raised. In particular, the effects of stimulation of cutaneous or proprioceptive afferents as well as monoaminergic descending pathways could be studied since they are known to elicit activation and modulation of locomotor activities[5,7,8,11-15]. Such studies are now in progress as well as a detailed quantification of the results.

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Diabetogenic action of alloxan-like derivatives of uric acid

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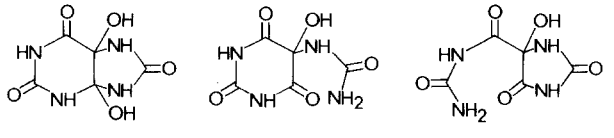
Summary. Two new potent diabetogenic substances 4,5-dihydro-4,5-dihydroxyuric acid (**1**) and 5-hydroxy-pseudouric acid (**2**) have been found.

The production of experimental diabetes by alloxan led to the early suggestion that in human diabetes an alloxan-like metabolite is formed in the course of purine catabolism[2]. Attempts to detect alloxan in vivo[3,4] and to demonstrate that it can be derived from uric acid[5,6] have also been reported. Our recent re-examination of the chemical and spectroscopical properties of alloxan-like compounds **1–3**, have resulted in the revision of previously accepted structures[7,8].



1 2 3

The structures **1** and **2** were assigned to Biltz' 5-hydroxy-pseudouric acid[9] and Behrend's compound $C_5H_6N_4O_5$[10], respectively. The structure **3** was established for the 3rd isomeric compound, originally formulated as 4,5-dihydro-4,5-dihydroxyuric acid[11].

An investigation of the biological activity of alloxan-like derivatives of uric acid seemed necessary in view of its far reaching importance in understanding the pathogenesis of diabetes mellitus.

Materials and methods. Male Lewis rats, weighing 180–230 g, were used throughout. The substances tested were injected i.v. or i.p. as saline solutions or suspensions, depending on solubility. A rat was considered strongly diabetic if glucosuria (> 1%) occurred within 24 h after injection and persisted for 5 days. Additional information was obtained by observation of blood sugar, ketonuria, and histological changes. The diabetogenic potency of the substance was expressed as the effective dose which caused diabetes in 50% of the animals (ED_{50})[12].

Results and discussion. The substances **1–3** were tested for diabetogenic activity. I.v. administration of **1** and **3** was inconvenient due to low solubility, therefore these substances were injected i.p. For comparison, activity of alloxan was also tested and the results are summarized in the following table.

A single i.p. or i.v. administration of **1** or **2** caused diabetes, whereas **3** produced neither diabetes nor toxic symptoms in rats. Nevertheless a reliable comparison is doubtful on account of remarkable differences in solubility; activities of **1** and alloxan, administrated i.p., were similar. The alloxan content at ED_{50} of **2**, however, corresponded to only 24 mg/kg (0.15 mmoles/kg), an amount which does not in itself cause diabetes when given i.v. Since the lowest observed active dose of alloxan is 30 mg/kg (0.19 mmoles/kg), there can be no doubt that the active species is the ureide **2**. Severe cases of diabetes with extreme hyperglycemia, ketonuria, and heavy glucosuria first began to appear in all animals injected with 50 mg/kg of the more potent diabetogenic substance **2**, although it seemed to be less toxic than alloxan. The permanent hyperglycemia was produced within 24 h after administration of the diabetogenic dose of **1** or **2**, and no typical triphasic change in the blood sugar curve as observed in alloxan diabetes was noted. The histological changes in the islets of Langerhans were similar to those in alloxan diabetes. Compounds **1** and **2** caused selective injury to the β-cells, resulting in the reduction of islets which consisted almost entirely of α-cells. The metabolic implications of these findings are of some interest. It seems likely that under certain conditions in vivo uric acid can be converted to intermediates **1** and/or **2** and thus explain the lesion of β-cells of the islands of Langerhans produced as the result

Effective diabetogenic doses (ED_{50}) in rats

Substance	No. of rats injected	(ED_{50}) mg/kg b.wt	mmole/kg b.wt
Alloxan	16 (i.v.)	50	0.31
Alloxan	16 (i.p.)	180	1.12
1	16 (i.p.)	215	1.06
2	24 (i.v.)	30	0.15
3	8 (i.p.)	inactive with 4 g/kg	

of the i.p. injection of uric acid in glutathione-depleted rabbits[13]. The particularly pronounced activity of **2** may also indicate that the actual diabetogenic agent in alloxan-induced diabetes could be formed through a combination of exogenous alloxan with blood urea. The formation of ureide **2** is a characteristic chemical property of alloxan[10] and may become useful in understanding its mode of action.

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Effects of aluminium hydroxide on restraint-induced and restraint delay-induced gastric ulceration in rats

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Summary. Rats given aluminium hydroxide after cold-restraint stress but before the 'post-stress delay' period, ulcerated significantly less severely and less frequently than rats given the drug before cold-restraint stress or those given water at either time period. Both aluminium hydroxide treated groups exhibited less ulceration than non-drug groups. These data suggest profound parasympathetic and hence, gastric acid, involvement in restraint delay-induced ulceration in rats.

The use of restraint as an ulcerogenic technique has been extensively documented[1-3]. Recently, a variation of the standard restraint procedure involving a 90-min post-stress delay in sacrificing the animals has been reported to enhance ulceration relative to animals sacrificed immediately following stress termination[4]. A similar phenomenon had previously been reported using shock stress[5,6]. The reasons for this phenomenon are unclear, however, parasympathetic 'rebound' following chronic sympathetic arousal during the stress of restraint is suggested by the work of Mason et al.[7] who observed marked elevation of parasympathetic function in monkeys given rest periods from a prolonged shock avoidance regimen. The present investigation was an attempt to examine the antiulcerogenic effects of a locally-acting antacid (aluminium hydroxide gel Amphojel) administered at various stages of the restraint delay paradigm.

Method. 50 male Wistar rats (175–200 g at the start of the experiment) were used. All animals were starved for 24 h and divided into equally-sized groups.

1 group of rats was given a single oral injection of 300 mg (in 5 ml) of aluminium hydroxide gel (Amphojel) prior to being subjected to the cold-restraint procedure in the supine position[8] for 3 h. Following this period, the animals were removed from the cold-restraint treatment and returned to their home cages without food or water for 90 min. Following this 'post stress delay' period[4-6], the rats were sacrificed with chloroform, their stomachs excised and examined for ulceration. The number, location (rumenal or glandular) and the cumulative length (mm) of the ulcers were recorded. A 2nd group of rats received treatment identical to that of the 1st group, except that the aluminium hydroxide injection was administered after the 3 h period of cold restraint and immediately prior to the 'post-stress delay' period. Rats in a 3rd and 4th group, received the same treatment as those in groups 1 and 2, except that they received oral injections of distilled water prior to or immediately following the 3 h period of supine cold-restraint, respectively. A final group of rats received no injection, but was subjected to both the supine cold-restraint period and the 'post-stress delay' period.

Results. Figure 1 shows mean cumulative glandular ulcer length (mm) for the 5 groups of rats. Rats given aluminium hydroxide prior to the cold-restraint period exhibited significantly less frequent ($p < 0.001$) and significantly less severe ($p < 0.001$) glandular stomach ulceration than either of the water-injected or non-injected groups. Rats given aluminium hydroxide after cold-restraint but prior to the 'post-stress delay' period, displayed significantly less frequent ($p < 0.001$) and significantly less severe ($p < 0.001$) glandular ulceration than any of the other groups. In the case of both aluminium hydroxide and water, administration after cold-restraint stress was more effective in