SOME 5-(AMINOACETYL)INDANES AND 1-(5-INDANYL)-2-AMINOETHANOLS*

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Substitution reactions of 5-(bromoacetyl)indane (*IIIa*) with a series of seven secondary amines led to amino ketones *IVa–Xa* which were then converted by reduction methods to the amino alcohols *IVb–Xb* and debenzylated to *Ib* and *IIb*. The products showed slight indications of central stimulant and antiarrhythmic activity.

Analogues of sympathomimetic and sympatholytic phenethylamines and phenylethanolamines are still attractive as potential cardiovascular and neurotropic drugs. As to the indane derivatives, such compounds have been studied so far as contain the five-membered ring incorporated into the phenylethylamine skeleton[1]. Only recently interest has been shown in indane derivatives where the ethylamine side chain is attached to the aromatic ring. Thus the first adrenaline analogue to be synthesized was 1-(5-indanyl)-2-methylaminoethanol (*Ib*)[2]; 5-(1-indanyl)-2-isopropylaminoethanol (*IIb*) was synthesized as a potential β-adrenolytic[3–6] and its pharmacology was studied in some detail[7,8]. In addition to these two compounds several other similar amino alcohols and corresponding amino ketones with a secondary or a tertiary amino group were described[2–6].

The present experimental work was stimulated by the finding of an interesting type of central depressant activity in the series of substituted N-phenacylpiperazines[9,10]. Several indane analogues of these compounds (*VIIIa–Xa*, *VIIIb–Xb*), several compounds not containing the piperazine residue (*IVa–VIIa*, *IVb–VIIb*) and finally, using a novel method, the amino alcohols *Ib* and *IIb* were synthesized.

The parent compound of the whole study was 5-(bromoacetyl)-indane[11,12] (*IIIa*) which was obtained by bromination of 5-acetylindane[13] through a modified procedure. A substitution reaction of this compound with 100% excess of the corresponding amine (benzylmethylamine[14], benzylisopropylamine[15–17], butylmethylamine[18,19], hexamethylenimine, 1-methylpiperazine, 1-phenylpiperazine[20], 1-benzylpiperazine[21]) in ether (method *A*) yielded amino ketones *IVa–Xa*. Compounds *VIa–Xa* were then reduced with lithium aluminium hydride in ether (method *B*) to the amino alcohols *VIb–Xb*. Amino ketones *IVa* and *Va* were hydrogenated in the form

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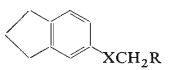
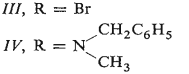
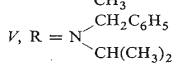
of hydrochlorides on Adams' catalyst in ethanol at room temperature and under normal pressure. The keto group was reduced preferentially, whereafter the uptake of hydrogen ceased spontaneously: this led to amino alcohols *IVb* and *Vb* (method *C*). Amino alcohol *IVb* was then debenzylated by hydrogenation on palladium catalyst on charcoal and yielded in a novel way the previously described[2,3] amino alcohol *Ib*.



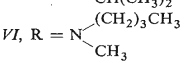
I, R = $NHCH_3$
II, R = $NHCH(CH_3)_2$
III, R = Br



IV, R = $N(CH_2C_6H_5)(CH_3)$

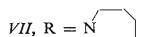


V, R = $N(CH_2C_6H_5)(CH(CH_3)_2)$

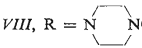


VI, R = $N((CH_2)_3CH_3)(CH_3)$

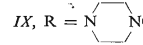
a, X = CO
b, X = CH(OH)



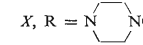
VII, R = N



VIII, R = $N(NCH_3)$



IX, R = $N(NC_6H_5)$



X, R = $N(NCH_2C_6H_5)$

Amino alcohol *Vb* in the form of a hydrochloride was then hydrogenated on Adams' catalyst which also resulted in debenzylation yielding the previously described[3–5] amino alcohol *IIb*. All the amino ketones, amino alcohols and their salts prepared, together with the experimental data, are shown in Table I.*

The amino ketones *VIa*–*VIIIa* and amino alcohols *VIb*, *VIIb* and *Xb* were pharmacologically tested by methods of general screening (for every compound the method of administration, the mean lethal dose LD_{50} in mg/kg in mice and the dose D in mg/kg in which the compound was applied *in vivo*, are shown). Hydrogen maleate of base *VIa* (*i.v.*, 75, 15) in doses greater than D exhibits some central depressant effects in mice. In agreement with this it slightly antagonizes the effect of phenmetrazine. In rats with normal tension it depresses briefly the blood pressure. In the *in vitro* test on rat duodenum it antagonizes slightly the acetylcholine contractions and very efficiently the barium chloride contractions (like papaverine). Compound *VIIa* (hydrogen maleate) (*p.o.*, 1 000, 200) at doses greater than D brings about signs of central excitation in mice. In agreement with this in antagonizes slightly the hypothermic effect of reserpine in mice. Further it shows a distinct hyperglycaemic effect on rats. Similarly, the di(hydrogen maleate) of *VIIIa* (*i.v.*, 70, 14) displays in higher doses a central stimulant effect which is not detectable at dose D. No antireserpine effect could be demonstrated. At the dose of D/2 it reduces briefly the blood pressure of normotensive rats which is followed by a pro-

* During the press of this paper a patent application[22] appeared dealing with some related compounds and describing also our substances *IXa* and *IXb*.

tracted increase of pressure. Further it exhibits some antiarrhythmic effects in mice toward chloroform arrhythmia; on the other hand, it is not effective against the aconitine arrhythmia in rats. After a *i.v.* application of D it depresses the blood sugar level in rats which could not be obtained after an oral application. In an isolated rat duodenum it displays a slight and nonspecific spasmolytic activity.

Hydrogen maleate of amino alcohol *VIb* (*i.v.*, 25, 5) is pharmacologically similar to the preceding compound. In a high dose it stimulates the CNS, in a D/2 dose it brings about a brief drop of blood pressure, a symptom of antiarrhythmic effect (chloroform), a slight hypoglycaemic effect after an *i.v.* application, which could not be found after *p.o.* administration. Similarly, the hydrogen maleate of *VIIb* (*p.o.*, 1 000, 200) shows in high doses signs of central stimulation; it showed some antireserpine activity (toward the effect on body temperature) in mice. It has a pronounced hyperglycaemic effect. Compound *Xb* (dihydrogen maleate) (*p.o.*, 1 000, 200) shows the most pronounced central stimulant effect on mice which is still apparent at a dose of 50 mg/kg (effect on motility). In agreement with this it has a hyperthermic effect: at a dose of 100–200 mg/kg it increases the body temperature of rats by 0·5°C. In the same dose it has a pronounced antiarrhythmic effect on rats toward aconitine arrhythmia. In a *p.o.* dose of 100 mg/kg it decreases the blood sugar level in rats by more than 20%. In isolated rat duodenum it shows a spasmolytic effect, specifically directed against acetylcholine.

Compounds *VIIIb* (dihydrogen maleate) and *IXa* (maleate) were tested by Dr M. Vaněček at the pharmacological department of this institute from the point of view of assumed hypotensive activity. A single application in a *p.o.* dose of 10 mg/kg does not reduce the blood pressure of hypertensive rats by more than 15%. For this reason the compounds are considered as uninteresting from this point of view. Compound *IXb* (maleate) was evaluated by Dr J. Metyš in this psychopharmacological group for its assumed central depressant activity: it was found to be uninteresting since in a dose of 500 mg/kg *p.o.* it is practically ineffective in the rotating-rod test in mice.

EXPERIMENTAL

The melting points of the analytical preparations were determined in Kofler's block and have not been corrected; the samples were dried at a suitable temperature (maximum 100°C) *in vacuo* of an oil pump over phosphorus pentoxide. The UV spectra (in methanol) were recorded in a Unicam SP 700 spectrophotometer, the IR spectra in an Infrascan (Hilger and Watts) spectrophotometer and the NMR spectrum in a ZKR 60 (Zeiss, Jena) spectrometer.

5-(Bromoacetyl)indane (*IIIa*)

Anhydrous $AlCl_3$ (0·8 g) was added to a solution of 6·6 g 5-acetylindane[13] in 140 ml ether, followed, under stirring, at 0–5°C, with 6·6 g bromine added dropwise. The mixture was stirred for 4 h at room temperature, the ether was evaporated, the residue was mixed with water and filtered, washed with water and some light petroleum and dried in air; 7·6 g (78%) m.p. 57–60°C.

TABLE I

5-(Aminoacetyl)indanes and 1-(5-Indanyl)-2-aminoethanols

Compound[a] Method	B.p., °C/Torr or m.p., °C (solvent)	Formula (M.w.)	Calculated/Found			
			% C	% H	% N	% Cl
Ib	130—131	$C_{12}H_{17}NO$	75·35	8·96	7·32	—
[b]	(benzene–light petroleum)	(191·3)	75·51	9·02	7·29	—
Ib-HCl	141—143	$C_{12}H_{18}ClNO$	63·29	7·96	6·15	15·57
—	(ethanol–ether)	(227·7)	63·48	8·13	6·16	15·84
IIb-HCl	213—214	$C_{14}H_{22}ClNO$	65·73	8·67	5·48	13·86
[b]	(ethanol–ether)	(255·8)	66·00	8·48	5·61	14·07
IVa	236—238/1	$C_{19}H_{21}NO$	81·70	7·57	5·01	—
A		(279·4)	81·50	7·81	4·94	—
IVa-HCl	187—188	$C_{19}H_{22}ClNO$	72·26	7·02	4·43	11·22
—	(ethanol–ether)	(315·8)	72·16	7·22	4·43	11·30
IVb-HCl	183—184	$C_{19}H_{24}ClNO$	71·80	7·61	4·41	11·15
C	(ethanol–ether)	(317·8)	71·98	7·90	4·33	11·43
Va-HCl[c]	163—165	$C_{21}H_{26}ClNO$	73·35	7·62	4·07	10·31
A	(ethanol–ether)	(343·9)	73·15	7·48	4·04	10·51
Vb-HCl	231	$C_{21}H_{28}ClNO$	72·91	8·16	4·05	10·25
C	(ethanol–ether)	(345·9)	73·07	8·03	4·01	10·41
VIa	150/1	$C_{16}H_{23}NO$	78·31	9·46	—	—
A		(245·4)	77·60	9·69	—	—
VIa-HM	104—105	$C_{20}H_{27}NO_5$	66·46	7·53	3·88	—
—	(ethanol–ether)	(361·4)	66·65	7·52	3·92	—
VIb-HM	71—72	$C_{20}H_{29}NO_5$	66·10	8·04	3·85	—
B	(ethanol–ether)	(363·4)	66·00	8·11	3·95	—
VIIa	170/0·5	$C_{17}H_{23}NO$	79·32	9·02	5·44	—
A		(257·4)	78·71	9·12	5·37	—
VII-HM	124—125	$C_{21}H_{27}NO_5$	67·53	7·29	3·75	—
—	(ethanol–ether)	(373·4)	67·38	7·32	3·73	—
VIIb-HM	126—127	$C_{21}H_{29}NO_5$	67·17	7·79	3·73	—
B	(ethanol–ether)	(375·5)	66·93	7·83	3·69	—
VIIIa	195/1[d]	$C_{16}H_{22}N_2O$	74·38	8·58	10·84	—
A		(258·4)	73·66	8·64	10·58	—
VIIIa·2 HCl[e]	211—213	$C_{16}H_{26}Cl_2N_2O_2$	—	—	8·02	20·33
—	(ethanol)	(349·3)	—	—	8·14	20·64

TABLE I
(*Continued*)

Compound[a] Method	B.p., °C/Torr or m.p., °C (solvent)	Formula (M.w.)	Calculated/Found % C	% H	% N	% Cl
VIIIa-2 HM	166–167	$C_{24}H_{30}N_2O_9$	58·77	6·16	5·71	—
—	(methanol)	(490·5)	58·84	6·25	5·74	—
VIIIb	82–83	$C_{16}H_{24}N_2O$	73·79	9·29	10·77	—
B	(benzene–light petroleum)	(260·4)	73·90	9·49	10·67	—
VIIIb-2 HM	178–179	$C_{24}H_{32}N_2O_9$	58·52	6·55	5·69	—
—	(ethanol)	(492·5)	58·50	6·67	5·93	—
IXa	112–113[f]	$C_{21}H_{24}N_2O$	78·71	7·55	8·75	—
A	(ethanol)	(320·4)	78·71	7·59	8·85	—
IXa-M	163–164	$C_{25}H_{28}N_2O_5$	68·78	6·47	6·42	—
—	(ethanol)	(436·5)	68·91	6·54	6·32	—
IXb	148–149	$C_{21}H_{26}N_2O$	78·22	8·13	8·69	—
B	(benzene–hexane)	(322·4)	78·13	8·16	8·51	—
IXb-M	165	$C_{25}H_{30}N_2O_5$	68·47	6·90	6·39	—
—	(ethanol–ether)	(438·5)	68·12	6·86	6·37	—
Xa-2 HM[e]	175–176	$C_{30}H_{36}N_2O_{10}$	61·63	6·21	—	—
A[g]	(ethanol)	(584·6)	61·51	6·45	—	—
Xb	134–135[h]	$C_{22}H_{28}N_2O$	78·52	8·39	8·33	—
B	(hexane)	(336·5)	78·43	8·41	8·18	—
Xb-2 HM	191–192	$C_{30}H_{36}N_2O_9$	63·36	6·38	4·93	—
—	(ethanol)	(568·6)	63·32	6·63	4·93	—

[a] M = maleate, HM = hydrogen maleate, 2 HM = di(hydrogen maleate). [b] See Experimental. [c] Crude base boils at 198–205°C/0·5 Torr. [d] UV spectrum: λ_{max} 257·5 nm (log ε 4·08), 288 nm (3·50). [e] Monohydrate. [f] UV spectrum: λ_{max} 254·5 nm (log ε 4·37), 286 nm (3·68). IR spectrum (KBr): 689 and 753 (5 vicinal aromatic C—H), 823 (2 vicinal aromatic C—H), 867 (isolated aromatic C—H), 1 502 and 1 599 (Ar), 1 680 (Ar—CO), 2 820 cm^{-1} (N—CH_2). NMR spectrum ($CDCl_3$): δ 7·95 (s, 1 H, 4 – H of indane), 7·88 (d, J = 9·0 Hz, 1 H, 6-H of indane), 7·11 (d, J = = 9·0 Hz, 1 H, 7-H of indane), 6·80–7·50 (m, 5 H, aromatic protons of phenyl), 3·83 (s, 2 H, $COCH_2$), 3·28 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·93 (m, 4 H, 2 CH_2 in positions 1 and 3 of indane), 2·75 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·06 (m, 2 H, CH_2 in position 2 of indane). [g] Crude base boils at 174–176°C/1 Torr. [h] IR spectrum (Nujol): 695 and 738 (5 vicinal aromatic C—H), 825 and 840 (2 vicinal aromatic C—H), 860 (isolated aromatic C—H), 1090 (CHOH) 2 780 (N—CH_2), 3 180 cm^{-1} (OH).

In this form it was used for further work. Ref.[11,12] give for a product obtained by a different method of bromination of 5-acetylindane m.p. of 58—59°C and 61°C.

5-(Benzylmethylaminoacetyl)indane (*IVa*)

Method A: A solution of 19·6 g *IIIa* in 200 ml ether was added to a solution of 19·8 g benzylmethylamine[14] in 50 ml ether, the mixture was stirred for 2 h at room temperature, then refluxed for 5 h and left to stand overnight. The suspension thus formed was agitated with 200 ml 10% solution of NaOH until the solid dissolved, the ether solution was separated, washed with water, dried with K_2CO_3 and evaporated. The residue was distilled to remove excess benzylmethylamine and the remaining base was redistilled: 19·0 g (83%), b.p. 236—238°C/1 Torr. Using an ether solution of hydrogen chloride, the base was converted to the hydrochloride, m.p. 187 to 188°C (ethanol–ether). Further data are shown in Table I which also includes the other aminoketones prepared. If the resulting base was crystalline it was not distilled but rather purified by recrystallization.

1-(5-Indanyl)-2-(4-methylpiperazino)ethanol (*VIIIb*)

Method B: A solution of 4·80 g 5-(4-methylpiperazinoacetyl) indane (*VIIIa*) in 75 ml ether was added dropwise under stirring to a solution of 2·0 g $LiAlH_4$ in 50 ml ether. The mixture was refluxed for 5 h, left to stand overnight at room temperature and decomposed by adding dropwise 8 ml 20% solution of NaOH. The solid was filtered and the filtrate evaporated. A total of 4·50 g (94%) crude base was obtained which was recrystallized from a mixture of benzene and light petroleum, to melt at 82—83°C. Neutralization with maleic acid in a mixture of ethanol and ether yields the di(hydrogen maleate) melting at 178—179°C (ethanol). Further data on the base and the maleate are shown in Table I which includes also other amino alcohols prepared by this method.

1-(5-Indanyl)-2-(benzylmethylamino)ethanol (*IVb*)

Method C: A solution of 14·0 g hydrochloride of amino ketone *IVa* was hydrogenated in the presence of 0·6 g PtO_2 in 50 ml ethanol at room temperature and under atmospheric pressure. Hydrogen consumption ceased after some 10% over the theoretical had been taken up, referred to H_2. After filtration, the filtrate was evaporated to dryness: 13·0 g (93%) crude hydrochloride which was purified by crystallization from a mixture of ethanol and ether, m.p. 183—184°C. The analytical data are shown in Table I.

1-(5-Indanyl)-2-methylaminoethanol (*Ib*)

A solution of 11·0 g hydrochloride of amino alcohol *IVb* in 150 ml ethanol was hydrogenated on 2·0 g 5% palladium catalyst on charcoal under normal conditions. After the consumption of hydrogen had ceased, the catalyst was filtered and the filtrate evaporated at reduced pressure. The remaining hydrochloride of the product (7·2 g, 92%) was crystallized from a mixture of ethanol and ether; m.p. 141—143°C. Decomposition of the aqueous solution of this hydrochloride with 20% NaOH liberated the base which was filtered and recrystallized from a mixture of benzene and light petroleum; m.p. 130—131°C. The analytical data are shown in Table I. Ref.[2] reports a preparation of the compound by hydrogenation of the corresponding methylamino ketone on palladium (m.p. of the base 132—132·5°C, of the hydrochloride 124—125·5°C), ref.[3] by reduction of the same amino ketone with sodium borohydride (m.p. of the base 131—132°C).

1-(5-Indanyl)-2-isopropylaminoethanol (*IIb*)

PtO_2 (1·0 g) was added to a solution of 14·0 g hydrochloride of amino alcohol *Vb* in 175 ml ethanol and the mixture was hydrogenated on a shaker until absorption of hydrogen ceased. After filtration of the catalyst the filtrate was evaporated, the residue was recrystallized from a mixture of ethanol and ether. A total of 8·50 g (91%) hydrochloride of the product was obtained (m.p. 213—214°C). The analytical data are shown in Table I. Ref.[3-5] described the preparation of the compound by reduction of the corresponding isopropylamino ketone with $NaBH_4$, and by the reaction of 1-(5-indanyl)-2-chloro (or bromo)ethanol with methylamine; only the m.p. of the base was reported as 99°C.

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REFERENCES

1. Ganellin C. R.: Advan. Drug. Research *4*, 163 (1967).
2. Pfleger R., Rauer K.: Chem. Ber. *90* (8), 1500 (1957).
3. Howe R., McLoughlin B. J., Rao B. S., Smith L. H., Chodnekar M. S.: J. Med. Chem. *12*, 452 (1969).
4. Howe R., Smith L. H., Stephenson J. S. (Imperial Chemical Industries Ltd.): Belg. 630 210; Brit. 1 019 772 (Appl. 28. III. 1962); Chem. Abstr. *61*, 625 (1964).
5. Howe R., Smith L. H., Stephenson J. S. (Imperial Chemical Industries Ltd.): U.S. 3 255 249 (Appl. 26. IV. 1963); Chem. Abstr. *65*, 15 294 (1966).
6. Hofmann A., Troxler F. (Sandoz Ltd.): French 1 503 368 (Swiss Appl. 8. XII. 1965); Chem. Abstr. *70*, 37 541 (1969).
7. Lacroix E., Weyne J., Leusen I.: Compt. Rend. Soc. Biol. 161 (*11*), 2338 (1967); Chem. Abstr. *69*, 25 850 (1968).
8. Marchetti G., Merlo L., Noseda V.: Arzneimittel-Forsch. *18(I)*, 43 (1968).
9. Protiva M., Vejdělek Z., Metyš J., Hradil F.: Czech. Appl. PV 8872—72 (22. XII. 1972).
10. Metyš J., Metyšová J., Votava Z., Kazdová E.: Activitas Nervosa Super. 15 (*2*), 96 (1973).
11. Braun J. V., Kirschbaum G., Schuhmann H.: Ber. *53*, 1155 (1920).
12. Borsche W., Pommer M.: *Ber.* 54, 102 (1921).
13. Dauben W. G., Jiu J.: J. Am. Chem. Soc. *76*, 4426 (1954).
14. Cromwell N. H., Babson R. D., Harris Ch. E.: J. Am. Chem. Soc. *65*, 312 (1943).
15. Lutz R. E., Bailey P. S., Rowlett R. J. jr, Wilson J. W. III, Allison R. K., Clark M. T., Leake N. H., Jordan R. H., Keller R. J. III, Nicodemus K. C.: J. Org. Chem. *12*, 760 (1947).
16. Steck E. A., Hallock L. L., Suter C. M.: J. Am. Chem. Soc. *70*, 4063 (1948).
17. Surrey A. R., Rukwid M. K.: J. Am. Chem. Soc. *77*, 3798 (1955).
18. Lukeš R., Přeučil J.: This Journal *10*, 384 (1938).
19. Borovička M., Šedivý Z., Protiva M.: Chem. listy *49*, 777 (1955).
20. Pollard C. B., MacDowell L. G.: J. Am. Chem. Soc. *56*, 2199 (1934).
21. Cymerman-Craig J., Young R. J.: Org. Syn, *42*, 19 (1962).
22. Bayssat M., Fontaine L., Grand M. (LIPHA-Lyonnaise Ind. Pharmac.): French Demande 2 138 488 (Appl. 71 19193, 27. V. 1971; Publ. 5. I. 1973).

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