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Mechanism of Drug Action at Receptor Surfaces—III. Chemical Reactivity and Conformation of Spiro-Ethylenimmonium Ions in Relation to Adrenergic Blocking Activity*

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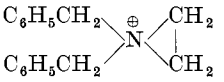
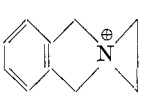
During the course of the extensive correlation studies of Nickerson, Gump and their collaborators[1,2] and Ullyot, Kerwin and their group[3] in the field of adrenergic blocking agents† related to Dibenamine-EI-ion (I), it was noted[3] that compounds in which the basic nitrogen is part of a ring (II, III, IV) are inactive in spite

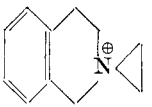


(I)

of their close structural similarity to Dibenamine. We suggested recently[4] that the rigidity of these spiro-structures (II, III and IV) introduces configurational restrictions that do not apply to



(II)



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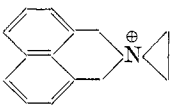


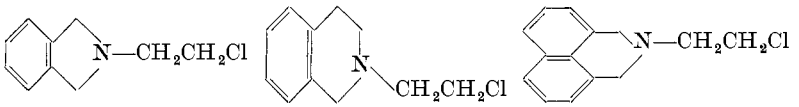
(IV)

open-chain EI-ions (I). Even though the phenethylamine pattern rule[4] applies to these ions, their rigidity should limit their ability to mould themselves onto the receptor surfaces. Obviously, with open-chain ions such as (I), variable degrees of freedom

* For the preceding paper in this series, see reference 13.

† The following abbreviations will be used: EI-ion for ethylenimmonium ion, ABAG for adrenergic blocking agent and ABAC for adrenergic blocking activity.

of rotation between the three-membered ring and the other substituents on the nitrogen are possible, thus allowing the molecule to fulfil the geometrical requirements of the receptors. These arguments formed the basis of our interpretation[4] of the inactivity of compounds (V), (VI) and (VII) which were assumed

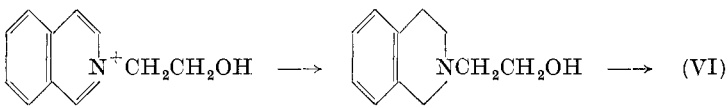


(V) (VI) (VII)

to yield their corresponding EI-ions (II), (III) and (IV) as relatively stable entities under physiological conditions. This latter assumption must now be critically examined from the quantitative point of view since it has been rigorously established that the only active species are the EI-ions themselves.[3,5] The kinetic behaviour of such cyclic β-chloroethylamines as (V), (VI) or (VII) does not appear to have been studied previously. It was of interest to include larger ring homologues of (VI) in these studies in view of our recent preliminary demonstration[4] that ABAC of spiro-EI-ions is a function of ring size. The synthesis of some new cyclic β-chloroethylamines, their kinetic behaviour and adrenergic blocking activity are the subject of this communication.

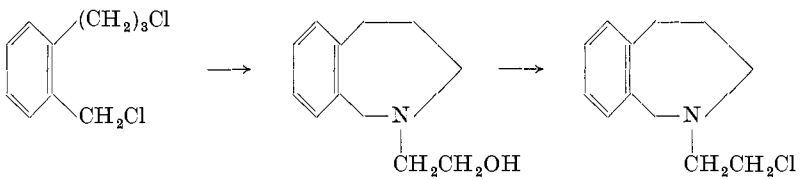
Synthesis of *N*-(β-Chloroethyl)-Benzaza*cyclo*alkanes

The lower homologue *N*-β-chloroethyl*iso*indoline (V) has been reported previously[1–3]. The tetrahydro*iso*quinoline derivative (VI) which has also been reported,[1–3] was prepared by a new method offering the advantage of convenience. *iso*Quinoline was quaternized in quantitative yield with 2-iodoethanol to give (VIII) which was reduced in high yield to (IX) by treatment with sodium borohydride.[6] Reaction of the latter with thionyl chloride in the usual manner afforded (VI).



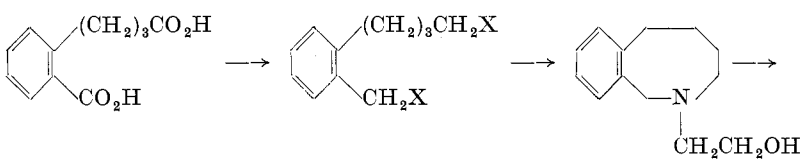
(VIII) (IX)

The seven-membered homologue (XII) is new and was prepared starting from *o*-chloromethyl-hydrocinnamyl chloride (X).[7] Reaction of the latter with ethanolamine gave (XI) in moderate yield which was readily converted to *N*-β-chloroethyl-1,2,3,4-tetrahydro-2-benzazepine (XII).



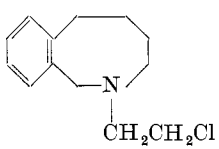
(X) (XI) (XII)

The next higher homologue (XVII) has not been reported previously. It was obtained starting from 4-(*o*-carboxyphenyl)-butyric acid (XIII) which in turn was prepared from 1-tetralone according to Johnson and Shelberg.[8] The sequence (XIII → XVII) was applied without any special difficulty. The final product *N*-β-chloroethyl-1,2,3,4,5,6-hexahydro-2-benzazocine (XVII) was obtained crystalline in moderate overall yield.



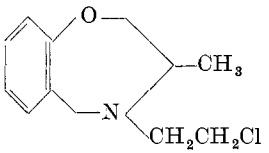
(XIII) (XIV, X = OH) (XV, X = Cl) (XVI)

Also included in our mechanism studies was the compound *N*-β-chloroethyl-3-methyl-1,2,3,4-tetrahydro-1,4-benzoxazepine



(XVII)

(XVIII) which represents a new heterocyclic ring system. We have already described its preparation[9] and it is noteworthy that this compound includes in a condensed form, the essential structural features of Dibenzyline.[3]



(XVIII)

Adrenergic Blocking Activity (ABAC)

The new β-chloroethylamine derivatives (XII), (XVII) and (XVIII) were tested for adrenergic blocking activity in the anaesthetized cat according to the procedure of Fellows, *et al.*[3,10] The minimum dose that consistently reversed the pressor effect of three standard doses of epinephrine was 4 mg/kg for XII and 0·8 mg/kg for (XVIII). These values represent blocking activity levels that are respectively 2·5 times and 12 times higher than Dibenamine. It was not possible to evaluate exactly the effective blocking dose for the benzazocine derivative (XVII) because of its potent hypotensive activity which was frequently fatal. However, at low doses, it was possible to establish that (XVII) possesses appreciable ABAC approaching Dibenamine in potency. This result is based on the establishment of a dose of Dibenamine producing a depth of blockade identical to that produced by a fixed dose of (XVII).

It is of considerable interest that the benzoxazepine compound (XVIII) proved orally effective in the dog at a dose level of 1·70 mg/kg. Therefore, this drug ranks amongst the most active and orally effective adrenergic blockers thus far reported.[3]

Kinetic Studies

In a previous communication,[11] a procedure was described for the measurement of the rate of cyclization of various β-chloroethylamines under pseudo-physiological conditions. Extension of this procedure to the homologous series (V), (VI) and (XII)

allowed accurate first-order rate constants (k_1) to be determined. The results are given in Table I which also includes results obtained with Dibenamine. In order to estimate the maximum effective concentration of EI-ions obtainable under these conditions, the procedure outlined by Ullyot and Kerwin[3] was followed. In this manner, the measurement of thiosulphate uptake in conjunction with titration for chloride ion led to the results included in Table I.

Table I. Measurements in 70% ethanol–water, 0·1M in $KHCO_3$ and at 37° C.

Compound	10^2k_1 min^{-1}	Max. EI-ion concentration, %	Time for max. EI-ion conc.	ABAC
(V)	0·41	0	—	nil [2]
(VI)	1·48	1±1	13–18 min	nil [2]
(XII)	20·4	60	8·5 min	4mg/kg
Dibenamine	1·65	5*	15 min*	10mg/kg

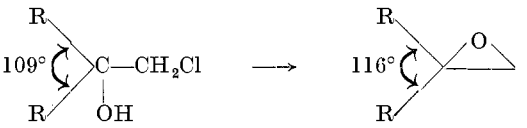
* This value is in excellent agreement with the one reported by Ullyot and Kerwin.[3]

It is interesting to note that the rates of cyclization as well as the maximum EI-ion concentrations increase as the size of the ring carrying the nitrogen increases. Insufficient quantities of the eight-membered compound (XVII) prevented its study by the kinetic method. However, as judged from the values obtained with (XII), it may be inferred that the rate of cyclization should fall within the range observed with (XII).

Discussion

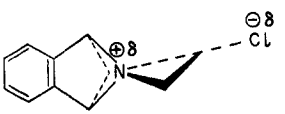
In the light of the present kinetic results it becomes clear that the inactivity as adrenergic blockers of compounds (V) and (VI) must be due at least in part to their inability to produce significant concentrations of EI-ions under physiological conditions. Another factor possibly contributing to inactivity is conformational rigidity of the spiro-ions (II) and (III). This point has already been discussed[4] and there remains to explain the inability of (V) and (VI) to yield measurable concentrations of EI-ions under favourable conditions. Although the dissociation constants of

the amines (V) and (VI) have not been measured, it is felt that the rather low pK values that can be expected for (V) and (VI) may not account for the low rates of cyclization (Table I). It has been our experience[11,12] that weakly basic and open-chain β-chloroethylamines ($pK_a \sim 7$) usually give rise to easily detectable concentrations of EI-ions. It appears that another factor of considerable importance may reside in the creation of additional ring strain upon formation of the EI-ion. To illustrate this point, it is only necessary to extrapolate Streitwieser's interpretation[13] of the effect of geminal substitution on the kinetics of cyclization of 2-halohydrins. Thus, upon cyclization of compound (XIX), the angle between the geminal groups increases



(XIX) (XX)

from the tetrahedral value of 109°28′ to 116°41′ in (XX). In the case of open-chain compounds, this spread in the bond angle leads to a faster rate of cyclization (greater entropy in the transition state). It is obvious that similar effects should operate in the cyclization of open-chain β-chloroethylamines. However, a spread in the bond angles of a small and rigid cyclic compound such as (V) should create strain in the five-membered ring and consequently should have an opposite effect on the rate of cyclization. This is shown in formula (XXI) where the solid lines

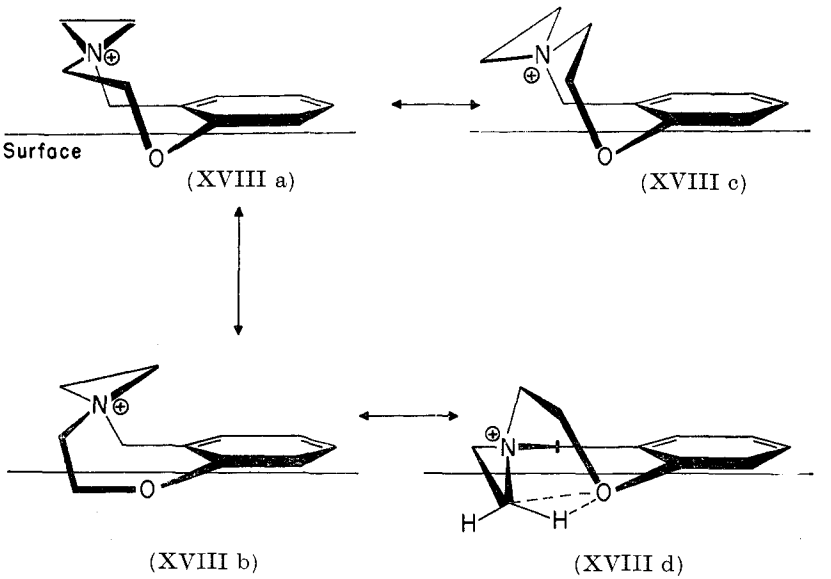


(XXI)

correspond to the uncyclized product and the dotted lines to the EI-ion. With the six-membered derivative (VI), the same effect should also operate and retard EI-ion formation. As the size of the ring increases, however, the spread in the bond angles should be better accommodated because of the greater flexibility of higher-membered rings. In fact, compound (XII) cyclizes

rapidly to give the corresponding EI-ion in high concentration. It can be seen, therefore, that ABAC of spiro-EI-ions is subject to conformational factors as well as chemical reactivity of the β-chloroethylamine moiety.

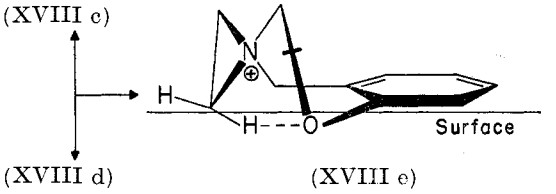
The high potency of the benzoxazepine derivative (XVIII) as compared to its isostere (XII) is of special interest in view of the possibility for an intramolecular interaction of the type previously discussed[11] in the case of open-chain phenoxyethylamine derivatives. It would seem reasonable to assume that (XVIII) is more active than (XII) because of a better 'fit' on the receptor surfaces (the chemical reactivity of (XII) being more than adequate). On that basis, some conformational differences between these two drugs should exist. In fact, if the assumption is made that an interaction with a receptor surface is favoured when an alkylating carbon is in the plane of a phenyl ring (as implied in a surface reaction), then it becomes possible to show that the oxygen of (XVIII) could facilitate the attainment of such a planar arrangement. A careful examination of Barton molecular models reveals that the four conformations (XVIIIa), (XVIIIb), (XVIIIc) and (XVIIId) are possible for compound (XVIII). However, only



(XVIII a) (XVIII c)

(XVIII b) (XVIII d)

the strainless and hybrid conformation (XVIIIe) allows a reactive methylene group to be in the plane of the phenyl ring. This latter arrangement should be especially favoured if an electrostatic interaction between the oxygen atom and a methylene group occurs as shown in conformation (XVIIId) (or if little non-bonded repulsion occurs between these two groups). This type of 1,5-interaction has been discussed in a preceding paper.[11] It



is obvious that replacement of the oxygen atom in (XVIII) by a methylene group as in (XII) would lead to non-bonding repulsions in the conformation analogous to (XVIIId) and hence de-stabilize the planar arrangement analogous to (XVIIIe). If this reasoning is correct, then the ideal blocking agent should be a molecule in which the EI-ion and the phenyl ring are 'frozen' in a conformation patterned after (XVIIIe). It is hoped that such compounds will become available for testing in the future.

Experimental*

N-(*2-Hydroxyethyl*)-*1,2,3,4-Tetrahydro*isoquinoline (*IX*)

Equimolar amounts of purified *iso*quinoline and 2-iodoethanol were heated under reflux in five volumes of dry benzene for 2 h. A crystalline mass separated in quantitative yield. Without purification, the quaternary salt was reduced as follows: to a solution of 70 g of the crystalline salt in 400 ml of 3 : 1 water–ethanol was added in portions a solution of 10 g of sodium borohydride in 50 ml of water. After standing for 1 h, the mixture was evaporated to dryness *in vacuo* and the residue extracted with a mixture of 5 per cent aqueous sodium hydroxide and chloroform. The chloroform layer was dried and evaporated to give an oil which was distilled *in vacuo*. There was obtained 33 g of

* B.P. and M.P. are uncorrected. Analyses by M. B. Mercier, Laval University.

pure *N*-(2-hydroxyethyl)-1,2,3,4-tetrahydro*iso*quinoline, b.p. 163–5°/14 mm (reported,[13] 164–6°/12 mm).

The corresponding chloride hydrochloride was prepared in high yield in the usual way.[11] The m.p. was 192–194°.

N-(*2-Hydroxyethyl*)-*1,2,3,4-Tetrahydro-2-Benzazepine* (*XI*)

Equimolar quantities of *o*-chloromethyl-hydrocinnamyl chloride[7] and 2-aminoethanol were mixed at room temperature in 10 volumes of methanol. After standing overnight at room temperature, the solution was evaporated to dryness, the residue dissolved in chloroform and the solution washed with 5 per cent aqueous sodium hydroxide. The organic phase was then extracted with dilute hydrochloric acid, the acid extract made alkaline and extracted with chloroform. The extract was dried and evaporated to yield an oil which was dissolved in Ethyl Cellosolve. One mole of anhydrous potassium carbonate was added and the suspension heated under reflux for 15 h. The mixture was filtered and the filtrate evaporated *in vacuo*. The residue was fractionally distilled *in vacuo* to give at 138–142°/2 mm a 45 per cent yield of colourless liquid.

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75·39; H, 8·90; N, 7.33. Found: C, 75·46; H, 8·81; N, 7·30.

N-(*2-Chloroethyl*)-*1,2,3,4-Tetrahydro-2-Benzazepine Hydrochloride* (*XII*)

The preceding amino alcohol (XI) (4 g) was dissolved in 15 ml of dry chloroform and the solution treated with dry hydrogen chloride until acid to congo red. The solution was cooled to 0° and treated drop-wise with 3 ml of purified thionyl chloride. The mixture was heated under reflux for 20 min and evaporated to dryness *in vacuo*. The residue was crystallized from acetone–ethyl acetate to give 3·5 g of colourless prisms, m.p. 192–194° (decomp.).

Anal. Calcd. for $C_{12}H_{17}Cl_2N$: N, 5·69; Cl, 28·86. Found: N, 5·64; Cl, 28·95.

4-(o-*Hydroxymethylphenyl*)-*1-Butanol* (*XIV*)

To a solution of 50 ml of concentrated sulphuric acid in 500 ml of dry methanol was added 33·7 g of 4-(*o*-carboxyphenyl)butyric

acid[8] and the mixture heated under reflux for 15 h. The mixture was worked up in the usual manner to give 34 g of liquid dimethyl ester which was used as such in the next operation without further purification. It was dissolved in 100 ml of dry ether and the solution added drop-wise to a solution of 7·5 g of lithium aluminium hydride in 200 ml of dry ether. The mixture was heated under reflux for 10 h and the product isolated in the usual way after decomposition of the complex with dilute hydrochloric acid. There was obtained 21 g of colourless viscous oil boiling at 141–2°/0·1 mm.

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73·33; H, 8·88. Found: C, 73·50; H, 9·01.

1-Chloro-4-(o-chloromethylphenyl)butane (XV)

The preceding 21 g of diol (XIV) was dissolved in 100 ml of dry chloroform containing 18 g of dry pyridine. While cooling to 0° there was added drop-wise 28 g of purified thionyl chloride. After the addition was completed the mixture was heated under reflux for 20 min and the product isolated in the usual manner. The yield of pure dichloride (XV) boiling at 95–96°/0·1 mm was 21 g. It is a colourless liquid with an irritating odour.

Anal. Calcd. for $C_{11}H_{14}Cl_2$: C, 60·82; H, 6·45. Found: C, 60·71; H, 6·32.

N-(*β-Hydroxyethyl*)-*1,2,3,4,5,6-Hexahydro-2-Benzazocine (XVI)*

A solution of 10 g. of 1-chloro-4-(*o*-chloromethylphenyl)butane in 100 ml of ethanol was treated with 2·5 molar equivalents of 2-aminoethanol and then allowed to stand at room temperature for 16 h. The solvent was removed *in vacuo* and the amino alcohol isolated in the usual way by extraction with chloroform. The crude amino alcohol was dissolved in 100 ml of propylene glycol and the solution heated under reflux for 12 h in the presence of 3·5 g of potassium carbonate. The solvent was removed *in vacuo*, the residue extracted with benzene and the benzene extract washed with several portions of 5 per cent aqueous hydrochloric acid. The acid extracts were decanted from an insoluble gum and made strongly alkaline. Extraction with ether followed by evaporation of the ether gave an oil which was

distilled *in vacuo*: at 122–4°/0·3 mm, there was obtained 2·50 g of a colourless syrup which did not give crystalline salts.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76·09; H, 9·26; N, 6·82. Found: C, 76·20; H, 9·14; N, 6·77.

N-(β-*Chloroethyl*)-*1,2,3,4,5,6-Hexahydro-2-Benzazocine* (*XVIII*)

The amino alcohol (XVI) was treated in 15 ml of dry chloroform with 5 ml of thionyl chloride. The mixture was allowed to stand 3 h and heated under reflux for 15 min. Evaporation of the solvent left a crystalline mass which after two re-crystallizations from acetone–methanol–ethyl acetate had m.p. 233–4°. The yield was 80 per cent.

Anal. Calcd. for $C_{13}H_{19}Cl_2N$: N, 5·38; Cl, 27·30. Found: N, 5·43; Cl, 27·41.

Kinetic Procedure

The rate measurements were carried out as described previously[11] using the same solvent system and buffer (70 per cent aqueous ethanol saturated with potassium bicarbonate). At various time intervals, suitable aliquots were divided into two equal portions; one portion was quenched with dilute nitric acid solution and titrated for chloride ion by the Volhard method and the other one allowed to stand for 3 h in excess sodium thiosulphate and back titrated with standard iodine solution. It was found necessary to adjust the pH of the thiosulphate solutions to 6·0 with monosodium phosphate buffer before titration with iodine in order to obtain accurate and reproducible results. The concentrations of EI-ions at time t were calculated using the relationship[3]

$$[EI] = [Cl^-]—a + [S_2O_3^-]$$

where a = initial concentration and $[S_2O_3^-]$ = uptake of thiosulphate at time t. The results are assembled in Table I.

Adrenergic Blocking Activities

These were measured according to the procedure of Fellows *et al.*[10] (see text).

Summary. The ability of various 2-chloroethylamines, in which the nitrogen is part of a ring, to produce effective concentrations of ethylenimmonium ions was measured under pseudo-physiological conditions. It was observed that the size of the ring carrying the nitrogen has a profound influence on ion formation as well as on adrenergic blocking activity. It is concluded that conformational factors can control ethylenimmonium ion formation and blocking activity. The activity of some new and highly effective blockers is rationalized on the basis of conformational properties.

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