Journal of Medicinal and Pharmaceutical Chemistry

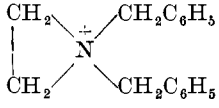
VOL. 1, No. 4 (1959)

Mechanism of Drug Action at Receptor Surfaces—II. Chemical Reactivity of *N*-(β-chloroethyl)-Phenoxyethylamines in Relation to Adrenergic Blocking Activity

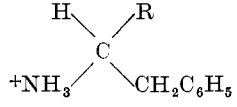
B. BELLEAU

Department of Chemistry, University of Ottawa, Ottawa, Ontario, Canada

In Part I of this series[1], a general interpretation of the adrenergic block activity of β-chloroethylamines was presented. On the basis of an empirical model receptor surface for adrenergic amines, it was shown that the pharmacologically active ethylenimmonium ion (I)* (hereon abbreviated as EI-ion) derivable from



(I)



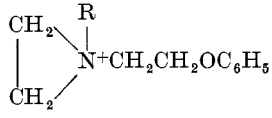
(II)

Dibenamine under physiological conditions, can be looked upon as a true isostere of sympathomimetic amines (II). From our study,[1] it emerged that all adrenergic blocking agents of this class have a common 'phenethylamine backbone' or 'pattern', a concept which led us to suggest that an anionic group may be the essential primary binding site on the adrenergic receptor surfaces. The nature of this binding site was not specified, however, but the proposal was made that a carboxylate or phosphate anion may be involved. Presently, it would seem more satisfactory to decide in favour of a phosphate anion on the basis of the fact that phosphate esters of β-aminoalcohols are much more stable towards hydrolysis[3,4] than carboxylate esters.[5] This is in better agreement with the prolonged duration of blockade produced by Dibenamine although it should be pointed out that the work of

* For a recent corroborative demonstration that EI-ions constitute the only active species, the paper by Graham[2] should be consulted.

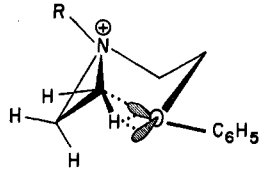
Harvey and Nickerson[6] appears to conflict with this interpretation. The contradiction may be superficial, however, since the binding of agonists or antagonists by a phosphate anion could be only a prerequisite for any subsequent surface reaction such as the alkylation of a thiol group.[6,7] However, this is not a requirement in our interpretation[1] and it remains that the alkylation of a phosphate anion alone explains the nature of the observed effects. It is hoped to discuss this point more fully in a future communication.

In connection with our interpretation of the adrenergic blocking activity of *N*-phenoxyethyl-β-haloalkylamines,[1] it was pointed out that EI-ions of the class III deviate from the phenethyl-



(III)

amine pattern rule. Mainly on the basis of analogies and theoretical considerations, it was suggested that the EI-ion (III) may owe its activity to the possibility that the molecule exists in the folded conformation (IV) which agrees with the phenethylamine

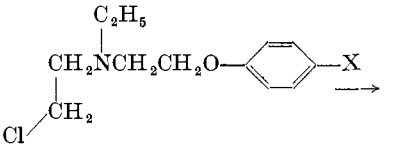


(IV)

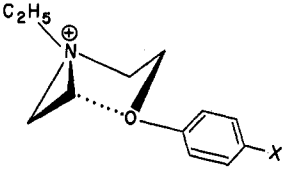
pattern rule. However, the type of interaction between the oxygen atom and a methylene group of the EI-ion as suggested in (IV) is unprecedented, and for this reason requires a careful evaluation of the factors involved. *A priori*, conformation (IV) is not unreasonable because a 1,5-interaction (low entropy demand[8]) is implied. Moreover, the methylene groups of EI-ions being strongly electrophilic, some electrostatic interaction with the orbitals of the phenolic oxygen is probable. This effect should

minimize the energy barrier associated with the eclipsing of groups and make possible a proper fitting on the receptor surfaces. However, the existence of significant concentrations of (IV) in solution is less certain and it became a matter of considerable importance to ascertain this point by experimental means, even though it is not an essential requirement that (IV) should exist as such in solution in order to exhibit blocking activity. It should suffice theoretically that the eclipsing of groups is not opposed by such energy barriers that cannot be overcome by the receptor surfaces.

In selecting an experimental approach to the problem of the possible interaction depicted in (IV), it may be expected that the magnitude of the 1,5-interaction should depend on the nucleophilicity of the oxygen atom, a property that is amenable to control by the introduction of suitable substituents in the *para*-position of the phenyl ring (V). This approach should have the



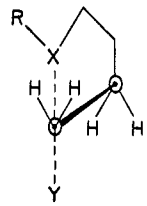
(V)



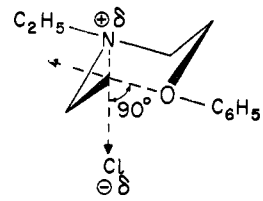
(VI)

important advantage that the presence of *para*-substituents should not in any foreseeable way affect the steric environment of the reacting centres, so that any effect of the substituent on a selected chemical behaviour of (V) could be ascribed only to the nucleophilic power of the oxygen atom. There remained to select the quantity to be measured that should reflect a participation effect by the oxygen atom. Normally, the operation of a neighbouring group participation effect in the sense advocated by Winstein[9] is associated with large deviations from an expected kinetic behaviour. Such effects are usually observed when the participating group and the leaving group form a planar transition state (VII). Under these conditions the rate of ejection of the leaving group Y (VII) is markedly enhanced. Clearly, such a participation effect cannot be extrapolated to the transformation (V) → (VI) since participation of the oxygen atom in the process of chloride ion ejection from (V) must occur at right angles with

the plane of the first transition state (VIII) itself involving participation of the basic nitrogen. It would seem, therefore, that the determination of the rate of chloride ion evolution from



(VII)

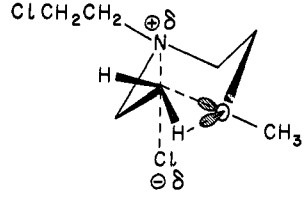


(VIII)

(V) to give (VI) may not yield any information on the magnitude of a possible interaction between a methylene group and the oxygen atom of (VI). Nevertheless, and in spite of these arguments, it has been observed by Cohen, Artsdalen and Harris[10] that the substitution of an oxygen atom for a methylene group in butyl nitrogen mustard (IX and X) led to a marked enhancement in the rate of the first cyclization step, an effect which is clearly reminiscent of a neighbouring group effect. Unfortunately, Cohen and his collaborators[10] could find no adequate explanation for these observations.

$CH_3CH_2CH_2CH_2N{=}(CH_2CH_2Cl)_2$ (IX)

$CH_3OCH_2CH_2N{=}(CH_2CH_2Cl)_2$ (X)

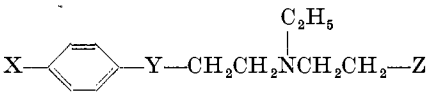


(XI)

It seems clear that the oxygen atom of (X) must interact in some way (possibly through hydrogen bonding) with the transition state leading to the corresponding EI-ion, and for our purposes structure (XI) may be used as a satisfactory representation of this

effect. We are aware, however, that further studies will be required to clarify the exact nature of this interaction. From these observations, it appeared that a study of the rates of cyclization of compounds such as (V) might yield the desired information on the possibility of interaction effects in the conversion of V to VI, and for this purpose the kinetic approach of Cohen *et al.*[10] appeared most suitable.

The following series of *N*-ethyl-*N*-(β-chloroethyl amines) (XII) was therefore synthesized according to conventional procedures (see experimental) and their properties are assembled in Table I. The corresponding *N*,*N*-diethyl analogues were also prepared (Table II) in order to determine their dissociation constants which could not be obtained in the chloroethyl series (XII, Z = Cl) due



(XII, Z = Cl)
(XIII, Z = H)

to rapid decomposition at alkaline pH. These dissociation constants were required in order to correlate the variations in the rates of cyclization to the corresponding EI-ions with the dissociation constants of the amines. In fact, Cohen and co-workers[10] have shown that in a strictly homologous series of β-chloroethylamines, there is a linear relationship between the logarithm of the rate constants and the logarithm of the dissociation constants of the amines so that any deviation from this relationship in our series may be ascribed to some kind of participation effect. It must be pointed out that the pK'_a values of series (XIII) are undoubtedly higher than the actual pK values of the chloroethyl series (XII) because of the inductive effect of the β-chlorine atom. It can be shown readily from Cohen's data[10] that a β-chlorine atom lowers the pK of a parent amine by at least two full pK units. Since the pK′s of series (XIII) should be related to the pK′s of series (XII) by a constant, it follows that a linear relationship between the pK'_a values of series (XIII) and the logarithm of the rate constants of series (XII) should obtain as long as complicating effects are absent.

The first-order rate constants for the cyclization of series (XII)

Table I. Properties of N-(β-chloroethyl)-N-ethylamines (XII, Z = Cl).

	X	Y	M.p. of hydrochloride	N		Cl		$10^2 k_1$ min^{-1}*
				calcd.	found	calcd.	found	
XIIa	H	CH_2 [21]	oil	5·34	5·20	27·1	27·2	34·5
XIIb	H	O [21]	107–8°	5·30	5·22	26·89	27·1	16·1
XIIc	OCH_3	O	110–2°	4·76	4·64	24·14	24·24	18·5
XIId	Cl	O	131–2°	4·69	4·60	35·67	35·31	15·2
XIIe	NO_2	O	161–3°	9·03	8·92	22·90	22·85	12·0
XIIf	H	S	76–8°	5·00	4·88	25·35	25·43	22·0
XIIg	H	OCH_2	107–9°	5·03	5·12	25·54	25·40	21·0

* Measured in 70% aqueous-ethanol saturated at 37°C with potassium bicarbonate.

Table II. Properties of *N*,*N*-Diethylamines (XIII, Z=H).

	X	Y	B.p.	pK′$_a$*	Ref.
XIIIa	H	CH_2	70°/0·25mm	9·20	23
XIIIb	H	O	75°/0·2mm	8·22	24
XIIIc	OCH_3	O	95–7°/0·15mm	8·28	25
XIIId	Cl	O	90–2°/0·3mm	8·20	26
XIIIe	NO_2	O	135°/0·3mm	7·90	27
XIIIf	H	S	88–92°/0·25mm	7·80	28
XIIIg	H	OCH_2	85°/0·2mm	8·60	29

* Determined at 25°C in 50 : 50 aqueous-ethanol from the titration curves.

to the corresponding EI-ions were measured in 70 per cent aqueous-ethanol saturated at 37°C with potassium bicarbonate by following the rate of chloride ion evolution. The pH of the medium was 9·5 so that under these conditions it can readily be shown using the relationship

$$\text{pH} = \text{pK} + \log \frac{[\text{dissociated amine}]}{[\text{undissociated amine}]}$$

that all the amines were fully dissociated. In this equation, the term pK is given by the pK′$_a$ values of Table II from which two pK units must be subtracted (see above). That the rate of chloride ion evolution gives a direct measure of the rate of cyclization to the corresponding EI-ions has been ascertained by Cohen *et al.*[10] who showed also that at alkaline pH, the reaction is essentially irreversible. A typical example is illustrated in Table III which clearly shows that the reaction obeys first-order kinetics on the basis of the constancy of the k values.

A comparison of the k_1 values of Table I with the pK′$_a$ values of Table II shows readily that there is a lack of correlation in some cases. In Fig. 1, the logarithm of the rate constants k_1 is plotted against the pK′$_a$ values of Table II from which it emerges that three compounds (XIIb, XIIc and XIIf) deviate from an otherwise perfect linear relationship. It is interesting to note that those compounds (XIIa, XIId, XIIe and XIIg) which lead to a

Table III. Rate of cyclization of compound (XIIg) in 70% ethanol–water saturated at 37°C with $KHCO_3$. Initial concentration = 0·01 M.

t_{min}	k_{min}^{-1}
0·5	0·220
1·5	0·200
2·0	0·210
2·5	0·215
3·0	0·208
5·0	0·213
10·0	0·209

Average k_1 = 0·210

(Since the amines are fully dissociated under these conditions, the rate constant k_1 need not be corrected.)

linear relationship are exactly those which would be expected to exhibit little or no participation effects.

Indeed, no 1,5-interaction is possible with (XIIa), whereas in (XIId) and XIIe) the nucleophilicity of the oxygen atom is

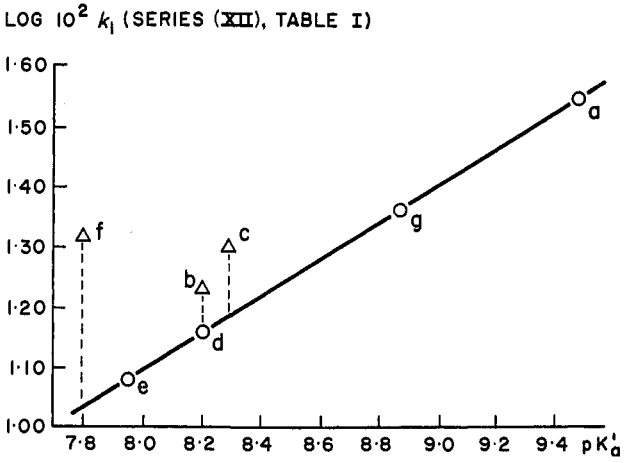
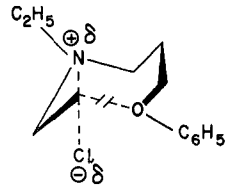


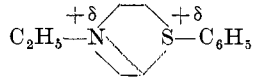
Fig. 1.

considerably reduced. Moreover, the phenoxypropyl derivative (XIIg) should exhibit little participation in view of the fact that a 1,6-interaction is involved (XIV), thus conducive to a higher entropy demand. This point has been illustrated in the case of



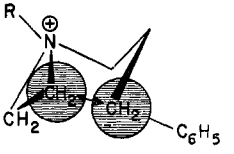
(XIV)

bromide ion displacement in 5-bromopentyl ethyl ether as opposed to 4-bromobutyl ethyl ether.[11] On the other hand, the phenoxyethyl derivative (XIIb) tends to deviate from the linear relationship and this effect is somewhat amplified by the introduction of a methoxy group in the *para*-position of the benzene ring (XIIc). It is significant that a *para*-methoxy group should increase nucleophilicity of the other oxygen atom as judged from the results of Bordwell and Cooper[12] on the acidity constants of substituted phenols. The largest deviation occurs in the case of the phenylthio derivative (XIIf) and this again agrees with the much greater nucleophilicity of sulphur as compared to oxygen. It appears, therefore, that the trend in the deviations is in the right direction but their magnitude is decidedly of little significance from the mechanism point of view. It is evident that a definite neighbouring group effect may be operative only in the case of the phenylthio derivative (XIIf). Nevertheless, this alone seems to justify the presumption that a 1,5-interaction of the type discussed above is possible. In the two other cases (XIIb and XIIc), it would be premature to specify the exact nature of the slight enhancements in the rates of cyclization. Recently, Blackadder and Hinshelwood[13] have re-emphasized the role of solvation in energy–entropy relations and it is probable that this factor may be involved in these two cases. To summarize, the following conclusions may be drawn: (1) the present kinetic data indicate that in the case of the phenylthio derivative (XIIf) the actual pharmacologically active species may be represented by structure (XV). This point will be discussed later in a separate communication. Structure (XV) is of interest as it represents a new type



(XV)

of alkylating agent. (2) In the case of phenoxyethylamine derivatives (XIIb and XIIc), the kinetic data eliminate the possibility of a participation effect but do not exclude the existence of an electrostatic 1,5-interaction as postulated above. It would seem preferable on that basis to ascribe adrenergic blocking activity in that series to a lowering of the energy barrier in the eclipsing of groups if folding of the molecule to species (IV) must occur at the receptor surface level. Since the rates of cyclization to EI-ions may not necessarily have a bearing on the type of interaction discussed above it is obvious that other approaches will be necessary to clarify this point. The importance of energy barriers in the eclipsing of groups is best illustrated by the case of the hydrocinnamyl derivative (XVI) which cannot spontaneously exist in that conformation because of the large non-bonded repulsion between the two eclipsed methylene groups. As a consequence, this compound is inactive in contrast to (XIIb).



(XVI)

Experimental*

Preparation of Starting Materials

All the amines were obtained from the corresponding bromides which were prepared according to the following general procedure: one mole of the appropriate commercially available phenol was mixed with three moles of ethylene bromide and one mole of sodium hydroxide in 250 ml of ethanol and the mixture heated under reflux for 24 h, after which time the solvent and excess ethylene bromide were removed by evaporation *in vacuo*. The residue was fractionally distilled after isolation in the usual manner by extraction with ether followed by successive washings with water and dilute sodium hydroxide solution. In this manner, the following ethers were obtained in yields ranging from 60 to 80 per cent.

* All b.p. and m.p. are uncorrected. Analyses by M. B. Mercier, Laval University and Midwest Microlab, Indianapolis.

Table IV. $R(CH_2)_nCH_2Br$

R	n	b.p.	m.p.	Ref.
C_6H_5O	1		—	14
p-Cl.C_6H_4.O	1	140°/0·5mm	—	—
p-NO_2.C_6H_4.O	1		64–5°	15
p-CH_3O.C_6H_4.O	1	142°/0·5mm	49–50°	16
C_6H_5O*	2	133–5°/15mm*	—	14
C_6H_5S†	1	134°/23mm	—	18

* Prepared by substituting trimethylene bromide for ethylene bromide.
† In this case, the *chloride* was prepared from the corresponding alcohol.[18]

Preparation of the Intermediate N-(*Aryloxyethyl*)-*Ethanolamines* ($ArOCH_2CH_2NHCH_2CH_2OH$) *and the* N-*Cinnamyl-Ethanolamine*

With the exception of the *p*-nitrophenoxy derivative (preparation described below), the bromides listed in Table IV including cinnamyl chloride were reacted with ethanolamine according to the following general procedure which is patterned after that of Kerwin, *et al.*[19,20]: three molar equivalents of ethanolamine was heated to gentle reflux, and while stirring one molar equivalent of the halide was added drop-wise over a period of 30 min. The mixture was heated and stirred for 3 h after which time it was cooled and poured into cold water followed by extraction with chloroform. The chloroform layer was washed several times with water, then dried and evaporated. The residue was fractionally distilled *in vacuo* to give the desired products in yields of 50 to 70 per cent. The properties are assembled in Table V.

Table V. $R{\cdot}NHCH_2CH_2OH$

R	b.p.	Anal.		Ref. (to prepara. tion)
		Calcd. N%	found N%	
$C_6H_5OCH_2CH_2$	115°/0·25mm	7·73	7·68	22
p-Cl.$C_6H_4OCH_2CH_2$	165°/0·8mm	6·49	6·41	—
p-CH_2O.$C_6H_4OCH_2CH_2$	146°/0·1mm; m.p. 67–68°	6·63	6·71	22
$C_6H_5OCH_2CH_2CH_2$	135–140°/0·5mm	7·17	7·08	—
$C_6H_5SCH_2CH_2$	145–150°/0·5mm	7·10	7·00	—
$C_6H_5CH{=}CH{-}CH_2$	150–155°/0·3mm	7·90	7·98	—

Preparation of N-*Ethyl*-N-(*Aryloxyethyl*)-*Ethanolamine*

The preceding aminoethanol derivatives (1 molar equivalent) in 5 volumes of ethanol were mixed with 1·33 molar equivalents of ethyl bromide and 0·5 molar equivalent of dry potassium carbonate. The mixture was heated under reflux while stirring for 24 to 30 h after which time it was cooled, filtered and the filtrate evaporated *in vacuo*. The residue was fractionally distilled *in vacuo* and the fraction with a constant boiling point re-distilled before analysis. The yields of tertiary amines were 30–60 per cent of the theoretical. The properties are given in Table VI.

Table VI. R·N(C_2H_5)CH_2CH_2OH

R	b.p.	Anal.				Ref. (to pre. para. ation)
		calcd.		found		
		C,	H,	C,	H,	
$C_6H_5OCH_2CH_2$	125°/0·5mm	—	—	—	—	22
p·Cl.$C_6H_4OCH_2CH_2$	151–3°/1·5mm	59·17	7·39	59·00	7·20	—
p·NO_2.$C_6H_4OCH_2CH_2$*	172–4°/0·7mm	56·69	7·08	56·51	7·17	—
p·CH_3O.$C_6H_4OCH_2CH_2$	145–7°/0·5mm	65·27	8·78	65·40	8·65	—
$C_6H_5OCH_2CH_2CH_2$	134–5°/0·7mm	69·95	9·41	70·04	9·28	—
$C_6H_5SCH_2CH_2$	135°/0·6mm	64·00	8·44	64·21	8·56	—
$C_6H_5CH = CH–CH_2$	125°/0·5mm	76·09	9·26	76·23	9·02	—

* Prepared according to the procedure described below.

N-*Ethyl*-N-(*p-Nitrophenoxyethyl*)-*2-Aminoethanol*

Although the reaction of *p*-nitrophenoxyethyl bromide with excess ethanolamine proceeded smoothly, it was found practically impossible to alkylate the reaction product with ethyl bromide, starting material being recovered unchanged. Therefore, the alternative method consisting of reacting the bromide with excess *N*-ethyl-2-aminoethanol was adopted: one molar equivalent of *p*-nitrophenoxyethyl bromide was mixed in ethanol with 2·5 molar equivalents of *N*-ethyl-2-aminoethanol and the solution heated under reflux for 48 h. The solvent was evaporated *in vacuo* and the residue dissolved in chloroform. The solution was washed thoroughly with water, dried and evaporated. The residue was distilled *in vacuo* to yield at 175–185°/0·7 mm a

yellowish viscous liquid in 50 per cent yield. It was re-distilled at 172–4°/0·7 mm prior to analysis (see Table VI).

Preparation of the 2-Chloroethylamine Hydrochlorides (XIIb to XIIg)

One molar equivalent of the preceding *N*,*N*-disubstituted ethanolamines was dissolved in 2 to 3 volumes of dry chloroform and dry hydrogen chloride passed into the solution until acid to congo red. The resulting solution of the hydrochloride was cooled in ice, and with stirring 1·2 molar equivalent of purified thionyl chloride was added drop-wise over a period of about 30 min. The solution was allowed to stand at room temperature for 2 h and then heated under reflux for 15–20 min. The solvent was evaporated *in vacuo* and the residue crystallized to constant melting point and composition from methanol–acetone mixtures or acetone–ethyl acetate mixtures. The properties of these compounds are assembled in Table I (see text).

N-*Ethyl*-N-(*2-Chloroethyl*)*Hydrocinnamylamine Hydrochloride (XIIa) from the Cinnamyl Analogue*

The *N*-ethyl-*N*-(2-chloroethyl)hydrocinnamylamine hydrochloride (XIIa, Table I) was an oil which failed to crystallize. When this compound was prepared from the corresponding alcohol by treatment with thionyl chloride as described above, the resulting dark syrup was highly contaminated with impurities so as to preclude its use in kinetic studies. It was, therefore, necessary to obtain this oily substance in pure form, and for that purpose it was decided to use the pure crystalline *N*-ethyl-*N*-(2-chloroethyl)-cinnamylamine hydrochloride as starting material which was found to hydrogenate cleanly to the desired hydrocinnamyl analogue in the presence of platinum oxide.

Thus, the *N*-cinnamyl derivative of Table VI above was treated with thionyl chloride according to the preceding procedure and the resulting *N*-ethyl-*N*-(2-cyloroethyl)cinnamylamine hydrochloride re-crystallized from ethanol–acetone until a constant melting point of 148–150° was obtained (reported without constants).[22]

Ten g of the pure material was dissolved in 100 ml of ethanol and some dry hydrogen chloride introduced into the solution. The mixture was hydrogenated over 0·1 g of platinum oxide

under 50 lb/in^2 of hydrogen. After 20 min hydrogen absorption ceased and corresponded to one molar equivalent. The catalyst was filtered off and the solvent evaporated *in vacuo*; alcohol was added to the residue and again removed *in vacuo*. This process was repeated 2 or 3 times to free the residue from excess hydrogen chloride. The colourless syrupy residue was finally dissolved in 70 per cent aqueous ethanol and the volume completed to 100 ml. Aliquots were used for analysis of the product (Table I) and for the determination of its exact concentration. The solution was found suitable for kinetic studies and gave reproducible results.

Preparation of the N,N-*Diethylamino Analogue of Table II*

The following general procedure for the preparation of the amines listed in Table II was followed: each of the bromides of Table (IV) was heated to 100° for 24 h in a pressure bottle with a large excess of diethylamine. The mixture was poured into dilute sodium hydroxide and extracted with ether. The ether extract was extracted with dilute hydrochloric acid which was then made basic with sodium hydroxide and re-extracted with ether. The ether was dried and evaporated and the residue distilled *in vacuo*. The main cut was re-distilled before analysis and a titration curve in 50 per cent aqueous ethanol and at 25°C obtained with the aid of a Beckman pH meter, Model G. The results are given in Table II. The pK values are accurate to $\pm 0{\cdot}04$ unit.

Kinetic Methods

The solvent system used in the kinetic determinations was prepared by dissolving 10–15 g of potassium bicarbonate in 300 ml of distilled water and completing the volume to 1 l. with 99 per cent ethanol whereupon some potassium bicarbonate separated. The salt was allowed to settle leaving a clear solution which was $0{\cdot}1$ M in bicarbonate. The mixture was immersed in a water-bath maintained at $37°C \pm 0{\cdot}05$ until the temperature of the solution was 37°C; 450 ml of the clear solution was measured in a volumetric flask and transferred to a 1 l. flask immersed in the water-bath. At time zero, 5 millimoles of the appropriate β-chloroethylamine made up to 50 ml in 70 per cent aqueous-ethanol was injected under nitrogen pressure (delivery time 1 sec)

into the buffer solution and under initial vigorous agitation. The mixture was continuously circulated in a closed circuit by a centrifugal pump equipped with a calibrated glass ampoule inserted in the circuit. At chosen intervals, the flow was interrupted with a stopcock and the glass ampoule allowed to drain through a stopcock (delivery time 0·5 sec) under nitrogen pressure into dilute nitric acid solution. The apparatus as well as the procedure were checked by injecting 0·01 N hydrochloric acid into the circulating liquid; in this way, it could be estimated that reproducibility of the results was of the order of ± 3 per cent. The quenched aliquots were then titrated by the Volhard method and the first-order rate constant calculated using the equation

$$k = \frac{2 \cdot 303}{t} \log \frac{a}{a-x}$$

where t = time in min, a = initial concentration of the amine, and x = concentration of chloride ion at time t. The results are assembled in Table I. Three separate kinetic runs were carried out for each of the compounds.

pK′$_a$ *Determinations on Series (XIII)*

Titration curves for each compound of series (XIII) were obtained using 50 per cent aqueous ethanol as the solvent and at 25°. A Beckman pH meter, model G, equipped with glass electrodes was used for the pH determinations. Initial concentration of the amines was 0·01 M and the titrations were carried out using 0·1 N hydrochloric acid. The pK′$_a$ values were obtained graphically from the titration curves. The results are given in Table II.

Summary. The nature of the anionic group postulated to be an essential part of adrenergic receptors (*cf.* Part I[1] of this series) is briefly discussed and it is suggested that a phosphate anion may be involved. The preparation of a series of *N*·phenoxyethyl·β·chloroethylamines carrying substituents in the *para*-position of the phenyl ring is described. Determinations of the cyclization rates of these amines under pseudo·physiological conditions were carried out in a search for possible neighbouring group effects in that series. The results indicate that no significant participation effects occur in the cases studied (excepting phenylthioethylamine derivatives). Our recent interpretation of adrenergic blocking activity in the phenoxyethylamine series is revised in the light of these kinetic

studies and it is pointed out that energy barriers in the eclipsing of groups at the receptor surface level may constitute a critical factor controlling intrinsic activity of adrenergic blocking agents.

Acknowledgements. Appreciation is expressed to the National Research Council of Canada for financial assistance.

(*Received 9 March, 1959*)

References

[1] Belleau, B. *Canad. J. Phys.* **36**, 731 (1958)
[2] Graham, J. D. P. *Brit. J. Pharmacol.* **12**, 489 (1957)
[3] Cherbuliez, E., Probst, H., Rabinowitz, J. and Sandrin, S. *Helv. chim. Acta*, **41**, 1163 (1958)
[4] Cherbuliez, E. and Bouvier, M. *Helv. chim. Acta* **36**, 1200, (1953)
[5] Davis, W. and Ross, W. C. J. *J. chem. Soc.* 3056 (1950)
[6] Harvey, S. C. and Nickerson, M. *J. Pharmacol.* **112**, 274 (1954)
[7] Nickerson, M. *Pharmacol. Rev.* **9**, 246 (1957)
[8] Streitwieser, A. *Chem. Rev.* **56**, 667 (1956)
[9] Winstein, S. and Grunwald, E. *J. Amer. chem. Soc.* **70**, 828 (1948); and subsequent papers
[10] Cohen, B., Artsdalen, E. R. V. and Harris, J. *J. Amer. chem. Soc.* **70**, 281 (1948); **74**, 1875 (1952)
[11] Oae, S. *J. Amer. chem. Soc.* **78**, 4030 (1956)
[12] Bordwell, F. G. and Cooper, G. D. *J. Amer. chem. Soc.* **74**, 1058 (1952)
[13] Blackadder, D. A. and Hinshelwood, C. *J. chem. Soc.* 2728 (1958)
[14] Marvel, C. S. and Tanenbaum, A. L. *Org. Synth.* Coll. Vol. I, 435 (1941)
[15] Wilson, W. C. and Adams, R. *J. Amer. chem. Soc.* **45**, 539 (1923)
[16] Renshaw, R. R. and Hopkins, C. Y. *J. Amer. chem. Soc.* **55**, 1524 (1933)
[17] Rumpf, P. *Bull. Soc. chim. Fr. Docum.* [5], **5**, 871 (1938)
[18] Amstutz, E. D. *J. org. Chem.* **9**, 310 (1944)
[19] Kerwin, J. F. *et al.* *J. Amer. chem. Soc.* **73**, 4162 (1951)
[20] Kerwin, J. F. and Ullyot, G. U.S. Pat. 2,683,719; *Chem. Abstr.* **49**, 11011e (1955)
[21] Gump, W. S. and Nikawitz, E. J. *J. Amer. chem. Soc.* **72**, 3846 (1950)
[22] Nickerson, M. and Gump, W. S. *J. Pharmacol.* **97**, 25 (1949)
[23] Peak, D. A. and Watkins, T. I. *J. chem. Soc.* 445 (1950)
[24] Burger, A., Wilson, E. L., Brindley, C. O. and Bernheim, F. *J. Amer. chem. Soc.* **67**, 1416 (1945)
[25] Kuroda, S. and Koyama, S. *J. pharm. Soc. Japan* **63**, 387 (1943)
[26] Drain, D. J., Peak, D. A. and Whitmont, F. F. *J. chem. Soc.* 2680 (1949)
[27] Rohmann, C. and Friedrich, K. *Ber. dtsch. chem. Ges.* **72B**, 1333 (1939)
[28] Benoit, G. and Bovet, D. *Bull. Sci. Pharmacol.* **45**, 97 (1938)
[29] Marvel, C. S., Zartman, W. H. and Bluthardt, O. D. *J. Amer. chem Soc.* **49**, 2299 (1927)