animals, particularly concerning the branched chain amino acids, may depend on the distinct mediating system for the transport of amino acids[18]. Further: the 'functional' temperature of the animal in deep hypothermia is about 5 °C, whereas after spontaneous arousal, a stupendous physiologic effort, it is about 35 °C.

Zusammenfassung. Die Serumkonzentration von 21 freien Aminosäuren wurde bei Igeln im Winterschlaf, bei spontanem Erwachen während des Winterschlafs und nach dem Aufwachen im Frühling bestimmt. Mit Ausnahme von Valin, Leucin, Isoleucin und Tryptophan sinken die Aminosäuren während des Schlafes signifikant ab und steigen beim Erwachen im Winter und Frühling an.

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Structure-Activity Relationship of Various Acyl Derivatives of 6-methyl-8β-aminomethyl-10α-ergoline (Dihydrolysergamine)

The natural ergot alkaloids and their derivatives have manifold activities (adrenolytic, anti-5-hydroxytryptamine, spasmogenic, on central nervous system etc.). In general they are not very specific, for instance ergometrine, which is mainly oxytocic, causes also peripheral vasoconstriction, hyperthermia, and antagonizes 5-hydroxytryptamine (5-HT); ergotamine, which is mainly adrenolytic, and methysergide (*N*-[1-(hydroxymethyl)-propyl]-1-methyl-D-lysergamide), which is mainly anti-5-HT, share also oxytocic and vasoconstrictor activities[1-3].

The following is a brief outline of the structure-activity (oxytocic, anti-5-HT, and adrenolytic) relationship of a new series of acyl derivatives of 6-methyl-8β-aminomethyl-10α-ergoline (dihydrolysergamine)[4-9] in the attempt to find compounds with a more specific activity. The pharmacological properties of 1 of these derivatives, the acetyl-dihydrolysergamine (compound I) which has specific oxytocic activity, were further studied in comparison with ergometrine and methergine (methylergometrine).

Structure-activity relationship of carboxylic acid derivatives. The nature of the acyl residue was found to influence strongly the pharmacological activities of the parent compound (dihydrolysergamine). Compounds I, III, IV, VIII, XI and XXVI showed specific oxytocic activity comparable or superior to that of ergometrine, while compound XXVIII showed high and specific adrenolytic activity. These findings contradict the general statement that ergoline derivatives are almost inactive oxytocics.

Acylation of dihydrolysergamine yielded compounds (from I–XXII) with a prominent oxytocic activity. This activity, and the toxicity also, increased up to a certain point with the lengthening of the carboxylic aliphatic chain (I, VIII, XI). Longer chains (XIII, XIV, XV) or the substitution of the aliphatic residue with an aromatic residue (XVI, XX, XXI, XXII) caused marked reduction of the activity on the uterus. Hydroxylation in position 10 (III and XIX) or methylation in 16 (IV and XVII) did not modify (but eventually reinforced) the specific oxytocic activity already present in the parent compounds (I and XVI). When either R_1 or R_4 were not hydrogen, the derivatives (II, IX, XII, V, VI, VII, X, and XVIII) lost the oxytocic properties of their parent compound (I, VIII, XI, and XVI). Nevertheless, methylation in position 1 afforded substances (II, IX, and XII) which showed prominent anti-5-HT and some adrenolytic properties.

Structure-activity relationship of carbonic acid derivatives. When R_3 was a carboalkoxy group, the compounds (from XXIII–XXIX) were found to be pharmacologically very active (as oxytocics, adrenolytics, and anti-5-HT) but less specific and more toxic than the acyl derivatives previously discussed. Here again, the oxytocic activity disappeared when R_3 was an aliphatic chain with more than 4 carbon atoms, whereas the adrenolytic activity was not similarly affected and in one instance it became specific (compound XXVIII).

Methylation in N_{17} (R_4) yielded an inactive compound (XXV), while methylation in N_1 strengthened the anti-5-HT activity (XXIV, XXVII, and XXIX) and left almost unaltered the other properties. The introduction of a hydroxyl group in position 10 yielded a compound with specific oxytocic activity (XXVI).

All the 10β-(*cis* junction) analogues[5] of the most active compounds here described were not reported in the Table, but were also examined and found to be inactive in all our tests.

Comparison between the pharmacological actions of compound I, ergometrine, and methergine. Since compound I showed a good specific oxytocic activity and a low toxicity, further pharmacological studies were performed on it in comparison with ergometrine and methergine.

It was seen that its oxytocic activity on the uterus in situ was comparable qualitatively and quantitatively to that of ergometrine and methergine. After small doses (0.02–0.1 mg/kg i.v.) it evoked contractions in silent uterus or increased in force and frequency those already present; after progressively larger doses, it caused first forceful and tetanic contractions with increased resting tonus and then sustained contracture. The approximate

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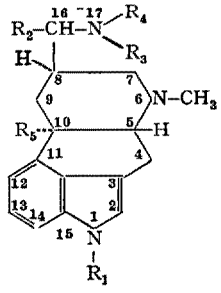

No. compounds	R_1	R_2	R_3	R_4	R_5	% Activity			LD_{50} in rabbit mg/kg i.v.
						Oxytocic[a]	Anti-5-HT[b]	Adrenolytic[c]	
Dihydrolysergamine[4]	H	H	H	H	H	30	5	< 5	
I[4]	H	H	$COCH_3$	H	H	60–90	10	< 5	40
II[4]	CH_3	H	$COCH_3$	H	H	< 10	50	14	
III[7]	H	H	$COCH_3$	H	OH	100	< 5	< 5	
IV[6]	H	CH_3	$COCH_3$	H	H	100	5	5	35
V[4]	H	H	$COCH_3$	CH_3	H	< 10	5	< 5	
VI[9]	H	H	$COCH_3$	CH_2CH_3	H	< 10	< 5	5	
VII[9]	H	H	$COCH_3$	$CH(CH_3)_2$	H	< 10	5	< 5	
VIII[4]	H	H	$COCH_2CH_3$	H	H	200	10	< 5	15
IX[4]	CH_3	H	$COCH_2CH_3$	H	H	< 10	80	70	10
X[9]	H	H	$COCH_2CH_3$	CH_3	H	< 10	< 5	5	
XI[4]	H	H	$COCH(CH_3)_2$	H	H	300	5	< 5	7.5
XII[4]	CH_3	H	$COCH(CH_3)_2$	H	H	< 10	80	70	7.5
XIII[4]	H	H	$COC(CH_3)_3$	H	H	< 10	5	5	
XIV[8]	H	H	$COCH(CH_2CH_3)_2$	H	H	< 10	< 5	5	
XV[4]	H	H	$CO(CH_2)_8CH_3$	H	H	< 10	< 5	< 5	
XVI[4]	H	H	COC_6H_5	H	H	40	< 5	5	
XVII[6]	H	CH_3	COC_6H_5	H	H	40	< 5	< 5	
XVIII[4]	H	H	COC_6H_5	CH_3	H	< 10	5	14	
XIX[7]	H	H	COC_6H_5	H	OH	40	< 5	< 5	
XX[4]	H	H	$CO(CH_2)_2C_6H_5$	H	H	< 10	< 5	< 5	
XXI[4]	H	H	Nicotinoyl	H	H	< 10	30	< 5	15
XXII[4]	H	H	Pyrazinoyl	H	H	< 10	5	5	
XXIII[4]	H	H	$CO_2CH_2CH_3$	H	H	200	30	140	4
XXIV[4]	CH_3	H	$CO_2CH_2CH_3$	H	H	200	300	120	4
XXV[4]	H	H	$CO_2CH_2CH_3$	CH_3	H	20	10	5	
XXVI[7]	H	H	$CO_2CH_2CH_3$	H	OH	200	5	5	
XXVII[4]	CH_3	H	$CO_2(CH_2)_2CH_3$	H	H	200	300	70	
XXVIII[8]	H	H	$CO_2(CH_2)_3CH_3$	H	H	< 10	5	140	
XXIX[4]	CH_3	H	$CO_2(CH_2)_3CH_3$	H	H	10	300	70	

[a] 100% = ergometrine (on the uterus in situ of rabbits following the procedure either of ROTHLIN[10], or of FREGNAN and GLÄSSER[11]. [b] 100% = lysergic acid diethylamide (on isolated rat uterus[12]). [c] 100% = ergotamine (on isolated guinea-pig seminal vesicle[12]).

LD_{50} in rabbits was 40 mg/kg i.v. for the N_{17} acetyl dihydrolysergamine, 3.5 mg/kg i.v. for ergometrine, and 2 mg/kg i.v. for methergine.

Compound I did not alter the electrocardiogram in anaesthetized (urethane 1 g/kg i.v.) vago-sympathectomized rabbits up to the dose of 0.5 mg/kg i.v., but after larger doses it caused first increase and sometimes inversion of the T wave, slight downward displacement of the S-T segment, increase in the amplitude of the QRS wave, and then ventricular arrhythmias. For either ergometrine or methergine the first alterations appeared already at the doses of 0.01–0.05 mg/kg i.v. and the ventricular arrhythmias at the doses of 0.1–0.5 mg/kg i.v.

Compound I seemed to be less active on the central nervous system, as it was less hyperpyretic and did not modify the respiration in rabbits up to the dose of 5 mg/kg i.v., while ergometrine and methergine caused hyperthermia and progressive reduction of the amplitude and arrhythmic respiration already at the dose of 1 mg/kg i.v. Besides, compound I did not evoke 'sham rage' in cats even at the dose of 5 mg/kg i.v., while ergometrine and methergine did at the dose of 1 mg/kg i.v.

In conclusion, it has been possible to find ergoline derivatives, namely the acetyl and isobutyryl dihydrolysergamine, which were more specific as oxytocics and less toxic than ergometrine.

Riassunto. Alcuni acil derivati dell'ergoline hanno dimostrato notevoli proprietà ossitociche, adrenolitiche ed anti-5-idrossitriptaminiche, (anti-5-HT). In particolare l'acetil e l'isobutirril diidrolisergamina possiedono una azione ossitocica altrettanto potente e più elettiva dell'ergometrina, della quale sono anche meno tossiche.

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