drogen the potency is greatly increased as AY-18,672 shows a high depletion at 2 mg/kg whereas comparable activity is exhibited by AY-14,948 at 20 mg/kg. The significance of the substituents on the aliphatic side chain is demonstrated by the finding that the compounds AY-20,213 and AY-20,214 containing an alcohol group are less active than the respective compounds AY-18,672 and AY-14,948 containing a carbonyl group.

The blockade of uptake of norepinephrine in the heart by AY-18,672 is not specific to the rat as the activity is also observed in the mouse. In this respect AY-18,672 is similar to AY-14,948 as this compound has also been shown to block the uptake of norepinephrine in both the rat and mouse[1].

None of the compounds examined cause a decrease in the endogenous norepinephrine in the rat under the conditions employed. In this respect they thus resemble the structurally-related 4-chlorinated aralkylamine 4-chloro-α,α-dimethylphenethylamine which has also been shown[2] to be ineffective. The compounds examined in the present studies are dialkylated in the α-position and this is of importance since it has been shown[6] that dialkylation of the α-position of mono-α-methylphenethylamine causes loss of the norepinephrine-releasing activity which is observed in the mono-α-methyl compounds in the mouse heart. AY-14,948 and AY-18,672 do not cause a decrease in the brain serotonin; in contrast, the structurally-related compound 4-chloro-N,α-methylphenethylamine does[3,5]. It is also of interest in this respect that in the 4-chloro-α-methylphenethylamine series the compound with the free amino group is the most effective in causing the decline in serotonin[7] and the compounds in the present studies are substituted amines.

In comparison with the drug imipramine, the compounds show similarities since imipramine has been demonstrated to interfere with the uptake of norepinephrine[8] and not to cause alterations in the endogenous levels of catecholamines and serotonin[9,10]. Further, imipramine inhibits gastric secretion in the rat[11–13] and the compounds examined in the present studies have also been found to inhibit gastric secretion[13]. It is of interest in this respect that, as found in the blocking of uptake of norepinephrine, AY-18,672 is also the most potent of the series in inhibiting gastric secretion and the level of this activity observed with AY-18,672 is similar to that found with imipramine[13]. In addition, the stimulation of gastric secretion induced by reserpine is blocked by both imipramine and AY-18,672[13,14].

Zusammenfassung. Es wurde gefunden, dass die strukturverwandte Verbindung α,α-Dimethylphenethylaminopropan-2-on (AY-18627) für das Blockieren der Norepinephrinaufnahme im Rattenherzen wirksamer ist als AY-14948. Unter gegebenen Versuchsbedingungen riefen diese Verbindungen weder eine Änderung im endogenen Bereich der Hirn- und Herzkatecholamine noch im Serotoningehalt des Rattenhirns hervor.

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[6] J. W. Daly, C. R. Creveling and B. Witkop, J. med. Chem. *9*, 273 (1966).
[7] R. W. Fuller, C. W. Hines and J. Mills, Biochem. Pharmac. *14*, 483 (1965).
[8] J. Axelrod, G. Hertting and L. Potter, Nature *194*, 297 (1962).
[9] K. G. Gey and A. Pletscher, J. Pharmac. *133*, 18 (1961).
[10] F. Sulser and B. B. Brodie, Biochem. Pharmac. *8*, 16 (1961).
[11] S. Bonfils, M. Dubrasquet and A. Lambling, J. appl. Physiol. *17*, 299 (1962).
[12] P. Bass and M. A. Patterson, J. Pharmac. *156*, 142 (1967).
[13] W. Lippmann, in preparation (1968).
[14] The author acknowledges the technical assistance of Miss Dorothy Mulrooney.

Antigastric Secretory Activity of 4-Chloro-α,α-Dimethylphenethylaminopropan-2-one and Related Compounds

In studies on the effects of 4-chlorinated aralkylamines on the monoamine levels in tissues of the rat it was found that 4-chloro-α,α-dimethylphenethylaminopropanon-2-one (AY-14,948) blocked the uptake of noradrenaline into the heart[1]. AY-14,948 did not cause any alterations in the catecholamine contents of the heart, brain or adrenals or 5-hydroxytryptamine content of the brain. Similar activities have been observed with imipramine[2–4]. Imipramine has been shown to inhibit gastric acid secretion[5–7]. The effects of AY-14,948 and structurally-related compounds on gastric acid secretion were determined and are reported here.

Materials and methods. Gastric acid secretion was determined by a modified method of Shay, Sun and Gruenstein[8]. Charles River female albino rats (Canadian Breeding Laboratories; 170–190 g) were caged individually 48 h prior to treating. For the first 24 h the animals were deprived of food and then were given access to 8% sucrose in 0.2% sodium chloride for 8 h. Water was permitted ad libitum except during the 8 h of sucrose. 3 h after the pyloric ligation the animals were anaesthetized with ether and the amount of acid in the stomach determined by titration against 0.1 *N* sodium hydroxide in a direct reading pH meter to 7.0. For the determination of the effect of AY-18,672 on the increase in gastric secretion induced by reserpine the method of Kim and Shore[9] as modified by Levine[10] was used. Rats (170–190 g) were starved as described above. The stomachs of the animals were ligated at the pyloric end and lavaged with 0.9% NaCl until clear.

[1] W. Lippmann, J. Pharm. and Pharmac. *20*, 385 (1968).
[2] K. G. Gey and A. Pletscher, J. Pharmac. *133*, 18 (1961).
[3] F. Sulser and B. B. Brodie, Biochem. Pharmac. *8*, 16 (1961).
[4] J. Axelrod, G. Hertting and L. Potter, Nature *194*, 297 (1962).
[5] S. Bonfils, M. Dubrasquet and A. Lambling, J. appl. Physiol. *17*, 299 (1962).
[6] P. Bass and M. A. Patterson, J. Pharmac. *156*, 142 (1967).
[7] W. Lippmann, in press (1968).
[8] H. Shay, D. C. H. Sun and M. Gruenstein, Gastrol. pol. *26*, 906 (1954).
[9] K. S. Kim and P. A. Shore, J. Pharmac. *141*, 321 (1963).
[10] R. J. Levine, Fedn Proc. Am. Socs exp. Biol. *24*, 1331 (1965).

1 ml 0.9% saline was returned to the stomach. The latter treatments and esophageal ligations were done under ether anaesthesia. Test drugs were given s.c. immediately following the operations. Reserpine (5 mg/kg s.c.) was given 15 min after the AY-18,672 and the animals were sacrificed 3 h later. The stomachs were removed and the gastric contents emptied into centrifuge tubes. The contents were centrifuged and volumes of solid matter and juice noted. An aliquot of each sample was titrated against 0.01 *N* sodium hydroxide in a direct reading pH meter to pH 3.5 to obtain the mean free acid content and then the total sample was titrated to pH 7.0 to obtain the total acid.

Reserpine was obtained from CIBA Ltd. and imipramine from Geigy Ltd. The compounds studied were synthesized by Dr. A. Langis (Ayerst Laboratories) and were in the form of the hydrochloride salts. Student's *t*-test was used in the evaluation of the data.

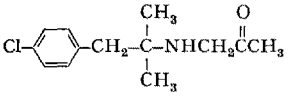
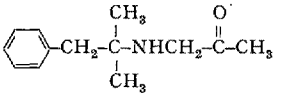
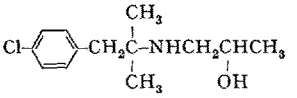
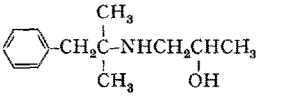
Results. AY-14,948 at 20 mg/kg, i.p., inhibited gastric secretion 56% (Table I). The structurally-related compounds AY-18,672 and AY-20,214 caused decreases in gastric secretion of 76 and 58%, respectively, while AY-20,213 did not cause any change. The gastric secretion decreased 26 and 62% after administration of AY-14,948 and AY-18,672, at 10 mg/kg, i.p., respectively; no change was observed after AY-20,214 and AY-20,213. Thus, AY-14,948 exhibits antigastric secretory activity; however, AY-18,672 is even more potent in this respect.

In Table II are shown the effects of AY-18,672 and imipramine on the stimulation of gastric secretion caused by reserpine. AY-18,672 (10 mg/kg s.c.) and imipramine (10 mg/kg s.c.) caused a decrease of 50 and 61% in mean free acid and a decrease of 60 and 66% in total acid, respectively. After administration of reserpine (5 mg/kg s.c.) there was an increase in mean free acid to 317% and total acid to 306%. When the animals received AY-18,672 or imipramine 15 min before reserpine the mean free acid and total acid were similar to the untreated animals; the total acid in the AY-18,672 treated animals was similar to that of the untreated animals and the total acid in the animals receiving imipramine was decreased. Thus, AY-18,672 inhibited the increase in gastric secretion induced by reserpine. Imipramine also exhibited this activity.

Discussion. In the present studies AY-14,948 was observed to inhibit gastric secretion in the rat. AY-14,948 has been demonstrated to block the uptake of noradrenaline into the heart[1]. In these respects AY-14,948 is similar to the drug imipramine since imipramine has been shown to interfere with the uptake of noradrenaline[4] and to inhibit gastric secretion[5–7]. Further, the drugs are similar since neither AY-14,948[1] nor imipramine[2,3] causes changes in the endogenous levels of catecholamines in the heart, brain or adrenals or 5-hydroxytryptamine in the brain.

Of the structurallyrelated compounds tested another compound AY-18,672 (α,α-dimethylphenethylaminopro-

Table I. Effect of AY-14,948 and structurally-related compounds on gastric secretion

Compound	Dose mg/kg, i.p.	Gastric secretion m Eq acid/3 h ± S.E.	% of control	*P*
None		0.54 ± 0.05		
AY-14,948 	20	0.29 ± 0.03	54	< 0.01
AY-18,672 	20	0.13 ± 0.02	24	< 0.001
AY-20,214 	20	0.23 ± 0.05	42	< 0.001
AY-20,213 	20	0.49 ± 0.06	91	> 0.10

There were 9 control and 4–6 treated animals.

None		0.58 ± 0.05		
AY-14,948	10	0.43 ± 0.04	74	< 0.05
AY-18,672	10	0.22 ± 0.04	38	< 0.001
AY-20,214	10	0.44 ± 0.06	76	> 0.10
AY-20,213	10	0.46 ± 0.04	79	> 0.05

There were 8 control and 5 treated animals.

Table II. Effects of AY-18,672 and imipramine on reserpine-induced gastric secretion

Compound	Dose mg/kg, s.c.	Mean free acid μ Eq/3 h ± S.E.	*P*	% of control	Gastric secretion Total acid μ Eq/3 h ± S.E.	*P*	% of control
None	–	23 ± 2.7			95 ± 20.0		
AY-18,672	10	12 ± 1.8	< 0.01	50	38 ± 4.7	< 0.05	40
Imipramine	10	9 ± 1.8	< 0.01	39	32 ± 2.8	< 0.02	34
Reserpine	5	73 ± 5.5	< 0.001	317	291 ± 48.0	< 0.01	306
AY-18,672 + Reserpine	10 5	18 ± 3.3	> 0.10 < 0.001[a]	78	52 ± 6.9	> 0.05 < 0.01[a]	55
Imipramine + Reserpine	10 5	18 ± 2.0	> 0.10 < 0.001[a]	78	45 ± 4.8	< 0.05 < 0.01[a]	47

There were 7 control and 4–6 treated animals; *P*-value is versus controls; [a]-value is versus reserpine-treated group.

pan-2-one) was more effective than AY-14,948 and was the most potent of the series in blocking the basal gastric secretion. The level of antigastric secretory activity of AY-18,672 is moreover similar to that observed with imipramine. Also, as with imipramine the stimulation of gastric secretion induced by reserpine is blocked by AY-18,672. It is of interest that AY-18,672 blocks the uptake of noradrenaline and is also more potent in this activity than AY-14,948[7]. Further, in studies utilizing the same compounds examined in the present studies AY-18,672 was the most active of the series in interfering in the uptake of noradrenaline[7]. Other drugs which prevent the uptake of noradrenaline, such as chlorpromazine and cocaine in addition to imipramine, are effective as inhibitors of the basal gastric secretion in the pylorus-ligated rat[6,11].

Zusammenfassung. AY-14,948 [4-Chlor-α,α-Dimethylphenethylaminopropan-2-on] setzt die basale Ausscheidung von Magensäure in der Ratte herab. Die Prüfung der strukturverwandten Verbindungen ergab, dass AY-18,672 [α,α-Dimethylphenethylaminopropan-2-on] in dieser Hinsicht wirksamer ist als AY-14,948, indem es auch die reserpinbedingte Erregung der Magensäureausscheidung blockiert.

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[11] The author acknowledges the technical assistance of Mrs. Ilse Marotta and Mrs. Susan Schaal.

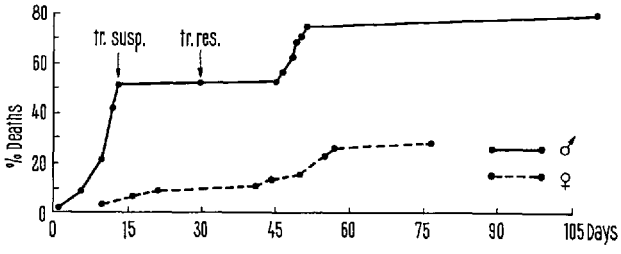
A Sex Difference in Some Toxic Effects of Lithium-Carbonate

Lithium carbonate is widely used in clinical trials against manic phases of the manic-depressive phychosis[1,2] and as prophylactic agent against recurrent depressions[3]. There is, therefore, a considerable interest in toxic effects after chronic treatment, using different ways of administration and different animal species[4-6].

Using lithium carbonate by gastric intubation in rats, consistently more pronounced toxic effects have been observed for male than for female animals under our experimental conditions. Male and female rats from Sprague Dawley strain weighing 180–210 g were kept on a standard diet (containing 5 g/kg of sodium chloride). The male rats were kept separated from the female animals, in a constant room temperature of 27 °C.

Lithium carbonate (Merck Co.) dissolved in water, (10 mg/ml) was administered daily by gastric intubation in a dose of 15 mg/100 g body weight.

Animals were allowed diet and tap water ad libitum. The parameters measured were body weight, survival time and blood non-proteic nitrogen. In all these parameters, in male rats more toxic effects than in the corresponding females have been observed.



Toxicity in rats receiving lithium carbonate (15 mg/100 g body weight per day).

Non-proteic nitrogen from blood of male and female rats after 15 days of treatment with lithium carbonate.

Control animals	Males	Females
0.33 ± 0.05	0.49 ± 0.02	0.35 ± 0.04

The results represent the average of 6 animals ± S.E.

In the Figure the survival time in both male and female animals is recorded. The toxic effect is higher in male rats. In this group the administration was interrupted after 15 days of treatment. During the days of interval no further deaths were observed while the animals rapidly died shortly after resumption of lithium carbonate.

The body weight decreased in both animal groups, but in male rats the decrease was about 30% more than in female rats.

The Table shows the changes in blood non-proteic nitrogen after 15 days of treatment in the 2 groups, again showing marked increase in male rats. The sex difference of lithium carbonate toxicity has not been reported in any of the reviews on the subject[7-10], and it is of interest to clinical investigators for the possibility that lithium carbonate may be more toxic in male human subjects during treatment of psychotic diseases.

Riassunto. Abbiamo notato una netta diversità di risposta tra ratti maschi e femmine durante il trattamento cronico con 15 mg/100 g di peso corporeo di carbonato di Litio, somministrato per sonda gastrica. La tossicità era molto più spiccata nei maschi che nelle femmine. Nei maschi la mortalità cessava con l'interruzione della somministrazione e riprendeva con il trattamento. L'azotemia determinata dopo 15 giorni di trattamento nei due gruppi, testimoniava pure valori significativamente più elevati negli animali maschi.

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[1] M. Schou, N. Juel-Nielsen, E. Strömgren and N. Voldby, J. Neurol. Psychiat. *17*, 250 (1954).
[2] R. Maggs, Br. J. Psychiat. *109*, 56 (1963).
[3] P. C. Baastrup and M. Schou, Archs gen. Psychiat. *16*, 162 (1967).
[4] J. L. Radomski, H. N. Fuyat, A. A. Nelson and P. K. Smith, J. Pharmac. *100*, 429 (1950).
[5] M. Schou, Acta pharmac. tox. *5*, 70 (1958).
[6] V. D. Davenport, J. Physiol. *163*, 673 (1950).
[7] J. R. Boissier, Actualité Pharmacologique 11e Série (1958), p. 5–40.
[8] M. Schou, Pharmac. Rev. *9*, 17 (1957).
[9] G. Andreani, G. Caseni and G. Martelli, G. Psichiat. Neuropatol. *86*, 273 (1958).
[10] A. Heffter and O. Eichler, *Handbuch der Experimentellen Pharmakologie XIII* (Springer, 1960).