4-(AMINOMETHYL)-*s*-HYDRINDACENES AND 4,8-BIS(AMINOMETHYL)-*s*-HYDRINDACENES; SYNTHESIS AND PHARMACOLOGICAL SCREENING*

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Received December 9th, 1976

Chloromethylation of crude *s*-hydrindacene yielded a mixture of compounds which was crystallized and distilled to produce some 65% monochloromethyl derivative *I* and 15% bis(chloromethyl) derivative *VIII*. Chromatography and crystallization produced further minor products (*II*, *III*, *IX* and *XV*). Reactions of *I* and *VIII* with N-benzylmethylamine, morpholine, 1-methylpiperazine, 1-(2-hydroxyethyl)piperazine, 1-phenylpiperazine and 1-benzylpiperazine yielded amines *IV*, *VII* and *X*–*XIV*. Catalytic debenzylation of *IV* provided the methylamino derivative *V* which was alkylated with propargyl bromide to *VI*. Hydrindacene-4-carboxylic acid (*XVI*) was prepared by oxidation of 4-acetyl-*s*-hydrindacene with sodium hypobromite and by hydrolysis of oxothiomorpholide *XVII* which is the sole isolated product of Willgerodt's reaction of 4-acetyl-*s*-hydrindacene. The propargylamine derivative *IV* potentiates tryptamine convulsions of rats similarly to pargyline and it has a slight stimulating effect. Piperazine derivatives *XI*, *XIII* and *XIV* act as central depressants in high doses. Practically all the compounds prepared are antimicrobially active *in vitro*, with specific effect on lower fungi.

In previous communications of this series[1,2] we dealt with amines derived from *s*-hydrindacene which had been rather overlooked from the point of view of pharmacology (only ref.[3]). We set out now to describe the synthesis and the properties of monoamines and diamines, the amino group of which is attached to the aromatic ring, *i.e.* to position 4, or to positions 4 and 8, by a single-carbon unit. Thus the compounds are derivatives of 4-(aminomethyl) and 4,8-bis(aminomethyl)-*s*-hydrindacene.

The starting compound was crude *s*-hydrindacene[4,5] obtained by reduction of crude *s*-hydrindacen-1-one[5] by a Wolff–Kishner method[6] in Huang-Minlon modification[7]. Chloromethylation with formaldehyde and hydrogen chloride in the presence of hydrochloric acid at 65–70°C yielded a mixture of compounds from which the 4,8-bis(chloromethyl) derivative *VIII* was separated by crystallization from cyclohexane. Distillation of the mother liquors yielded 15% unaltered *s*-hydrindacene plus a higher-boiling fraction which contained some 85% monochloromethyl deriva-

* Part CXIV in the series Neurotropic and Psychotropic Agents; Part CXIII: This Journal *42*, 3079 (1977).

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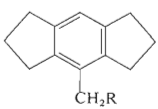
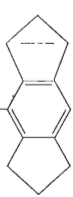
tive *I* which can be obtained in a pure state by recrystallization. Chromatography permitted to isolate some 2% *s*-hydrindacene from the distillate, plus 2% compound *VIII* and 3–4% somewhat more polar substance which was identified as ether *II* with the aid of analyses and spectra. The most polar components to be eluted were two alcohols. The first of these (about 7%) was identified as *s*-hydrindacene-4-methanol (*III*); besides the spectra, its identification was aided by the transformation of the compound to the chloromethyl derivative *I* in a reaction with thionyl chloride. The second of the alcohols (about 1%) is 4,8-bis(hydroxymethyl)-*s*-hydrindacene (*IX*). The identification was accomplished with the aid of spectra and of transformation of the compound to the bis(chloromethyl) derivative *VIII*. After crystallization of the bis(chloromethyl) derivative, the mother liquors yielded another compound which is isomeric with *VIII* and which, according to the ^{1}H-NMR spectrum, is 4,5-bis(chloromethyl)-*as*-hydrindacene (*XV*). The source of this compound is apparently *as*-hydrindacene[8] which is present as contaminant of our starting crude *s*-hydrindacene. The primary source, however, is *as*-hydrindacen-3-one[8] which is formed, together with *s*-hydrindacen-1-one, by cyclization of 5-(3-chloropropionyl)indane[1,5]. According to gas chromatography, our crude *s*-hydrindacene contains about 2% of the isomer. Repeated crystallization of crude *s*-hydrindacene-1-one and *s*-hydrindacene yielded the pure compounds and their spectra were recorded.



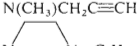
I, R = Cl

II, R = OCH_2



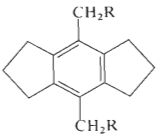
III, R = OH

IV, R = $N(CH_3)CH_2C_6H_5$
V, R = $NHCH_3$
VI, R = $N(CH_3)CH_2C{\equiv}CH$

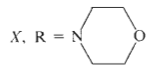
VII, R = 

A substitution reaction of chloromethyl derivative *I* with a 100% excess of benzylmethylamine at 120°C (method *A*) prepared amine *IV* which was debenzylated by catalytic hydrogenation on palladium to secondary amine *V*. Alkylation with propargyl bromide yielded the methylpropargylamino derivative *VI* which is the *s*-hydrindacene analogue of "pargyline"[9]. Substitution reaction of chloromethyl derivative *I* with 1-phenylpiperazine[10] according to method *A* resulted in the phenylpiperazine

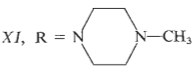
derivative *VII*. Using this method, substitution reactions of the 4,8-bis(chloromethyl) derivative *VIII* were done with morpholine, 1-methylpiperazine, 1-(2-hydroxyethyl)-piperazine, 1-phenylpiperazine[10] and 1-benzylpiperazine[11]; diamines *X* – *XIV* were formed. All the prepared amines are shown together with experimental data in Table I.



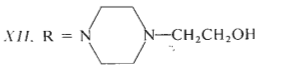
VIII, R = Cl
IX, R = OH



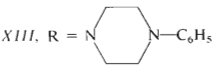
X, R = N O



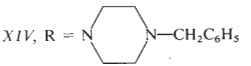
XI, R = N N—CH$_3$



XII, R = N N—CH$_2$CH$_2$OH

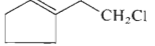


XIII, R = N N—C$_6$H$_5$

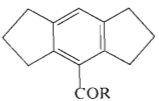


XIV, R = N N—CH$_2$C$_6$H$_5$

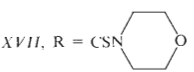
In an attempt to prepare *s*-hydrindacene-4-acetic acid, we subjected 4-acetyl--*s*-hydrindacene[2,5] to Willgerodt's reaction in Kindler's modification[12]. A high yield of a neutral product was obtained and identified with the aid of analyses and spectra as oxothiomorpholide *XVII*. Willgerodt's reaction with this sterically hindered ketone



XV



XVI, R = OH



XVII, R = CSN O

XVIII, R = OCH$_2$CH$_3$

thus does not proceed all the way to the usual final product but it stops at an intermediate stage as encountered in other cases[13,14]. The identity of the product is supported by the course of alkaline hydrolysis which requires rather drastic conditions and which yields *s*-hydrindacene-4-carboxylic acid (*XVI*). The same acid was obtained in a very low yield by oxidation of 4-acetyl-*s*-hydrindacene[2,5] with sodium hypobromite

TABLE I

4-(Aminomethyl)-*s*-hydrindacenes, 4,8-Bis(aminomethyl)-*s*-hydrindacenes and Their Salts

Compound[a]	Method yield, %	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found			
				% C	% H	% N	% Cl
IV-HCl	*A*[b]	210–211 (ethanol–ether)	$C_{21}H_{26}ClN$ (327·9)	76·92 76·54	8·00 8·11	4·27 3·99	— —
V-HCl	[b]	290–292 (ethanol)	$C_{14}H_{20}ClN$ (237·1)	70·72 71·25	8·48 8·63	5·89 5·70	14·91 14·97
VI-HM	[b]	117–118 (ethanol–ether)	$C_{21}H_{25}NO_4$ (355·4)	70·96 70·65	7·09 6·99	3·94 3·64	— —
VII-M	*A* (77)	168–169 (ethanol)	$C_{27}H_{32}N_2O_4$ (448·5)	72·30 71·99	7·19 7·25	6·24 6·16	— —
X	*A* (96)	177–178 (ethanol)	$C_{22}H_{32}N_2O_2$ (356·5)	74·12 73·98	9·05 9·07	7·86 7·75	— —
X-2 HCl	—	>300 (aqueous ethanol)	$C_{22}H_{34}Cl_2N_2O_2$ (429·4)	61·53 61·49	7·98 8·10	6·53 6·78	16·51 16·71
XI	*A* (75)	175–176[c] (ethanol)	$C_{24}H_{38}N_4$ (382·6)	75·34 75·58	10·01 9·72	14·65 14·67	— —
XI-4 HCl	—	>340 (aqueous ethanol)	$C_{24}H_{42}Cl_4N_4$ (528·4)	54·55 54·58	8·01 8·15	10·61 10·45	26·83 26·73
XII	*A* (83)	223–224 (benzene)	$C_{26}H_{42}N_4O_2$ (442·6)	70·55 70·73	9·56 9·64	12·66 12·31	— —
XII-4 HCl[d]	—	>330 (aqueous ethanol)	$C_{26}H_{48}Cl_4N_4O_3$ (606·5)	51·49 51·56	7·97 7·69	9·24 9·11	23·37 23·05
XIII	*A* (80)	223–224 (benzene–hexane)	$C_{34}H_{42}N_4$ (506·7)	80·60 81·07	8·34 8·25	11·06 10·58	— —
XIII-2 HCl[d]	—	>300 (aqueous ethanol)	$C_{34}H_{46}Cl_2N_4O$ (597·6)	68·34 68·77	7·76 7·94	9·37 9·13	11·86 12·15
XIV	*A* (86)	219–220 (benzene)	$C_{36}H_{46}N_4$ (534·8)	80·85 80·55	8·67 8·65	10·48 10·13	— —
XIV-4 HCl	—	>330 (ethanol–ether)	$C_{36}H_{50}Cl_4N_4$ (680·6)	63·53 62·70	7·41 7·52	8·23 7·87	20·83 20·47

[a] HCl hydrochloride, HM hydrogen maleate, M maleate. [b] See Experimental. [c] ^{1}H-NMR spectrum: δ 3·42 (m, 4 H, NCH_2ArCH_2N), 2·92 (t, 8 H, remaining 4 $ArCH_2$), 2·44 (bs, 16 H, 8 NCH_2 of piperazine), 2·28 (s, 6 H, 2 NCH_3), 2·00 (m, 4 H, remaining isolated 2 CH_2). [d] Monohydrate.

in aqueous dioxane. Our value of the melting point of *XVI* does not agree with literature data[5,15] for the acid obtained by oxidation of 4-acetyl-*s*-hydrindacene with sodium hypochlorite in aqueous methanol. The identity of the present product is supported by the IR spectrum and further by the ^{1}H-NMR spectrum of ethyl ester *XVIII* prepared from the acid *via* the chloride. The discrepancy may be explained by the existence of two crystal modifications.

Of the compounds prepared here, more attention was paid to the propargylamine derivative *VI* (tested as maleate VÚFB-10.643), the pargyline analogue, *i.e.* N-benzyl--N-methylpropargylamine[9]. In the observation test according to Ther[16] on mice the compound at *p.o.* doses of 10 and 30 mg/kg displayed only a slight and brief stimulating effect. A higher dose (100 mg/kg) is slightly inhibitory in this test. In the rotating-rod test in mice it causes ataxia only at the mean effective dose of ED_{50} = 130 mg/kg *p.o.* (maximum at 90 min after application). Like pargyline, the present compound potentiates with nearly equal intensity the tryptamine convulsions of rats, thus resembling a monoamine oxidase inhibitor (Dr A. Dlabač, pharmacological department of this institute).

Other compounds were evaluated orientatively by methods of general pharmacological screening. The first to be mentioned is the form in which the compound was applied, then the code number, way of application, orientation value of the mean lethal dose (LD_{50} in mg/kg) in mice and further dose D (mg/kg) at which the compound was applied in tests *in vivo*: *VII*-maleate, VÚFB-10.642, *p.o.*, >2500, 300; *X*-dihydrochloride, VÚFB-10.645, *i.v.*, 100, 20; *XI*-tetrahydrochloride, VÚFB-10.640, *i.v.*, 25, 5; *XII*-tetrahydrochloride (monohydrate), VÚFB-10.637, *i.v.*, 62, 12; *XIII*-dihydrochloride (monohydrate), VÚFB-10.646, *p.o.*, >2500, 300; *XIV*-tetrahydrochloride, VÚFB-10.638, *i.v.*, 175, 35; *XVII*, VÚFB-10.696, *p.o.*, >2500, 300.

The *p.o.* applied compounds *VII*, *XIII* and *XVII* which appear to be practically nontoxic, did not exhibit any demonstrable effect in any of the tests used. This may be due to their low resorption from the intestinal tract. At the dose shown, even the parenterally applied *X* was ineffective. The relatively highly toxic *XI* acts as a central inhibitor even in doses lower than D (it depresses the spontaneous motility of mice). At concentrations of 5–25 μg/ml it depresses heart inotropy by 25% using an isolated rabbit atrium. At an oral dose of 25 mg/kg it depresses the blood sugar level of rats by 20%. The highest depressant activity was found with *XII* which, at a subcutaneous dose of 12 mg/kg, depresses significantly the spontaneous motility of mice in known surroundings. At an oral dose of 60 mg/kg it increases the blood sugar level of rats by 20%. When using a respiratory pump, at an *i.v.* dose equal to twice the LD_{50}, it shows indications of a myorelaxant effect of the curare type using rat gastrocnemius. Finally, it has an antiarrhythmic effect; in an *i.v.* dose of 12 mg/kg it inhibits significantly heart arrhythmias caused by aconitine. Compound *XIV* has a depressant action in mice at doses greater than D. Like the previous one, it increases the blood sugar level of rats by 20%, but only at an oral dose of 175 mg/kg. While it does not affect inotropy (isolated rabbit atrium), at

a concentration of 50 μg/ml it increases heart frequency by 25%. At an *i.v.* dose lower than D it inhibits significantly aconitine arrhythmias of the rat heart.

Most of the compounds prepared here were evaluated (as the salts shown) by Dr J. Turinová and Dr A. Čapek (bacteriological department of this institute) in tests *in vitro* as to their antimicrobial activity toward a standard set of microorganisms (the minimum inhibitory concentrations are shown in μg/ml unless they exceed 100 μg/ml): *Mycobacterium tuberculosis* H37Rv, *VI* 50, *XI* 100; *Saccharomyces pasterianus*, *VI* 100, *VII* 100, *X* 100, *XI* 100, *XII* 100, *XIII* 100, *XIV* 50, *XVII* 100; *Trichophyton mentagrophytes*, *VI* 25, *VII* 25, *X* 50, *XI* 50, *XII* 50, *XIII* 50, *XIV* 25, *XVII* 6·2; *Candida albicans*, *VI* 100, *VII* 100, *X* 100, *XI* 100, *XII* 50, *XIII* 100, *XIV* 50, *XVII* 100; *Aspergillus niger*, *VI* 100, *VII* 100, *X* 100, *XI* 100, *XII* 50, *XIII* 100, *XIV* 25, *XVII* 100. Up to 100 μg/ml, all the compounds were ineffective against *Streptococcus* β-*haemolyticus*, *Streptococcus faecalis*, *Staphylococcus pyogenes aureus*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Proteus vulgaris*. Thus there is a specific action of the compounds against lower fungi and yeasts. The oxothiomorpholide *XVII* is remarkably effective against *Trichophyton mentagrophytes*.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried at about 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; IR spectra (in Nujol) in a Unicam SP 200G spectrophotometer, ^{1}H-NMR spectra (in $CDCl_3$) in a Tesla BS 487C (80 MHz) spectrometer and the mass spectra in a MS 902 (AEI) spectrometer. Gas chromatographic estimations were done in a Perkin–Elmer F 7 Fraktometer. The homogeneity of the compounds was checked by chromatography on a thin layer of silica gel. The analyses of the amines and of their salts are summarized in Table I.

s-Hydrindacen-1-one

The crude product prepared according to literature data[1,5] melted at 59—61°C and in this state it was used for reduction. After a triple crystallization from hexane it melted at 79—80°C which is almost identical with the literature reference[5] (80—81°C). With this pure product the spectra were measured. Mass spectrum: *m/e* 172·0888 ($C_{12}H_{12}O$; M^+; 100%), 158 (28%), 144 (74), 130 (90), 129 (100), 115 (76). UV spectrum: λ_{max} 217 nm (log ε 4·11), 255 nm (4·14), 303 nm (3·78). IR spectrum: 870, 883 (solitary Ar—H), 1 580, 1 620, 3 050 (Ar), 1 699 cm^{-1} (Ar—CO). ^{1}H-NMR spectrum: δ 7·50 (s, 1 H, 8-H), 7·21 (s, 1 H, 4-H), c. 2·90 (m, 6 H, CH_2 in positions 3, 5 and 7), 2·60 (m, 2 H, CH_2CO), 2·08 (m, 2 H, 6-CH_2).

s-Hydrindacene

A mixture of 96 g crude *s*-hydrindacen-1-one[1,5], 450 ml triethylene glycol, 130 ml 80% hydrazine hydrate and 75 g ground KOH was refluxed for 1 h. The volatile fractions were then distilled in the course of 16 h at reduced pressure until a temperature of 175°C has been reached. The mixture was then refluxed for 3 h at this temperature. The distillate was returned to the mixture and, after dilution with 700 ml water, the mixture was extracted with benzene. After drying the extract with Na_2SO_4 it was distilled: 75 g (86%) oil boiling at 122—125°C/15—18 Torr which solidified on standing to a semicrystalline substance. According to gas chromatography it contains about 2% of a contaminant of similar polarity, apparently *as*-hydrindacene[8]. Due to large losses associated with removing this contamination, the crude hydrocarbon was used for further work. Ref.[4,5]

describe its preparation by ketone reduction using Clemmensen's method, for the crude product it reports a b.p. of 116—120°C/9 Torr and for the pure substance a m.p. of 52—54°C.

In analogy to the preceding case, pure *s*-hydrindacen-1-one was reduced to yield a product boiling at 130—132°C/12 Torr and melting at 49—51°C. Recrystallization from ethanol yielded a product melting at 53—54°C. According to gas chromatography, the product contains before as well as after crystallization 99·8% pure substance. It was used for recording the spectra. Mass spectrum: *m/e* 158 ($C_{12}H_{14}$; M^+; 100%), 144 (8%), 130 (80), 116 (20). UV spectrum: λ_{max} 276 nm (log ε 3·61), 280 nm (3·63), 286 nm (3·62). IR spectrum: 869 (solitary Ar—H), 1486, 3020, 3115 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·02 (s, 2 H Ar—H), 2·80 (t, 8 H, 4 $ArCH_2$), 2·00 (m, 4 H, CH_2 in positions 2 and 6).

4,8-Bis(chloromethyl)-*s*-hydrindacene (*VIII*)

A. A mixture of 123 g crude *s*-hydrindacene, 82 ml 37% formaldehyde and 270 ml hydrochloric acid was heated to 65—70°C and, at that temperature, it was saturated under vigorous stirring with hydrogen chloride for 8 h. It was cooled, diluted with 250 ml water and extracted with benzene. The extract was washed with water, dried with Na_2SO_4 and evaporated. The residue (158 g) was dissolved in 160 ml boiling cyclohexane and the solution was left overnight to crystallize; 25·2 g (13% per conversion) crude product *VIII*, melting at 175—177°C (for processing the mother liquor see below). Repeated crystallization from benzene yielded the pure product, m.p. 199 to 201°C. ^{1}H-NMR spectrum: δ 4·50 (s, 4 H, 2 CH_2Cl), 2·90 (t, 8 h, 4 $ArCH_2$), c. 2·10 (m, 4 H, CH_2 in positions 2 and 6). For $C_{14}H_{16}Cl_2$ (255·2) calculated: 65·90% C, 6·32% H, 27·78% Cl; found: 66·20% C, 6·35% H, 27·55% Cl.

B. A solution of 40 mg *IX* (see below) in 2 ml chloroform was combined with 0·5 ml $SOCl_2$, the mixture was refluxed for 30 min, evaporated *in vacuo*, and the residue was dissolved in a mixture of benzene and ether. The solution was washed with a solution of $NaHCO_3$, dried and evaporated; 45 mg, m.p. 197—199°C. After recrystallization from benzene, the m.p. was 198—199°C and the substance melted without depression in a mixture with the product prepared under *A*.

4-Chloromethyl-*s*-hydrindacene (*I*)

A. The cyclohexane mother liquor from the preceding experiment (under *A*) was evaporated and the residue was distilled. The first to be regenerated was 18 g (15%) starting *s*-hydrindacene, b.p. up to 125°C/2 Torr. This was followed by 91 g (67% per conversion) of a fraction boiling at 138—150°C/2 Torr which is the crude monochloro derivative *I*. On standing it crystallizes and on repeated crystallization from hexane it yields the pure compound melting at 57—58°C. ^{1}H-NMR spectrum: δ 7·10 (s, 1 H, Ar—H), 4·57 (s, 2 H, $ArCH_2Cl$), 2·90 (m, 8 H, 4 $ArCH_2$), 2·14 (m, 4 H, CH_2 in positions 2 and 6). For $C_{13}H_{15}Cl$ (206·7) calculated: 75·53% C, 7·32% H, 17·15% Cl; found: 75·11% C, 7·29% H, 17·66% Cl.

Since crude substance *I* (distillate) showed in TLC the presence of admixtures, 15 g of this distillate was dissolved in 75 ml hexane and chromatographed on a column of alumina (400 g, activity II). The first to be eluted with hexane was 8·4 g *I*. The last hexane fractions (0·3 g) were found to contain the bis(chloromethyl) derivative *VIII*, m.p. 195—197°C (cyclohexane). Benzene eluted 0·6 g of a substance which was identified as bis(*s*-hydrindacen-4-ylmethyl) ether (*II*), m.p. 115—116°C (ethanol). Mass spectrum: *m/e* 358 (corresponds to $C_{26}H_{30}O$; the most intense fragment at *m/e* 170). IR spectrum: 862, 890 (solitary Ar—H), 1072, 1243 (C—O—C), 1492, 1570, 1594, 1612, 1632, 1708 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·00 (s, 2 H, Ar—H), 4·48 (s, 4 H, $ArCH_2OCH_2Ar$), 2·95 (t, 16 H, 8 $ArCH_2$), 2·00 (m, 8 H, remaining 4 CH_2). For $C_{26}H_{30}O$ (358·5) calculated: 87·10% C, 8·44% H; found: 86·97% C, 8·48% H.

On continuing the chromatography and eluting with benzene with 10% ethanol the first to be eluted was 1·4 g substance, m.p. 84°C (cyclohexane). It was identified as *s*-hydrindacene-4-methanol (*III*). IR spectrum: 862 (solitary Ar—H), 972, 1003, 1021 (CH_2OH), 3320, 3390 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 7·00 (s, 1 H, Ar—H), 4·58 (s, 2 H, $ArCH_2O$), 2·80 (m, 8 H, 4 $ArCH_2$), 2·00 (m, 4 H, remaining 2 CH_2), 1·55 (s, 1 H, OH). For $C_{13}H_{16}O$ (188·3) calculated: 82·93% C, 8·57% H; found: 82·68% C, 8·54% H.

The same mixture of solvents was then used to elute 4·1 g of a mixture of alcohol *III* with another polar admixture which was separated on the basis of low solubility in cyclohexane; 80 mg, m.p. 202—203°C (ethanol). It was identified as 4,8-bis(hydroxymethyl)-*s*-hydrindacene (*IX*). Mass spectrum: *m/e* 218·1305 which corresponds by its composition to $C_{14}H_{18}O_2$. ^{1}H-NMR spectrum (CD_3SOCD_3): δ 4·55 (t, J = 6·0 Hz, 2 H, 2 OH), 4·30 (d, J = 6·0 Hz, 4 H, OCH_2Ar . . CH_2O), 2·78 (t, J = 7·0 Hz, 8 H, 4 $ArCH_2$), 1·90 (m, 4 H, remaining 2 CH_2). For $C_{14}H_{18}O_2$ (218·3) calculated: 77·04% C, 8·31% H; found: 77·08% C, 8·32% H.

The distillation residue after the above broad fraction of crude monochloromethyl derivative *I* was also characterized; compounds *I*, *VIII* and *IX* were isolated and characterized.

B. One ml $SOCl_2$ was added to a solution of 216 mg *III* in 1·5 ml chloroform and the mixture was refluxed for 30 min. After evaporation *in vacuo*, the residue was dissolved in a mixture of benzene and ether, the solution was washed with a saturated solution of $NaHCO_3$, dried and evaporated. The residue crystallized from 1·5 ml hexane to 215 mg substance, melting at 62—63°C and showing no depression on mixing with pure *I* obtained under *A*.

4,5-Bis(chloromethyl)-*as*-hydrindacene (*XV*)

The benzene mother liquors after crystallization of 107 g crude *VIII* were evaporated (residue 24 g) and a part of the residue (15·7 g) crystallized from 130 ml cyclohexane. A total of 7·1 g nonhomogeneous substance melting at 110—115°C precipitated; a part of this (2·0 g) was chromatographed on a column of 40 g alumina (activity II), using elution with a mixture of cyclohexane and benzene. The middle fraction obtained was 1·21 g homogeneous substance which crystallizes from ethanol and melts at 122—123°C. ^{1}H-NMR spectrum: δ 4·70 and 4·50 (2 s, 4 H, $ClCH_2ArCH_2Cl$), 2·92 and 2·82 (2t, 8 H, remaining 4 $ArCH_2$), c. 2·10 (m, 4 H, remaining 2 CH_2). For $C_{14}H_{16}Cl_2$ (255·2) calculated: 65·90% C, 6·32% H, 27·78% Cl; found: 66·38% C, 6·31% H, 27·49% Cl.

N-Benzyl-N-(*s*-hydrindacen-4-ylmethyl)methylamine (*IV*) (Method *A*)

A mixture of 3·17 g *I* and 4·0 g N-benzylmethylamine was heated under stirring to homogeneity and then refluxed for 1 h at 120°C. After cooling, it was mixed with 50 ml benzene, the precipitated benzylmethylamine hydrochloride was filtered (2·4 g) and the filtrate was washed with water, dried and evaporated *in vacuo*; 4·8 g (quantitative yield) oily base, most of which distils at 180 to 190°C/1 Torr. Dissolving in ethanol and addition of an ether solution of hydrogen chloride led to precipitation of hydrochloride, m.p. 210—211°C (ethanol–ether). For further work we used the pure base which was released from the hydrochloride with NH_4OH and extracted with benzene.

N-(*s*-Hydrindacen-4-ylmethyl)methylamine (*V*)

A solution of 4·8 g *IV* in 80 ml ethanol was hydrogenated under normal conditions on 2 g 10% palladium catalyst on charcoal. The theoretical amount of hydrogen was consumed after 5 h of agitation. The catalyst was filtered and the filtrate evaporated to dryness; 3·2 g (97%) oily base.

Like in the preceding case, crystalline hydrochloride was prepared, m.p. 290—292°C (ethanol). For further work we used the pure base (oil) liberated from the hydrochloride.

N-(*s*-Hydrindacen-4-ylmethyl)-N-methylpropargylamine (*VI*)

K_2CO_3 (2·6 g) and propargyl bromide (2·2 g) were added to a solution of 3·3 g *V* in 40 ml 1-butanol and the mixture was refluxed under stirring for 2 h. After standing overnight, the precipitated inorganic salts were filtered and the filtrate was evaporated *in vacuo*. The residue was dissolved in benzene, the solution was washed with water and shaken with 50 ml dilute hydrochloric acid (1 : 5). The precipitated hydrochloride was filtered, combined with the acid aqueous phase of the filtrate and the base was liberated by alkalification. Extraction with benzene yielded 3·4 g (87%) oily base. After dissolving in ether, the solution was neutralized with a solution of 1·7 g maleic acid in ethanol; hydrogen maleate, m.p. 117—118°C (ethanol–ether).

Thiomorpholide of *s*-Hydrindacen-4-ylglyoxylic Acid (*XVII*)

A mixture of 40·0 g 4-acetyl-*s*-hydrindacene[2,5], 26·2 g morpholine and 9·6 g powdery sulfur was refluxed for 15 h. After cooling, the mixture was dissolved in 200 ml ether, filtration removed the small undissolved fraction, the filtrate was washed consecutively with 5% NaOH, 5% HCl and with water, dried with Na_2SO_4 and evaporated. The residue was dissolved in 60 ml benzene and 45 ml ethanol and the solution was combined with 150 ml hexane. On standing overnight, 21·3 g yellow crystalline solid precipitated and was identified as *XVII*. Another fraction of the substance (6·6 g) was obtained by chromatography of the mother liquor on a column of alumina (600 g, activity II), eluting first with benzene to recover 17·1 g of the starting 4-acetyl-*s*-hydrindacene (m.p. 63·5—64·5°C). A total of 27·9 g (78% per conversion) compound *XVII* was thus obtained; m.p. 130—131°C (ethanol). UV spectrum: λ_{max} 264·5 nm (log ε 4·26), infl. 322 nm (3·82). IR spectrum: 871, 900 (solitary Ar—H), 1109, 1250, 1270 (C—O), 1500 (CSN), 1570 (Ar), 1641 cm^{-1} (ArCO—CSN). ^{1}H-NMR spectrum: δ 7·22 (s, 1 H, Ar—H), 3·60—4·40 (m, 8 H, 4 CH_2 of morpholine), 2·20—3·20 (m, 8 H, 4 $ArCH_2$), 1·80—2·30 (m, 4 H, remaining 2 CH_2). For $C_{18}H_{21}NO_2S$ (315·4) calculated: 68·55% C, 6·71% H, 4·44% N, 10·15% S; found: 68·55% C, 6·80% H, 4·95% N, 10·16% S.

s-Hydrindacene-4-carboxylic Acid (*XVI*)

A. A solution of sodium hypobromite prepared in a reaction of 40 g NaOH in 200 ml water with 48 g bromine at below 10°C was added dropwise under stirring to a solution of 20 g 4-acetyl-*s*-hydrindacene[2,5] in 100 ml dioxane, kept at 25—30°C. The mixture was stirred for 2 h at room temperature and then its temperature was raised over 2 h to 70°C. Dioxane was then distilled off, replaced with water, the neutral compounds were isolated by extraction with benzene (recovering most of the starting ketone) and the alkaline water solution was then filtered with charcoal and acidified with hydrochloric acid to precipitate 1·5 g (7·5%) acid which crystallizes from aqueous ethanol and melts at 183—184°C. UV spectrum: λ_{max} 242 nm (log ε 3·89), 304 nm (3·56). IR spectrum: 872 (solitary Ar—H), 957, 1286 (COOH), 1571 (Ar), 1670 cm^{-1} (Ar—COOH). For $C_{13}H_{14}O_2$ (202·2) calculated: 77·20% C, 6·98% H; found: 76·69% C, 7·07% H. Ref.[5] reports a m.p. of 229·5—231°C.

B. A mixture of 7·5 g *XVII*, 40 ml 1-butanol and a solution of 20 g KOH in 60 ml water was refluxed for 10 h. After dilution with water, the butanol was steam-distillated and the remaining aqueous liquid was cooled and extracted with benzene to yield 2·2 g starting *XVII*. The aqueous phase was filtered with charcoal and acidified with hydrochloric acid to yield 2·6 g (77% per

conversion) acid which was dried and crystallized from octane to melt at 182—183°C. It is identical with the product obtained under *A*.

Ethyl *s*-Hydrindacene-4-carboxylate (*XVIII*)

A suspension of 10·0 g *XVI* in 30 ml 1,2-dichloroethane was combined with 6 ml $SOCl_2$, the mixture was left to stand for 15 min at room temperature and then was heated for 2 h to 70°C and evaporated *in vacuo*. The residue (10·8 g) is crude *s*-hydrindacene-4-carbonyl chloride. It was dissolved in 15 ml 1,2-dichloroethane, 50 ml ethanol was added under stirring, the mixture was refluxed for 1 h and evaporated. The residue was chromatographed on a column of 250 g alumina (activity II). The benzene-eluted product was distilled; 7·50 g (68%), n_D^{22} 1·5471, b.p. 155°C/2 Torr. A sample of the ester crystallized only after chromatography on alumina, using elution with hexane and then with a mixture of hexane and benzene; m.p. 42—43°C (pentane). UV spectrum: δ_{max} 240 nm (log ε 3·98), 305 nm (3·67). IR spectrum: 864 (solitary Ar—H), 1 236 (C—O—C), 1 712 cm^{-1} (ArCOOR). ^{1}H-NMR spectrum: δ 7·20 (s, 1 H, Ar—H), 4·35 (q, J = = 7·0 Hz, 2 H, $COOCH_2$), 3·18 (t, J = 7·0 Hz, 4 H, 2 CH_2 in positions 3 and 5), 2·80 (t, J = = 7·0 Hz, 4 H, remaining 2 $ArCH_2$), 2·10 (m, 4 H, remaining isolated CH_2), 1·42 (t, J = 7·0 Hz, 3 H, C—CH_3). For $C_{15}H_{18}O_2$ (230·3) calculated: 78·22% C, 7·88% H; found: 78·16% C, 7·92% H.

The authors are indebted to Dr E. Svátek (department of physical chemistry of this institute) for measuring and interpreting the UV and IR spectra, further to Dr M. Ryska, Institute of Macromolecular Chemistry, Czechoslovak Academy of Sciences, Prague, and to Dr O. Matoušová (this institute) for measuring and interpreting the mass spectra, to Mr L. Tůma for skilled technical assistance with the preparatory part of the work, to Mr S. Vaněček (department of chromatography on this institute) for gas-chromatographic analyses, and finally to Mrs J. Komancová, Mrs V. Šmidová, Mr M. Čech, Mrs J. Hrdá and Mrs A. Slaviková (analytical department of this institute) for carrying out the analyses.

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Translated by A. Kotyk.