SYNTHETICAL EXPERIMENTS IN THE GROUP OF SYMPATHOMIMETICS—PART III

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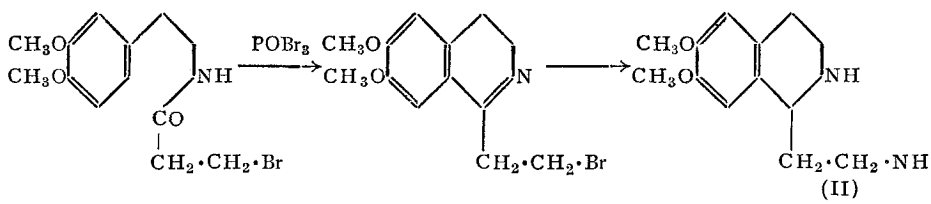
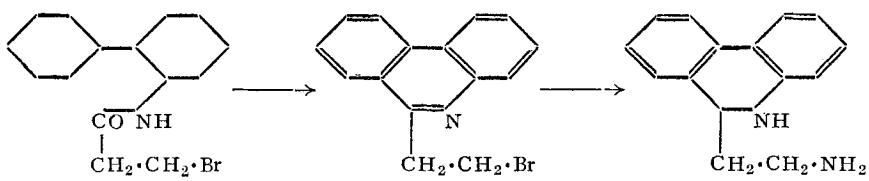
In continuation of the study[1] on the relationship between chemical constitution and physiological activity of sympathomimetic amines derived from various ring-systems, one member of the group of β, β-bis-aryl-β-hydroxy ethylamines belonging to the phenanthrene series, *viz.*, β, β-bis (9-phenanthryl)-β-hydroxy ethylamine (I), has now been synthesised in the usual way.[1,2] The present study also included the synthesis of a β-aminoethyl isoquinoline (II) and a β-aminoethyl phenanthridine (III) on the following lines:

$$9\text{—}C_{14}H_9MgBr + H_2N\cdot CH_2\cdot CO_2Et,\ HCl \longrightarrow (9\text{—}C_{14}H_9\text{—})_2C(OH)\cdot CH_2\cdot NH_2$$

(I)

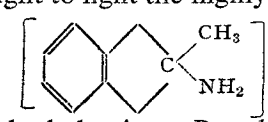


(II)

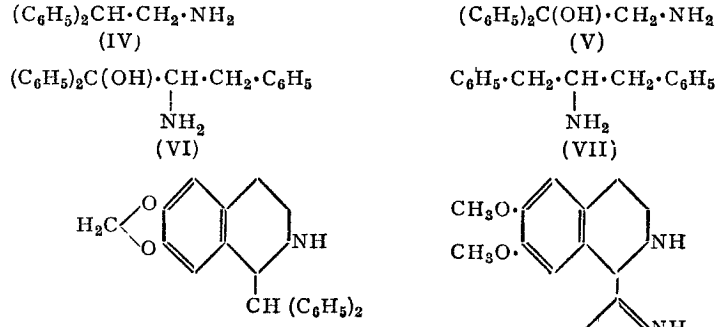


(III)

The scheme for the synthesis of compounds (II) and (III) had, however, to be ultimately abandoned owing to very low yields of the intermediate β-bromoethyl isoquinoline with the former and the failure of the cyclisation to 9-β-bromoethyl phenanthridine in the case of the latter.

A survey of the literature on sympathomimetics brought to light the highly significant observation[3] that methylaminohydrindene  is intensely active by virtue of its being doubly a β-phenyl ethylamine. Based

on the above finding and actuated by considerations of the relative ease with which such bodies could be synthesised, the following compounds, possessing the requisite structure necessary for sympathomimetic activity, have been prepared:



(VIII) (IX)

A close examination of the formulæ-picture of the compounds IV to VIII reveals the active groups, Ar. C.C.N, being repeated in their molecules. The compound (IX), in addition to falling structurally in the class of the sympathomimetic norhydro hydrastinines, constitutes an interesting variation of a β-amino ethyl tetrahydro isoquinoline, wherein the α- and β-carbon atoms are linked by a double bond and form part of an aromatic nucleus.

A few of these compounds (IV, V and VI), although known in literature, were included for purposes of a comparative pharmacological study in progress elsewhere. β, β-Diphenyl ethylamine[4] (IV) has advantageously been prepared now in good yields by the Hoffmann degradation of β, β-diphenyl propionamide.[5] The customary methods were adopted for the synthesis of the other members of the group.

The results of pharmacological examination of about twenty final compounds, hitherto synthesised, compared to tyramin as control, have been reserved for a future communication.

Experimental

β, β-Bis-(9-phenanthryl)-β-hydroxyethylamine (I) hydrochloride.—A Grignard solution was prepared according to Bachmann[6] from magnesium (3·54 g.), 9-bromophenanthrene[7] (38·3 g.) and a mixture of ether (100 c.c.) and benzene (100 c.c.) in an atmosphere of dry nitrogen. Glycine ester hydrochloride (6·7 g.) was added and the mixture refluxed for 1 hour on the water-bath, cooled, decomposed with dilute hydrochloric acid and the

separated solid filtered. The hydrochloride was recrystallised once from alcohol-ether and once from dilute hydrochloric acid as almost colourless needles, m.p. 239–40° (dec.). [Found: Cl, 8·23; $C_{30}H_{24}ONCl$ requires Cl, 7·90%.]

The *picrate* was obtained as greenish-yellow needles, m.p. 209–10° (dec.). [Found: N, 8·36; $C_{36}H_{26}O_8N_4$ requires N, 8·73%.]

1-β-Bromoethyl-3 : 4-dihydro-6 : 7-dimethoxy isoquinoline:

β-Bromopropionyl chloride.—β-Bromopropionic acid[8] (20 g.) and thionyl chloride (18 c.c.) were heated together on the water-bath for 2 hours, and the reaction mixture fractionated. The acid chloride was obtained as an almost colourless, lachrymatric oil, b.p. 115-17°/30 mm. Yield 15·4 g.

β-Bromopropionyl homoveratrylamide.—A mixture of homoveratrylamine[9] (5 g.) and β-bromopropionyl chloride (5 g.) in a little petrol was strongly cooled and gradually treated with dilute sodium carbonate under shaking. The amide separated from water in long, colourless, prismatic needles, m.p. 120–21°; yield 2·5 g. [Found: N, 4·28; $C_{13}H_{18}O_3NBr$ requires N, 4·43%.]

1-β-Bromoethyl-3 : 4-dihydro-6 : 7-dimethoxy isoquinoline.—The above amide (2·4 g.) in chloroform (20 c.c.) was allowed to react at the room temperature with phosphorus oxybromide (10 g.) for 1 week with the exclusion of moisture. The isoquinoline was obtained as a thick brown oil; yield, 0·4 g. One half of the unreacted amide was recovered at the end of the experiment. The *picrate* separated from acetic acid as a yellow powder, decomposing at 166–68°. [Found: N, 10·12; $C_{19}H_{19}O_9N_4Br$ requires N, 10·63%.]

β-Bromopropionyl-o-amino-diphenyl, obtained in 50% yield, crystallised from alcohol in colourless needles, m.p. 118°. [Found: N, 4·80; $C_{15}H_{14}ONBr$ requires N, 4·83%.]

β, β-Diphenyl ethylamine (IV) hydrochloride:

β, β-Diphenyl propionamide.[5]—β, β-Diphenyl propionic acid[10] (15 g.) in chloroform (50 c.c.) was treated with thionyl chloride (10 c.c.), the mixture allowed to stand overnight and gradually added to well-cooled liquor ammonia (75 c.c.) containing a little sodium hydroxide (5 g.). The amide, isolated in the usual way, was obtained in a yield of 12 g., m.p. 124–25°. [Found: N, 6·34; $C_{15}H_{15}ON$ requires N, 6·22%.]

β, β-Diphenyl ethylamine[4] *hydrochloride.*—The above amide (12 g.) was shaken with a cold solution of sodium hypochlorite (from 4 g. of potassium permanganate and 125 c.c. of 10% sodium hydroxide). The temperature was gradually raised to 65° and maintained at 65–70° for 1 hour, cooled, treated

with solid potassium hydroxide (45 g.), heated at 70–80° for half-an-hour, cooled and thoroughly extracted with ether. The ethereal extract was washed and extracted with dilute hydrochloric acid. The aqueous acid solution was evaporated to dryness on the water-bath and the residual hydrochloride recrystallised from alcohol-ether in colourless needles, m.p. 256°; yield, 5 g. [Found: Cl, 14·94; $C_{14}H_{16}NCl$ requires Cl, 15·20%.]

The *picrate* separated from alcohol as greenish-yellow crystals, m.p. 210° (dec.). [Found: N, 13·10; $C_{20}H_{18}O_7N_4$ requires N, 13·14%.]

β, β-Diphenyl-β-hydroxy-ethylamine (*V*) *hydrochloride*, prepared according to Thomas and Bettzieche[2] from phenyl magnesium bromide and glycine ester hydrochloride, crystallised from alcohol-ether in colourless needles, m.p. 191° (dec.). [Found: Cl, 13·85; $C_{14}H_{16}ONCl$ requires Cl, 14·23%.]

The *picrate* separated from alcohol in yellow needles, m.p. 179° (dec.). [Found: N, 12·95; $C_{20}H_{18}O_8N_4$ requires N, 12·67%.]

β, β-Diphenyl-β-hydroxy-α-benzyl ethylamine (*VI*) *hydrochloride*,[2] obtained by reaction of phenyl magnesium bromide (from 35 g. of bromobenzene) and β-phenylalanine ester hydrochloride[11] (6 g.) in fairly good yield (4·5 g.), recrystallised from alcohol-ether as a white crystalline powder, m.p. 225–26° (dec.).

Dibenzylaminomethane (*VII*) *hydrochloride*.—The attempt to reduce dibenzyl ketoxime[12] with sodium amalgam to the desired amine was unsuccessful due, probably, to strong steric hindrance. The amine was, however, prepared by the modified Leuckart method.[13]

Dibenzyl ketone (30 g.) and formamide (20–25 c.c.) were heated together at 175–85° for 8 hours and, thereafter, worked up in the usual way.

The *hydrochloride* recrystallised from dilute hydrochloric acid or alcohol-ether in colourless needles, m.p. 200–01°; yield 25 g. [Found: C, 72·14; H, 6·85; Cl, 14·20; $C_{15}H_{18}NCl$ requires C, 72·73; H, 7·27; Cl, 14·34%.]

The *N-formyl-derivative* separated from alcohol in colourless needles, m.p. 88-89°. [Found: N, 5·57; $C_{16}H_{17}ON$ requires N, 5·86%.]

The *picrate* separated from alcohol in yellow plates, m.p. 191–92° (dec.). [Found: N, 12·59; $C_{21}H_{20}O_7N_4$ requires N, 12·70%.]

1-*Diphenylmethyl*-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*methylenedioxy isoquinoline* (*VIII*) *hydrochloride*:

Diphenylacetyl homopiperonylamide.—Homopiperonyl amine[14] (3·3 g.) and a solution of the crude diphenyl acetyl chloride (from 4·5 g. of the acid and excess of thionyl chloride) in petroleum-ether were condensed together

in the presence of dilute alkali. The separated amide was filtered and recrystallised from alcohol in long, colourless needles, m.p. 139–40°; yield, 2·6 g. [Found: N, 3·84; $C_{23}H_{21}O_3N$ requires N, 3·90%.]

1-*Diphenylmethyl*-3 : 4-*dihydro*-6 : 7-*methylenedioxy isoquinoline*.—A mixture of the above amide (2·5 g.), phosphorus oxychloride (7·5 c.c.) and dry toluene (20 c.c.) was gently refluxed on the sand-bath for 1½ hours with the exclusion of the moisture, cooled and poured on to crushed ice with stirring. The solution, after freeing from non-basic impurities by extraction with ether, was cooled in ice, basified with excess of sodium hydroxide and the separated solid filtered. The dihydro isoquinoline recrystallised from alcohol in colourless needles, m.p. 125–26°, after sintering at 120°; yield, 2·2 g. [Found : N, 4·01; $C_{23}H_{19}O_2N$ requires N, 4·11%.]

1-*Diphenylmethyl*-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*methylenedioxy isoquinoline hydrochloride*.—The crude dihydro base (2 g.), zinc dust (10 g.) and dilute sulphuric acid (60 c.c. of 1 : 4) were heated together on the boiling water-bath for 4 hours, filtered, cooled, basified with a large excess of ammonia and extracted with ether. The isoquinoline was purified twice through a dilute hydrochloric acid solution and the hydrochloride, obtained by evaporation of a dilute acid solution, crystallised from alcohol-ether in faintly yellowish, prismatic needles, m.p. 239° (dec.); yield 1·6 g. [Found: Cl, 10·10; $C_{23}H_{22}O_2NCl$ requires Cl, 9·34%.]

The *N-acetyl derivative* separated from alcohol in colourless needles, m.p. 172°. [Found: C, 77·26; H, 5·43; $C_{25}H_{23}O_3N$ requires C, 77·91; H, 5·97%.]

The *picrate* crystallised from dilute acetic acid in yellow needles, m.p. 212–13° (dec.). [Found: N, 10·32; $C_{29}H_{24}O_9N$ requires N, 10·15%.]

1-(o-*Amino*)-*phenyl*-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy isoquinoline* (IX) *hydrochloride*:

o-*Nitrobenzoyl homoveratrylamide*.—Homoveratryl amine (2·4 g.) by condensation with *o*-nitrobenzoyl chloride in the usual way gave the crude amide (4·6 g., m.p. 138–40°). The amide crystallised from alcohol in colourless, silky needles, m.p. 142°. [Found: N, 8·44; $C_{17}H_{17}O_5N_2$ requires N, 8·51%.]

1-(o-*Nitro*)-*phenyl*-3 : 4-*dihydro*-6 : 7-*dimethoxy isoquinoline*.—The crude amide (4·5 g.), phosphorous oxychloride (15 c.c.) and toluene (40 c.c.) were gently refluxed together for 1 hour and worked up as usual. The isoquinoline separated from alcohol in faint-yellow needles, m.p. 117°, after slight

shrinking at 112°; yield 4·2 g. [Found: N, 8·87; $C_{17}H_{15}O_4N_2$ requires N, 9·00%.]

1-(o-*Amino*)-*phenyl*-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy isoquinoline.*—The nitro dihydro base (1 g.), zinc dust (10 g.) and dilute sulphuric acid (60 c.c. of 1 : 4-) were heated together on the boiling water-bath for 6 hours and worked up. The base separated from alcohol as hard, colourless crystals, m.p. 162°. [Found: C, 72·21; H, 6·36; $C_{17}H_{19}O_2N_2$ requires C, 72·07; H, 6·71%.]

The *monohydrochloride* separated from alcohol-ether in clusters of colourless needles, m.p. 189° (dec.), after sintering at 183°. [Found: Cl, 11·50; $C_{17}H_{20}O_2N_2Cl$ requires Cl, 11·06; %.]

The *diacetyl derivative* crystallised from alcohol as colourless needles, m.p. 196°. [Found: N, 7·42; $C_{21}H_{23}O_4N_2$ requires N, 7·63%.]

Summary

With the object of studying the relationship between chemical constitution and physiological activity of sympathomimetically active amines, one member of the group $Ar_2 : C(OH) \cdot CH_2NH_2$, belonging to the phenanthrene series has been synthesised.

A number of simple bases derived from benzene and the isoquinoline ring-systems, possessing the requisite structure for sympathomimecity, have also been prepared for purposes of a comparative pharmacological study.

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