition of the viral enzyme neuraminidase. A highly significant relationship has been shown to exist between enzyme inhibition and the hydrophobicity constant, π, and also between enzyme inhibition and group dipole moment, μ. The significance of terms in μ and μ^2 is discussed; these terms are believed to represent dipole–charge (μ) and dipole-induced dipole (μ^2) interactions between drug and receptor. The Hansch analysis has thus been used as a diagnostic tool rather than in any predictive sense and affords evidence as to the nature of the receptor site on the enzyme, or enzyme–substrate complex.

In continuing our work on structure–activity relationships in the 1-phenoxymethyl-3,4-dihydroisoquinoline series,[1] we realized that here was the ideal situation for study of drug–receptor interaction using the methods described by Hansch and his coworkers,[2] based on a linear free-energy relationship between relative biological response and various substituent constants, these being used as parameters in a multiple regression analysis. The choice of parameters is arbitrary and the statistical method allows the testing of each of the corresponding coefficients by the application of a *t* test. A semiempirical approach has been tried here, using first the constants found by Hansch to be generally useful, namely the hydrophobic bonding constant π and the Hammett constant σ.[2b] This report describes how we have applied these constants, and then tried others, namely group dipole moment μ and polarizability α, which we had reason to believe could be especially significant to the analysis of a simple interaction between drug and receptor *in vitro*.

Method.—The standard equation to be solved in multiple regression analysis is of the form of eq 1

$$y = k_1x_1 + k_2x_2 + k_3x_3 + \cdots + k \qquad (1)$$

where y represents relative biological response and where x_1, x_2, x_3, ... are substituent constants. A computer program was written for the solution of this equation by the method of least squares, to provide the regression coefficients k_1, k_2, k_3, ... the constant k, the multiple correlation coefficient, and the standard

(1) Part I: M. S. Tute, K. W. Brammer, B. Kaye, and R. W. Broadbent, *J. Med. Chem.*, **13**, 44 (1970).

(2) (a) C. Hansch, *Ann. Rept. Med. Chem.*, 348 (1967); (b) C. Hansch and T. Fujita, *J. Am. Chem. Soc.*, **86**, 1616 (1964); (c) T. Fujita, J. Iwasa, and C. Hansch, *ibid.*, **86**, 5175 (1964).