termine which THC isomer, if any, the hydroxy-metabolite simultates in its electroencephalographic effects.

LERNER and ZEFFERT[19] reported that the ratio of $\Delta^1(^6)$ THC/Δ^1 THC found in fresh Mexican marihuana was 0.4/99.6, whereas in older samples of hashish[19] and in Maryland marihuana[20] the $\Delta^1(^6)$ THC isomer represented 10% of the active THC fraction. In the light of this evidence and the different electroencephalographic responses induced by the Δ^1 and $\Delta^1(^6)$ isomers, the ratio of Δ^1 to $\Delta^1(^6)$ THC may be a necessary factor to take into account when assessing the behavioral, pharmacological and clinical effects of marihuana in animals and man[21].

Bien que le Δ^1 ainsi que le $\Delta^1(^6)$ tétrahydrocannabinol élevent le seuil de la formation réticulaire chez le chat, les réponses électroencéphalographiques fournies par ces composés sont distinctes. Il faut considérer ces différences dans l'évaluation pharmacologique et clinique des effets de marihuana chez l'homme et chez des animaux.

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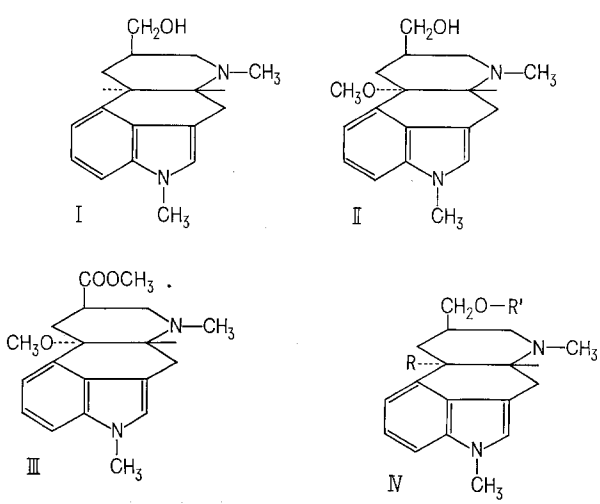
10-Methoxyergoline Derivatives as α-Adrenergic Blocking Agents[1]

Natural ergot alkaloids possess various pharmacological actions and among them a strong alpha adrenergic blocking activity[2,3]. Hydrogenation of ergotamine and ergotoxine yields drugs with enhanced adrenolytic activity and reduced toxicity, however the specifity of action of these compounds is still unsatisfactory. For instance dihydroergotoxine, a combination of dihydroergocristine, dihydroergocryptine and dihydroergocornine in equal proportions, has a central blood pressure depressing activity and a latent vasoconstrictor action becoming manifest in spinal cats when the destruction of the medulla oblongata prevents its central hypotensive effect[4]. Furthermore in dogs, this drug is a powerful emetic agent at i.v. doses close to those found to block the alpha receptors[5].

Although modifications of the ergoline nucleus are known to alter the pharmacological profile of the ergot alkaloids[2], most of the compounds so far reported are substituted amides of lysergic acid. In order to obtain more specific pharmacological agents and, notably, a more specific alpha adrenergic blocking agent, we have subjected, in the last years, both the ergoline nucleus and the amide linkage to a series of chemical modifications[6,7]. In the course of this work we have examined various esters of 1-methyldihydrolysergol (I)[8] and, among them, the benzoate (No. 1) and the nicotinate (No. 2) were found to have a certain adrenolytic activity. The corresponding esters of 1-methyl-10α-metoxydihydrolysergol (II)[9] were next investigated (No. 3 and 4). The nicotinate (No. 4) was found to be remarkably active, whereas the picolinate (No. 5), the isonicotinate (No. 6) and 3-pyridylacetate (No. 7) were practically devoid of adrenolytic activity. On the basis of these results, a series of nicotinic esters bearing various substituents in the pyridine nucleus were synthesized. The physico-chemical data and the biological activities of the compounds IV so far synthesized are reported in the table[10].

Chemistry. Reduction of the ester III[11] with an excess of $LiAlH_4$ in tetrahydrofuran afforded 10 α-methoxydihydrolysergol, m.p. 225–227° (Anal. Calcd. for $C_{17}H_{22}N_2O_2$: C 71.3; H 7.7%. Found C 71.2; H 8.0%) which was methylated with CH_3I and KNH_2 in liq. NH_3[12] to give II, m.p. 212–214°, $[\alpha]_D^{20}$-10° (c 0.5, pyridine). The esters were prepared by condensation of II with an excess of acyl chloride in pyridine: comp. No. 19 was obtained by reaction of II (1 mol) with 5-carboxamidonicotinic acid[13] (2 mol) in pyridine, in the presence of dicyclohexylcarbodiimide (2 mol) (24 h, room temp)[14].

Pharmacology. The data reported in the Table show that among the pyridyl carboxylic esters of 1-methyl-10α-methoxydihydrolysergol, the nicotinates, and notably



[1] Ergoline derivatives. Note X, Note IX: W. BARBIERI, L. BERNARDI, G. BOSISIO and A. TEMPERILLI, Tetrahedron *25*, 2401 (1969).
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[13] Swiss Pat. No. 284.073.
[14] We are indebted to Dr. P. ULIVI for this preparation.

Compound No.	R	R′	Formula	m.p.	Alpha-adrenergic blockade: In vitro[a] Relative activity Ergotamine = 100	Alpha-adrenergic blockade: In vivo[b] ED_{50} mg/kg i.v.	Anti-5-HT: In vitro[a] Relative activity LSD_{25} = 100
1	H	Benzoyl	$C_{24}H_{26}N_2O_2$	141–143°	70	—	< 3
2	H	Nicotinoyl	$C_{23}H_{25}N_3O_2$	142–144°	120	0.3	10
3	CH_3O	Benzoyl	$C_{25}H_{28}N_2O_3$	167–169°	85	—	3
4	CH_3O	Nicotinoyl	$C_{24}H_{27}N_3O_3$	202–203°	700	0.03	30
5	CH_3O	Picolinoyl	$C_{24}H_{27}N_3O_3$	150–151°	14	>1	—
6	CH_3O	Isonicotinoyl	$C_{24}H_{27}N_3O_3$	162–165°	28	>1	—
7	CH_3O	3-Pyridylacetyl	$C_{25}H_{29}N_3O_3$	amorphous[c]	14	>1	2
8	CH_3O	6-Methylnicotinoyl	$C_{25}H_{29}N_3O_3$	152–154°	60	—	100
9	CH_3O	6-t.Butylnicotinoyl	$C_{28}H_{35}N_3O_3$	136–138°	<7	—	<30
10	CH_3O	2,4-Dimethylnicotinoyl	$C_{26}H_{31}N_3O_3$	amorphous[d]	70	—	30
11	CH_3O	2,6-Dimethyl-4-methoxynicotinoyl	$C_{27}H_{33}N_3O_4$	amorphous[e]	14	—	30
12	CH_3O	6-Methyl-2,4-dichloronicotinoyl	$C_{25}H_{27}Cl_2N_3O_3$	177–179°	25	—	30
13	CH_3O	5,6-Dichloronicotinoyl	$C_{24}H_{25}Cl_2N_3O_3$	156–158°	40	—	10
14	CH_3O	6-Chloronicotinoyl	$C_{24}H_{26}ClN_3O_3$	165–167°	40	—	10
15	CH_3O	2-Chloronicotinoyl	$C_{24}H_{26}ClN_3O_3$	126–129°	140	0.1	15
16	CH_3O	5-Chloronicotinoyl	$C_{24}H_{26}ClN_3O_3$	127–128°	3500	0.02	5
17	CH_3O	5-Fluoronicotinoyl	$C_{24}H_{26}FN_3O_3$	122–124°	1400	0.02	—
18	CH_3O	5-Iodonicotinoyl	$C_{24}H_{26}IN_3O_3$	141–143°	7000	0.05	2
19	CH_3O	5-Carboxamidonicotinoyl	$C_{25}H_{28}N_4O_4$	138–140°	140	0.02	10
20	CH_3O	5-Bromonicotinoyl	$C_{24}H_{26}BrN_3O_3$	136–138°	7800	0.02	10
Dihydroergotoxine					700	0.05	2
Dihydroergocryptine					700	0.05	2

[a] Alpha-receptor blockade was determined against adrenaline on the isolated guinea-pig seminal vescicle and anti-5-HT (5-hydroxytryptamine) activity on the isolated rat uterus in artificial oestrus. Concentrations producing 50% inhibition of the spasmogenic effects of the agonists were estimated graphically for each antagonist. [b] Alpha-receptor blockade was determined in rats. ED_{50} is the graphically estimated dose of antagonist protecting 50% of animals from the lethal effect of 0.2 mg/kg adrenaline, injected i.v. 5 min later. [c] Acid tartrate, m.p. 84–85°. [d] Acid oxalate dihydrate, m.p. 110°. [e] Acid oxalate dihydrate, m.p. 130°.

those having an electron-withdrawing group in position 5, are characterized by a strong alpha adrenergic blocking activity which is not associated with antagonistic properties towards other biogenic amines such as 5-HT or histamine. To investigate further the biological profile of these interesting and apparently specific compounds, it was decided to select comp. No. 20[15] for a widespread testing on different functional parameters. Comp. No. 20 (as tartrate) was chosen on the basis of its low toxicity (LD_{50} i.v. in rats = 72 mg/kg) and for the absence of any emetic effect in dogs. In these animals an intravenous dose of 1 mg/kg, which is about 50 times higher than the ED_{50} in the adrenaline mortality test, did not cause vomiting, whereas dihydroergotoxine was found to be emetic at 0.02 mg/kg i.v. Comp. No. 20 did not influence systemic arterial blood pressure in conscious animals up to 0.6 mg/kg in cats and in dogs; however, under anesthesia, a moderate pressure fall could be observed when lower doses (0.05–0.15 mg/kg) were injected i.v.

Compound No. 20 increases regional blood flows following both intra-arterial and intravenous administration to dogs which were anesthetized and prepared for recording blood flow changes. Systemic administration of moderately hypotensive doses of comp. No. 20 increase the total femoral blood flow (+47% at 50 µg/kg i.v.). Intraarterial doses as low as 0.1–2 µg/kg produce a vasodilatation in the muscle-cutaneous vascular districts of the hind limb in the absence of any systemic effect, as shown by recording either the total femoral blood flow with an electromagnetic flow-meter, or the perfusion pressure in hind limbs perfused at constant volume. Using a similar procedure, Benzi et al.[16] found that local administration of comp. No. 20 reduces also the vascular resistance and increases the cerebral metabolic activities in the isolated in situ perfused canine brain. Cardiac output measured as blood flow through the ascending aorta as well as stroke volume increase moderately in the range of doses from 0.05 to 0.5 mg/kg i.v.

In pithed rats and spinal cats comp. No. 20 has no hypertensive activity up to 2.5 mg/kg i.v., while dehydroergotoxine and dehydroergokryptine increase blood pressure in rats at 0.1–0.5 mg/kg.

In conclusion a highly specific alpha-adrenergic blocking activity has been found among a group of new ergoline derivatives: the former[17] and present data suggest the opportunity of further investigations in both animals and men.

Riassunto. Vengono descritte le attività adrenolitiche di una nuova classe di derivati dell'ergolina di formula generale IV. Uno di questi composti (No. 20) è stato esaminato su diversi reattivi biologici che hanno messo in luce la sua attività vasodilatatrice e adrenolitica e l'assenza di attività indesiderate tipiche degli alcaloidi dell'Ergot.

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