4-AMINO-*s*-HYDRINDACENE AND DERIVATIVES: SYNTHESIS AND PHARMACOLOGICAL SCREENING*

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Rearrangement of 4-acetyl-*s*-hydrindacene oxime (*III*) with trifluoroacetic acid resulted in 4-acetamido-*s*-hydrindacene (*IV*). Treatment of oxime *III* with benzenesulfonyl chloride in pyridine yielded sulfo ester *V* as the main product while amides *IV* and *VI* were only obtained in small amounts. Hydrolysis of anilide *IV* gave rise to 4-amino-*s*-hydrindacene (*VII*) which was converted *via* Schiff bases *VIII* and *IX* to secondary amines *X* and *XI*. Amine *VII* was used for preparation of the piperazine derivative *XII* by fusion with diethanolamine hydrochloride and by alkylation with N,N-bis(2-chloroethyl)amine. Acylation of *XII* with phenylacetyl chloride and subsequent reduction resulted in the N-(2-phenylethyl) derivative *XIV*. Alkylation with phenacyl halogenides led to *XV* and *XVI*. The phenylethyl derivative *XIV* was centrally depressant in higher doses. Compounds *XII* and *XIV*—*XVI* had antimicrobial activity in tests *in vitro*.

In an earlier communication[1] the rationale for studying *s*-hydrindacene-derived amines was explained and the synthesis and pharmacology of 1-amino-*s*-hydrindacene and some of its derivatives were described. A sequel to this study was the preparation of 1,2,3,4,7,8-hexahydro-6*H*-cyclopent(*g*)isoquinoline and its N-substitution derivatives[2]. Now we shall study systematically amines where the amino group is a part of the substituent in position 4 of the *s*-hydrindacene skeleton. The synthesis of 4-amino-*s*-hydrindacene and some of its N-substitution derivatives will be described.

s-Hydrindacene[3,4] (*I*) prepared by Clemmensen's a reduction of *s*-hydrindacen-1-one was subjected to a Friedel–Crafts reaction with acetyl chloride and aluminium chloride in benzene and converted to 4-acetyl-*s*-hydrindacene (II). This preparation of ketone *II* was found to be more suitable from the point of view of efficiency than the reported method[4] based on the use of acetic anhydride in tetrachloroethane. Ketone *II* was converted to the oxime *III* in a reaction with hydroxylamine in pyridine; here again a modification of the described method is used[5]. In the present arrangement we obtained roughly identical amounts of a higher- and lower-melting form of the oxime, the lower-melting form being unstable and

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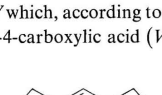
readily crystallizing to the higher-melting form. Beckmann's rearrangement of this oxime was described[5] using the Beckmann mixture, the sole product being 4-acetamido-*s*-hydrindacene (*IV*). This is in agreement with data in the literature[6] according to which Beckmann's rearrangement of oximes of acetophenone-type ketones gives rise exclusively or mainly to anilides ArNHCOR, occasional minor by-products being benzamides ArCONHR. This selectivity is particularly pronounced in the case of 2,6-disubstituted acetophenonoximes for which there are theoretical reasons[7]. This is the case of oxime *III* and it is thus not surprising that in the present design of the rearrangement where the agent used was trifluoroacetic acid (for method see[8]) there was an almost theoretical yield of anilide *IV*. On the other hand, the attempt to rearrange oxime *III* with benzenesulfonyl chloride in pyridine (see[9]) was not usable for preparative purposes, there arising a mixture of substances which were crystallized to mere 20% of anilide *IV*. Chromatography of the residue produced the main reaction product – the benzenesulfonyl ester *V*; the more polar product isolated (in a 20% yield) was an isomer of *IV* which, according to UV spectra, has the structure of methylamide of *s*-hydrindacene-4-carboxylic acid (*VI*).

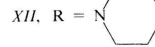


I, R = H
II, R = $COCH_3$
III, R = $C(=NOH)CH_3$
IV, R = $NHCOCH_3$
V, R = $C(=NOSO_2C_6H_5)CH_3$
VI, R = $CONHCH_3$
VII, R = NH_2
VIII, R = $N=CHC_6H_5$
IX, R = $4\text{-}N=CHC_6H_4OCH_3$
X, R = $NHCH_2C_6H_5$
XI, R = $4\text{-}NHCH_2C_6H_4OCH_3$

XII, R =

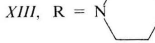
XIII, R =

XIV, R =



XV, R =

XVI, R =



The sterically protected amide *IV* was found to be resistant to attempts at hydrolysis: is not hydrolyzed even in boiling dilute hydrochloric acid or ethanolic or aqueous–ethanolic potassium hydroxide. The goal was attained only by heating with 100% phosphoric acid to 160–170°C which is the recommended method for hydrolyzing

sterically hindered amides[10]. After diluting with water, the precipitated product was identified as metaphosphate of amine *VII* from which the desired 4-amino-*s*-hydrindacene (*VII*) was set free by alkalification. Reactions of amine *VII* with benzaldehyde and anisaldehyde yield Schiff bases *VIII* and *IX* which were reduced by lithium aluminium hydride in ether (for method see[11]) to secondary amines *X* and *XI*.

For transforming amine *VII* to the piperazine derivative *XII* both methods described[12,13] for converting arylamines to arylpiperazines were used with almost the same effect (yields of 30–40%). In the first of these[12], the hydrochloride of amine *VII* was heated with diethanolamine hydrochloride to 220–240°C; in the second method[13] amine *VII* was heated with N,N-bis(2-chloroethyl)amine[14,15] and potassium carbonate in boiling 1-butanol (see[16]). The 1-(*s*-hydrindacen-4-yl)piperazine (*XII*) was acylated with phenylacetyl chloride[17] in benzene in the presence of triethylamine and the amide *XIII* formed was reduced with lithium aluminium hydride in ether to the phenylethyl derivative *XIV*. Piperazine *XII* was further alkylated with phenacyl chloride and 4-(methylsulfonyl)phenacyl bromide[16] in benzene in the presence of triethylamine; amines *XV* and *XVI* were obtained in nearly theoretical yields.

Of the compounds prepared, the piperazine derivatives *XII* and *XIV*–*XVI* were subjected to general pharmacological screening (compound *XVI* was studied in more detail by Dr J. Metyš of the pharmacological department of this institute). The form of the salt tested is shown, followed by its code number, the mean lethal dose LD_{50} (mg/kg) for mice after oral administration and finally the dose D (mg/kg) in which the substance was applied in the *in vivo* tests: *XII*-maleate (hemihydrate), VÚFB-10.606, 1 000, 200; *XIV*-hydrochloride, VÚFB-10.639, 1 500, 300; *XV*-hydrochlode, VÚFB-10.641, 2000, 300; *XVI*-maleate, VÚFB-10.644, >2000 (following this dose, applied in suspension, no animal of a group of ten died within seven days).

The only apparent effect of *XII* was a slight central depression of mice in the orientation toxicity test with doses greater than D. On the other hand, compound *XIV* acts as a mild tranquilizer: in the rotating-rod test in mice it brings about ataxia with a means effective dose of about 200 mg/kg while at 75 mg/kg it brings about a drop of rat body temperature by 1°C measured *in recto*. In the same dose it prolongs thiopental sleep in mice to twice the control value and at 100 mg/kg it depresses significantly the spotaneous motility of mice in known surroundings. At the dose applied (D), compound *XV* showed no pronounced activity. Compound *XVI* which is an analogue of mesylphenacyrazine[16,18–21] had a slight (statistically insignificant) depressant effect on mice at a dose of 50 mg/kg in the locomotor activity test using the photo-cell method (decrease to 71% of control group activity). In the same dose in the rotating-rod test in mice it caused ataxia in at most 20% animals (within 45–60 min after application). In rats it did not alter general activity, registered in the Animex apparatus, with statistical significance even after a dose of 5 mg/kg. Only a slight increase of activity to 120% of the control group value was observed.

In a dose of 300 mg/kg it did not affect apomorphine-induced chewing of rats and it depressed slightly agitation.

Compounds *XII* and *XIV*—*XVI* were further evaluated (in the form of salts) by Dr J. Turinová and Dr A. Čapek (bacteriological department of this institute) *in vitro* for antimicrobial activity (the minimum inhibitory concentration in μg/ml are shown unless they exceed 100 μg/ml:

Streptococcus β-*haemolyticus*, *XII* 50; *Streptococcus faecalis*, *XII* 100; *Staphylococcus pyogenes aureus*, *XII* 50; *Pseudomonas aeruginosa*, *XII* 100; *Escherichia coli*, *XII* 100; *Mycobacterium tuberculosis* H37Rv, *XII* 50, *XV* 25, *XVI* 50; *Saccharomyces pasterianus*, *XII* 100, *XIV* 100, *XV* 100, *XVI* 100; *Trichophyton mentagrophytes*, *XII* 50, *XIV* 25, *XV* 25, *XVI* 25; *Candida albicans*, *XII* 100, *XIV* 100, *XV* 100, *XVI* 100; *Aspergillus niger*, *XII* 100, *XIV* 100, *XV* 50, *XVI* 100. Up to 100 μg/ml, all the four compounds were ineffective against *Proteus vulgaris*. It follows from the results that piperazine *XII* is a wide-spectrum agent with mild antimicrobial activity while *XIV*—*XVI* are specifically active against lower fungi.

EXPERIMENTAL

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

4-Acetyl-*s*-hydrindacene (*II*)

Powdered $AlCl_3$ (30 g) was added over a period of 1 h at below 7°C and under stirring to a mixture of 30·0 g *s*-hydrindacene[3,4] (*I*, b.p. 122—125°C/15—18 Torr, solidifies on standing), 120 ml benzene and 14·2 ml acetyl chloride. The mixture was stirred for 30 min under cooling, for 5 h at room temperature. After decomposition of the mixture with 270 g ice and 45 ml hydrochloric acid, the benzene layer was separated, the aqueous phase was extracted with benzene and the benzene fractions were combined. After washing with dilute hydrochloric acid and water, it was dried with Na_2SO_4 and distilled; 35·0 g (92%), b.p. 150—153°C/2 Torr. Ref.[4] describes a similar reaction with acetic anhydride in tetrachloroethane with a yield of 63%; for the product it reports a b.p. of 145—147°C/4 Torr and a m.p. of 64—64·5°C. Our product crystallized on standing but for further work the above distillate was used.

Oxime (III): A mixture of 33·0 g *II*, 250 ml ethanol, 58·5 g hydroxylamine hydrochloride and 80 ml pyridine was refluxed for 12 h, evaporated at reduced pressure, the residue was decomposed with 500 ml water and the precipitated oxime was isolated by extraction with a mixture of ether and benzene. A part of the oxime precipitated in a crystalline form and was filtered; 17·3 g, m.p. 169—171°C. Evaporation of the organic layer of the filtrate and crystallization of the residue from hexane yielded further 14·5 g oxime which melts at 105—110°C. Both fractions behave during TLC as identical compounds and the lower-melting form is converted by crystallization from benzene to the higher-melting one. The total amount of product obtained was thus 31·8 g (90%). Analytical product, m.p. 173—175°C (benzene–ethanol). IR spectrum (Nujol): 880 (solitary Ar—H), 965 (C=NOH), 3 300 cm^{-1} (OH in H-bond). ^{1}H-NMR spectrum: δ 8·68 (bs. 1 H, NOH). 7·10 (s, 1 H, Ar—H), 2·85 (t, J = 6·0 Hz, 8 H, 4 $ArCH_2$), 2·15 (s, 3 H, CH_3), 2·01 (m, 4 H, remaining 2 CH_2). For $C_{14}H_{17}NO$ (218·3) calculated: 78·10% C, 7·96% H, 6·51% N; found:

78·24% C, 8·22% H, 6·46% N. Ref.[5] describes the preparation of this oxime in a similar way using NaOH instead of pyridine; the m.p. reported is 161—163°C and no mention of the lower-melting form is made.

4-Acetamido-*s*-hydrindacene (*IV*)

A solution of 37 g oxime *III* in 120 ml trifluoroacetic acid was added dropwise under stirring over a period of 20 min to 40 ml boiling trifluoroacetic acid and the mixture was refluxed for 1 h. The volatile fractions were then evaporated at reduced pressure and then residue was mixed with 60 ml light petroleum. A total of 35 g (95%) product crystallized, m.p. 239—241°C. Crystallization from benzene led to a compound melting at 249—250°C. UV spectrum: λ_{max} 234·5 nm (infl.) (log ε 3·96), 269 nm (3·46), 283 nm (3·48). IR spectrum: 875 (solitary Ar—H), 745, 1545, 1669 (CONH), 1590 (Ar), 3271 cm^{-1} (NH). Ref.[5] reports a m.p. of 248—250°C for a product obtained by rearrangement in the presence of Beckmann's mixture.

4-(1-Benzenesulfonyloximinoethyl)-*s*-hydrindacene (*V*)

Benzenesulfonyl chloride (20 ml) was added dropwise under stirring over a period of 15 min at a temperature below 15°C to a solution of 18·0 g oxime *III* in 130 ml pyridine. The mixture was stirred for 3 h at room temperature and poured into a mixture of 260 g ice and 130 ml hydrochloric acid. After 1 h of standing the precipitated inhomogeneous product was filtered, washed with water and dried in air (20 g). After dissolving in 500 ml chloroform the solution was washed with dilute hydrochloric acid, 5% solution of Na_2CO_3 and water, dried and evaporated. The residue was dissolved in 850 ml boiling benzene. Standing and cooling led to crystallization of 3·60 g (20%) product *IV*, m.p. 246—248°C which was recrystallized from benzene to homogeneity; m.p. 249—250°C.

The benzene filtrate was partly evaporated and placed on a column of 400 g alumina (activity II). Benzene eluted 10·95 g (38%) sulfo ester *V*, melting at 135—138°C which was recrystallized from a mixture of benzene and hexane to purity; m.p. 142—143°C. IR spectrum (Nujol): 688, 759 (C_6H_5), 800 (N—O—S), 866 (solitary Ar—H), 1190 and 1361 cm^{-1} (O—SO_2). ^{1}H-NMR spectrum: δ 7·97 (mcd, J = 8·5; 2·0 Hz, 2 H, 2,6-H_2 of phenyl), 7·40—7·80 (m, 3 H, remaining protons of phenyl), 7·06 (s, 1 H, 8-H of the skeleton), 2·82 (t, J = 7·0 Hz, 4 H, 2 CH_2 in positions 1 and 7), 2·50 (t, J = 7·0 Hz, 4 H, 2 CH_2 in positions 3 and 5), 2·06 (s, 3 H, CH_3), 2·00 (q, J = = 7·0 Hz, 4 H, 2 CH_2 in positions 2 and 6). For $C_{20}H_{21}NO_3S$ (355·4) calculated: 67·63% C, 5·95% H, 3·92% N; found: 67·94% C, 6·19% H, 3·84% N.

Continuation of chromatography and elution with chloroform produced 3·07 g homogeneous product; m.p. 158—160°C which was recrystallized from a mixture of benzene and hexane to melt at 160—161°C. According to analysis and spectra we are dealing here with N-methyl-*s*-hydrindacene-4-carboxamide (*VI*). UV spectrum: λ_{max} 237 nm (log ε 3·89), 278 nm (3·32). IR spectrum: 869 (solitary Ar—H), 735, 1545, 1669 (CONH), 1610 (Ar), 3280 cm^{-1} (NH). ^{1}H-NMR spectrum: δ 7·45 (s, 2 H, NH and 8-H), 2·70 (t, 8 H, 4 $ArCH_2$), 2·06 (s, 3 H, NCH_3), 2·00 (m, 4 H, 2 CH_2 in positions 2 and 6). For $C_{14}H_{17}NO$ (218·3) calculated: 78·10% C, 7·96% H, 6·51% N; found: 78·36% C, 8·28% H, 6·26% N.

4-Amino-*s*-hydrindacene (*VII*)

A mixture of 35 g crude *IV* and 110 ml 100% H_3PO_4 was heated for 2 h to 160—170°C. The warm mixture was poured into 2 liters water, left to stand overnight and then 16 g metaphosphate of amine *VII* was filtered; m.p. 205—208°C. This was purified by crystallization from ethanol;

m.p. 213–214°C (needles). IR spectrum: 875 (solitary Ar—H), 995 (PO_3), 1542, 1608 (Ar), 1630, 3160, 3265 (NH_2), 2610 cm^{-1} (NH_2^+). The compound gives a positive reaction with 4-dimethylaminobenzaldehyde which confirms the presence of an aniline amino group. For $C_{12}H_{16}NO_3P$ (253·2) calculated: 56·92% C, 6·38% H, 5·52% N, 12·24% P; found: 56·96% C, 7·08% H, 5·45% N, 12·60% P.

The mother liquors after crystallization of the metaphosphate were evaporated and extracted with benzene to regenerate 5·0 g starting *IV* (m.p. 246–248°C). The benzene-insoluble fraction was filtered, suspended in the original mother liquor and the suspension was strongly made alkaline with 10% NaOH. The released base was isolated by further shaking with 1 litre warm benzene. Evaporation yielded 24 g (99% per conversion) of crude base *VII* which crystallizes from hexane in the form of needles and which melts in the pure state at 87–88°C. UV spectrum: λ_{max} 234 nm (infl.) (log ε 3·93). IR spectrum: 840 (solitary Ar—H), 1465 (CH_2), 1590 (Ar), 1645, 3205, 3315, 3430 cm^{-1} (NH_2). ^{1}H-NMR spectrum: δ 6·53 (s, 1 H, Ar—H), 3·36 (bs, 2 H, NH_2), 2·79 and 2·61 (2 t, 8 H, 4 $ArCH_2$), 2·05 (m, 4 H, 2 CH_2 in positions 2 and 6). For $C_{12}H_{15}N$ (173·2) calculated: 83·19% C, 8·73% H, 8·08% N; found: 83·56% C, 8·81% H, 7·77% N.

The *hydrochloride* was obtained from a benzene solution of the base and from an ether solution of hydrogen chloride; m.p. 205–206°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: 68·67% C, 7·95% H, 16·66% Cl, 6·38% N.

4-(Benzylidenamino)-*s*-hydrindancene (*VIII*)

A solution of 11·4 g amine *VII* and 7·2 g benzaldehyde in 350 ml methanol was refluxed for 5 h. Evaporation to a small volume and crystallization yielded 12·8 g (75%) Schiff base; m.p. 76–78°C. Crystallization from ethanol resulted in yellow needles; m.p. in a capillary 77–78°C, in Kofler's block 85–86°C. For $C_{19}H_{19}N$ (261·4) calculated: 87·30% C, 7·34% H, 5·36% N; found: 87·41% C, 7·41% H, 5·26% N.

4-(4-Methoxybenzylidenamino)-*s*-hydrindacene (*IX*)

In analogy to the preceding case, 10·4 g *VII* and 8·3 g anisaldehyde yielded 12·1 g (70%) product melting at 89–91°C which crystallized from ethanol to melt at 95–96°C. For $C_{20}H_{21}NO$ (291·4) calculated: 82·45% C, 7·26% H, 4·80% N; found: 82·50% C, 7·40% H, 4·55% N.

4-(Benzylamino)-*s*-hydrindacene (*X*)

A solution of 12·0 g *VIII* in 120 ml ether was added dropwise to a solution of 2·2 g $LiAlH_4$ in 50 ml ether and the mixture was refluxed for 4 h. After cooling, 9 ml 20% NaOH was added dropwise, the precipitate was filtered after 30 min and washed with benzene. Evaporation of the filtrate yielded 12·0 g (99%) oil which crystallized after 4 days of standing. Recrystallization from hexane yielded a pure base melting at 47–48°C. For $C_{10}H_{21}N$ (263·4) calculated: 86·64% C, 8·04% H, 5·32% N; found: 86·90% C, 8·01% H, 5·22% N.

The *hydrochloride* was obtained by treatment with hydrogen chloride in ether, m.p. 208 to 209°C (ethanol–ether). For $C_{19}H_{22}ClN$ (299·8) calculated: 76·09% C, 7·41% H, 11·83% Cl, 4·67% N; found: 76·31% C, 7·53% H, 12·00% Cl, 4·56% N.

4-(4-Methoxybenzylamino)-*s*-hydrindacene (*XI*)

Like in the preceding case, reduction of 12·0 g *IX* with 2·2 g $LiAlH_4$ yielded 12·1 g (theoretical amount) of an oily product which crystallized on standing; m.p. 96°C (hexane). ^{1}H-NMR spec-

trum: δ 7·24 (d, J = 8·5 Hz, 2 H, 2,6-H_2 of benzyl), 6·84 (d, J = 8·5 Hz, 2 H, 3,5-H_2 of benzyl), 6·65 (s, 1 H, 8-H), 4·32 (s, 2 H, NCH_2Ar), 3·85 (s, 3 H, OCH_3), 3·18 (bs, 1 H, NH), c. 2·78 (m, 8 H, 4 $ArCH_2$ of the skeleton), 2·05 (m, 4 H, 2 CH_2 in positions 2 and 6). For $C_{20}H_{23}NO$ (293·4) calculated: 81·87% C, 7·90% H, 4·77% N; found: 82·25% C, 8·00% H, 4·67% N.

1-(*s*-Hydrindacen-4-yl)piperazine (*XII*)

A. Volatile fractions were slowly distilled from a mixture of 9·3 g amine *VII*, 6·2 g diethanolamine, 20 ml water, 6 ml ethanol and 10 ml hydrochloric acid at normal pressure and the residue was heated for 7 h to 200—240°C. It was dissolved in 300 ml warm water, filtered and the filtrate was made alkaline with 20% NaOH. The released bases were isolated by extraction with a mixture of benzene and ether and separated crudely by distillation. The fraction distilling at 170°C/1 Torr is basically the regenerated *VII*. The fraction at 175—180°C/1 Torr (4·1 g, 32%) represents the crude base *XII* which does not crystallize even on longer standing. Neutralization with 2·0 g maleic acid in 5 ml ethanol and addition of ether yielded 5·50 g crude maleate, melting at 175 to 177°C. Crystallization from aqueous ethanol yielded the pure product melting at 182—183°C, its analysis indicating that it is a hemihydrate. For $C_{20}H_{26}N_2O_4 + 0{\cdot}5\ H_2O$ (367·4) calculated: 65·40% C, 7·41% H, 7·60% N; found: 65·92% C, 7·52% H, 7·68% N.

B. A mixture of 26·0 g amine *VII*, 26·8 g N,N-bis(2-chloroethyl)amine hydrochloride[14,15] and 120 ml 1-butanol was refluxed under stirring for 8 h. On the following day it was combined with 10·4 g K_2CO_3 and refluxing continued for 8 h. The addition of K_2CO_3 and refluxing was repeated twice more. After cooling, it was filtered, the solid fraction was washed with benzene and the filtrate was evaporated *in vacuo*. The residue was dissolved in 80 ml hexane, a minor solid fraction was removed by filtration and the filtrate was distilled after evaporation. Fraction boiling at 168—185°C/2 Torr was collected as the crude product (17·0 g, 47%). This was then converted to the maleate (20·6 g, m.p. 179—181°C). Decomposition of this maleate with ammonium hydroxide and extraction with benzene yielded 13·8 g (38%) pure base which crystallized; m.p. 57—58°C (hexane). ^{1}H-NMR spectrum: δ 6·90 (s, 1 H, 8-H), 2·75—3·20 (m, 16 H, 4 $ArCH_2$ and 4 NCH_2), 2·72 (s, 1 H, NH), 2·08 (m, 4 H, 2 CH_2 in positions 2 and 6). For $C_{16}H_{22}N_2$ (242·3) calculated: 79·29% C, 9·15% H, 11·56% N; found: 79·19% C, 9·40% H, 11·43% N.

1-(*s*-Hydrindacen-4-yl)-4-(phenylacetyl)piperazine (*XIII*)

A solution of 3·0 g phenylacetyl chloride[17] in 20 ml benzene was added dropwise to a solution of 4·6 g *XII* and 5 ml triethylamine in 30 ml benzene and the mixture was refluxed for 3 h. After cooling, it was washed with water and 5% Na_2CO_3, dried with Na_2SO_4 and evaporated at reduced pressure. The yield was 6·0 g (89%) crude amide which crystallized after adding 30 ml hexane and acetone to the boiling mixture until a solution formed; m.p. 161—163°C. Recrystallization from hexane yielded pure amide melting at 165—166°C. IR spectrum: 694, 766 (C_6H_5), 864 (solitary Ar—H), 1 578, 1 597 (Ar), 1 695 cm^{-1} (NCOR). For $C_{24}H_{28}N_2O$ (360·5) calculated: 79·96% C, 7·83% H, 7·77% N; found: 79·69% C, 7·80% H, 7·60% N.

1-(*s*-Hydrindacen-4-yl)-4-(2-phenylethyl)piperazine (*XIV*)

A solution of 5·2 g *XIII* in 60 ml ether was added dropwise to a solution of 2·0 g $LiAlH_4$ in 60 ml ether and the mixture was refluxed for 4 h. After cooling, it was decomposed with 8 ml 20% NaOH, the precipitated fraction was filtered and washed with benzene and the filtrate was evaporated *in vacuo*. A total of 5·0 g (theoretical amount) oil was obtained. After dissolving in 80 ml ether, a slight excess of an ether solution of hydrogen chloride was added, the precipitated mono-

hydrochloride was filtered, washed with ether and dried in air; 5·50 g (99%), m.p. 245—248°C. Recrystallization from ethanol yielded an analytical product melting at 247—249°C. For $C_{24}H_{31}ClN_2$ (383·0) calculated: 75·26% C, 8·16% H, 9·26% Cl, 7·32% N; found: 74·89% C, 8·36% H, 9·54% Cl, 7·03% N.

1-(*s*-Hydrindacen-4-yl)-4-phenacylpiperazine (*XV*)

A solution of 4·6 g *XII*, 5 ml triethylamine and 3·0 g phenacyl chloride in 50 ml benzene was refluxed under stirring for 7 h. After cooling, it was washed with water and the benzene solution was shaken with excess dilute (1 : 4) hydrochloric acid. The precipitated monohydrochloride was filtered, washed with some water and ether and dried in air; 7·55 g (theoretical amount) of a compound melting at 208—210°C. Recrystallization from 95% ethanol and addition of ether led to an analytical sample melting at 209—210°C. For $C_{24}H_{29}ClN_2O$ (397·0) calculated: 72·61% C, 7·36% H, 8·95% Cl, 7·06% N; found: 72·84% C, 7·43% H, 9·46% Cl, 6·90% N.

Decomposition of the hydrochloride sample with ammonium hydroxide and extraction with benzene yielded a base which was crystallized from ethanol to melt at 113—114°C. UV spectrum: λ_{max} 243 nm ($\log \varepsilon$ 4·23), infl. 268 nm (3·86), infl. 282 nm (3·67). IR spectrum: 694 and 766 (C_6H_5), 862 (solitary Ar—H), 1124, 1158, 1694 (Ar—CO—R), 1578 and 1596 cm^{-1} (Ar). For $C_{24}H_{28}N_2O$ (360·5) calculated: 79·96% C, 7·83% H, 7·77% N; found: 79·45% C, 7·71% H, 7·59% N.

1-(*s*-Hydrindacen-4-yl)-4-(4-methylsulfonylphenacyl)piperazine (*XVI*)

A solution of 4·0 g *XII*, 5 ml triethylamine and 4·7 g 4-(methylsulfonyl)phenacyl bromide[16] in 80 ml benzene was heated under stirring for 2 h to 70—75°C. After standing overnight, it was diluted with 100 ml benzene and washed with water. The benzene solution was dried with Na_2SO_4 and evaporated at reduced pressure. A total of 7·1 g (theoretical yield) of crude base melting at 138—141°C was obtained. Crystallization from a mixture of benzene and ethanol yielded an analytical sample melting at 155—156°C. IR spectrum: 769 (2 adjacent Ar—H, effect of SO_2R?), 862 (solitary Ar—H), 1155, 1317 (SO_2), 1222, 1704 (Ar—CO—R), 1575 cm^{-1} (Ar). For $C_{25}H_{30}N_2O_3S$ (438·6) calculated: 68·46% C, 6·90% H, 6·39% N, 7·31% S; found: 69·03% C, 6·93% H, 6·18% N, 7·32% S.

Maleate was prepared from a solution of the base in chloroform and a solution of maleic acid in ethanol; m.p. 189—190°C (needles from aqueous ethanol). For $C_{29}H_{34}N_2O_7S$ (554·6) calculated: 62·80% C, 6·18% H, 5·05% N, 5·78% S; found: 62·93% C, 6·22% H, 4·94% N, 5·70% S.

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REFERENCES

1. Vejdělek Z. J., Bartošová M., Protiva M.: This Journal *41*, 2020 (1976).
2. Vejdělek Z. J., Kakáč B., Holubek J., Svátek E., Bartošová M.: Protiva M.: This Journal *42*, 1200 (1977).
3. Arnold R. T., Barnes R. A.: J. Amer. Chem. Soc. *66*, 960 (1944).
4. Arnold R. T., Rondestvedt E.: J. Amer. Chem. Soc. *67*, 1265 (1945).
5. Arnold R. T., Craig P. N.: J. Amer. Chem. Soc. *72*, 2728 (1950).

6. Donaruma L. G., Heldt W. Z.: Org. Reactions *11*, 1 (1960).
7. Greer F., Pearson D. E.: J. Amer. Chem. Soc. *77*, 6649 (1955).
8. Huber M. L. (E. I. du Pont de Nemours & Co.): U.S. 2 721 199 (18. X. 1955); Chem. Abstr. *50*, 10 762 (1956).
9. McLeish N., Campbell N.: J. Chem. Soc. *1937*, 1103.
10. Moureu H., Chovin P., Rivoal G.: C. R. Acad. Sci. *223*, 951 (1946); Chem. Abstr. *41*, 2032 (1947).
11. Nystrom R. F., Brown W. G.: J. Amer. Chem. Soc. *70*, 3738 (1948).
12. Pollard C. B., MacDowell L. G.: J. Amer. Chem. Soc. *56*, 2199 (1934).
13. Prelog V., Dříza G. J.: This Journal *5*, 497 (1933).
14. Mann F. G.: J. Chem. Soc. *1934*, 461.
15. Ward K., jr: J. Amer. Chem. Soc. *57*, 914 (1935).
16. Vejdělek Z. J., Metyš J., Hradil F., Protiva M.: This Journal *40*, 1204 (1975).
17. Fourneau E., Nicolitch B.: Bull. Soc. Chim. Fr. (4) *43*, 1239 (1928).
18. Metyš J., Metyšová J., Votava Z.: Activ. Nerv. Super. *15*, 96 (1973).
19. Metyš J., Metyšová J.: Activ. Nerv. Super. *16*, 161 (1974).
20. Metyš J., Metyšová J., Kazdová E.: J. Pharmacol. (Paris) *5*, Suppl. 2 (9th. Congr. CINP, Paris, July 1974), 67 (1974).
21. Kulísková O., Náhunek K., Mišurec J., Sláma B., Švestka J., Kamenická V.: Activ. Nerv. Super. *17*, 236 (1975).

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