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

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s-Hydrindacen-1-one (*I*) was converted to oxime *II* which was O-aminoalkylated to derivatives *III* and *IV*. Reduction of ketone *I* led to alcohol *V* which reacted with thionyl chloride to the unstable chloride *VI*. Its reaction with 1-methylpiperazine resulted in a minute amount of amine *VII*. Reduction of oxime *II* with sodium and ethanol yielded 1-amino-*s*-hydrindacene (*IX*) which was methylated to the dimethylamino derivative *VIII*. Acylation reactions of amine *IX* led to amides *X*—*XIV*, the last of which was condensed with N-benzylisopropylamine, pyrrolidine, piperidine, morpholine, 1-methylpiperazine and 1-phenylpiperazine, to amides *XV*—*XX*. Reduction of amides with lithium aluminium hydride led to amines *XXI*—*XXVI*. Reaction of ketone *I* with methylmagnesium iodide and subsequent dehydration led to olefin *XXVII*. While the amides are at higher doses centrally depressant the amines and the diamines are generally central stimulants. With many compounds (amines, basic oximes and basic amides) structurally nonspecific neurotropic effects were observed, in particular a locally anaesthetic and a spasmolytic one.

A special position among neurotropic and psychotropic agents is held by amines derived from tricyclic systems[1-3]. Mainly the linearly condensed tricyclic systems were studied where the outside rings are aromatic or heteroaromatic while the central ring is 5—7-membered, heterocyclic or alicyclic. The amino group is usually attached to the carbon or nitrogen of the central ring through a side chain, in some cases it is attached directly to the central ring carbon[4], rarely to an outside ring carbon[5]. In this situation we thought it useful to attempt to find neurotropic agents among amines derived from tricyclic systems which, in contrast with the above, contain an aromatic central ring while the outside rings are either alicyclic or partly saturated heterocyclic. The first object of a more systematic approach was *s*-hydrindacene (1,2,3,5,6,7-hexahydrocyclopent[*f*]indene, RRI 2551), the chemistry of which is rather little known and which lies in a region untouched by pharmacological studies.

For the present purposes the most suitable starting compound was *s*-hydrindacen-1-one (*I*), the preparation of which was described either *via* cyclization of 3-(5-in-

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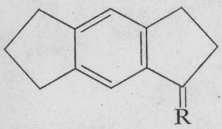
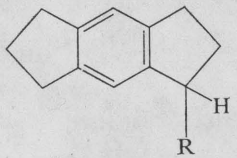
danyl)propionyl chloride with stannic[6] or aluminium[7] chloride or of the free acid with polyphosphoric acid[8], or *via* cyclization of 5-(3-chloropropionyl)indane with sulfuric acid[9]. In both cases the process is accompanied by the formation of a small amount of the isomeric ketone from the *as*-hydrindacene series, *i.e.* in the first case *as*-hydrindacen-1-one[7,8] (see also[10]), in the second *as*-hydrindacen-3-one[11] which are mostly removed during crystallization of the crude ketone *I*. For the synthesis of larger amounts of ketone *I* we used the path *via* 5-(3-chloropropionyl)-indane[9], the preparation of which was modified, obtaining a substantially greater yield than reported in the literature[9]. Moderation of the reaction conditions during the cyclization step resulted in greater yields of ketone *I*.

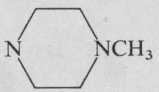
Ketone *I* was converted to oxime II which was alkylated with 2-dimethylamino-ethyl chloride and 3-dimethylaminopropyl chloride in dimethylformamide (metallation with sodium ethoxide) (method *A*) and yielded the basic oximes *III* and *IV* which were isolated and characterized as hydrochlorides. Reduction of ketone *I* with lithium aluminium hydride in a mixture of ether and benzene resulted in alcohol *V* which was further treated by a reaction with thionyl chloride in benzene at room temperature. The expected chloride *VI* could not be obtained in the pure state. Using the crude product, an attempt at a substitution reaction was done with excess 1-methylpiperazine in boiling benzene. The desired reaction took place in a small extent only and hence 1-(*s*-hydrindacen-1-yl)-4-methypiperazine (*VII*) was obtained in a low yield and was isolated as hydrochloride. The principal reaction apparently proceeds *via* elimination which yields the corresponding conjugated olefin which, like indene[12], polymerizes to tar products.



I, R = O
II, R = NOH
III, R = $NO(CH_2)_2N(CH_3)_2$
IV, R = $NO(CH_2)_3N(CH_3)_2$



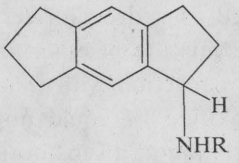
V, R = OH
VI, R = Cl

VII, R = 

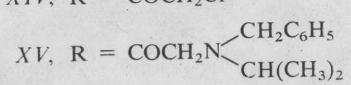
VIII, R = $N(CH_3)_2$

Reduction of oxime *II* with sodium and ethanol yielded solid 1-amino-*s*-hydrindacene (*IX*) which was converted *via* reaction with formaldehyde and formic acid to the N,N-dimethyl derivative *VIII*. Heating of amine *IX* with excess ethyl formate led to the formyl derivative *X*. The reaction can be conducted in an autoclave at 120°C but it proceeds at sufficient rate even on refluxing the mixture. Amine *IX* was acylat-

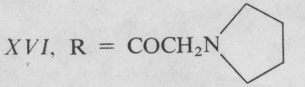
ed with acetyl chloride, isovaleroyl chloride and benzoyl chloride in pyridine (method *B*) to amides *XI*–*XIII*. Acylation of amine *IX* with chloroacetyl chloride in benzene in the presence of potassium carbonate resulted in amide *XIV* which reacted with N-benzylisopropylamine[13]. pyrrolidine, piperidine, morpholine, 1-methylpiperazine and 1-phenylpiperazine[14]. In the first case the reaction of chloroacetamide *XIV* with two equivalents of N-benzylisopropylamine was conducted in boiling dimethylformamide. In all the other cases, reactions of amide *XIV* with two equivalents of the above amines proceeded satisfactorily in boiling benzene (method *C*). Amides *X*–*XIII*, *XVII* and *XX* were reduced with lithium aluminium hydride in a mixture of ether and benzene (method *D*) to amines *XXI*–*XXVI*. All the amines and basic amides prepared were converted to crystalline hydrochlorides for characterization and pharmacological testing.



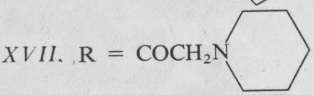
IX, R = H
X, R = CHO
XI, R = $COCH_3$
XII, R = $COCH_2CH(CH_3)_2$
XIII, R = COC_6H_5
XIV, R = $COCH_2Cl$



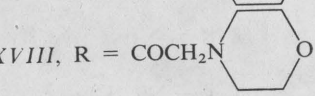
XV, R = $COCH_2N(CH_2C_6H_5)CH(CH_3)_2$



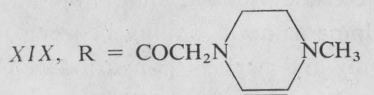
XVI, R = $COCH_2N$



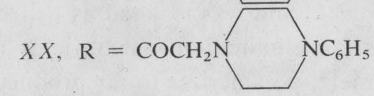
XVII, R = $COCH_2N$



XVIII, R = $COCH_2N$O

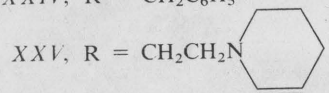


XIX, R = $COCH_2N$NCH$_3$

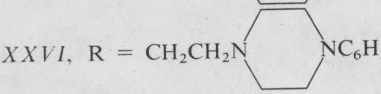


XX, R = $COCH_2N$NC$_6$H$_5$

XXI, R = CH_3
XXII, R = CH_2CH_3
XXIII, R = $(CH_2)_2CH(CH_3)_2$
XXIV, R = $CH_2C_6H_5$



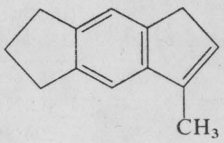
XXV, R = CH_2CH_2N



XXVI, R = CH_2CH_2NNC$_6$H$_5$

Reaction of ketone *I* with methylmagnesium iodide in a mixture of ether and benzene and subsequent decomposition with a solution of ammonium chloride yielded a nonhomogeneous product with the nonpolar component (a hydrocarbon) markedly predominating over the polar one (a tertiary alcohol). Chromatography on alumina led to isolation of the nonpolar product in a pure state – using NMR spectrum, it was identified as 1-methyl-3,5,6,7-tetrahydro-*s*-indacene (*XXVII*). An attempt

to convert the polar fraction (alcohol) present in the crude product to hydrocarbon *XXVII* by an acid-catalyzed dehydration (*4*-toluenesulfonic acid) was unsuccessful as the whole mixture polymerized.



XXVII

All the amines and amides prepared are summarized in Table I, including all the usual experimental data. If the compounds were prepared by a uniform method (methods *A* – *D*), only examples of the methods used are shown in the experimental section.

The compounds prepared were evaluated biologically by methods of general pharmacological screening, the results being shown in Table II. The toxicity is very low with the poorly soluble amides which were applied *per os* (incomplete resorption from the digestive tract cannot be excluded). On the other hand, toxicity is rather high with the soluble amine hydrochlorides which were applied intravenously, the maximum being reached with the dimethylamine derivative *VIII*. The central neurotropic effects are generally slight. A depressant effect is observed only at high doses with oxime *II* and with amides *X*, *XI*, *XVI*, *XVII* and *XX*. In no case was it reflected in an incoordinating effect in the rotating-rod test. On the other hand, in some cases, a potentiation of thiopental sleep (*II*, *X*) was observed which is particularly pronounced with the basic oxime *IV*, and further a hypothermic effect (*II*, *IV*, *X*, *XI*). Only formamide *X* displayed an anticonvulsant activity in the electroshock test but the compound is ineffective against pentetrazol convulsions. The basic amides *XVIII* and *XIX* and the amines *III*, *VIII*, *IX*, *XXI*–*XXIV* show at high doses a short-lived stimulant effect. An antireserpine effect was observed only with the basic oxime *IV* in the test of antagonization of reserpine hypothermia. In the ptosis test the compound is ineffective. An anorectic activity was found with the methylamino derivative *XXI*.

Many amine salts displayed further structurally little specific neurotropic effects: a local anaesthetic effect (*XV*–*XVII*, *XXIII*–*XXVI*), a slight spasmolytic activity toward acetylcholine *in vitro* (*IX*, *XVI*, *XVII*, *XXV*, *XXVI*) and especially toward barium chloride (*III*, *XV*–*XVII*, *XXIII*–*XXV*). Only exceptionally did the compound affect blood pressure of normotensive rats (brief drops after *IV*, *XI* and *XV*). On the other hand, many of the substances were negatively inotropic (*III*, *VIII*, *IX*, *XVI*–*XVIII*, *XXI*, *XXII*, *XXIV*, *XXVI*) accompanied in a single case by a negatively chronotropic effect (*XVII*), in several cases by a positively chronotropic effect

TABLE I

1-Substituted *s*-Hydrindacenes

Compound	Method (yield, %)	B.p., °C/Torr or m.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found			
				% C	% H	% N	% Cl
III-HCl	*A*[a] (73)	214—215 (ethanol)	$C_{16}H_{23}ClN_2O$ (294·8)	65·17 64·74	7·87 7·70	9·50 9·37	12·03 11·94
IV-HCl[b]	A (78)	188—191[c] (ethanol–ether)	$C_{17}H_{26}ClN_2O_{1.5}$ (317·8)	64·24 64·50	8·25 8·43	8·81 8·60	11·15 11·41
VII-2HCl	[a]	216—217 (ethanol)	$C_{17}H_{26}ClN_2$ (329·3)	61·99 61·76	7·96 8·05	8·51 8·48	21·54 21·40
VIII-HCl	[a]	205—206 (ethanol–ether)	$C_{14}H_{20}ClN$ (237·8)	70·72 70·45	8·48 8·63	5·89 5·95	14·91 15·14
IX-HCl	[a]	270 decomp. (water)	$C_{12}H_{16}ClN$ (209·7)	68·72 69·05	7·69 8·26	6·68 6·66	16·91 16·65
IX-HS[d]	[a]	210—212 (aqueous ethanol)	$C_{12}H_{17}NO_{2.5}S_{0.5}$ (231·3)	62·30 61·74	7·41 7·58	6·06 6·48	6·93[e] 6·78
X	[a]	139—140 (benzene)	$C_{13}H_{15}NO$ (201·3)	77·58 77·18	7·51 7·64	6·96 6·75	— —
XI	*B*[a] (94)	184—185 (benzene)	$C_{14}H_{17}NO$ (215·3)	78·10 78·22	7·96 8·08	6·50 6·49	— —
XII	*B* (83)	139—140 (benzene–hexane)	$C_{17}H_{23}NO$ (257·4)	79·32 79·11	9·02 9·55	5·44 5·37	— —
XIII	*B* (94)	180—182 (ethanol)	$C_{19}H_{19}NO$ (277·4)	82·26 81·80	6·92 6·45	5·05 4·98	— —
XIV	[a]	182—183 (ethanol)	$C_{14}H_{16}ClNO$ (249·7)	67·33 67·31	6·45 6·68	5·61 5·51	14·20 14·50
XV	[a]	81—82 (hexane)	$C_{24}H_{30}N_2O$ (362·5)	79·50 79·14	8·35 8·82	7·73 7·64	— —
XV-HCl[f]	—	56—58 (ethanol–ether)	$C_{24}H_{33}ClN_2O_2$ (417·0)	69·12 68·50	7·99 7·92	6·69 6·32	8·51 8·78
XVI	*C*[a]	92—93 (hexane)	$C_{18}H_{24}N_2O$ (284·4)	76·01 76·01	8·51 8·30	9·85 9·38	— —
XVI-HCl	—	179—180 (ethanol–ether)	$C_{18}H_{25}ClN_2O$ (320·8)	67·37 67·18	7·86 7·80	8·73 8·77	11·05 11·09
XVII	*C* (97)	82—83[g] (hexane)	$C_{19}H_{26}N_2O$ (298·4)	76·45 76·20	8·79 8·83	9·40 9·31	— —
XVII-HCl	—	181—182 (ethanol–ether)	$C_{19}H_{27}ClN_2O$ (334·9)	68·13 67·44	8·13 8·59	8·37 8·11	10·59 10·39

TABLE I
(Continued)

Compound	Method (yield, %)	B.p., °C/Torr or m.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found			
				% C	% H	% N	% Cl
XVIII-HCl	*C*	180–182	$C_{18}H_{25}ClN_2O_2$	64·17	7·48	8·32	10·53
	(93)	(ethanol–ether)	(336·8)	63·93	7·68	8·30	10·29
XIX-2HCl	*C*	209–211	$C_{19}H_{29}Cl_2N_3O$	59·05	7·57	10·88	18·36
	(90)	(ethanol–ether)	(386·4)	59·88	7·61	10·93	18·39
XX	*C*[h]	175–176[i]	$C_{24}H_{29}N_3O$	76·76	7·79	11·19	—
	(79)	(benzene– hexane)	(375·5)	76·80	7·66	10·69	—
XX-HCl	—	144–145	$C_{24}H_{30}ClN_3O$	69·97	7·34	10·20	8·61
		(ethanol–ether)	(412·0)	69·46	7·46	9·83	8·44
XXI-HCl	*D*[a]	112–115	$C_{13}H_{18}ClN$	69·79	8·11	6·26	15·84
	(91)	(ethanol–ether)	(223·6)	69·36	8·52	6·08	15·68
XXII	*D*	120–122/1	—	—	—	—	—
	(87)						
XXII-HCl	—	160–161	$C_{14}H_{20}ClN$	70·72	8·48	5·89	14·91
		(ethanol–ether)	(237·8)	70·43	8·85	5·87	15·04
XXIII	*D*	163–165/1	—	—	—	—	—
	(93)						
XXIII-HCl	—	166–167	$C_{17}H_{26}ClN$	72·95	9·37	5·01	12·67
		(ethanol–ether)	(279·8)	72·67	9·77	4·88	12·78
XXIV	*D*	190–192/1	$C_{19}H_{21}N$	86·64	8·04	5·32	—
	(96)		(263·4)	85·82	8·45	5·07	—
XXIV-HCl	—	173–175	$C_{19}H_{22}ClN$	76·09	7·41	4·67	11·83
		(ethanol–ether)	(299·8)	75·51	7·33	4·59	11·98
XXV-2HCl[b]	*D*[j]	213–214	$C_{19}H_{31}Cl_2N_2O_{0.5}$	62·29	8·53	7·65	19·35
	(92)	(ethanol–ether)	(366·4)	62·47	8·69	7·64	19·21
XXVI-2HCl[b]	*D*[j] [k]	204–205	$C_{24}H_{34}Cl_2N_3O_{0.5}$	64·98	7·74	9·48	16·00
		(ethanol–ether)	(443·5)	64·35	7·87	9·40	15·95

[a] See the experimental section. [b] Hemihydrate. [c] IR spectrum: 868 (solitary Ar—H), 1635 (N=C), 2465, 2565 (NH^+), 3460 cm^{-1} (H_2O). [d] Hemisulfate, hemihydrate. [e] Content of sulfur. [f] Monohydrate. [g] IR spectrum (Nujol): 870 (solitary Ar—H), 1520, 1650, 1690 (NHCO), 3250 cm^{-1} (NH); ^{1}H-NMR spectrum: δ 7·45 (bs, 1 H, NH), 7·08 (s, 2 H, aromatic protons), 5·40 (m, 1 H, Ar—CH—N), 2·95 (s, 2 H, $COCH_2N$), 1·20–2·90 (m, 10 CH_2). [h] In this case the crude reaction mixture was not washed with water but filtered to remove the precipitated phenylpiperazine hydrochloride; the filtrate was then processed as described for the preparation of *XVI*. [i] IR spectrum: 698, 767, 874 (5 adjacent and solitary Ar—H), 1500, 1582, 1602 (Ar), 1525, 1654 (NHCO), 3280 cm^{-1} (NH); ^{1}H-NMR spectrum: δ 6·50–7·40 (m, 8 H, NH and aromatic protons), 5·35 (m, 1 H, Ar—CH—N), 1·50–3·30 (m, 10 CH_2). [j] The base was not distilled but converted to the salt directly in the crude state. [k] Yield of crude base was almost theoretical.

TABLE II

Biological Properties of 1-Substitution Derivatives of *s*-Hydrindacene

Compound (VÚFB-Code No)	Way of application[a]	LD_{50}[b] mg/kg	D[c] mg/kg	CNS[d] effects	Other neurotropic	Cardiovascular	Other pharmacodynamic	Antimicrobial[e]
II (10·095)	*p.o.*	2 500	300	*f,g,h*	—	—	—	—
III-HCl (10·096)	*i.v.*	50	10	*i*	*j,k*	*l*	—	—
IV-HCl[m] (10·097)	*p.o.*	750	150	*n,o,p*	*q*	*r*	—	—
VIII-HCl (10·102)	*i.v.*	15	3	*s*	*t*	*u*	—	—
IX-HCl (10·072)	*i.v.*	35	7	*s*	*v*	*u*	*w*	—
X (10·093)	*p.o.*	2 000	300	*f,o,x,y*	*z*	—	*aa*	—
XI (10·103)	*p.o.*	2 500	300	*f,h*	*bb*	*r*	—	—
XII (10·544)	*p.o.*	>2 500	300	—	—	—	—	*cc*
XIII (10·094)	*p.o.*	>2 500	300	—	—	—	—	—
XIV (10·098)	*p.o.*	>2 500	300	*x*	—	—	—	—
XV-HCl[dd] (10·052)	*i.v.*	62·5	12	—	*k,ee*	*ff,gg*	—	*cc,hh*
XVI-HCl (10·550)	*i.v.*	50	10	*f*	*k,v,ii*	*jj*	*kk*	*cc*
XVII-HCl (10·551)	*i.v.*	50	10	*f*	*k,v,ii*	*ll*	*kk*	*cc*
XVIII-HCl (10·099)	*i.v.*	87·5	15	*i*	—	*u*	—	—
XIX-2 HCl (10·100)	*i.v.*	100	20	*i*	—	—	—	—
XX-HCl (10·547)	*p.o.*	>2 500	300	*f*	—	—	—	*cc*
XXI-HCl (10·101)	*i.v.*	25	5	*s,mm*	—	*jj*	*nn*	—
XXII-HCl (10·104)	*i.v.*	20	4	*i*	—	*l*	—	—

TABLE II
(Continued)

Compound (VÚFB-Code No)	Way of application[a]	LD_{50}[b] mg/kg	D[c] mg/kg	CNS[d] effects	Other neurotropic	Cardiovascular	Other pharmacodynamic	Antimicrobial[e]
XXIII-HCl (10·553)	*i.v.*	17·5	3	*i*	*k,ii*	—	—	*cc,oo*
XXIV-HCl (10·105)	*i.v.*	25	5	*s*	*j,k,ee*	*pp*	—	—
XXV-2 HCl[m] (10·549)	*i.v.*	25	5	—	*k,v,ee*	—	—	*cc*
XXVI-2 HCl[m] (10·545)	*i.v.*	35	7	—	*j,v,ii*	*jj*	—	*cc*

[a] *p.o. per os*, *i.v.* intravenously, *s.c.* subcutaneously, *i.p.* intraperitoneally. [b] Orientative value of the mean lethal dose determined in mice. [c] Dose at which the compound was applied *in vivo*. [d] The basic idea about a central neurotropic effect of compounds follows from observations of mice in acute toxicity tests when doses greater than D are also used. [e] If numerical values are shown, the minimum inhibitory concentrations in μg/ml *in vitro* are meant. [f] At a dose greater than D mouse motility is inhibited. [g] At a dose of 50—100 mg/kg *p.o.* it prolongs thiopental sleep of mice to twice the control value. [h] At a dose of 100—300 mg/kg *p.o.* it decreases the rectal temperature of rats by 1°C. [i] At a dose greater than D it has a brief excitatory effect on mice (it increases motility). [j] In the test of infiltration anaesthesia in guinea pigs it is effective at concentrations of 1% or more. [k] In an isolated rat duodenum it inhibits barium chloride contractions by 50% at 10 μg/ml. [l] In an isolated rabbit atrium it decreases inotropy by 25% at 10—25 μg/ml, while frequency is unaffected. [m] Hemihydrate. [n] Like *g* at a dose of 2·5 mg/kg *p.o.* [o] Like *h* at a dose of 25—50 mg/kg *p.o.* [p] At a dose of 150 mg/kg it antagonizes the hypothermic effect of reserpine in mice but it does not affect ptosis. [q] At a dose of 25—50 mg/kg *p.o.* it causes mouse miosis amounting to 30%. [r] At dose D it depresses blood pressure of normotensive rats by 10%. [s] Like *i*, but at dose D applied *s.c.* [t] At doses greater than 30 mg/kg *i.v.* (respiratory pump) it has a myorelaxing effect on rat gastrocnemius muscle. [u] Like *l*, but at 25—50 μg/ml. [v] In an isolated rat duodenum it inhibits acetylcholine contractions by 50% at 10 μg/ml (weaker than adiphenin). [w] At a dose of 35 mg/kg *p.o.* it increases the diuresis of mice by 100% as compared with the control. [x] Like *g* but at dose D. [y] At doses above D it has an anticonvulsant effect in the electroshock test in mice; it is ineffective against pentetrazol convulsions. [z] Like *q*, but at 100—300 mg/kg. [aa] At a dose lower than D it increases the blood sugar level in rats by 20%. [bb] Like *q*, but at a dose higher than D. [cc] It inhibits the growth of (concentrations shown): *Saccharomyces pasterianus* 100, *Trichophyton mentagrophytes* 50, *Candida albicans* 100, *Aspergillus niger* 100. [dd] Monohydrate. [ee] At 1% concentration, it has a locally anaesthetic effect in a test of corneal anaesthesia in rabbits (with 50% animals). [ff] Like *r*, the pressure drop being deep and brief and accompanied by pronounced bradycardia. [gg] At a dose of 12 mg/kg *i.p.* it extends with statistical significance the survival of mouse myocard during asphyxia. [hh] It inhibits the growth of the following microorganisms (concentrations are shown): *Streptococcus* β-*haemolyticus* 12·5, *Streptococcus faecalis* 12·5, *Staphylococcus pyogenes aureus* 12·5. [ii] Like *ee*, but at 0·1—0·5% concetration (it irritates

TABLE II

(*Continued*)

in the case of XVI). [jj] Like *u* but it increases frequency by 25%. [kk] Like *aa* but at 50 mg/kg *p.o.* [ll] Like *u* but it decreases frequency. [mm] It has an anorectic effect in mice; at 25 mg/kg *p.o.* it decreases food uptake as compared with control by 50%. [nn] Like *w* but at 10—25 mg/kg *p.o.* [oo] It inhibits the growth of *Mycobacterium tuberculosis* H37Rv at 25 μg/ml. [pp] Like *l* but it increases frequency.

(*XVI*, *XXI*, *XXIV*, *XXVI*). Among other effects one should mention a diuretic one (*IX*, *XXI*) and a hyperglycemic one (*X*, *XVI*, *XVII*)

The compounds prepared were further evaluated by Dr J. Turinová and Dr A. Čapek (bacteriological department of this institute) using *in vitro* tests, for their antimicrobial activity toward a standard set of microorganisms. Most of the compounds were found to be ineffective, several of them are inhibitory toward yeasts and lower fungi (*XII*, *XV—XVII*, *XX*, *XXIII*, *XXV*, *XXVI*); a rather singular effect is that against cocci (*XV*) and mycobacteria (*XXIII*). Most of the compounds prepared were tested in the Research Institute for Biofactors and Veterinary Drugs at Pohoří—Chotouň (director Dr B. Ševčík) for their anthelminthic and coccidiostatic activity. While in the first direction they were all ineffective, a number of them showed signs (*II*, *VIII—X*, *XII*, *XIII*, *XXIII*, *XXV*) of a coccidiostatic effect (tested in chicks infected with oocysts of *Eimeria tenella*), the effect being quite pronounced with two of the compounds (*XXI*, *XXVI*).

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 spectrum (in methanol) was recorded in a Unicam SP-700 spectrophotometer, IR spectra (in KBr unless stated otherwise) were recorded in a Unicam SP 200G spectrophotometer and ^{1}H-NMR spectra (in $CDCl_3$) in a Zeiss Jena ZKR 60 spectrometer. The homogeneity of compounds was tested chromatographically on thin layers of silica gel. The analyses of the amides, amines and salts prepared are shown in Table I. Compounds *V—XXVI* are racemates.

5-(3-Chloropropionyl)indane

Aluminium chloride (376 g) was added under stirring at about 0°C over a period of 3 h to a solution of 300 g indane (b.p. 73—75°C/10—12 Torr; prepared by hydrogenation of indene on Raney nickel at 100°C and initial pressure of 50 atm. H_2; see ref.[15]) and 323 g 3-chloropropionyl chloride[16] in 1 850 ml thiophene-free benzene. The mixture was stirred for 20 min under cooling, then for 4 h at room temperature, left to stand overnight and decomposed by pouring into a mixture of 3·5 kg ice and 700 ml hydrochloric acid. The benzene layer was separated and the aqueous one was extracted with benzene. The benzene fractions were washed with dilute hydrochloric acid and water, dried with Na_2SO_4 and evaporated. The residue (470—500 g, 89—95%, depending of batch) melted at 62—65°C and was used without purification for the next step. Reference[9] described the reaction in nitromethane with a yield of 74%; for a pure product a m.p. of 68 to 69°C has been reported.

s-Hydrindacen-1-one (*I*)

Cyclization of 137 g 5-(3-chloropropionyl)indane with 540 ml H_2SO_4 was carried out according to the literature[9] with the difference that a temperature of 90–95°C was used. After cooling, the reaction mixture was poured onto 4·75 kg of a mixture of ice and water, the product was filtered after standing overnight, washed with water and dried in air; 89 g (79%), m.p. 62–64°C. After crystallization from hexane, the product melts at 69–72°C. In this form it was used for further work. Ref.[9] describes cyclization at 100°C with a 50% yield. For sublimed and recrystallized product, a m.p. of 80–81°C has been reported.

1-Oximino-*s*-hydrindacene (*II*)

A mixture of 120 g *I*, 224 g $NH_2OH.HCl$, 1050 ml ethanol and 350 ml pyridine was refluxed for 15 h. After evaporation of the volatile components at reduced pressure, the residue was diluted with 1200 ml water, the precipitated product was filtered, washed with dilute hydrochloric acid and with water and dried in air; 128 g (98%), m.p. 141–144°C; analytical product, m.p. 146–147°C (benzene). UV spectrum: λ_{max} 213 nm (log ε 4·41), 257 nm (4·14), 301 nm (3·93), 313 nm (3·90). IR spectrum: 870 (solitary Ar—H), 1610 (Ar), 1656 (C=N), 3200 and 3300 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 9·45 (bs, 1 H, NOH), 7·50 and 7·08 (2 s, 2 H, aromatic 4,8-H_2), 2·92 (s, 4 H, 2 CH_2 in positions 2, 3), 2·83 (t, 4 H, 2 CH_2 in positions 5, 7), 2·00 (m, 2 H, CH_2 in position 6). For $C_{12}H_{13}NO$ (187·2) calculated: 76·97% C, 7·00% H, 7·48% N; found: 77·26% C, 7·38% H, 7·34% N.

1-(2-Dimethylaminoethoximino)-*s*-hydrindacene (*III*) (Method *A*)

Sodium (1·2 g), followed by 9·2 g *II*, were added to 75 ml ethanol, the solution was refluxed for 1 g and ethanol was evaporated *in vacuo*; the remaining ethanol was removed by adding 20 ml dimethylformamide and distillation *in vacuo* in a 100°C bath. The residue was combined with 50 ml dimethylformamide and 5·8 g 2-dimethylaminoethyl chloride (liberated from hydrochloride[17] and redistilled) and the mixture was heated for 1 h to 90–100°C and refluxed for 30 min. After coolling, the precipitated NaCl was filtered and the filtrate was evaporated. The remaining oily base (12·2 g) was dissolved in ether, the solution was filtered and the filtrate was neutralized with an ether solution of hydrogen chloride; 10·5 g (73%) hydrochloride, m.p. 214–215°C (ethanol). IR spectrum: 869 (solitary Ar—H), 1645 (C=N), 2645, 2500, 2535 (NH^+), 2945, 2980 (CH_2), 3040 cm^{-1} (Ar).

s-Hydrindacen-1-ol (*V*)

A solution of 50 g *I* in 200 ml benzene was added dropwise under stirring to a solution of 7·0 g $LiAlH_4$ in 200 ml ether and the mixture was refluxed for 3 h. After cooling, 28 ml 20% solution of NaOH was added dropwise, the mixture was diluted with 400 ml benzene and the insoluble fraction was filtered at 50°C and washed with hot benzene. Evaporation of the filtrate yielded the crude product in a theoretical yield (50·8 g) and purified by crystallization from benzene, m.p. 119–120°C. IR spectrum: 871 (solitary Ar—H), 1067 (cyclic CHOH), 3160 and 3270 cm^{-1} (OH). For $C_{12}H_{14}O$ (174·2) calculated: 82·72% C, 8·10% H; found: 82·68% C, 8·06% H.

1-(*s*-Hydrindacen-1-yl)-4-methylpiperazine (*VII*)

Suspension of 7·0 g *V* in 50 ml benzene was combined under stirring at room temperature with 6·0 ml $SOCl_2$ added dropwise. After 1 h of stirring the solution cleared and the volatile fractions

were removed by evaporation at reduced pressure (max. temperature 40°C). The remaining crude 1-chloro-*s*-hydrindacene (*VI*) (7·5 g) was dissolved in 30 ml benzene and the solution was added dropwise to a solution of 8·0 g 1-methylpiperazine in 40 ml benzene. The mixture was stirred for 1 h at room temperature and refluxed for 1 h. After cooling, the precipitated 1-methylpiperazine hydrochloride was filtered, the filtrate was washed with water and shaken with 50 ml 5% hydrochloric acid. After separation, the acid aqueous phase was made alkaline with 20% NaOH and the base was isolated by extraction with benzene; 0·30 g (3%). In an ether solution, it was neutralized with hydrogen chloride, to give the hydrochloride of m.p. 216—217°C (ethanol).

1-Amino-*s*-hydrindacene (*IX*)

A warm-prepared solution of 117 g *II* in 1 500 ml ethanol was added dropwise under a reflux condenser to 280 g Na. The mixture was refluxed for 4 h, during which 1 500 ml ethanol was added until sodium completely dissolved. After partial cooling, 600 ml water was added dropwise and the mixture was steam-distilled into a solution of 200 ml hydrochloric acid in 200 ml water, until the volume of the distillate reached 9 litres. Even then, the distillation flask contained some of the oily base *IX* which was isolated by extraction with benzene. The acid distillate was evaporated at reduced pressure, the residue was made alkaline with 20% NaOH and shaken with some benzene. Both benzene extracts were combined and evaporated after cooling. Distillation of the residue yielded 101 g (95%) base *IX*, b.p. 125—130°C/1—2 Torr. The hydrochloride crystallizes from water and melts under decomposition at about 270°C. Neutralization of the base with a calculated amount of H_2SO_4 yields the hemisulfate which crystallizes from aqueous ethanol as hemihydrate and melts at 210—212°C.

1-Dimethylamino-*s*-hydrindacene (*VIII*)

A mixture of 8·0 g base *IX*, 9 ml 85% formic acid, 12 ml water and 17 ml 28% formaldehyde was refluxed for 5 h. After cooling, 30 ml hydrochloric acid was added and the mixture was evaporated *in vacuo*. The residue was dissolved in 40 ml warm water with an addition of 2 ml hydrochloric acid, the solution was washed with ether, made alkaline with 20% NaOH and the base was isolated by extraction with a mixture of ether and benzene. Distillation of the extract yielded 4·3 g (47%) base boiling at 128—130°C/1 Torr. The hydrochloride crystallizes from a mixture of ethanol and ether and melts at 205—206°C.

N-(*s*-Hydrindacen-1-yl)formamide (*X*)

A mixture of 7·5 g *IX* and 15 ml ethyl formate was heated in an autoclave for 6 h at 120°C. After cooling, it was diluted with light petroleum and the crystalline product was filtered; 8·0 g (93%). m.p. 124—127°C. The analytical product was obtained by crystallization from benzene m.p. 139—140°C. IR spectrum: 885 (solitary Ar—H), 1547, 1660 (NHCO), 3300 cm^{-1} (NH). ^{1}H-NMR spectrum: δ 8·10 (bs, 1 H, CHO), 6·95 (bs, 2 H, aromatic protons in positions 4,8), 6·00 (bs, 1 H, NH), 5·38 (m, 1 H, Ar—CH—N), 2·78 (t, 6 H, 3 $ArCH_2$), 1·50—2·60 (m, 4 H, 2 CH_2 in positions 2,6). A practically identical yield of the product was obtained by a 4-h refluxing of a mixture of amine *IX* (7·0 g) with 15 ml ethyl formate.

N-(*s*-Hydrindacen-1-yl)acetamide (*XI*) (Method *B*)

Acetyl chloride (9·0 ml) was added dropwise under stirring to a mixture of 15·0 g amine *IX* and 20 ml pyridine and the mixture was refluxed for 3 h on a 120—130°C bath. After partial cooling,

it was poured into 1 litre water. The separated oil crystallized on standing: 17·6 g (94%), m.p. 184—185°C (benzene). IR spectrum: 869 (solitary Ar—H), 1550, 1632 (NHCO), 3260 cm^{-1} (NH). ^{1}H-NMR spectrum: δ 7·03 and 6·98 (2 s, 2 H, aromatic protons in positions 4, 8), 5·90 (d, 1 H, NH), 5·25 (m, 1 H, Ar—CH—N), 2·78 (t, J = 6·0 Hz, 6 H, 3 $ArCH_2$), 1·50—2·50 (m, 4 H, 2 CH_2 in positions 2, 6), 1·92 (s, 3 H, $COCH_3$).

N-(*s*-Hydrindacen-1-yl)chloroacetamide (*XIV*)

Potassium carbonate (14·5 g) was added to a solution of 35·0 g amine *IX* in 150 ml benzene and, at 5—8°C, a solution of 24·0 g chloroacetyl chloride in 100 ml benzene was added dropwise over a period of 1 h. The mixture was left for 1 h at that temperature and for 1 h at room temperature, diluted with 3 litres benzene and heated to 60—65°C, 300 ml water was added and stirred for 20 min at the temperature shown. The benzene layer was separated and evaporated after drying. Crystallization of the residue yielded 37·4 g (75%) crude product melting at 172—175°C. The pure substance was obtained by crystallization from ethanol, m.p. 182—183°C. ^{1}H-NMR spectrum: δ 7·02 (s, 2 H, aromatic protons in positions 4, 8), 6·70 (bs, 1 H, NH), 5·30 (m, 1 H, Ar—CH—N), 3·98 (s, 2 H, CH_2Cl), 2·81 (t, J = 6·0 Hz, 6 H, 3 $ArCH_2$), 1·50—2·60 (m, 4 H, 2 CH_2 in positions 2, 6).

N-(*s*-Hydrindacen-1-yl)-2-(N-benzyl-N-isopropylamino)acetamide (*XV*)

A mixture of 5·4 g *XIV*, 6·4 g N-benzylisopropylamine[13] and 20 ml dimethylformamide was refluxed for 6 h (a 160—165°C bath). After evaporation of dimethylformamide *in vacuo*, the residue was separated by shaking between 70 ml benzene and 70 ml water, the benzene solution was washed with water and shaken with 150 ml 4% hydrochloric acid. After separation, the acid aqueous solution was made alkaline with 20% NaOH and the base was isolated by extraction with a mixture of benzene and ether: 6·7 g (86%), m.p. 81—82°C (hexane). IR spectrum (Nujol): 744 and 875 (5 adjacent and solitary Ar—H), 1518 and 1659 cm^{-1} (NHCO). ^{1}H-NMR spectrum: δ 7·55 (d, J = 9·0 Hz, 1 H, NH), 7·25 (s, 5 H, C_6H_5), 7·10 and 6·94 (2 s, 2 H, aromatic protons in positions 4, 8), 5·30 (m, 1 H, Ar—CH—N), 3·55 (s, 2 H, $ArCH_2N$), 3·10 (s, 2 H, $COCH_2N$), 1·40—3·00 (m, 11 H, 5 CH_2 of the skeleton and NCH in the side chain), 1·00 (d, 6 H, 2 C—CH_3). Neutralization of the base with hydrogen chloride in a mixture of benzene and ether yielded the hydrochloride which crystallizes from a mixture of 95% ethanol and ether as a monohydrate, melting at 56—58°C.

N-(*s*-Hydrindacen-1-yl)-2-pyrrolidinoacetamide (*XVI*) (Method *C*)

A mixture of 5·4 g *XIV*, 120 ml benzene and 3·0 g pyrrolidine was refluxed for 6 h. After standing overnight, it was thoroughly washed with water, the benzene solution was dried and evaporated. The crude base was obtained in a theoretical yield (6·1 g) as an oil which crystallized on standing. The pure base was obtained by crystallization from hexane, m.p. 92—93°C. IR spectrum: 871, 884 (solitary Ar—H), 1550, 1653 (NHCO), 2810 (NCH_2), 3080 (Ar), 3275 cm^{-1} (NH). ^{1}H-NMR spectrum: δ 7·30 (bs, 1 H, NH), 7·02 (s, 2 H, aromatic protons in positions 4, 8), 5·40 (m, 1 H, Ar—CH—N), 3·15 (s, 2 H, $COCH_2N$), 2·81 (t, 6 H, 3 $ArCH_2$), 2·55 (m, 4 H, CH_2NCH_2 of pyrrolidine), 1·50—2·40 (m, 8 H, 2 CH_2 in positions 2, 6 and remaining 2 CH_2 of pyrrolidine). Hydrochloride was obtained by neutralization of the base in a mixture of ethanol and ether with hydrogen chloride; m.p. 179—180°C (ethanol–ether).

1-Methylamino-*s*-hydrindacene (*XXI*) (Method *D*)

A solution of 10·6 g amide *X* in 50 ml benzene was added under stirring dropwise to a solution of 5·0 g $LiAlH_4$ in 100 ml ether and the mixture was refluxed for 5 h. After cooling, 20 ml 20% solution of NaOH was added dropwise, the precipitated solid was filtered and washed with benzene. Evaporation of the filtrate yielded the crude base which was distilled; 9·0 g (91%), b.p. 120 to 122°C/1—1·5 Torr. The hydrochloride crystallizes from a mixture of ethanol and ether and melts at 112—115°C.

1-Methyl-3,5,6,7-tetrahydro-*s*-indacene (*XXVII*)

Reaction of 37·5 g methyl iodide with 5·9 g Mg in 130 ml ether gave rise to the Grignard reagent which was combined with a solution of 37·8 g *I* in 150 ml benzene added dropwise. The mixture was refluxed for 3 h, cooled and decomposed with a solution of 30 g NH_4Cl in 150 ml water. The organic phase was separated, dried and the solvents were evaporated *in vacuo* (at 40°C at the most). The remaining oil (37·3 g was characterized by chromatography on a thin layer of silica gel as a mixture of about 90% nonpolar and 10% polar component. A part of the mixture (32 g) was chromatographed on a column of 300 g Al_2O_3 (activity II). Hexane eluted 27 g nonpolar component boiling at 100—102°C/1 Torr, $n_D^{18.5}$ 1·5809. According to the ^{1}H-NMR spectrum we are dealing here with hydrocarbon *XXVII* with an endocyclic double bond. ^{1}H-NMR spectrum: δ 7·20 and 7·15 (2 s, 2 H, aromatic protons in positions 4, 8), 6·13 (m, 1 H, CH= in position 2), 3·25 (m, 2 H, CH_2 in position 3), 2·94 (t, 4 H, 2 CH_2 in positions 5, 7), 2·15 (mcs, J = 2·0 Hz, 3 H, CH_3), 2·15 (m, 2 H, CH_2 in position 6). For $C_{13}H_{14}$ (170·2) calculated: 91·71% C, 8·29% H; found: 91·26% C, 8·55% H.

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