Blockade of Adrenergic α-Receptors by a Carbonium Ion

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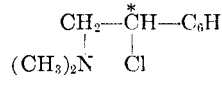
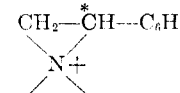
Our recent extension and refinement of the concept of isosterism[2,3] led to the proposal that alkylammonium ions and carbonium ions should be interchangeable species in a drug in so far as affinity for anionic sites of receptors is concerned. The adrenergic blocking activity of the ethyleniminium ion (EI-ion) derivable from a variety of β-haloalkylamines[3] could then be pictured as resulting from the inability of an α-receptor anionic site to discriminate against the positively charged ring carbons of the strained three-membered ring, thereby permitting the establishment of non-competitive blockade through alkylation of the negatively charged site. However, as yet no experimental support for the possible intermediacy and role of positive carbon in the complementation mechanism at the α-receptor level could be adduced. For the potential alkylation reaction to be eventually successful, optimal chemical complementation must initially be achieved in the Michaelis complex with the receptor. The energy for complex formation must be applied by the receptor and it is not known whether this energy can be used to modify the ground state carbonium ion character of an EI-ion assuming this to be a prerequisite for binding. One of us[2,3] already has offered the postulate that the positive character of the carbons of EI-ions is necessary for complementation with the receptors. Indirect evidence now has been obtained which shows that in some cases the species involved in complex formation with α-receptors may not be the intact EI-ion but the corresponding open carbonium ion, which in a subsequent step would eventually alkylate the active site.

The potent (but short acting) adrenergic blocking agent *N*,*N*-dimethyl-β-chlorophenethylamine (I)[4] was selected for our mecha-



I



II

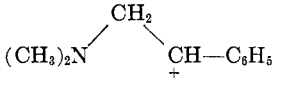
(1) National Research Council of Canada Postdoctoral Fellow, 1959–1961.

(2) B. Belleau, in "Ciba Foundation Symposium on Adrenergic Mechanisms," J. R. Vane, G. E. W. Wolstenholme and M. O'Connor, Editors, J. and A. Churchill Ltd., Publishers, London, 1960, pp. 223, 531, and 533.

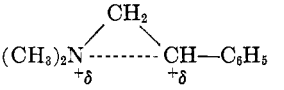
(3) B. Belleau, *Can. J. Biochem. Physiol.*, **36**, 731 (1958).

(4) F. C. Ferguson, Jr., and W. C. Wescoe, *J. Pharmacol. Exp. Ther.*, **100**, 100 (1950).

nism studies because as the corresponding EI-ion (II), it provides for the possibility of relating the effect of the configuration of the β-carbon on blocking potency to the electronic structure of the latter when complementation with the receptor surface is achieved. In view of the well-known optical specificity of α-receptors toward the β-carbon of norepinephrine, it is logical to expect a similar specificity toward the enantiomers of II *as long as alkylation of the receptor does*



(III)



(IV)

not proceed by way of the open carbonium ion III in which the asymmetry is lost. The fact that the optical forms of the blocking agent, 2-(*N*-benzyl-*N*-β-chloroethylamino)-1-phenylpropane have different potencies[5] even though the asymmetric center does not involve the alkylating carbons, certainly justifies the expectation that differences in activity would be detectable between the enantiomers of (II) if the extended ion (III) is not an intermediate in the blocking reaction. These considerations appear to provide an approach to the problem of the significance of positive carbon in the complementation phenomenon at the receptor level.

The required enantiomers of (I) were prepared from the corresponding optically active alcohols the preparation of which already has been described.[6] Treatment of both alcohols with either phosphorus pentachloride or thionyl chloride afforded pure (+)(I)-hydrochloride, m.p. 206–208°, $[\alpha]^{20}D$ 75° (ethanol) and (−)(I)-hydrochloride, m.p. 206–208°, $[\alpha]^{20}D$ 75° (ethanol). The starting stereoisomeric amino alcohols were characterized as the methiodides, m.p. 258–259°, $[\alpha]^{20}D$ 45.5° (ethanol) and m.p. 259–259.5°, $[\alpha]^{20}D$ −45° (ethanol).

The mechanism of solvolysis[7] of (I) was first confirmed by treatment of (+)(I) with one equivalent of sodium hydroxide in 1:1 aqueous acetone and allowing the mixture (0.1 molar in I) to stand at room temperature for 24 hr. Isolation of the product in the usual manner and treatment with methyl iodide afforded *N*,*N*-dimethyl-2-phenylethanolamine methiodide (95% yield), m.p. 219–238°, $[\alpha]^{20}D$ 24.5° (ethanol). Identical results were obtained when (−)(I) was solvolyzed. It is clear on the basis of these results that racemiza-

(5) G. E. Ullyot and J. F. Kerwin, Chapter on "β-Haloalkylamine Adrenergic Blocking Agents," in Medicinal Chemistry, Vol. II, F. F. Blicke and C. M. Suter, eds., John Wiley and Sons Inc., New York, N. Y., 1956, p. 276.

(6) S. Ose and Y. Yoshimura, *Yakugaku Zasshi*, **77**, 730 (1957); *Chem. Abstr.*, **51**, 17856b (1957).

(7) N. B. Chapman and D. J. Triggle, to be published.

tion occurs to the extent of 45% accompanied by 55% net retention of configuration during solvolysis. Hence an SN1 mechanism (open carbonium ion intermediate) is operative but appreciable shielding of the carbonium ion IV occurs since configuration is retained to the extent of 55%. The EI-ion (II) which must be optically stable over a period of several hours provides a possibility for the receptor to react preferentially either with the shielded or the opened carbonium ion excluding an SN2 attack on the ground that it can be observed only under conditions of extreme alkalinity.[7]

Pharmacological comparison of racemic I, (+) I, and (−) I in the usual manner[5] revealed that within the limits of experimental error (±15% of the dose administered) no difference in blocking potencies could be detected in atropinized cats. The results of the tests are assembled in Table I where it can be seen that if the potencies differ, the difference cannot exceed 15%.

TABLE I

Adrenergic blocking activity (intravenous route) of racemic I, (+) I, and (−) I; the minimum doses required to reverse consistently the effect of 8μg./kg. of epinephrine on the blood pressure and to abolish the nictitating membrane contraction of the cat are recorded. The results represent an average of three separate experiments in which the doses were carefully graded.

	Reversal of blood pressure (cat)	Blocking of the contraction of the nictitating membrane
Racemic I	250 μg. ± 25	500 μg. ± 75
(+)I	270 μg. ± 25	500 μg. ± 75
(−)I	250 μg. ± 25	500 μg. ± 100

The conclusion becomes acceptable that the α-receptor surface forces the EI-ion (II) to adopt exclusively the carbonium ion configuration (III) in order to achieve complex formation and that it would be this latter species which performs the postulated alkylation reaction. This predilection for a carbonium ion supports our previous rationalizations on the affinity of α-receptors for positive carbon.[2,3] Finally, in the almost extended and weakly shielded form (IV), the ion (III) satisfies the required distance relationship between the nitrogen and the phenyl ring for successful approach to the receptor,[3] thus eliminating a difficulty which initially led to a misinterpretation of the mechanism of action of the EI-ion (II) and which recently had attracted some valid criticism.[8] The involvement of the carbonium ion form of an EI-ion at the receptor level recently has been suggested on speculative grounds.[9]

(8) Discussion by N. B. Chapman, see ref. 2, p. 270–273.
(9) Discussion by G. W. James, see ref. 2, p. 273.

Of interest is the report[10] that substitution of the β-hydrogen on (III) by a methyl group[7] abolishes blocking activity even though the carbonium ion is remarkably stable in solution.[7] However this result is in agreement with the postulate that close approach of a positive ion to the receptor anionic site is hindered when the ion is bulky. It may be recalled that the triggering of an excitatory response has been attributed to ion-pair formation between the small cationic head (primary ammonium group) of norepinephrine[2,3] and an anionic active site and that the effect of substituents on the cationic head would be to prevent ion-pair formation, thus precluding the initiation of an excitatory response. It can be seen, therefore, that very similar trends would actually operate both in the carbonium ion and the ammonium ion series, the effect of substitution being presumably to hinder close approach to the anionic site. These considerations fully support the hypothesis that carbonium ions and ammonium ions may be bound by the same anionic site.

Acknowledgments.—Financial support of this work by the National Research Council of Canada is gratefully acknowledged. Grateful appreciation is expressed to Dr. M. Pindell of Bristol Laboratories for the pharmacological data.

(10) J. D. P. Graham and G. W. L. James, *J. Med. Pharm. Chem.*, **3**, 489 (1961).

Pyrimidines. VIII. Pyrimidine Derivatives of Thioguanine[1]

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The antitumor activity of 2-amino-6-purinethiol (thioguanine, I; R_1, R_2 = H) has been well established.[2] The high toxicity of this compound has prompted many investigators to modify the structure of thioguanine in order to obtain less toxic derivatives with greater specificity at enzyme sites. As a part of our general investigating program on pyrimidines, some pyrimidine derivatives of thioguanine have been synthesized Elion, *et al.*, prepared some imidazole deriva-

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(2) *Cf. Cancer Chemotherapy Reports*, **11**, 202 (1961).