SYNTHETICAL EXPERIMENTS IN THE GROUP OF SYMPATHOMIMETICS, PART IV

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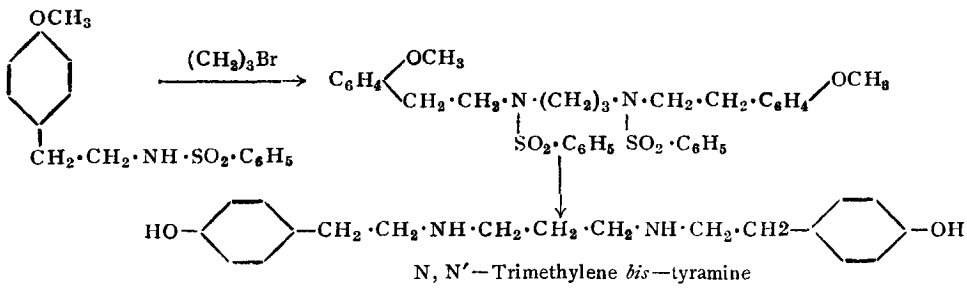
An earlier paper[1] described attempts to synthesise 9-β-aminoethyl-9: 10-dihydro-phenanthridine and a series of possible sympathomimetics derived from some carbocyclic ring systems. The latter had the repeating pressor active, atom-patterns, Ar.C.C.N.—as features of their molecular architectures and, on the basis of von Braun's conception of the mode of action of the intensely sympathomimetic methyl amino hydrindene[2], were entitled to consideration as β-phenylethylamines many times over. The present communication is concerned with attempts to synthesise further 9-β-amino ethyl-9: 10-dihydro-phenanthridine and N,N′-trimethylane *bis*-tyramine which also comes under the same category.

The scheme for the synthesis of the β-aminoethyl phenanthridine derivative could not be pursued owing to failure at the cyclisation stage of cyanacetamido diphenyl to 9-cyanomethyl phenathridine, a necessary intermediate. However, success was encountered in the scheme for the synthesis of the trimethylene *bis*-tyramine. 4-Methoxy phenyl ethylamine[3] was transformed in good yield to its N-benzenesulphonyl derivative[4]; the potassium salt of the latter gave with trimethylene bromide the corresponding alkali insoluble di-amide, which on hydrolysis, furnished the desired N,N[1]-trimethylene *bis*-tyramine.



N, N′—Trimethylene *bis*—tyramine

N,N′-Trimethylene *bis*-tyamine has recently been subjected by Capt. K. Venkatachalam of the Madras Medical College to preliminary biological tests in respect of its pressor activity and compared to tyramine in the spinal cat. The tests, so far conducted, reveal that while its intensity of action

is nearly equal to that of tyramine, trimethylene *bis*-tyramine is superior to the standard sympathomimetic in the matter of its duration of action.

Experimental

2-Cyanoacetamido diphenyl.—A mixture of 2-amino diphenyl (4 g). and ethyl cyanoacetate (2·8 g.) was heated under reflux at 200–10° for 2 hours and cooled; the solid (2·5 g.) which separated was washed with dilute hydrochloric acid followed by water and crystallised from water. It was obtained as colourless needles, m.p. 126° (Found: N, 11·3. $C_{15}H_{12}ON_2$ requires N, 11·9 per cent.)

N,N'-Trimethylene bis-*tyramine hydrochloride.* The postasium salt of N-benzenesulphonyl tyramine-methyl ether was prepared *in situ* by adding the calculated quantity of potassium to a hot solution of the benzene sulphonamide (7 g.) in xylene (15 c.c.) Trimethylene bromide (2·4 g.) was then added and the mixture refluxed for 4 hours. The reaction mixture, after pouring into water and steam distillation to remove xylene completely, furnished the trimethylene diamide. The crude product was freed from the unreacted starting amide by washing successively with dilute alkali and water. The purified diamide was then heated with concentrated hydrochloric acid (10 c.c.) in a sealed tube at 160-170° for 6 hours so as to obtain hydrochloride of N,N'-trimethylene *bis*-tyramine.

The crude, dark coloured product of the pressure reaction was dissolved in absolute alcohol and fractionally precipitated with anhydrous ether, the first oily portions being rejected. The partly purified hydrochloride (1·4 g.) then recrystallised from alcohol-ether in colourless needles, m.p. 149°. (Found: N, 7·8; Cl, 18·6. $C_{19}H_{26}O_2N_2$, 2 HCl requires N, 7·2; Cl, 19·0 per cent.)

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Summary

In continuation of an earlier line of work, synthesis has been effected of N,N'-trimethylene *bis*-tyramine which fulfils the requisite structural specifications for sympathomimecity. The results of subjecting this to preliminary biological tests in respect of its pressor action in the spinal cat are also indicated.

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