above. Furthermore, the mean half-life in group 2 was not significantly longer than in group 1, and the mean half-life in group 4 with hyperbilirubinemia was significantly longer than in group 1, although there was no significant difference in serum albumin from group 1. These observations indicate that the increase in half-life of antipyrine was not primarily due to the presence of tumor, but rather to the nutritional status and liver function of the individual. In contrast with our results, Ambre et al.[4] demonstrated a shortened plasma elimination half-life of antipyrine in lung cancer patients. This discrepancy indicates that changes in the metabolic fate of antipyrine in cancer patients might not be due to cancer itself. It is particularly important that the metabolism of antipyrine might be altered in patients with cancer since patients with cancer usually receive a number of drugs that are metabolized by the hepatic microsomal system[9].

Anticancer agents are seldom used alone but rather in combination with other anticancer agents. Anticancer angents and extracts from bacteria are also currently used in combination for the chemoimmunotherapy of a number of neoplastic diseases. Recent studies reported that extracts from bacteria cause a significant reduction in hepatic microsomal enzyme activities[10-12]. Decreased activities of hepatic microsomal enzyme have been reported in rats treated with some anticancer agents[13]. It may be predicted that these substances such as antimetabolic and alkylating agents, which interfere with the synthesis of nucleic acids, would inhibit hepatic microsomal enzyme. On the other hand, it has been reported that a long-term administration of 6-mercaptopurine in humans increased the requirement for warfarin[14]. These results suggest the possibility that 6-mercaptopurine might induce hepatic microsomal enzyme. Because of these observations, information about changes in drug metabolism in patients with cancer deserves serious consideration.

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Antiprolactinic ergolines

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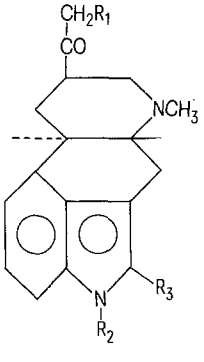
Summary. The synthesis and the antiprolactin activity of a group of 8-acetylergolines are reported.

The inhibitory activity toward prolactin secretion of ergot alkaloids and their derivatives has been recently reviewed[1]. In the present note we report the preliminary data on the preparation and antiprolactin activity of a group of new ergolines (**I**) bearing a hydroxyacetyl side chain present in many biologically active compounds, synthesized in the course of our extensive screening program for semi-synthetic ergot derivatives[2,3].



(1)

Chemistry. The synthesis of 8-acetylergoline (No. 1) has been previously reported[4], however all attempts to brominate it to **I** (R_1 = Br; R_2 = R_3 = H) yielded only 2-bromoacetylergoline and 2,13-dibromoacetylergoline. Reaction of diazomethane with the mixed ethoxyformic anhydride of dihydrolysergic acid in tetrahydrofuran yielded a diazoketone (m.p. 163–165 °C) that by reaction with ethanol[5] in the presence of BF_3 etherate gave the ether No. 14 and by reaction with HBr gave the required bromoketone **I** (R_1 = Br; R_2 = R_3 = H)[6]. Condensation of the rather unstable bromoketone with the sodium salt of an appropriate carboxylic acid or with the acid itself in the presence of KF in DMF[7] yielded the esters No. 3 ÷ 10 and 16. Likewise the phenyl ether No. 15 was obtained by condensation of the bromoketone with sodium phenate in refluxing ethanol. Chlorination of compound 7 to give compound 12 was performed with sulphuryl chloride in the presence of BF_3 etherate complex[8] whereas the 2-bromo compound 11 was obtained by treatment of compound 7 with NBS[9] in dichloroethane at 45 °C. Compound 2 was obtained by methanolysis at room temperature of compound 4 in the presence of a trace of triethylamine and compound 13 was prepared by

No.	R^1	R^2	R^3	m.p. (°C)	Nidation inhibition ED_{50} (mg/kg) s.c.	p.o.
1	H	H	H	204–206	>4	>4
2	OH	H	H	202–203	0.5	0.5
3	Acetyloxy	H	H	158–160	>4	–
4	5-Bromonicotinoyloxy	H	H	185–187	1–2	1
5	Isonicotinoyloxy	H	H	158–161	2–4	2–4
6	Hexanoyloxy	H	H	135–137	1–2	0.5–1
7	Benzoyloxy	H	H	164–166	1	0.5
8	Pivaloyloxy	H	H	155–156	1–2	0.5–1
9	2,6-Dimethoxybenzoyloxy	H	H	142–146	2–4	2–4
10	2,6-Dimethylbenzoyloxy	H	H	184–186	4	2
11	Benzoyloxy	H	Br	200–202	2	4
12	Benzoyloxy	H	Cl	198–200	0.7	1.5
13	Benzoyloxy	CH_3	H	168–170	>16	9
14	Ethoxy	H	H	121–123	>4	–
15	Fenoxy	H	H	128–130	>4	>4
16	Benzoylthio	H	H	165–167	>4	>4
17	2-Bromo-α-ergocryptine				1.3	7.7

methylation[10] of compound 7 with CH_3J and $NaNH_2$ in liq. NH_3.

Pharmacology. The antiprolactin activity of the derivatives has been indirectly evaluated utilizing the nidation inhibition test in rats[11], prolactin being the single pituitary hormone responsible for the function of the corpora lutea in early pregnancy in this species[12]. Pregnant Sprague-Dawley rats weighing 200–250 g were used. The compounds to be tested, suspended in 5% acacia gum, were administered p.o. or s.c. on day 3 of pregnancy (day 1 = day of sperms or plug detection).

On day 14 the animals were anesthetized and the uteruses were examined for the presence of implantation sites.

Each substance was administered at the screening dose of 4 mg/kg to groups of 5–7 rats: the active compounds were tested at lower doses for the approximate ED_{50} evaluation.

2-Bromo-α-ergocryptine well known for both its anti-nidation and anti-prolactin activity[13] has been used as reference standard.

The results are summarized in the table. These data suggest that, with the notable exception of compound 3, all the esters are hydrolyzed in vivo to the active ketol (No. 2), although an activity per se of the esters cannot be excluded. Compounds No. 1, 14, 15, 16 that cannot yield the ketol No. 2 are inactive at the screening dose level. Halogenation in position 2 does not modify the antiprolactin activity whereas methylation in position 1 practically abolishes it.

On the basis of these data and of the stability tests, the benzoate (No. 7) has been selected for further investigation.

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Inhibition of Ca^{2+}-induced noradrenaline release from central noradrenergic neurons by morphine

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Summary. Morphine inhibited the noradrenaline release from slices of rat brain cortex induced by introduction of Ca^{2+} ions after superfusion with Ca^{2+}-free, K^+-rich solution. The degree of inhibition was inversely related to the Ca^{2+} concentration used for stimulation.

Morphine[2,3] and the endogenous compounds enkephalin[3,4] and β-endorphin[5] inhibit the noradrenaline release from rat brain slices evoked by electrical pulses or high extracellular K^+ concentration; the inhibition is probably mediated by opiate receptors, since it was antagonized by naloxone. These receptors appear to be located on the varicosities of the terminal noradrenergic fibres[3], and it has been suggested that their activation may decrease the availability of Ca^{2+} ions for stimulus-release coupling[6]. On the basis of these suggestions we studied whether the noradrenaline release induced by introduction of Ca^{2+} ions after superfusion of brain cortex slices with Ca^{2+}-free, K^+-rich solution is decreased by morphine and whether the degree of inhibition is dependent on the Ca^{2+} concentration used for