SYNTHESIS OF SOME ARALKYLDIMETHYLHYDRAZINE DERIVATIVES AS BLOCKING AGENTS OF ADRENERGIC NEURONS

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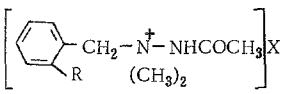
N-benzyl-N,N-dimethyl-N'-acetylhydrazinium chloride, N-(o-bromobenzyl)-N,N-dimethyl-N'-acetylhydrazinium bromide, and N-(o-chlorobenzyl)-N,N-dimethyl-N'-acetylhydrazinium bromide, which are blocking agents for adrenergic neurones, have been synthesized. N-(o-bromobenzyl) -N,N-dimethyl-N'-acetylhydrazinium bromide has the most pronounced inhibiting activity.

In preceding investigations [1-4] it was established that some aralkylguanidines – in particular, N-benzyl-N',N''-dimethylguanidine sulfate (Benzanidin) and its o-bromo and o-chloro analogs – are blocking agents for adrenergic neurones. Like Ornid, they inhibit the release of the mediator from the terminations of the sympathetic nerves. For a further search for blocking agents of adrenergic neurones with possible new pharmacodynamic properties, it is of interest to synthesize and study such substances as may also be regarded as products of the addition of the benzyl grouping forming part of Ornid and Benzanidin to hydrazine, which enters into the composition of the blocking agents for monoamino oxidase (MAO) mentioned above (Iprazid, nialamide). For this purpose, we have synthesized N-benzyl-N,N-dimethyl-N'-acetylhydrazinium salts and their o-bromo and o-chloro derivatives with the general formula:



R = H, Cl, Br X = Cl, Br

In these compounds, the acetylation of the hydrazine may lead to a decrease in toxicity and an increase in lipophilicity. The second hydrogen remains free, which permits the assumption of its reaction with a specific substrate and the inhibition of the activity of the enzyme. The starting material for these compounds is N,N-dimethyl-N'-acetylhydrazine, which was obtained by the acetylation of unsymmetrical dimethylhydrazine with acetic anhydride. This method gives the best yields of N,N-dimethyl-N'-acetylhydrazine (62-65%). Other methods of acetylation – for example, with ethyl acetate, glacial acetic acid, or acetyl chloride – gave unsatisfactory results. The condensation of the N,N-dimethyl-N'-acetylhydrazine with benzyl chloride and o-bromobenzyl and o-chlorobenzyl bromides in dry acetone gave the corresponding aralkylacetyldimethylhydrazinium salts. They are all slightly hygroscopic, readily soluble in water and ethanol, sparingly soluble in acetone, and insoluble in ether and benzene.

The results of the investigations carried out have shown that all three compounds exhibit a two-phase action in experiments on mice: the first phase is sympathomimetic (exophthalmos, dishevelled fur, motor agitation, passing with toxic doses into clonic-tetanic spasms), and the second phase is inhibition. The LD_{50} on intraperitoneal injection into mice is 1280 (1242.7-1318.4) mg/kg for N-benzyl-N,N-dimethyl-N'-acetylhydrazinium chloride, 920 (851.2-993.6) mg/kg for the o-bromo derivative, and 1020 (957.7-1086.3) mg/kg for the o-chloro derivative. When injected intravenously into anaesthetized cats, a two-phase action on the blood pressure is observed: the first phase is a pressor action and the second phase depressor. Some specific features of the action of the individual compounds were noted. In doses of 6 and 7 mg/kg, the nonbrominated analog causes a pressor reaction and an increase in the tonus of the nictitating mem-

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brane. The depressor phase is not always shown. The introduction of chlorine and, particularly, bromine into the o-position of the aromatic nucleus decreases the intensity of the first phase of the reaction and increases the depressor component. The administration of the latter compound in a dose of 7 mg/kg causes, after a small and brief hypertension, a gradual development of hypotension lasting 3-4 h (sometimes even longer) with the subsequent restoration of the blood pressure. Simultaneously a decrease in the pressor reaction and a compression of the aa. carotis com., a decrease in the contraction of the nicititating membrane in response to stimulation of the jugular sympathetic ganglion, and a spontaneous decrease in the tonus of the denervated nictitating membrane are observed. The reaction of the blood pressure to the stimulation of the peripheral segment of the n. vagus changes little and inconstantly. In a dose of 7 mg/kg, N-(o-bromobenzyl)-N,N-dimethyl-N'-acetylhydrazinium bromide does not lower, and in the first few hours even enhances the pressor action of administered epinephrine. The pressor reaction to the intravenous injection of the ganglion stimulator 1,1-dimethyl-1,4-phenylpiperazine in a dose of 50 mg/kg is not blocked either. Thus, the depressor action of the compound is not connected with an adrenolytic and ganglion-blocking activity. N-(o-bromobenzyl) -N,N-dimethyl-N'-acetylhydrazinium bromide also exhibits anti-reserpine activity, which is expressed as an inhibition of the development of reserpine ptosis in the mouth and a decrease in the reserpine hypothermia. The investigations carried out have shown that N-(o-bromobenzyl)- and N-(o-chlorobenzyl)-N,N-dimethyl-N'-acetylhydrazinium salts are blocking agents of adrenergic neurones acting in the same way as Ornid and Benzanidin.

EXPERIMENTAL

Unsymmetrical dimethylhydrazine was obtained by a published method [5] for unsymmetrical dimethylhydrazine hydrochloride with the only difference that the concentrated aqueous solution of the latter was treated with solid NaOH and the base was distilled from an iron retort in the presence of solid KOH. The fraction with b.p. 60-68°C was collected. Yield 69-70%.

N,N-dimethyl-N'-acetylhydrazine. A three-necked round-bottomed flask cooled with water and fitted with a stirrer with a seal, a reflux condenser, and a dropping funnel was charged with 40 g of dimethylhydrazine and, with stirring, 68 g of freshly distilled acetic anhydride was added over 20 min, after which the mixture was kept at 10-12°C for 1 h and was then heated in the boiling water bath for 4 h. After cooling, the mixture was transferred to a Wurtz flask, the excess of acetic anhydride was distilled off (up to 156°C in the vapor), and the residue was distilled in vacuum; b.p. 91-96°C (12 mm). Yield 43 g (68%).

o-Bromobenzyl Bromide. Obtained by the method that we have reported previously [6]. B.p. 120-129°C (12 mm). Yield 73-75%.

o-Chlorobenzyl Bromide. The starting material was technical o-toluidine, which was converted into o-chlorotoluene by diazotization with subsequent replacement of the diazonium group with chlorine [7]. The o-chlorotoluene was brominated with bromine by the method that we have described for o-bromobenzyl bromide [6], being converted into o-chlorobenzyl bromide. B.p. 97-110°C (8 mm). Yield 65%.

General Method for Obtaining N-aralkyl-N,N-dimethyl-N'-acetylhydrazinium Salts. With stirring, 0.11 mole of benzyl chloride or o-bromo- or o-chlorobenzyl bromide was added to an acetonic solution of 0.1 mole of N,N-dimethyl-N'-acetylhydrazine. The mixture was heated in the water bath for 3-5 h and, after cooling, the precipitate formed was filtered off. The acetonic solution was evaporated to $^1/_2$-$^1/_3$ of its volume, the residue was treated with absolute ether, and the precipitate that formed was filtered off and twice reprecipitated from absolute ethanol. The yield of hydrazinium salt was 48-50%. The following compounds were obtained in this way:

1. N-benzyl-N,N-dimethyl-N'-acetylhydrazinium chloride, m.p. 124-125°C. Found, %: N 12.65, 12.92. $C_{11}H_{17}ON_2Cl$. Calculated, %: N 12.81.

2. N-(o-bromobenzyl)-N,N-dimethyl-N'-acetylhydrazinium bromide, m.p. 114-116°C; literature: 119-120°C [8]. Found, %: N 7.98, 8.02. $C_{11}H_{16}ON_2Br_2$. Calculated, %: N 8.33.

3. N-(o-chlorobenzyl)-N,N-dimethyl-N'-acetylhydrazinium bromide, m.p. 119-120°C, slightly hygroscopic. Found, %: N 10.90, 11.10. $C_{11}H_{16}ON_2BrCl$. Calculated, %: N 11.52.

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