[CONTRIBUTION FROM THE DEPARTMENT OF PATHOLOGY, THE GEORGETOWN UNIVERSITY MEDICAL CENTER]

Hypotensive Agents. XII. The *Exo* and *Endo* Isomers of *N*-Dimethylaminoethyl-4-methyl-4,7-*endo*-oxyperhydroisoindole Bis-methonium Cation[1,2]

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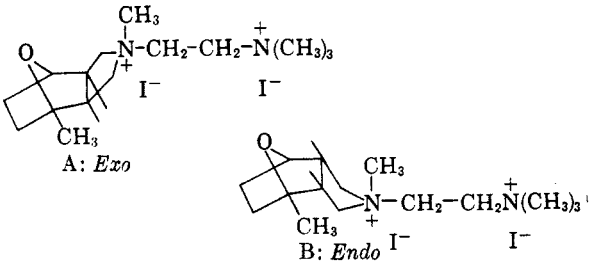
In studying the structure-activity relationship of bis-quaternary ammonium salts in lowering blood pressure, the compound *exo-cis*-*N*-dimethylaminoethyl-4-methyl-4,7-*endo*-oxyperhydroisoindole bis-methonium cation was found to be a very potent agent and nontoxic. The *endo-cis* stereoisomer was synthesized and its activity in this respect was essentially the same as that of the previously reported *exo-cis* derivative.

It has been demonstrated that the bis-methonium salt of *N*-dimethylaminoethyl-4-methyl-4,7-*endo*-oxyperhydroisoindole, our code H-2, is a very potent hypotensive agent both in animals and man[5] with an extremely large therapeutic index.[6] In the various series of symmetrical and unsymmetrical quaternary ammonium compounds prepared previously by us[7] and others, mainly Cavallito and co-workers,[8] changing the size of the cationic group greatly influenced the pharmacological activity. We have recently shown[9] that changing the bridging within the ring system making up the cationic group, a change in the molecular size and shape, greatly influenced the usefulness of the resultant compounds as hypotensive agents.

Examination of the structure of H-2, shows that there are two forms of this compound depending on the position of the pyrrolidine ring with respect to the oxygen atom in space. These are shown by the structures A and B. In practice the *exo* isomer, A, is generally represented as having the pyrrolidine ring and oxygen atom on the same side of the plane and the *endo* form, B, as having them on the opposite sides. It was felt that this type of space-structure relationship might furnish another means of obtaining additional information on structure-activity relationships. With these facts in mind, we have now prepared the *exo* and *endo* isomers of H-2 and compared their pharmacological activity.



The synthesis of the desired *exo* and *endo* isomers was carried out by first preparing the phthalic anhydrides of the proper configuration. When maleic anhydride and 2-methyl furan are condensed according to the method of Alder and Backendorf,[10] the resultant Δ^4-monoene adduct, I, has the *exo* configuration. Woodward and Baer[11] have shown this to be the case with maleic anhydride and furan. On hydrogenation of I, the *exo-cis* perhydrophthalic anhydride, II, is obtained. Condensation of diethyl acetylene-1,2-carboxylate with 2-methyl furan based on the procedures of Alder and Rickert,[12] Alder and Backendorf[10] and Diels and Olsen[13] yields the $\Delta^{1,4}$-diene adduct, III. This adduct on hydrogenation absorbed one mole of hydrogen and yielded the Δ^1-cyclohexene,[12,14] IV. On saponification the corresponding acid, V, was obtained. On further hydrogenation of V, one mole of hydrogen was absorbed and the *endo-cis* perhydrophthalic acid, VI, was obtained. This acid was converted to the corresponding anhydride, VII, on treatment with acetyl chloride and acetic anhydride.

The Δ^4-acid from I differed from the Δ^1-acid, V. The anhydride, VII, in view of the work of Woodward and Baer,[11] is thus the *endo* form, although the opposite assignment was applied by earlier German workers.[10,12]

The anhydrides II and VII were treated with dimethylaminoethylamine as previously described[5] to yield the amic acids which were cyclized to the

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(5) L. M. Rice, C. H. Grogan, and E. E. Reid, *J. Am. Chem. Soc.*, **75**, 4911 (1953).

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(10) K. Alder and K. H. Backendorf, *Ann.*, **535**, 101 (1938).

(11) R. B. Woodward and H. Baer, *J. Am. Chem. Soc.*, **70**, 1161 (1948).

(12) K. Alder and H. F. Rickert, *Ber.*, **70**, 1354 (1957).

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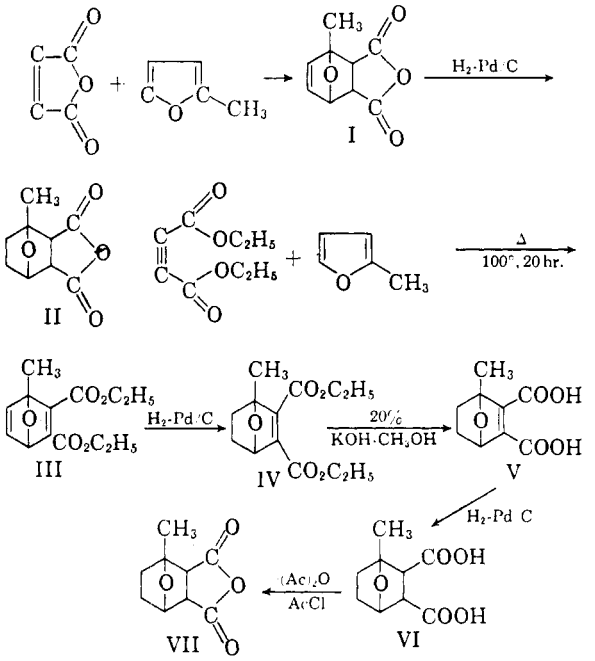
TABLE I

ANALYTICAL DATA

Compound	Analysis											
	Carbon, %		Hydrogen, %		Nitrogen, %		Oxygen, %		Chlorine, %		Iodine, %	
	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
Exo imide	61.88	61.74	7.99	8.07	11.10	11.12	—	—	12.28	12.38[a]	—	—
Endo imide	61.88	61.67	7.99	7.74	11.10	11.15	19.02	19.03	12.28	12.21[a]	—	—
Exo base	69.60	69.38	10.78	10.61	12.49	12.19	—	—	23.86	23.94[b]	—	—
Endo base	69.60	69.50	10.78	10.61	12.49	12.69	7.13	7.14	23.86	23.78[b]	—	—
Exo H-2	35.45	35.34	5.95	5.82	5.51	5.45	—	—	—	—	49.94	49.90
Endo H-2	35.45	35.40	5.95	5.71	5.51	5.45	—	—	—	—	49.94	49.84

[a] Imide hydrochloride. [b] Base dihydrochloride.

corresponding imides. These were in turn reduced with lithium aluminum hydride to yield the desired isoindole bases from which derivatives were prepared.



A comparison of the melting points of the derivatives of the *exo* and *endo* forms is shown in Table II. Except in the case of the starting anhydrides and the base dihydrochlorides they are nearly identical. However, a marked depression of the melting points was obtained in all cases on mixing the isomeric forms.

Although there was little doubt from the analytical data, (Table I) that the materials were pure and, as shown by the mixed melting points, (Table II) different, additional evidence was obtained from the infrared spectra and x-ray diffraction patterns of the crystalline dimethonium salts. The infrared spectra of each stereoisomeric form, although generally similar, exhibited distinct differences. The spectra were obtained in potassium bromide pellets using a Perkin Elmer Model 221 spectrophotometer. The multiplicity of frequencies associated with single bond C–N, C–C, and C–O stretching modes, and the large influence of the environment on them, renders them less useful in identifying structural units than in the identification of particular molecules. With these facts in mind, the major differences between 7 and 13 μ are summarized. The *exo* form had absorption bands at 7.09M, 8.12M, 9.19W, 10.55W, 11.64S and 12.20μW which did not occur in the spectrum of the *endo* form. The *endo* form had bands at 7.53-WW, 7.70W, 8.64W, 10.08S and 11.80μS which did not occur in the *exo* spectrum. In addition there were significant shifts in corresponding bands with accentuation or attenuation throughout the spectra. The two bands 7.53μWW and 7.61μW of the *endo* form were replaced by a single 7.61μS band in the *exo* spectrum and the very weak band at 7.97μ of the *endo* form was resolved into a very weak doublet at 7.94μ and 7.99μ in the *exo* form.

TABLE II

Compound	Melting Point °		
	Exo	*Endo*	Mixed *exo-endo*
Anhydride	105–106	87	68–70
Imide·HCl	260	261–262	247
Isoindole·2 HCl	237	213–214	205–208
Isoindole·2 CH_3I	233–234	233–234	220–222

The x-ray diffraction patterns, kindly obtained for us by Dr. Herman Noelther of the Celanese Corporation of America, also showed distinct differences in structure.

These two *exo* and *endo* isomeric forms of H-2 when evaluated as hypotensive agents in dogs[15] displayed, as far as we were able to discern, almost identical activity. Hence it has been shown that this change in shape in the molecule of the very active hypotensive agent, H-2, from *exo* to *endo* produced little or no change in toxicity or pharmacological activity.

EXPERIMENTAL

Exo-cis-3-methyl-3,6-endo-oxyhexahydrophthalic anhydride. Maleic anhydride, 49 g. (0.50 mole) was mixed in anhydrous ether solution with 41.1 g. (0.50 mole) of 2-methyl furan and let stand two days. The ether was removed *in vacuo* and the resultant Δ^4 adduct hydrogenated in ethyl acetate at room

(15) W. E. O'Malley, G. Winkler, L. M. Rice, and C. F. Geschickter, *J. Am. Pharm. Assoc. Sci. Ed.*, 46, 346 (1957).

temperature over 5% palladium on charcoal. The catalyst was filtered and the solvent removed *in vacuo*. The desired anhydride was obtained in colorless blocks in nearly quantitative yield, m.p. 99–101°. Recrystallization from benzene or ethyl acetate raised the m.p. to 105–106°. The unrecrystallized material is suitable for subsequent steps without further purification. The Δ^4 adduct cannot be recrystallized with heating as it decouples.

Endo-cis-3-methyl-3,6-endo-oxyhexahydrophthalic anhydride. Acetylene-1,2-diethyl carboxylate, 85 g. (0.50 mol.) and 2-methyl furan, 41.1 g. (0.50 mol.) were heated together at 100° for 20 hr. without solvent essentially as described[12,13,14] for furan and homologs. At the end of this period, all volatile products were removed by heating *in vacuo* at 70–80°. The adduct, a reddish brown oil, shown to be a $\Delta^{1,4}$ *endo*-oxycyclohexadiene[12] in the case of furan and acetylene-1,2-diethyl carboxylate, was hydrogenated in acetone with 5% palladium-charcoal to yield the Δ^1-adduct which was saponified with 20% methanolic potassium hydroxide to the free acid. This was obtained by evaporation to dryness on the water bath and extraction of the residue with two 200-ml. portions of ether. The ether was stripped and the resultant Δ^1-acid hydrogenated in methanol with 5% palladium-charcoal to yield the saturated acid. This was converted to the *endo-cis* anhydride by treatment with acetic anhydride containing 10% acetyl chloride and melted at 77–80° after distillation of excess reactants. Recrystallization from benzene, ethyl acetate, or acetone-ligroin raised the melting point to 87°.

Imides. The dimethylaminoethylimides of both anhydrides were prepared as previously described[6] by direct reaction of molar equivalents of the anhydrides and dimethylaminoethylamine without solvent. The imides were isolated as colorless oils boiling in the range 120–130°/0.2 mm. Imide hydrochlorides were prepared in isopropyl alcohol with alcoholic-hydrochloric acid. The boiling points of the imides and the melting points of their hydrochlorides were essentially identical (see Table II).

Isoindoles. The *exo-cis* and *endo-cis* isoindoles from the above imides were prepared[5] by reduction of 25.2 g. (0.10 mol.) quantities of the imides in anhydrous ether with lithium aluminum hydride and isolated by vacuum distillation. They were converted into dihydrochlorides and dimethiodides. Again the boiling points of the isoindoles, 100–105°/0.2 mm., and the melting points of the dimethonium salts were identical. The melting points of the dihydrochloride salts, however, differed considerably (see Table II).

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[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY,[1] SOUTHERN RESEARCH INSTITUTE]

Synthesis of Potential Anticancer Agents. XXII.[2] Reactions of Orthoesters with 4,5-Diaminopyrimidines

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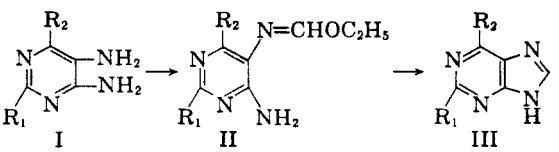
The usefulness of the reactions of triethyl orthoformate, triethyl orthoacetate, and triethyl orthopropionate with 4,5-diaminopyrimidines for the preparation of purines is discussed.

The preparation of chloropurines by the reaction of chloro-4,5-diaminopyrimidines with triethyl orthoformate–acetic anhydride[3] and with diethoxymethyl acetate (prepared from triethyl orthoformate and acetic anhydride)[4] has previously been reported from these laboratories.

In contrast to the behavior of 4,5-diamino-2-(or -6-)chloropyrimidine and 4,5-diamino-2,6-dichloropyrimidine, the reaction of 4,5-diaminopyrimidine with triethyl orthoformate–acetic anhydride gave 4,5-diacetamidopyrimidine[5] as the principal product and only a small amount of the expected purine. The reaction of 4,5-diaminopyrimidine and acetic anhydride alone also produced 4,5-diacetamidopyrimidine,[5] whereas 4,5-diamino-2-chloropyrimidine and acetic anhydride alone gave only the monoacetylated product, 5-acetamido-4-amino-2-chloropyrimidine. Apparently a chlorine atom in the 2 or the 6 position (or both) of the pyrimidine ring determines the course of the orthoester–acetic anhydride reaction.

Since hypoxanthine is readily formed from 4,5-diamino-6-pyrimidinol by merely refluxing the pyrimidine with formic acid, it seemed that treatment of the pyrimidine or one of its salts with triethyl orthoformate alone might also produce hypoxanthine. This surmise proved to be true, since the pyrimidine, its sulfate, and its hydrochloride gave hypoxanthine in good yield on refluxing with triethyl orthoformate, although the reaction mixture was heterogeneous in each case. The free pyrimidine



I II III

$CH_3COOC(OC_2H_5)=CHC(CH_3)(OC_2H_5)_2$

IV

$CH_3COOC(R)(OC_2H_5)_2$

V

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