superior cervical ganglion with supramaximal electrical stimuli, 25/sec, for 20 sec, with an automatic stimulator[6]. Spinal cords of cats, anesthetized with ether, were pithed by passing a steel wire into the spinal canal via the foramen magnum.

Sympathetic cardio-accelerator nerves in vagotomized dogs, anesthetized with chloralose, 75 mg/kg i.v., were stimulated postganglionically for 20 sec with square wave impulses, 1–8 V, 10/sec, 1 msec duration. Blood pressure and heart rate were recorded with a Grass polygraph.

At 0.3 mg/kg orally, all 4 compounds lowered systolic blood pressure in conscious hypertensive dogs. The maximum hypotensive effect was obtained 2–6 h after treatment, and ranged from 10–60 mmHg. III and IV were the most potent of the 4 compounds; the minimum effective dose of either was 20 μg/kg orally, and the maximum hypotensive effect was obtained with 0.15 mg per kg orally. All 4 compounds were more potent than hydralazine. The duration of the hypotensive effect was dose dependent, and varied from compound to compound. I and II had a shorter duration of action than III and IV. At 0.625 mg/kg, the hypotensive effect of both III and IV persisted for at least 24 h. By oral administration to conscious dogs all 4 compounds had no significant effect on the heart rate. In contrast, hydralazine, 1.25 mg/kg orally increased the heart rate by more than 50 beats/min and for longer than 6 h. By i.v. administration to anesthetized dogs all 4 compounds increased heart rate, but by only 10 beats/min and for less than 5 min. Hydralazine, 1 mg/kg i.v. increased the heart rate by approximately 15 beats/min and for longer than 30 min.

All 4 aminoquinazolines at doses of from 0.4–4.0 mg/kg i.v. lowered blood pressure and calculated total peripheral vascular resistance in dogs. Intravenous administration of II, 1 mg/kg, or of IV, 0.4 mg/kg, moderately increased cardiac output; but neither III, 0.4–1.6 mg/kg, nor I, 0.25–1.0 mg/kg, had a significant effect on cardiac output. Femoral arterial blood flow increased following intra-arterial administration of either of the 4 compounds at doses ranging from 1–256 μg. In cats, the compounds either reduced or reversed the pressor effect of epinephrine, 5–10 μg i.v. but did not alter the pressor effect of angiotensinamide. Equal reductions of contractions of the cat nictitating membrane induced by pre- or postganglionic stimulation suggested that the drugs had no conventional hexamethonium-like ganglionic blocking activity.

In pithed cats infused with epinephrine, all 4 compounds lowered blood pressure.

III, 0.1 mg/kg i.v. and II, 4.0 mg/kg i.v. reduced cardiac acceleration caused by stimulation of cardiac sympathetic fibers in dogs; IV at 0.1 mg/kg had no effect.

The mechanism of hypotensive activity of these compounds appears to involve a component of sympathetic inhibition at peripheral site or sites, but this action differs in important respects from conventional blockade of α-receptors. A detailed study of the site and mechanism of action of 1 member of this group will be published shortly[7].

Zusammenfassung. 4 neue Aminoquinazolin-Derivate, die den Blutdruck von Hunden und Katzen herabsetzen, werden beschrieben. Ihre wirksamen Dosen liegen im Bereiche von 20 bis 300 μg/kg peroral. Diese Substanzen setzen den peripheren Widerstand herab und reduzieren die blutdrucksteigernde Wirkung von Adrenalin, unterscheiden sich aber von den typischen α-Sympatholytika.

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Blockade of Uptake of Norepinephrine in Rodents by α,α-Dimethylphenethylaminopropan-2-one

In previous studies on the effects of 4-chlorinated aralkylamines on the monoamine levels in tissues of the rat it has been shown that 4-chloro-α,α-dimethylphenethylaminopropan-2-one (AY-14,948) blocks the uptake of norepinephrine into the heart[1]. Other 4-chlorinated aralkylamines have been shown to have effects on the monoamines in tissues and to differ in their actions[2–5]. In studies on the effects of compounds structurally related to AY-14,948 on the uptake and storage of the monoamines in rodent tissues, it was found that AY-18,672 (α,α-dimethylphenethylaminopropan-2-one) was more potent than AY-14,948 in causing a blockade of uptake of norepinephrine in the heart and these results are reported here. The methods used in the present study were identical to those described in the previous related publication[1].

The effects of compounds structurally related to AY-14,948 on the uptake and release of H^3-norepinephrine (H^3-NE) in the rat heart are shown in Table I. When the compounds were administered before the H^3-NE, AY-14,948 (20 mg/kg) caused a 49% decline in the H^3-NE. A decrease (33%) was observed in the H^3-NE after AY-18,672 at the lower dose of 2 mg/kg. AY-20,213 (20 mg/kg) and AY-20,214 (20 mg/kg) decreased the H^3-NE 32% and 22%, respectively. At 10 mg/kg AY-14,948, AY-18,672 and AY-20,213 caused declines of 30, 69 and 20%, respectively; no change was observed after AY-20,214. When AY-14,948, AY-20,213 and AY-20,214 at 20 mg/kg and AY-18,672 at 2 mg/kg were injected after the H^3-NE, no changes in the H^3-NE were observed after any of the compounds. Thus,

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[5] W. Lippmann and M. Wishnick, Life Sci. *4*, 849 (1965).

each of the compounds blocked the uptake, and did not cause a release, of H^3-NE in the rat heart. Further, AY-18,672 was much more potent than AY-14,948 and the latter was more effective than AY-20,213, followed by AY-20,214.

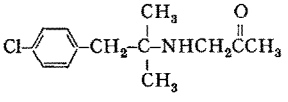
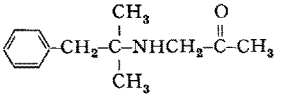
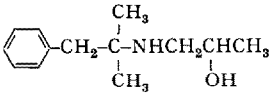
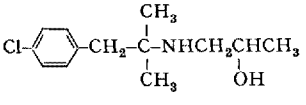
The effects of the most active compound AY-18,672 on the H^3-NE were also determined in the mouse. At 50, 25 and 10 mg/kg there were decreases of 86, 65 and 57%, respectively, in the H^3-NE in the mouse heart when the compound was given before the H^3-NE (Table II). No change in H^3-NE was observed when AY-18,672 (50 mg/kg) was given after the H^3-NE. Thus, AY-18,672 also caused an interference in the uptake, and not a release, of H^3-NE in the mouse heart.

In Table III are shown the effects of AY-18,672 (0.1 mM/kg) on the catecholamine and serotonin contents of tissues of the rat after 16 h. AY-18,672 did not cause any changes in the levels of catecholamines in the brain and heart or serotonin in the brain. Similar results were observed after AY-14,948. The levels of catecholamines in the adrenals were also not changed after AY-18,672. AY-20,213 and AY-20,214 did not alter the levels of catecholamines in the brain or heart.

The monoamine oxidase activities in brains and livers of rats 1 h after injection (0.1 mM/kg) of AY-18,672, AY-14,948, AY-20,213 or AY-20,214 were not changed. Tranylcypromine (0.33 mM/kg) caused an inhibition of the monoamine oxidase activity of 89% in the brain and of 87% in the liver. In vitro none of the compounds caused inhibition of monoamine oxidase activity in the rat brain at $10^{-4}M$; pargyline caused a 70% inhibition at $10^{-6}M$.

As with AY-14,948 the structurally-related compounds AY-18,672, AY-20,213 and AY-20,214 also cause a blockade of the uptake, and not a release, of norepinephrine in the rat heart. With respect to the structure-activity relationship it appears that the substituent in the para-position of the aromatic ring is of major importance. Thus, when the chlorine in the 4-position is replaced by a hy-

Table I. Effects of compounds structurally related to AY-14,948 on the uptake and release of H^3-norepinephrine in the rat heart

Compound	Dose (mg/kg, i.p.)	Radioactivity content cpm/g ± S.E.	% of control	P
None		9030 ± 319		
AY-14,948 	20	4635 ± 203	51	< 0.001
AY-18,672 	2	6065 ± 303	67	< 0.001
AY-20,213 	20	6118 ± 348	68	< 0.001
AY-20,214 	20	7160 ± 324	79	< 0.001

Compound	Dose (mg/kg, i.p.)	Radioactivity content cpm/g ± S.E.	% of control	P
None		11408 ± 677		
AY-14,948	10	7931 ± 356	70	< 0.001
AY-18,672	10	3515 ± 189	31	< 0.001
AY-20,213	10	9162 ± 644	80	< 0.05
AY-20,214	10	10503 ± 900	92	> 0.3

The compounds were administered 15 min before the H^3-NE and the rats (60–80 g) were killed 105 min later. There were 15–17 animals in the control and 8–10 in the treated groups.

None		6164 ± 387		
AY-14,948	20	6787 ± 426	109	> 0.3
AY-18,672	2	6170 ± 611	100	> 0.9
AY-20,213	20	5602 ± 466	91	> 0.5
AY-20,214	20	5807 ± 508	94	> 0.5

The compounds were injected 15 min after H^3-NE and the animals were killed 2 h later. There were 15 animals in the control and 8 in the treated groups.

Table II. Effects of AY-18,672 on the uptake and release of H^3-norepinephrine in the mouse heart

Drug	Dose (mg/kg, i.p.)	Time drug given before or after H^3-NE	Radioactivity content cpm/g ± S.E.	% of control	P
None		45 min before	7883 ± 390		
AY-18,672	50	45 min before	1116 ± 142	14	< 0.001
AY-18,672	25	45 min before	2760 ± 131	35	< 0.001
AY-18,672	10	45 min before	3404 ± 223	43	< 0.001
None		45 min after	5740 ± 460		
AY-18,672	50	45 min after	5691 ± 399	99	> 0.5

There were 9–11 animals in the control and 7 in the treated groups. Animals were killed 2 h after receiving drug.

Table III. Effect of AY-18,672 on the catecholamine and serotonin contents of tissues of the rat after 16 h

Compound	Brain catechol-amines µg/g ± S.E.	P	Brain serotonin µg/g ± S.E.	P
None	0.40 ± 0.02		0.60 ± 0.03	
AY-18,672	0.39 ± 0.02	> 0.3	0.55 ± 0.03	> 0.2
AY-14,948	0.34 ± 0.02	> 0.05	0.53 ± 0.03	> 0.2
	Heart catechol-amines µg/g ± S.E.			
None	0.42 ± 0.02			
AY-18,672	0.41 ± 0.02	> 0.7		
AY-14,948	0.43 ± 0.03	> 0.7		

The compounds were administered (0.1 mM/kg, i.p.) to rats (160 to 180 g) and the tissues were removed 16 h later. There were 15 animals in the control and 7–8 in the treated groups.

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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Biogenic Amines Laboratory, Ayerst Laboratories, Montreal (Que., Canada), 10 May 1968.

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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.

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