# 1,2,3,4,7,8-HEXAHYDRO-6H-CYCLOPENT[*g*]ISOQUINOLINE AND N-SUBSTITUTED DERIVATIVES; SYNTHESIS AND PHARMACOLOGICAL SCREENING*

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The Beckmann rearrangement of 1-oximino-*s*-hydrindacene (*I*) with polyphosphoric acid gives rise to a mixture of isomeric lactams *II* and *III*, the predominant component *II* having been isolated. The presence of isomer *III* was demonstrated only after reduction of the mixture of mother liquors with lithium aluminium hydride by isolating its reduction product *XII*. A similar reduction of pure lactam *II* yielded 1,2,3,4,7,8-hexahydro-6*H*-cyclopent[*g*]isoquinoline (*IV*) which was converted to derivatives *V*—*XI*. Reduction of oxime *I* with lithium aluminium hydride yielded as principal products the primary amine *XIV* and the rearranged amine *XII*. Pharmacological screening demonstrated a slight centrally depressant activity of *IX* and *X* while amine *IV* is rather a slight stimulant. Amines *IV* and *V* are adrenolytic in rats and adrenomimetic in monkeys.

The present communication proceeds from an earlier study[1] on 1-amino-*s*-hydrindacene and its derivatives, using as the starting compound the previously described 1-oximino-*s*-hydrindacene (*I*) which was subjected to a Beckmann rearrangement and to a reduction with lithium aluminium hydride. The first reaction was found to be a preparatively feasible approach to the little known series of derivatives of 6*H*-cyclopent[*g*]isoquinoline (RRI 3096; other approaches in ref.[2-5]). Both reactions provide a poor yield of derivatives of isomeric 6*H*-cyclopenta[*g*]quinoline (RRI 3099; see also[6-9]).

The Beckmann rearrangement of 1-oximino-*s*-hydrindacene[1] (*I*) was done with the aid of polyphosphoric acid (for method see[10-13]) at 130°C. A mixture of lactams resulted, the principal product isolated by crystallization having been identified as 1-oxo-1,2,3,4,7,8-hexahydro-6*H*-cyclopent[*g*]isoquinoline (*II*) by means of spectra and chemical transformations. The isomeric lactam *III* could not be isolated but its presence in the reaction product was demonstrated by reduction of the residue of mother liquors after lactam *II* with lithium aluminium hydride. Chromatography of a mixture of bases isolated the little polar 1,2,3,4,7,8-hexahydro-6*H*-cyclopenta-

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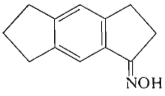
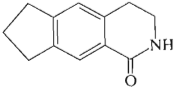
[*g*]quinoline (*XII*) formed apparently by reduction of lactam *III*. Pure lactam *II* was reduced similarly to 1,2,3,4,7,8-hexahydro-6*H*-cyclopent[*g*]isoquinoline (*IV*). Alkaline hydrolysis of lactam *II* yielded the amino acid *XIII*.

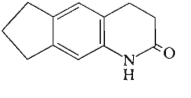
The secondary amine *IV* was used as the starting compound for preparing several derivatives where a neurotropic or a cardiovascular pharmacodynamic activity could be expected. Thus, in a reaction of amine *IV* with formaldehyde and formic acid, the 2-methyl derivative *V* was formed. Acylation of amine *IV* with phenylacetyl chloride[14], 3,4-dimethoxyphenylacetyl chloride[15] and 3,3-diphenylpropionyl chloride[16] in benzene in the presence of pyridine gave rise to amides *VI* – *VIII* which were reduced with lithium aluminium hydride to amines *IX* – *XI*.



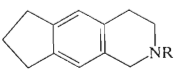

*I*



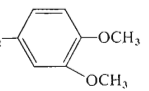

*II*



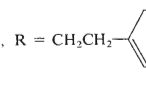

*III*




*IV*, R = H
*V*, R = $CH_3$
*VI*, R = $COCH_2C_6H_5$

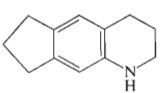
*VII*, R = $COCH_2$  

*VIII*, R = $COCH_2CH(C_6H_5)_2$
*IX*, R = $CH_2CH_2C_6H_5$

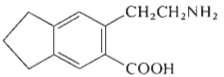
*X*, R = $CH_2CH_2$  

*XI*, R = $CH_2CH_2CH(C_6H_5)_2$

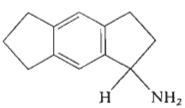
During the reduction of oxime *I* with lithium aluminium hydride which was carried out in a mixture of ether and tetrahydrofuran one could expect a more complicated course, the reduction of ketoximes with complex hydrides being known to yield the corresponding primary amines[17] plus the rearranged secondary amines[10,18,19] and aziridines[18–21]. In agreement with this, we obtained a mixture of bases which was isolated *via* a mixture of hydrochlorides. After dissolving the mixture of bases in light petroleum some 10% crystalline polar compound precipitated on standing. The mother liquors contain approximately equal parts of two compounds which were separated by chromatography on alumina. The less polar product was identified as 1,2,3,4,7,8-hexahydro-6*H*-cyclopenta[*g*]quinoline (*XII*) formed by rearrangement and reduction. The more polar product is the previously described[1] 1-amino-*s*-hydrindacene (*XIV*).



*XII*



*XIII*



*XIV*

The compounds prepared (hydrochlorides) were biologically evaluated using methods of general pharmacological screening, the results being shown in Table I. The readily soluble compounds *IV* and *V* were administered parenterally and their toxicity is rather high. On the other hand, the values of acute toxicity of orally applied compounds may be 10 times higher which may be due to poor resorption. The phenethylamine derivatives *IX* and *X* have the character of centrally depressant compounds; in high doses they inhibit motility of mice, bring about ataxia, potentiate thiopental sleep and possess a slight hypothermic effect. On the other hand, the basic amine *IV* at high doses shows signs of excitatory effects (it increases mouse motility). This compound alone showed a slight local anaesthetic effects in the corneal anaesthesia test. The N-methyl derivative *V* is slightly spasmolytic *in vitro* toward acetylcholine spasms and, in a high dose, shows signs of a peripheral myorelaxing effect. Compounds *IV* and *V* depress the pressor effect of epinephrine in rats. In contrast with this finding, *IV* applied to monkeys brought about a slight pressor reaction with a generally adrenomimetic rather than adrenolytic character (Dr V. Trčka, pharmacological department of this institute). The hypotensive effect in rats was found only after an oral application of a high dose of *XI*. The basic compound *IV* has a positively inotropic and a negatively chronotropic character. The phenethylamine derivatives *IX* and *X* prolong the survival of a mouse myocard during asphyxia. Compounds *IV*, *IX* and *X* slightly increase the blood sugar level and *X* is antiinflammatory.

The antimicrobial activity of the compounds prepared was evaluated by Dr J. Turinová and Dr A. Čapek (bacteriological department of this Institute) in tests *in vitro*. Microorganisms where an activity was found are shown, together with compound numbers and minimum inhibitory concentrations in μg/ml: *Streptococcus* β-*haemolyticus*, *IX* 50; *Streptococcus faecalis*, *IX* 50; *Staphylococcus pyogenes aureus*, *IX* 50; *Mycobacterium tuberculosis* H37Rv, *IV* 100, *IX* 25, *X* 50; *Saccharomyces pasterianus*, *IV* 100, *V* 50, *IX* 100, *X* 100, *XI* 100; *Trichophyton mentagrophytes*, *IV* > 100, *V* 50, *IX* 50, *X* 100, *XI* 50; *Candida albicans*, *IV* 100, *V* 100, *IX* 100, *X* > 100, *XI* > 100;

TABLE I

Pharmacological Properties of Hydrochlorides of 1,2,3,4,7,8-Hexahydro-6*H*-cyclopent[*g*]isoquinolines

| Hydrochloride | Code No VÚFB | Method of application[a] | Acute toxicity[b] $LD_{50}$ mg/kg | D[c] mg/kg | Pharmacological effects |
|---|---|---|---|---|---|
| *IV* | 10·554 | *i.v.* | 25 | 5 | [d] |
| *V* | 10·546 | *i.v.* | 20 | 4 | [e] |
| *IX* | 10·555 | *p.o.* | 1 500 | 300 | [f] |
| *X* | 10·557 | *p.o.* | 1 000 | 200 | [g] |
| *XI* | 10·548 | *p.o.* | >2 500 | 300 | [g,h] |

[a] *p.o.* orally, *i.v.* intravenously. [b] Orientation value of the mean lethal dose estimated in mice. [c] Dose in which the compound was administered *in vivo*. [d] In a dose greater than D it increases mouse motility, suggesting a central excitation; in a dose of 1—5 mg/kg *i.v.* it decreases the pressor response after epinephrine in rats by 50%; in an isolated rabbit atrium, at a concentration of 25—50 μg/ml, it increases inotropy by 25% and decreases heartbeat frequency by the same factor; in a dose of 25 mg/kg *p.o.* it brings about an increase of the blood sugar level in rats by 20%; at 1%, it has a local anaesthetic effect in a corneal anaesthesia test in rabbits (in 50% animals). In a dose of 50 mg/kg *p.o.* it increased the blood pressure in 2 monkeys within 1—3 h after application by 15—20 Torr, it increased heart frequency and in one case there was a pronounced breath arrhythmia, after further 3 h the blood pressure was at the starting level; no changes in behaviour were observed. [e] In a dose of 2—4 mg/kg *i.v.* it decreases the pressor response to epinephrine in rats by 50%; in isolated rat duodenum it inhibits acetylcholine contractions at a concentration of 10 μg/ml by 50% (1% of activity of atropine); at 40 mg/kg *i.v.* (under artificial ventilation) it acts as a myorelaxant for rat gastrocnemius. [f] In a dose of 100—300 mg/kg *p.o.* it inhibits mouse motility in known as well as unknown surroundings; in a dose of 200 mg/kg it brings about ataxia in mice in the rotating-rod test; in a dose of 300 mg/kg *p.o.* it depresses rectal temperature of rats by 1°C; in doses of 100—300 mg/kg *p.o.* it prolongs thiopental sleep of mice to twice the control; at 100 mg/kg *p.o.* it prolongs with statistical significance the survival of a mouse myocard during asphyxia. [g] Like the preceding compound, in doses of 100—200 mg/kg *p.o.* it inhibits mouse motility in known as well as unknown surroundings; in a dose of 100 mg/kg *p.o.* it brings about ataxia of mice on a rotating rod; in a dose of 200 mg/kg *p.o.* it prolongs thiopental sleep of mice to twice the control; in doses of 100—200 mg/kg *p.o.* it prolongs with statistical significance the survival of a mouse myocard during asphyxia; in doses of less than 100 mg/kg *p.o.* it increases the blood sugar level in rats by 20%; in a dose of 200 mg/kg *p.o.* it brings about a decrease of pupil diameter of mice by 30% (miosis); in doses of 50—100 mg/kg *p.o.* it inhibits with statistical significance the development of a kaolin arthritis in rats, especially at 24 h after application. [h] In a dose of 300 mg/kg *p.o.* it depresses the blood pressure of normotensive rats by 10% 3 h after application.

*Aspergillus niger*, *IV* 100, *V* 50, *IX* 100, *X* >> 100, *XI* 100. The anthelminthic and coccidiostatic activities of the compounds were tested at the Research Institute of Biofactors and Veterinary Drugs, Pohoří – Chotouň. While *X* showed signs of anthelminthic activity toward *Nippostrongylus brasiliensis*, *IV* was clearly coccidiostatic (*Eimeria tenella*) and *XI* slightly so.

## EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* at 0·1 Torr over $P_2O_5$ at room temperature or at 77°C. The UV spectra shown (in methanol) were recorded in a Unicam SP 8000 spectrophotometer, the IR spectra (in KBr unless stated otherwise) in a Unicam SP 200G spectrophotometer or in an Infrascan (Hilger and Watts) and the $^1$H-NMR spectra (in $CDCl_3$) in a ZKR 60 (Zeiss, Jena) spectrometer. Homogeneity of the compounds was tested by chromatography on thin layers of silica gel.

1-Oxo-1,2,3,4,7,8-hexahydro-6*H*-cyclopent[*g*]isoquinoline (*II*)

1-Oximino-*s*-hydrindacene[1] (*I*, 37·0 g) was added at 70°C to polyphosphoric acid prepared from 356 ml 85% $H_3PO_4$ and 540 g $P_2O_5$ (stirred for 1 h at 130°C). The mixture was heated to 130°C for 15 min. After cooling, it was decomposed with 3·2 litres ice-cold water, left to stand for 12 h and the precipitated product was filtered, washed with water and dried in air (30 g). The filtrate was extracted with chloroform and the residue of the extract (4·5 g) was combined with the filtered fraction. Crystallization from 160 ml ethanol yielded 23·0 g (63%) product melting at 197–199°C; analytical product, m.p. 200–202°C (ethanol). UV spectrum: $\lambda_{max}$ 241·5 nm (log $\varepsilon$ 3·98), 286 nm (3·44), 294 nm (3·44). IR spectrum: 891 (solitary Ar—H), 1478, 1570, 1616 (Ar), 1276, 1316, 1664, 3060, 3190 cm$^{-1}$ (ArCONH). $^1$H-NMR spectrum: $\delta$ 7·85 (s, 1 H, 9-H), 7·51 (bs, 1 H, NH), 6·99 (s, 1 H, 5-H), 3·48 (m, 2 H, $NCH_2$), 2·85 (m, 6 H, 3 $ArCH_2$), 2·00 (m, 2 H, 7-$CH_2$). For $C_{12}H_{13}NO$ (187·2) calculated: 76·97% C, 7·00% H, 7·48% N; found: 77·27% C, 7·11% H, 7·11% N. Residue (10·0 g) of the mother liquor after *II* does not crystallize on standing; according to TLC it does not contain the starting oxime *I* and consists of approximately equal parts of *II* and of another more polar component.

1,2,3,4,7,8-Hexahydro-6*H*-cyclopent[*g*]isoquinoline (*IV*)

A warm-prepared solution of 20·0 g *II* in 450 ml benzene was added dropwise to a stirred suspension of 10·0 g $LiAlH_4$ in 150 ml dibutyl ether and the mixture was refluxed for 6 h. After cooling, it was decomposed by adding dropwise 44 ml 20% NaOH, the mixture was stirred for a while and the precipitated inorganic fractions were filtered and the filtrate was evaporated *in vacuo* to a half volume. This was shaken at 50°C with dilute hydrochloric acid (410 ml, 1 : 15), the separated acid aqueous phase was cooled, made alkaline with 20% NaOH and the base was isolated by extraction with benzene. After drying with $Na_2SO_4$ the extract was evaporated, the residue crystallizing on standing: 18·0 g (97%), m.p. 52–57°C. Crystallization from hexane yielded the analytical product which melts in a capillary at 57–58°C. In Kofler's block, most of the substance melts at the same temperature but the rest only at 97–98°C. UV spectrum: $\lambda_{max}$ 273 nm (log $\varepsilon$ 3·31), 277 nm (3·30) 283 nm (3·43). IR spectrum (Nujol): 871 (solitary Ar—H), 1440, 1555, 1621 (Ar), 3380 cm$^{-1}$ (NH). $^1$H-NMR spectrum: $\delta$ 6·95 and 6·82 (2 s, 2 H, 5,9-$H_2$), 3·95 (bs, 2 H, $ArCH_2N$), 2·94 (s) disappears after $D_2O$, 1 H, NH), 2·50–3·30 (m, 8 H, 2 $ArCH_2$ and $ArCH_2CH_2N$), 1·98 (m, 2 H, 7-$CH_2$). For $C_{12}H_{15}N$ (173·2) calculated: 83·20% C, 8·73% H, 8·07% N; found: 82·87% C, 8·99% H, 7·94% N.

*Hydrochloride*, m.p. 245–247°C (ethanol–ether). For $C_{12}H_{16}ClN$ (209·7) calculated: 68·72% C, 7·69% H, 16·91% Cl, 6·68% N; found: 68·35% C, 8·06% H, 16·77% Cl, 6·55% N.

1,2,3,4,7,8-Hexahydro-6*H*-cyclopenta[*g*]quinoline (*XII*)

A part of the residue (1·3 g) of the mother liquor after lactam *II* was dissolved in 30 ml warm benzene and the solution was added to a stirred suspension of 0·8 g $LiAlH_4$ in 20 ml dibutyl ether. The mixture was refluxed for 5 h, cooled and decomposed by adding dropwise 3·5 ml 20% NaOH. The precipitated product was filtered and the filtrate evaporated. The residue (1·0 g) is a mixture of bases which contains according to TLC a minor amount of amine *IV* and mostly the less polar base *XII*. This was isolated by chromatography on a column of 25 g alumina (activity II) and by elution with hexane: 0·7 g (16% referred to oxime *I*), m.p. 65–66°C (hexane). $^1$H-NMR spectrum: $\delta$ 6·63 (s, 1 H, 9-H), 6·23 (s, 1 H, 5-H), 3·44 (s, disappears after $D_2O$, 1 H, NH), 3·14 (t, 2 H, $NCH_2$), 2·67 (t, 6 H, 3 $ArCH_2$), 1·91 (m, 4 H, 2 $CH_2$ in positions 3 and 7). For $C_{12}H_{15}N$ (173·2) calculated: 83·19% C, 8·73% H, 8·09% N; found: 83·28% C, 8·75% H, 8·06% N.

*Hydrochloride*, m.p. 200–202°C (ethanol–ether). For $C_{12}H_{16}ClN$ (209·7) calculated: 68·72% C, 7·69% H, 16·91% Cl, 6·68% N; found: 68·20% C, 7·35% H, 16·99% Cl, 6·51% N.

6-(2-Aminoethyl)indane-5-carboxylic Acid (*XIII*)

A mixture of 1·0 g *II*, 1·5 g KOH and 3 ml ethanol was refluxed for 2 h in a 120°C bath. After evaporation of ethanol, the residue was diluted with 30 ml water, filtered and 0·5 g starting *II* was recovered. The alkaline filtrate was diluted with water and neutralized with a calculated amount of acetic acid. Standing precipitated 0·45 g amino acid which was recrystallized from a mixture of 5 ml water and 1·5 ml ethanol; m.p. 196–197°C. IR spectrum (Nujol): 889 (solitary Ar—H), 1515, 1562 (Ar), 1370, 1590 and 2700 $cm^{-1}$ ($COO^-$). For $C_{12}H_{15}NO_2$ (205·3) calculated: 70·22% C, 7·37% H, 6·82% N; found: 70·13% C, 7·45% H, 6·66% N.

*Hydrochloride*, m.p. 188–189°C (under decomposition, ethanol–ether). For $C_{12}H_{16}ClNO_2$ (241·7) calculated: 59·63% C, 6·67% H, 14·67% Cl, 5·79% N; found: 59·22% C, 6·63% H, 14·84% Cl, 5·56% N.

2-Methyl-1,2,3,4,7,8-hexahydro-6*H*-cyclopent[*g*]isoquinoline (*V*)

A mixture of 5·5 g *IV*, 8 ml water, 6 ml 85% formic acid and 9 ml 28% formaldehyde was refluxed for 5 h (in a 120–130°C bath). After partial cooling, 15 ml hydrochloric acid was added and the mixture evaporated *in vacuo*. The residue was dissolved under adding 2 ml hydrochloric acid in 50 ml water, the solution was washed with ether, filtered with charcoal and the filtrate was made alkaline with 20% NaOH. The base was isolated by extraction with benzene and the extract was dried and evaporated; 5·30 g (90%), m.p. 44–45°C (hexane). $^1$H-NMR spectrum: $\delta$ 6·99 and 6·90 (2 s, 2 H, 5,9-$H_2$), 3·52 (s, 2 H, $ArCH_2N$), 2·50–3·00 (m, 8 H, 2 $ArCH_2$ and $ArCH_2CH_2N$), 2·41 (s, 3 H, $N—CH_3$), 1·70–2·30 (m, 2 H, 7-$CH_2$). For $C_{13}H_{17}N$ (187·3) calculated: 83·37% C, 9·15% H, 7·48% N; found: 83·48% C, 9·36% H, 7·36% N.

*Hydrochloride*, m.p. 200–201°C (ethanol–ether). For $C_{13}H_{18}ClN$ (223·7) calculated: 69·78% C, 8·11% H, 15·85% Cl, 6·26% N; found: 69·85% C, 8·55% H, 15·91% Cl, 6·23% N.

2-(Phenylacetyl)-1,2,3,4,7,8-hexahydro-6*H*-cyclopent[*g*]isoquinoline (*VI*)

A solution of 3·3 g phenylacetyl chloride[14] in 50 ml benzene was added dropwise over a period of 30 min to a stirred solution of 3·8 g *IV* in 50 ml benzene and 3 ml pyridine. The mixture was

refluxed for 2 h, cooled, washed with water, dilute hydrochloric acid, 5% $NaHCO_3$ and again with water; the benzene solution was dried with $Na_2SO_4$ and evaporated. The residue (5·0 g, 78%) crystallized on adding hexane; m.p. 102–103°C (benzene–hexane). IR spectrum: 700, 755, 882 ($C_6H_5$ and solitary Ar—H), 1 502, 1 593 (Ar), 1 655 $cm^{-1}$ (CON). For $C_{20}H_{21}NO$ (291·4) calculated: 82·45% C, 7·26% H, 4·80% N; found: 82·32% C, 7·41% H, 4·55% N.

2-(3,4-Dimethoxyphenylacetyl)-1,2,3,4,7,8-hexahydro-6*H*-cyclopent[*g*]isoquinoline (*VII*)

This was prepared in analogy to *VI* by a reaction of 3·60 g *IV* and 4·5 g 3,4-dimethoxyphenylacetyl chloride (b.p. 135–138°C/1 Torr)[15] in 100 ml benzene in the presence of 3 ml pyridine; 7·0 g (96%) crude, oily product. It crystallizes from a mixture of benzene and hexane as a solvate with one-half benzene molecule; m.p. 84–85°C. IR spectrum (Nujol): 800, 879 (2 adjacent and solitary Ar—H), 1038, 1242, 1271 ($ArOCH_3$), 1521, 1581 (Ar), 1640 $cm^{-1}$ (CON). $^1$H-NMR spectrum: $\delta$ 7·36 (s, protons of benzene), 6·70–7·10 (m, 5 H, Ar—H), c. 4·60 (m, 2 H, $ArCH_2N$), 3·80 (s, 6 H, 2 $OCH_3$), 3·30 (s, 2 H, $ArCH_2CO$), c. 3·70 (m, 2 H, 3-$CH_2$), 2·80 (m, 6 H, remaining 3 $ArCH_2$), 1·80–2·30 (m, 2 H, 7-$CH_2$). For $C_{22}H_{25}NO_3 + 1/2\ C_6H_6$ (390·5) calculated: 76·90% C, 7·23% H, 3·58% N; found: 76·99% C, 7·50% H, 3·74% N.

2-(3,3-Diphenylpropionyl)-1,2,3,4,7,8-hexahydro-6*H*-cyclopent[*g*]isoquinoline (*VIII*)

This was prepared in analogy to the above in a reaction of 4·80 g *IV* with 6·80 g 3,3-diphenylpropionyl chloride[16] in 80 ml benzene in the presence of 3 ml pyridine; 10·0 g (95%), m.p. 117 to 118°C (benzene–hexane). IR spectrum: 712, 750, 760, 880 ($C_6H_5$ and solitary Ar—H), 1455, 1505 (Ar), 1640 $cm^{-1}$ (CON). For $C_{27}H_{27}NO$ (381·5) calculated: 85·00% C, 7·13% H, 3·67% N; found: 84·92% C, 7·38% H, 3·94% N.

2-(2-Phenylethyl)-1,2,3,4,7,8-hexahydro-6*H*-cyclopent[*g*]isoquinoline (*IX*)

A solution of 4·7 g amide *VI* in 50 ml benzene was added dropwise under stirring to a solution of 3·0 g $LiAlH_4$ in 40 ml ether and the mixture was refluxed for 5 h. After cooling, it was decomposed with 12 ml 20% NaOH, the solid was filtered and the filtrate evaporated. The residue (4·50 g, 100%) crystallized; m.p. 75–76°C (hexane). $^1$H-NMR spectrum: $\delta$ 7·29 (s, 5 H, $C_6H_5$), 6·99 and 6·91 (2 s, 2 H, 5,9-$H_2$), 3·65 (s, 2 H, $ArCH_2N$), 2·50–3·00 (m, 12 H, 2$ArCH_2$ and 2 $ArCH_2CH_2$), 1·80–2·30 (m, 2 H, 7-$CH_2$). For $C_{20}H_{23}N$ (277·4) calculated: 86·60% C, 8·35% H, 5·05% N; found: 87·11% C, 8·65% H, 4·89% N.

*Hydrochloride*, m.p. 225–226°C (ethanol–ether). For $C_{20}H_{24}ClN$ (313·9) calculated: 76·54% C, 7·71% H, 11·29% Cl, 4·46% N; found: 76·94% C, 8·00% H, 11·06% Cl, 4·58% N.

2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4,7,8-hexahydro-6*H*-cyclopent[*g*]isoquinoline (*X*)

Like in the preceding case, 6·5 g *VII* was reduced with 3·0 g $LiAlH_4$ in a mixture of 60 ml ether and 30 ml benzene. A total of 5·60 g (90%) oil was obtained and this crystallized on standing in the refrigerator: m.p. 76–78°C (hexane). $^1$H-NMR spectrum: $\delta$ 7·00 and 6·92 (2 s, 2 H, 5,9-$H_2$), 6·80 (s, 3 H, Ar—H of dimethoxyphenyl), 3·84 (s, 6 H, 2 $OCH_3$), 3·65 (bs, 2 H, $ArCH_2N$), 2·80 (m, 12 H, 2 $ArCH_2$ and 2 $ArCH_2CH_2$), 2·00 (m, 2 H, 7-$CH_2$). For $C_{22}H_{27}NO_2$ (337·4) calculated: 78·30% C, 8·07% H, 4·15% N; found: 78·35% C, 8·07% H, 4·08% N.

*Hydrochloride*, m.p. 230–231°C (ethanol). For $C_{22}H_{28}ClNO_2$ (373·9) calculated: 70·67% C, 7·55% H, 9·48% Cl, 3·74% N; found: 70·74% C, 7·52% H, 9·68% Cl, 3·64% N.

2-(3,3-Diphenylpropyl)-1,2,3,4,7,8-hexahydro-6*H*-cyclopent[*g*]isoquinoline (*XI*)

Like in the preceding cases, 9·0 g *VIII* was reduced with 3·0 g $LiAlH_4$ in a mixture of 60 ml ether and 50 ml benzene. A crude oily product was obtained in a theoretical yield (8·7 g); it crystallized on standing; m.p. 86—87°C (hexane). $^1$H-NMR spectrum: $\delta$ 7·31 (s, 10 H, 2 $C_6H_5$), 6·99 and 6·90 (2 s, 2 H, 5,9-$H_2$), 4·07 (t, 1 H, $Ar_2CH$) 3·55 (s, 2 H, $ArCH_2N$), 2·30—3·00 (m, 12 H, 2 $ArCH_2$ and $CH_2CH_2NCH_2CH_2$), 1·80—2·30 (m, 2 H, 7-$CH_2$). For $C_{27}H_{29}N$ (367·5) calculated: 88·23% C, 7·96% H, 3·81% N; found: 88·05% C, 8·34% H, 3·83% N.

*Hydrochloride*, m.p. 178—179°C (ethanol–ether). For $C_{27}H_{30}ClN$ (404·0) calculated: 80·26% C, 7·49% H, 8·78% Cl, 3·47% N; found: 80·43% C, 7·82% H, 8·88% Cl, 3·41% N.

Reduction of 1-Oximino-*s*-hydrindacene (*I*) with $LiAlH_4$

A solution of 8·0 g *I* in 40 ml tetrahydrofuran was added dropwise uder stirring to a solution of 3·0 g $LiAlH_4$ in 80 ml ether and the mixture was refluxed for 5 h. After cooling, it was decomposed by adding dropwise 12 ml 20% NaOH and the solid fraction was filtered. The filtrate was evaporated and the residue was dissolved in 120 ml ether. An ether solution of hydrogen chloride was used to convert the substance to a hydrochloride (8·2 g, m.p. 178—185°C) which is nonhomogeneous. A part (7·8 g) was dissolved in 100 ml warm water, the solution was filtered with charcoal, the filtrate was made alkaline with 20% NaOH and the mixture of bases was isolated by extraction with benzene (6·0 g oil). After dissolving in 50 ml light petroleum, 0·60 g of a polar compound crystallized and was filtered. The filtrate was evaporated and the residue (5·4 g oil) was chromatographed on a column of 150 g alumina (activity II). Elution with hexane yielded first 2·7 g of a homogeneous base which crystallized from hexane and melted at 65—66°C. It is amine *XII* which (an authentic sample) does not depress the melting point. It yields a hydrochloride melting at 200—201°C. Benzene eluted then 2·4 g of a more polar homogeneous base boiling at 142 to 144°C/10 Torr and yielding a crystalline hydrochloride melting at 265—270°C. It is 1-amino-*s*-hydrindacene (*XIV*) which was found to be identical with the authentic product[1].

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