4-(AMINOACYLAMIDO)-*s*-HYDRINDACENES AND RELATED COMPOUNDS: SYNTHESIS AND PHARMACOLOGICAL SCREENING*

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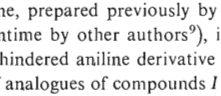
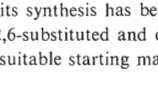
Received March 22nd, 1982

Chloracylamido derivatives *IIIa—Va* were obtained by acylation of 4-amino-*s*-hydrindacene with chloroacetyl chloride, 2-chloropropionyl chloride and 3-chloropropionyl chloride; their reactions with excessive diethylamine, pyrrolidine, piperidine and morpholine afforded the title compounds *IIIbcde—Vbcde*. A reaction of 4-amino-*s*-hydrindacene with benzoyl isothiocyanate gave 1-benzoyl-3-(*s*-hydrindacen-4-yl)thiourea (*VI*) whose mild alkaline hydrolysis resulted in N-(*s*-hydrindacen-4-yl)thiourea (*VII*). The following treatment with methyl iodide and then with ethylenediamine afforded the imidazoline derivative *VIII* in a low yield. N-(*s*-Hydrindacen-4-yl)-2-piperidinoacetamide (*IIId*) in the form of the hydrochloride revealed a high degree of local anaesthetic and antiarrhythmic activity.

Derivatives of some 2,6-substituted anilines revealed interesting and useful pharmacological properties. The local anaesthetic lidocaine (*I*) (ref.[1-4]) and the adrenolytic and antihypertensive agent clonidine (*II*) (ref.[5-7]) are the examples. 4-Amino-*s*-hydrindacene, prepared previously by our group[8] (its synthesis has been described in the meantime by other authors[9]), is likewise a 2,6-substituted and consequently a sterically hindered aniline derivative considered a suitable starting material of the synthesis of analogues of compounds *I* and *II*.



I

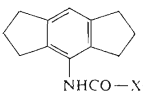


II

First of all we have prepared a series of lidocaine analogues. Reactions of 4-amino-*s*-hydrindacene[8] with chloroacetyl chloride, 2-chloropropionyl chloride[10,11] and 3-chloropropionyl chloride[12] in boiling chloroform in the presence of potassium

* Part CLXXII in the series Neurotropic and Psychotropic Agents; Part CLXXI: This Journal *47*, 3134 (1982).

carbonate gave the chloroacylamido derivatives *IIIa – Va*. These were transformed by reactions with excessive diethylamine, pyrrolidine, piperidine and morpholine to the aminoacylamides *IIIbcde – Vbcde* either in boiling benzene (method *A*) or without solvent in the refluxing amine (method *B*), and in the case of the combination of diethylamine with compound *IVa*, without a solvent in the autoclave at 140 to 150°C (method *C*). In the experimental part only the preparation of compounds *IIId*, *IVb* and *IVd* is described. The other compounds were obtained by similar methods and the usual experimental data are assembled in Table I. In addition to the bases, the hydrochlorides were also prepared.

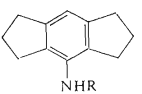


III, X = $-CH_2-$
IV, X = $-CH(CH_3)-$
V, X = $-CH_2CH_2-$

In formulae *III – V*: *a*, R = Cl; *b*, R = $N(C_2H_5)_2$; *c*, R =  ;

d, R =  ; *e*, R = 

In an attempt at synthesizing the analogue of clonidine we used methods which are usual in the series of analogous 2-imidazoline derivatives[5,13,14]. Benzoyl isothiocyanate, resulting from a reaction of ammonium thiocyanate with benzoyl chloride in acetone, was transformed *in situ* by treatment with 4-amino-*s*-hydrindacene[8] to 1-benzoyl-3-(*s*-hydrindacen-4-yl)thiourea (*VI*) (method, *cf.*[15–17]). Mild alkaline hydrolysis effected the debenzoylation to compound *VII*. A reaction with methyl



VI, R = $CSNHCOC_6H_5$
VII, R = $CSNH_2$
VIII, R = 

TABLE I

Compounds *IIIbcde*— *Vbcde* and their hydrochlorides

Compound	Method (yield, %)	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found			
				% C	% H	% N	% Cl
IIIb	*A* (75)	81—82[a] (hexane)	$C_{18}H_{26}N_2O$ (286·4)	75·47 75·16	9·15 9·12	9·79 9·96	— —
IIIb·HCl		175—176 (ethanol–ether)	$C_{18}H_{27}ClN_2O$ (322·9)	66·95 66·24	8·43 8·28	8·68 8·80	10·98 11·34
IIIc	*A* (88)	151—152[b] (benzene–hexane)	$C_{18}H_{24}N_2O$ (284·4)	76·01 75·65	8·51 8·66	9·85 9·62	— —
IIIc·HCl		254—255 (ethanol–ether)	$C_{18}H_{25}ClN_2O$ (320·9)	67·37 67·03	7·86 7·79	8·73 8·66	11·05 11·19
IIId	*A*[c] (96)	119—120 (benzene–hexane)	$C_{19}H_{26}N_2O$ (298·4)	76·46 76·81	8·79 8·92	9·39 9·19	— —
IIId·HCl		253—254 (aqueous ethanol)	$C_{19}H_{27}ClN_2O$ (334·9)	68·13 68·25	8·13 8·23	8·37 8·39	10·59 10·76
IIIe	*A* (76)	148—149[d] (benzene–hexane)	$C_{18}H_{24}N_2O_2$ (300·4)	71·97 71·22	8·05 7·90	9·33 9·80	— —
IIIe·HCl		220—221 (aqueous ethanol–ether)	$C_{18}H_{25}ClN_2O_2$ (336·8)	64·17 63·80	7·48 7·53	8·32 8·26	10·53 10·75
IVb	*C*[c] (88)	96—97 (hexane)	$C_{19}H_{28}N_2O$ (300·4)	75·94 75·94	9·40 9·23	9·33 9·36	— —
IVb·HCl		229—230 (ethanol–ether)	$C_{19}H_{29}ClN_2O$ (336·9)	67·72 67·22	8·68 8·71	8·32 8·15	10·53 10·37
IVc	*B* (91)	171—172[e] (ethanol)	$C_{19}H_{26}N_2O$ (298·4)	76·45 76·70	8·79 8·88	9·39 9·09	— —
IVc·HCl[f]		184—185 (aqueous ethanol–ether)	$C_{19}H_{27}ClN_2O + 0·5\ H_2O$ (343·9)	66·38 66·94	8·20 8·17	8·14 8·19	10·31 10·61
IVd	*B*[c] (91)	139—140 (ethanol)	$C_{20}H_{28}N_2O$ (312·4)	76·88 76·44	9·03 9·02	8·97 8·82	— —
IVd·HCl		219—220 (ethanol–ether)	$C_{20}H_{29}ClN_2O$ (348·9)	68·84 68·52	8·38 8·53	8·03 7·90	10·16 9·99
IVe	*B* (92)	168—169[g] (ethanol)	$C_{19}H_{26}N_2O_2$ (314·4)	72·56 72·56	8·34 8·40	8·91 8·94	— —
IVe·HCl		228—229 (ethanol–ether)	$C_{19}H_{27}ClN_2O_2$ (350·9)	65·01 65·01	7·76 7·89	7·99 8·07	10·11 10·30

TABLE I
(*Continued*)

Compound	Method (yield, %)	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found			
				% C	% H	% N	% Cl
Vb	*A* (76)	153—154[h] (benzene–hexane)	$C_{19}H_{28}N_2O$ (300·4)	75·94 76·14	9·40 8·94	9·33 9·28	— —
Vb-HCl[i]		182—183 (aqueous ethanol–ether)	$C_{19}H_{29}ClN_2O + H_2O$ (354·9)	64·28 64·36	8·79 8·41	7·92 8·41	10·00 10·59
Vc	*A* (91)	193—194[j] (benzene–hexane)	$C_{19}H_{26}N_2O$ (298·4)	76·45 77·02	8·79 9·00	9·39 9·69	— —
Vc-HCl		242—243 (ethanol–ether)	$C_{19}H_{27}ClN_2O$ (334·9)	68·13 68·58	8·13 8·19	8·37 8·30	10·59 10·62
Vd	*A* (97)	189—190[k] (benzene–hexane)	$C_{20}H_{28}N_2O$ (312·4)	76·88 76·69	9·03 9·00	8·97 8·92	— —
Vd-HCl		216—217 (ethanol–ether)	$C_{20}H_{29}ClN_2O$ (348·9)	68·84 68·73	8·38 8·50	8·03 8·17	10·16 10·15
Ve	*B* (87)	190—191[l] (benzene–hexane)	$C_{19}H_{26}N_2O_2$ (314·4)	72·56 72·67	8·34 8·26	8·91 8·74	— —
Ve-HCl		219—220 (aqueous ethanol)	$C_{19}H_{27}ClN_2O_2$ (350·9)	65·01 64·34	7·76 7·65	7·99 8·18	10·11 10·08

[a] IR spectrum (KBr): 869 (solitary Ar—H), 1 530, 1 660 (NHCO), 3 015, 3 045 (Ar), 3 260 cm^{-1} (NH); ^1H NMR spectrum: δ 9·89 (bs, 1 H, NH), 6·98 (s, 1 H, 8-H), 3·17 (s, 2 H, $COCH_2N$), 2·87 and 2·69 (2 t, 8 H, 4 $ArCH_2$), 2·11 (q, J = 7·0 Hz, 4 H, CH_2NCH_2 in diethylamino), 2·08 (m, 4 H, 2 CH_2 in positions 2 and 6 of hydrindacene), 1·11 (t, J = 7·0 Hz, 6 H, 2 CH_3 of diethylamino). [b] IR spectrum: 861, 890 (solitary Ar—H), 1 533, 1 659, 1 684 (NHCO), 3 010, 3 050 (Ar), 3 240 cm^{-1} (NH); ^1H NMR spectrum: δ 9·69 (bs, 1 H, NH), 6·98 (s, 1 H, 8-H), 3·25 (s, 2 H, $COCH_2N$), 2·80 (m, 8 H, 4 $ArCH_2$), 2·70 (m, 4 H, CH_2NCH_2 of pyrrolidine), 2·05 (m, 4 H, 2 CH_2 in positions 2 and 6 of hydrindacene), 1·80 (m, 4 H, remaining 2 CH_2 of pyrrolidine). [c] See Experimental. [d] IR spectrum (KBr): 862 (solitary Ar—H), 1 120 (ROR), 1 532, 1 650 (NHCO), 3 020, 3 050 (Ar), 3 280 cm^{-1} (NH); ^1H NMR spectrum: δ 8·65 (bs, 1 H, NH), 7·00 (s, 1 H, 8-H), 3·75 (m, 4 H, CH_2OCH_2 of morpholine), 3·14 (s, 2 H, $COCH_2N$), 2·50—3·00 (m, 12 H, 4 $ArCH_2$ and CH_2NCH_2 of morpholine), 2·05 (m, 4 H, 2 CH_2 in positions 2 and 6 of hydrindacene). [e] IR spectrum (KBr): 868 (solitary Ar—H), 1 535, 1 670 (NHCO), 3 019, 3 045 (Ar), 3 248 cm^{-1} (NH); ^1H NMR spectrum: δ 8·52 (bs, 1 H, NH), 6·98 (s, 1 H, 8-H), 3·05 (q, J = 7·0 Hz, 1 H, COCHN), 2·89 and 2·79 (2 t, 8 H, 4-$ArCH_2$), 2·70 (m, 4 H, CH_2. .NCH_2 of pyrrolidine), 2·05 (m, 4 H, 2 CH_2 in positions 2 and 6 of hydrindacene), 1·82 (m, 4 H, remaining 2 CH_2 of pyrrolidine), 1·42 (d, J = 7·0 Hz, 3 H, CH_3 in propionyl). [f] Hemihydrate. [g] IR spectrum: 866 (solitary Ar—H), 1 121 (ROR), 1 552, 1 650 (NHCO), 3 018, 3 045 (Ar), 3 150, 3 185, 3 225 cm^{-1} (NH); ^1H NMR spectrum: δ 8·75 (bs, 1 H, NH), 7·00 (s, 1 H, 8-H),

TABLE I
(*Continued*)

3·80 (t, 4 H, CH_2OCH_2 of morpholine), 3·18 (q, J = 7·0 Hz, 1 H, COCHN), 2·89 and 2·79 (2 t, 8 H, 4 $ArCH_2$), *c.* 2·65 (m, 4 H, CH_2NCH_2 of morpholine), 2·05 (m, 4 H, 2 CH_2 in positions 2 and 6 of hydrindacene), 1·38 (d, J = 7·0 Hz, 3 H, CH_3 in propionyl). [h] IR spectrum (KBr): 869 (solitary Ar—H), 1 550, 1 650 (NHCO), 3 020, 3 050 (Ar), 3 235 cm^{-1} (NH); ^1H NMR spectrum: δ 10·41 (bs, 1 H, NH), 6·98 (s, 1 H, 8-H), 2·89 and 2·79 (2 t, 8 H, 4 $ArCH_2$), 2·80 to 2·90 (m, 2 H, $COCH_2$), *c.* 2·60 (m, 6 H, CH_2NCH_2 in diethylamino and CH_2N in the chain), 2·05 (m, 4 H, 2 CH_2 in positions 2 and 6 of hydrindacene), 1·07 (t, J = 7·0 Hz, 6 H, 2 CH_3 of diethylamino). [i] Monohydrate. [j] IR spectrum: 872, 889 (solitary Ar—H), 1 532, 1 652 (NHCO), 3 018, 3 045 (Ar), 3 260 cm^{-1} (NH); ^1H NMR spectrum: 10·60 (bs, 1 H, NH), 6·99 (s, 1 H, 8-H), 2·89 and 2·79 (2 t, 8 H, 4 $ArCH_2$), 2·80—2·90 (m, 2 H, $COCH_2$), *c.* 2·65 (m, 6 H, CH_2. .NCH_2 of pyrrolidine and CH_2N in the chain), 2·05 (m, 4 H, 2 CH_2 in positions 2 and 6 of hydrindacene), 1·82 (m, 4 H, remaining 2 CH_2 of pyrrolidine). [k] IR spectrum (KBr): 864 (solitary Ar—H), 1 532, 1 650 (NHCO), 3 015, 3 045 (Ar), 3 260 cm^{-1} (NH); ^1H NMR spectrum: δ 10·39 (bs, 1 H, NH), 7·00 (s, 1 H, 8-H), 2·80—2·90 (2 t, and m, 10 H, 4 $ArCH_2$ and $COCH_2$), *c.* 2·60 (m, 6 H, CH_2NCH_2 of piperidine and CH_2N in the chain), 2·05 (m, 4 H, 2 CH_2 in positions 2 and 6 of hydrindacene), 1·55 (bm, 6 H, remaining 3 CH_2 of piperidine). — [l] IR spectrum (KBr): 879 (solitary Ar—H), 1 121 (ROR), 1 530, 1 650 (NHCO), 3 020, 3 040 (Ar), 3 260 cm^{-1} (NH): ^1H NMR spectrum: δ 9·81 (bs, 1 H, NH), 7·00 (s, 1 H, 8-H), 3·75 (m, 4 H, CH_2OCH_2 of morpholine), 2·80—2·90 (2 t and m, 10 H, 4 $ArCH_2$ and $COCH_2$), 2·60 (m, 6 H, CH_2NCH_2 of morpholine and CH_2N in the chain), 2·05 (m, 4 H, 2 CH_2 in positions 2 and 6 of hydrindacene).

iodide in methanol gave the crude isothiuronium salt which was subjected to heating with excessive ethylenediamine. In addition to a great quantity of the recovered 4-amino-*s*-hydrindacene there was obtained in a low yield a further substance whose spectra confirm its identity as the desired imidazoline derivative *VIII*; the analysis indicates that the compound is solvated by a non-stoichiometric quantity of benzene.

The compounds prepared were tested in the form of salts described in the Experimental and in Table I by methods of the pharmacological general screening. According to their solubility in water they were administered either parenterally (*i.v.*) or orally (*p.o.*). The medium lethal doses (LD_{50}) from the tests of acute toxicity in mice and the basic doses D (doses throughout in mg/kg), used in the screening, are given: *IIIb*, *i.v.*, 30, 6; *IIIc*, *i.v.*, 30, 6; *IIId*, *i.v.*, 35, 7; *IIIe*, *p.o.*, 2 000, 300; *IVb*, *i.v.*, 30, 6; *IVc*, *i.v.*., 25, 5; *IVd*, *i.v.*, 35, 7; *IVe*, *i.v.*, 125, 25; *Vb*, *i.v.*, 25, 5; *Vc*, *i.v.*., 35, 7; *Vd*, *i.v.*, 30, 6; *Ve*, *p.o.*, 2 500, 300. Compounds *IIIb*, *IVc* and *Vc* in doses D (after *s.c.* administration) reduce mildly the motility of mice in known surroundings, compound *IIIc*, on the contrary, exhibits a mild excitation. Most of the compounds tested bring about at doses above D first an increase of the activity of mice followed by ataxia, tremor and convulsions. Compound *IIIe* in oral doses of 100—300 mg/kg showed an anticonvulsant effect in mice towards pentetrazole. Only with compounds *IIId*, *IVb* and *IVd* the expected local anaesthetic activity was found. In this line, the most

active one is compound *IIId*, for which in the first stage of screening the medium active concentrations of 0·1 – 0·05% were found in the tests of infiltration anaesthesia (guinea-pigs), as well as of corneal anaesthesia (rabbit's eye). In the second stage of testing the values of 0·1% for infiltration anaesthesia and 0·5% for corneal anaesthesia were found. This indicates that we are dealing here with a substance which is at least 10 times more active than trimecaine (infiltration anaesthesia) and at least twice as active as procaine (corneal anaesthesia). This compound was further tested for antiarrhythmic activity (Dr V. Trčka, pharmacological department of this institute) by estimation of the refractory phase of the electrically stimulated rabbit's heart atria. Its effective concentration $ED_{50} = 5{\cdot}3 \cdot 10^{-8}$ mol ml^{-1}. It is thus practically equipotent with quinidine ($ED_{50} = 0{\cdot}4 \cdot 10^{-8}$ mol ml^{-1}). Grewal and coworkers[18] described a high degree of local anaesthetic activity for N-(2,3,5,6-tetramethylphenyl)-2-pyrrolidinoacetamide which is a structural analogue of our compound *IIIc*.

The compounds were also tested for antimicrobial activity *in vitro* (Dr J. Turinová, bacteriological department of this institute). The microorganisms and the minimum inhibitory concentrations (IC) in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus* β-*haemolyticus*, *IIIb* 25, *IIIc* 50, *IIId* 25, *IIIe* 25, *IVb* 25, *IVc* 50, *IVd* 25, *IVe* 50, *Vb* 50, *Vc* 25, *Vd* 25, *Ve* 25; *Streptococcus faecalis*, *IIIb* 100, *IIIc* 100, *IIId* 100, *IIIe* 100, *Vc* 100, *Vd* 100; *Staphylococcus pyogenes aureus*, *IIId* 50, *IIIe* 100; *Pseudomonas aeruginosa*, *IVb* 50, *IVc* 50, *IVe* 50, *Ve* 50; *Escherichia coli*, *IIId* 50; *Proteus vulgaris*, *IIIb* 50, *IIIc* 50, *IIId* 100, *IIIe* 50, *IVb* 100, *IVc* 100, *IVd* 50, *IVe* 100, *Vb* 50, *Vc* 50, *Vd* 50, *Ve* 50; *Mycobacterium tuberculosis* H37Rv, *IIIb* 50, *IIIc* 50, *IIId* 50, *IIIe* 50, *IVd* 50, *Vd* 50; *Trichophyton mentagrophytes*, *IIIb* 50, *IIIc* 50, *IIId* 50, *IIIe* 50, *IVb* 50, *Vb* 50, *Vc* 50. The IC of all compounds for *Saccharomyces pasterianus*, *Candida albicans* and *Aspergillus niger* are above 50 μg/ml.

EXPERIMENTAL

The melting points were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 60 Pa over P_2O_5 at room temperature or at 77°C. The UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (in Nujol unless stated otherwise) with a Unicam SP 200G spectrophotometer and the ^{1}H NMR spectra (in C^2HCl_3) with a Tesla BS 487C (80 MHz) spectrometer. The mass spectrum was recorded on a MS 902 (AEI) spectrometer. The homogeneity of the compounds was checked by chromatography on thin layers of silica gel.

N-(*s*-Hydrindacen-4-yl)chloroacetamide (*IIIa*)

A stirred mixture of 21·6 g 4-amino-*s*-hydrindacene[8], 100 ml chloroform and 20·7 g K_2CO_3 was trated dropwise over 50 min with a solution of 14·2 g chloroacetyl chloride in 140 ml chloroform and the mixture was refluxed for 90 min. After cooling, 180 ml water was added and the product was extracted with chloroform. The extract was dried with Na_2SO_4 and evaporated; 27·8 g (89%) crude product, m.p. 212–215°C. Analytical sample, m.p. 237–238°C (benzene). IR spectrum: 872 (solitary Ar—H), 1 541, 1 550, **1 678** (NHCO), 3 027, 3 057 (Ar), 3 255 cm^{-1} (NH). For $C_{14}H_{16}ClNO$ (249·7) calculated: 67·34% C, 6·45% H, 14·20% Cl, 5·60% N; found: 67·40% C, 6·33% H, 14·35% Cl, 5·58% N.

N-(*s*-Hydrindacen-4-yl)-2-chloropropionamide (*IVa*)

The reaction of 21·6 g 4-amino-*s*-hydrindacene[8] with 19·0 g 2-chloropropionyl chloride[10,11] in 230 ml chloroform in the presence of 20·7 g K_2CO_3 was carried out similarly like in the preceding case and the mixture similarly processed; 19·3 g (59%), m.p. 208–210°C. Analytical sample, m.p. 218–219°C (dioxane). IR spectrum: 875 (solitary Ar—H), 1 550, **1 670** (NHCO), 3 020, 3 053 (Ar), 3 253 cm^{-1} (NH). For $C_{15}H_{18}ClNO$ (263·8) calculated: 68·30% C, 6·88% H, 13·44% Cl, 5·31% N; found: 68·29% C, 7·06% H, 13·30% Cl, 5·46% N.

N-(*s*-Hydrindacen-4-yl)-3-chloropropionamide (*Va*)

A similar reaction of 21·6 g 4-amino-*s*-hydrindacene[8] with 19·0 g 3-chloropropionyl chloride[12] and 20·7 g K_2CO_3 in 230 ml chloroform gave 32·1 g (97%) crude *Va*, m.p. 201–204°C. Analytical sample, m.p. 211–212°C (ethanol). IR spectrum: 879 (solitary Ar—H), 1 550, **1 670** (NHCO), 3 020, 3 050 (Ar), 3 250 cm^{-1} (NH). For $C_{15}H_{18}ClNO$ (263·8) calculated: 68·30% C, 6·88% H, 13·44% Cl, 5·31% N; found: 67·91% C, 6·79% H, 13·19% Cl, 5·44% N.

N-(*s*-Hydrindacen-4-yl)-2-piperidinoacetamide (*IIId*) (Method *A*)

A mixture of 7·0 g *IIIa*, 280 ml benzene and 5·2 g piperidine was refluxed for 8 h. After cooling the precipitated piperidine hydrochloride (3·0 g) was filtered off, the filtrate was washed with water, dried with Na_2SO_4 and evaporated; 8·0 g (96%) crude product, m.p. 89–92°C (hexane). Analytical sample, m.p. 119–120°C (benzene–hexane). IR spectrum: 865 (solitary Ar—H), 1 529, **1 651** (NHCO), 3 298 cm^{-1} (NH). ^1H NMR spectrum: δ 8·85 (bs, 1 H, NH), 6·98 (s, 1 H, 8-H), 3·08 (s, 2 H, $COCH_2N$), *c.* 2·80 (m, 8 H, 4 $ArCH_2$), 1·60, 2·08 and 2·55 (3 m, 14 H, 5 CH_2 of piperidine and 2 CH_2 in positions 2 and 6 of hydrindacene). Hydrochloride, m.p.253–254°C (aqueous ethanol). The analyses in Table I.

N-(*s*-Hydrindacen-4-yl)-2-piperidinopropionamide (*IVd*) (Method *B*)

A mixture of 6·1 g *IVa* and 15 ml piperidine was refluxed for 5 h (bath temperature 130–150°C). It was then poured into 150 ml water, the separated product was filtered, washed with water and dried *in vacuo*; 6·50 g (91%), m.p. 122–124°C. Analytical sample, m.p. 139–140°C (ethanol). IR spectrum (KBr): 863 (solitary Ar—H), 1 552, **1 652** (NHCO), 3 020, 3 050 (Ar), 3 192, 3 228 cm^{-1} (NH). ^1H NMR spectrum: δ 9·00 (bs, 1 H, NH), 7·00 (s, 1 H, 8-H), 3·20 (q, J = 7·0 Hz, 1 H, COCHN), 2·89 and 2·79 (2 t, 8 H, 4 $ArCH_2$), *c.* 2·60 (m, 4 H, CH_2NCH_2 in piperidine), 2·05 (m, 4 H, 2 CH_2 in positions 2 and 6 of hydrindacene), 1·65 (m, 6 H, remaining 3 CH_2 of piperidine), 1·32 (d, J = 7·0 Hz, 3 H, CH_3). Hydrochloride, m.p. 219–220°C (ethanol–ether). Analyses of *IVd* and its hydrochloride, *cf.* Table I.

N-(*s*-Hydrindacen-4-yl)-2-diethylaminopropionamide (*IVb*) (Method *C*)

A mixture of 6·5 g *IVa* and 15 ml diethylamine was heated for 5 h to 140–150°C in an autoclave. Similar processing like in the preceding case gave 6·2 g (88%) crude *IVb*, m.p. 70–73°C. Analytical sample, m.p. 96–97°C (hexane). IR spectrum (KBr): 863 (solitary Ar—H), 1 549, **1 650** (NHCO), 3 021, 3 050 (Ar), 3 230 cm^{-1} (NH). ^1H NMR spectrum: δ 9·05 (bs, 1 H, NH), 7·00 (s, 1 H, 8-H), 3·51 (q, J = 7·0 Hz, 1 H, COCHN), 2·89 and 2·79 (2 t, 8 H, 4 $ArCH_2$), 2·60 (m, 4 H, CH_2NCH_2 in diethylamino), 2·05 (m, 4 H, 2 CH_2 in positions 2 and 6 of hydrindacene), 1·32 (d, J = 7·0 Hz, 3 H, CH_3 in propionyl), 1·11 (t, J = 7·0 Hz, 6 H, 2 CH_3 in diethylamino). Hydrochloride, m.p. 229–230°C (ethanol–ether). The analyses in Table I.

1-Benzoyl-3-(*s*-hydrindacen-4-yl)thiourea (*VI*)

A solution of 6·0 g NH_4SCN in 25 ml acetone was stirred and treated over 15 min with 9·4 g benzoyl chloride, added dropwise. The mixture was refluxed for 5 min, the heating was then discontinued and a warm solution of 11·5 g 4-amino-*s*-hydrindacene[8] in 35 ml acetone was slowly added which maintained the mixture in refluxing. The mixture was stirred for 10 min and poured into 500 ml cold water. After 1 h standing the precipitated yellow crystals were filtered, washed with water and dried *in vacuo*; 20·0 g (90%) crude product, m.p. 177–179°C. Analytical sample, m.p. 194–195°C (ethanol). UV spectrum: λ_{max} 243 nm (log ε 4·29), 276 nm (4·26). IR spectrum: 670, 721, 874 (5 adjacent and solitary Ar—H), 1 520 (N—C=S), 1 565, 1 603, 3 020, 3 060 (Ar), 1 676 (ArCONH), 3 150, 3 200, 3 225 cm^{-1} (NH). For $C_{20}H_{20}N_2OS$ (336·4) calculated: 71·40% C, 5·99% H, 8·33% N, 9·53% S; found: 71·31% C, 6·06% H, 8·46% N, 9·76% S.

N-(*s*-Hydrindacen-4-yl)thiourea (*VII*)

A mixture of 14·6 g *VI* and 150 ml 10% NaOH was stirred and refluxed for 20 min. After cooling the precipitate was filtered, washed with water and dried *in vacuo*; 13·2 g (96%), m.p. 229–230°C (ethanol). UV spectrum: λ_{max} 248 nm (log ε 4·05), inflexes at 275 nm (3·86) and 283 nm (3·76). IR spectrum: 881 (solitary Ar—H), 1 520 (N—C=S), 1 618 ($CSNH_2$), 3 160, 3 220, 3 250, 3 420 cm^{-1} (NH, NH_2). For $C_{13}H_{16}N_2S$ (232·3) calculated: 67·20% C, 6·94% H, 12·06% N, 13·80% S; found: 67·69% C, 6·91% H, 11·72% N, 13·60% S.

2-(*s*-Hydrindacen-4-ylamino)-2-imidazoline (*VIII*)

A mixture of 13·0 g *VII*, 6·5 ml methyl iodide and 200 ml methanol was refluxed for 3 h. The solution was evaporated *in vacuo* at 70°C and the residue (20·7 g, 99%, S-methylisothiuronium iodide) was heated with 6·5 ml anhydrous ethylenediamine under reflux to 135–145°C for 1 h. After cooling the mixture was diluted with a solution of 45 ml acetic acid in 230 ml water and the suspension obtained was made alkaline with 20% NaOH. The precipitate was filtered, washed with water and extracted with ether. The undissolved material was discarded and the extract was evaporated. The residue crystallized from a mixture of hexane, benzene and ethanol; 3·8 g, m.p. 89–90°C. The substance was identified as 4-amino-*s*-hydrindacene (lit.[8], m.p. 87–88°C). The mother liquor was chromatographed on 400 g Al_2O_3 (neutral, activity II). Chloroform with 5% ethanol eluted first 2·1 g 4-amino-*s*-hydrindacene (m.p. 87–90°C). Elution with chloroform with 15% ethanol yielded 1·05 g (7%) a substance which crystallized from a mixture of ether and hexane and then from benzene, m.p. 210–211°C. It was identified as *VIII* solvated with 1/3 C_6H_6. Mass spectrum, *m/z*: 241·158 (M^+ corresponding to $C_{15}H_{19}N_3$). IR spectrum (KBr): 843 (solitary Ar—H), 1 473, 1 572 (Ar), 1 639, 1 695 (C=N), 3 145, 3 390 cm^{-1} (NH). ^1H NMR spectrum: δ 7·20 (s, 1 H, ArNH), 6·72 (s, 1 H, 8-H), 4·90 (bs, 1 H, NH in the imidazoline ring), 3·38 (s, 4 H, NCH_2CH_2N), 2·80 and 2·72 (2 t, 8 H, $ArCH_2$), 2·00 (m, 4 H, 2 CH_2 in positions 2 and 6 of hydrindacene). For $C_{15}H_{19}N_3 + 1/3\ C_6H_6$ (267·4) calculated: 76·37% C, 7·92% H, 15·72% N; found: 75·68% C, 7·98% H, 15·85% N.

The authors are indebted to Drs E. Svátek and M. Ryska and Mrs A. Hrádková for recording and interpreting the UV, IR *and* MS *spectra (physico-chemical department of this institute), to Mr L. Tůma for technical assistance with the syntheses, and to Mrs J. Komancová, Mrs V. Šmídová, Mrs J. Kropáčová and Mr M. Čech (analytical department of this institute) for carrying out the analyses.*

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Translated by the author (M. P.).