3-(*s*-HYDRINDACEN-4-YL)PROPYLAMINES AND 4-(*s*-HYDRINDACEN-4-YL)BUTYLAMINES; SYNTHESIS AND PHARMACOLOGICAL SCREENING*

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4-Chloromethyl-*s*-hydrindacene (*VIIa*) was transformed *via* the malonic acid derivatives *VIIIa* and *IXa* to the acid *Xb* which afforded in four steps the homological acid *Xc*. Reactions of chlorides of both acids (*XIbc*) with dimethylamine, 1-methylpiperazine and 1-(2-hydroxyethyl)piperazine led to the amides *XIIbc*—*XIVbc* which were reduced with lithium aluminium hydride to the title compounds *IVcd*—*VIcd*. The amines obtained show central neurotropic effects only in subtoxic doses; they are also potent local anaesthetics and have significant spasmolytic activity of the neurotropic as well as musculotropic type.

According to the present knowledge, the ability to block the dopamine receptors in the brain is the basis of the mechanism of action of all types of the antipsychotic neuroleptics[1,2]. In his effort to find a common structural fragment in molecules of the importantly differing various types of neuroleptic agents, Janssen[3,4] concluded in formulating the partial structure *I* (*cf.*[5,6]); this structure represents a combination of an aromatic nucleus with a tertiary amino group connected by a four-membered chain in which the members A and B may be carbon atoms or hetero atoms. This structure can be found in molecules of such heavily differing substances like haloperidol (*II*), representative of the fluorobutyrophenone type neuroleptics, and chlorpromazine (*III*), prototype of tricyclic neuroleptics. It is not clear whether the presence of the fragment *I* in molecules of compounds is a prerequisite for attaining the neuroleptic activity and it is doubtful that it would be sufficient to this end. The present paper represents a contribution to answering these questions; it deals with the synthesis of three 4-(*s*-hydrindacen-4-yl)butylamines *IVd*—*VId*. Molecules of these compounds contain the fragment *I* suggested by Janssen[3]. In addition, their molecules reveal some similarity with molecules of the tricyclic neuroleptics: the basis of their structure is a tricyclic skeleton and the basic side chain is connected to the central ring of the skeleton. For structures of neuroleptic agents it is unusual to locate the aromatic nucleus to the centre of the system and to use alicyclic residues as the

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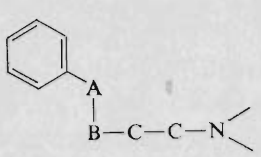
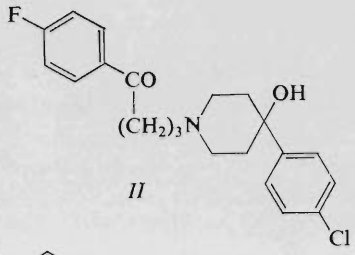
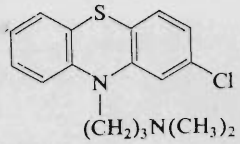
external nuclei of the system. The new compounds lack further the "neuroleptic substituent" which, however, was omitted also in the Janssen's formulation of the partial structure *I*. Our synthetic investigation is a continuation of the preceding systematic pharmaco-chemical studies in the series of hydrindacene derivatives[7-10].



I



II

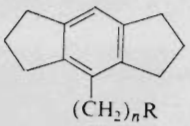


III

In one of the preceding papers[8] we have described the preparation of 4-chloromethyl-*s*-hydrindacene (*VIIa*); this compound has now been used in the synthesis of amines *IVd*–*VId* as well as their lower homologues *IVc*–*VIc*. Alkylation of ethyl malonate with the chloride *VIIa* gave the ester *VIIIa* which was hydrolyzed to the malonic acid *IXa*. Thermic decarboxylation resulted in 3-(*s*-hydrindacen-4-yl)propionic acid (*Xb*). Its chloride *XIb* was subjected to reactions with excessive dimethylamine, 1-methylpiperazine and 1-(2-hydroxyethyl)piperazine in benzene (method *A*); the amides *XIIb*–*XIVb* were obtained. Reduction of the amides with lithium aluminium hydride in a mixture of ether and benzene (method *B*) gave 3-(*s*-hydrindacen-4-yl)propylamines *IVc*–*VIc*.

The ethyl ester *XVb*, obtained by esterification of the acid *Xb*, afforded by reduction with lithium aluminium hydride in ether the alcohol *XVIc* which was reacted with thionyl chloride in benzene to give the chloro derivative *VIIc*. Treatment with sodium cyanide in dimethyl sulfoxide resulted in the nitrile *XVIIc* which was hydrolyzed with sulfuric acid in aqueous acetic acid to 4-(S-hydrindacen-4-yl)butyric acid (*Xc*). The crude chloride *XIc*, obtained by treatment with thionyl chloride, was processed using method *A* and transformed to the amides *XIIc*–*XIVc* which were reduced in crude state (method *B*) to the desired amines *IVd*–*VId*. Compounds prepared using methods *A* and *B* are summarized in Table I with the usual experimental data. The oily amines *IVcd*–*VIcd* were characterized and purified in the form of hydrochlorides.

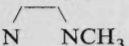
The amine hydrochlorides were pharmacologically tested by methods of the general screening; their solubility in water enabled the parenteral administration and carrying out the *in vitro* experiments. Numbers of compounds, their acute toxicities in mice on intravenous administration (LD_{50}, mg/kg) and the basic doses D (mg/kg, *i.v.*), which were used in the screening, are given: *IVc*-HCl, 35, 7; *Vc*-2 HCl, 50, 10; *VIc*-2 HCl, 62·5, 12; *IVd*-HCl, 40, 8; *Vd*-2 HCl, 40, 8; *VId*-2 HCl, 54, 10. In doses D the substances did not show any CNS effects; some of them appeared in doses higher than D (subtoxic doses): Compound *IVc* is central depressant for mice and brings about ataxia in the rotarod test; *VIc*, on the other hand, enhances activity and reactivity of mice; *IVd* in a subcutaneous dose of 8 mg/kg increases significantly the motor

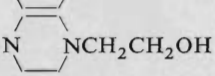


$(CH_2)_nR$

a, $n = 1$
b, $n = 2$
c, $n = 3$
d, $n = 4$

IV, R = $N(CH_3)_2$

V, R = 

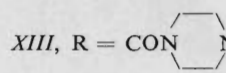
VI, R = 

VII, R = Cl

VIII, R = $CH(COOC_2H_5)_2$
IX, R = $CH(COOH)_2$
X, R = COOH

XI, R = COCl

XII, R = $CON(CH_3)_2$

XIII, R = 

XIV, R = 

XV, R = $COOC_2H_5$
XVI, R = OH
XVII, R = CN

activity of mice. Compound *VId*, the molecule of which contains the Janssen's fragment and the side chain, typical for active neuroleptics, was tested with negative results for cataleptic activity in rats: an intraperitoneal dose of 10 mg/kg as well as an oral dose of 50 mg/kg were completely inactive. It must be concluded that the compounds prepared lack completely the neuroleptic character; the presence of the Janssen's fragment (*I*) (ref.[3,4]) in their molecules is evidently not a sufficient condition for attaining this character.

The testing revealed some other effects of the compounds (partly of neurotropic nature): In concentrations of 0·1–0·5% compounds *IVc* and *IVd*–*VId* are active in the test of infiltration anaesthesia in rabbits (bring about a complete anaesthesia in 50% of the animals); in the same concentrations compounds *IVd*–*VId* are effective in the test of corneal anaesthesia (complete anaesthesia of the rabbit eye cornea in 50% animals). These activities surpass that of procaine and equal that of trimecaine. In concentrations of 1–10 μg/ml compounds *IVc* and *IVd*–*VId*

have spasmolytic effect of the neurotropic as well as musculotropic type (exhibit a reduction of the acetylcholine and barium chloride contractions of the isolated rat duodenum by 50% which is 1% of the atropine activity and the full activity of papaverine). On the isolated rabbit atrium the compounds depress inotropy and the heartbeat frequency by 25% in the following concentrations (in μg/ml): inotropy, *IVc* 5–10, *Vc* 25–50, *VIc* 50, *IVd* 50, *VId* 50; chronotropy, *IVc* 5–10, *VIc* 50, *IVd* 5–50. Compound *IVc* in the dose D brings about deep and brief drops of the blood pressure in normotensive rats. Compound *VIc* showed the hypoglycaemic effect; an oral dose of 60 mg/kg decreased the blood sugar level in rats by 20% (50% of the tolbutamide activity).

The compounds prepared were also tested for antimicrobial activity *in vitro* (Dr J. Turinová, bacteriological department of this institute). The used microorganisms, numbers of compounds and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus β-haemolyticus*, *IVc* 100, *IVd* 25, *Vc* 100, *Vd* 25, *VIc* 100, *VId* 25, *XIIb* 100, *XIIIb* 50; *Streptococcus faecalis*, *IVc* 100, *IVd* 25, *Vd* 25, *VIc* 100, *VId* 100; *Staphylococcus pyogenes aureus*, *IVd* 50, *Vd* 50, *VId* 100; *Mycobacterium tuberculosis* H37Rv, *IVc* 25, *IVd* 6·25, *Vc* 25, *Vd* 25, *VIc* 50, *VId* 25, *XIIb* 100, *XIIIb* 100; *Saccharomyces pasterianus*, *IVc* 100, *IVd* 100, *Vc* 100, *Vd* 100, *VIc* 100, *VId* 100, *XIIb*100, *XIIIb* 100, *XIVb* 100; *Trichophyton mentagrophytes*, *IVc* 50, *IVd* 100, *Vc* 50, *Vd* 100, *VIc* 50, *VId* 100, *XIIb* 50, *XIIIb* 50, *XIVb* 50; *Candida albicans*, *IVc* 100, *IVd* 100, *Vc* 100, *Vd* 100, *VIc* 100, *VId* 100, *XIIb* 100, *XIIIb* 100, *XIVb* 100; *Aspergillus niger*, *IVc* 100, *IVd* 100, *Vc* 100, *Vd* 100, *VIc* 100, *VId* 100, *XIIb* 100, *XIIIb* 100, *XIVb* 100.

EXPERIMENTAL

The melting points of analytical samples were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 20 Pa over P_2O_5 at room temperature or at 77°C. The IR spectra (mostly in Nujol) were recorded with a Unicam SP 200G spectrophotometer and ^{1}H-NMR spectra (in $CDCl_3$ unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer. The homogeneity of the compounds was checked by chromatography on thin layers of silica gel.

Diethyl (*s*-Hydrindacen-4-ylmethyl)malonate (*VIIIa*)

Na (7·0 g) was dissolved in 150 ml ethanol, the solution was treated at 50°C with 48 g diethyl malonate and then under stirring with 62 g 4-chloromethyl-*s*-hydrindacene (*VIIa*) (ref.[8]), added dropwise over 80 min. The mixture was refluxed for 2 h, ethanol was evaporated under reduced pressure, the residue was decomposed with water and the product was extracted with benzene. The extract was dried with Na_2SO_4 and processed by distillation; 75·6 g (77%), b.p. 205–215°C/0·35 kPa. Analytical sample, b.p. 185°C/0·13 kPa, n_D^{20} 1·5226. For $C_{20}H_{26}O_4$ (330·4) calculated: 72·70% C, 7·93% H; found: 72·84% C, 8·03% H.

(*s*-Hydrindacen-4-ylmethyl)malonic Acid (*IXa*)

A solution of 80 g *VIIIa* in 110 ml ethanol was added to a solution of 51 g KOH in 100 ml water and the mixture was refluxed for 2 h. The mixture was then evaporated *in vacuo*, the residue

was dissolved in 350 ml water at 50°C, the solution was filtered with charcoal and after cooling below 15°C, the filtrate was acidified with 120 ml 1 : 1 dilute hydrochloric acid. The product was filtered, washed with water and dried *in vacuo*; 65·5 g (99%), m.p. 164—167°C (capillary). Analytical sample, m.p. 174—177°C (aqueous ethanol). IR spectrum: 861 (solitary Ar—H), 943, 1 211, 1 710, 2 620 cm^{-1} (COOH). ^{1}H-NMR spectrum ($C^2H_3SOC^2H_3$): δ 12·60 (bs, 2 H, 2 COOH), 6·80 (s, 1 H, Ar—H), 3·35 (t, J = 7·0 Hz, 1 H, COCHCO), 2·90 (d, J = 7·0 Hz, 2 H, $ArCH_2$ in the side chain), 2·64 (t, 8 H, 4 $ArCH_2$ in the skeleton), 1·85 (m, 4 H, remaining 2 CH_2 in the skeleton). For $C_{16}H_{18}O_4$ (274·3) calculated: 70·04% C, 6·62% H; found: 69·77% C, 6·81% H.

3-(*s*-Hydrindacen-4-yl)propionic Acid (*Xb*)

The acid *IXa* (64·5 g) was heated to 180—185°C to effect the decarboxylation. After the termination of CO_2 formation, the melt was kept for additional 30 min at the mentioned temperature *in vacuo*. After cooling, the solidified melt was dissolved in 700 ml boiling cyclohexane, the solution was filtered with charcoal and the filtrate cooled. Crystallization resulted in 55·5 g (100%) product melting at 136—138°C. Analytical sample, m.p. 140—141°C (cyclohexane). IR spectrum: 861 (solitary Ar—H), 935, 1 221, 1 303, 1 691, 2 640 cm^{-1} (COOH). ^{1}H-NMR spectrum: δ 10·90 (bs, 1 H, COOH), 6·98 (s, 1 H, Ar—H), 2·80 (t, 8 H, 4 $ArCH_2$ in the skeleton), *c.* 2·50 (m, 4 H, $ArCH_2CH_2$ in the side chain), 2·00 (m, 4 H, 2 CH_2 in positions 2 and 6 of the skeleton). For $C_{15}H_{18}O_2$ (230·3) calculated: 78·22% C, 7·88% H; found: 77·85% C, 7·49% H.

The acid chloride *XIb* (30 g, 100%) was prepared by refluxing a mixture of 25 g *Xb*, 150 ml benzene and 25 ml $SOCl_2$ for 60 min and by the following evaporation of the solvent and excess of $SOCl_2$ *in vacuo* (bath of 100°C). The chloride was used in this crude state without further characterization.

Ethyl 3-(*s*-Hydrindacen-4-yl)propionate (*XVb*)

A mixture of 27 g *Xb*, 270 ml ethanol and 8 ml H_2SO_4 was refluxed for 4 h, ethanol was evaporated under reduced pressure, the residue decomposed with water and the product extracted with a mixture of benzene and ether. The extract was washed with water, a saturated solution of $NaHCO_3$, dried with Na_2SO_4 and evaporated; 30·2 g (100%) crude oily ester. A sample was crystallized from aqueous ethanol, m.p. 34—35°C. IR spectrum: 860 (solitary Ar—H), 1 160, 1 745 cm^{-1} (COOR). For $C_{17}H_{22}O_2$ (258·3) calculated: 79·02% C, 8·58% H; found: 79·45% C, 8·62% H.

3-(*s*-Hydrindacen-4-yl)propanol (*XVIc*)

A solution of 29 g *XVb* in 130 ml benzene was added dropwise over 30 min to a suspension of 7·0 g $LiAlH_4$ in 120 ml ether and the mixture was refluxed for 2·5 h. After cooling it was decomposed by a slow addition of 28 ml 20% NaOH, the solid was filtered off and the filtrate evaporated; 24·3 g (100%) residue, m.p. 65—67°C. Analytical sample, m.p. 82°C (cyclohexane). IR spectrum (KBr): 859 (solitary Ar—H), 1 070 (CH_2OH), 3 220, 3 320 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 6·92 (s, 1 H, Ar—H), 3·65 (t, J = 6·0 Hz, 2 H, CH_2O), 2·80 (t, 8 H, 4 $ArCH_2$ in the skeleton), 2·60 (t, 2 H, $ArCH_2$ in the chain), *c.* 1·90 (m, 6 H, remaining 3 CH_2 in the skeleton and in the chain), 1·60 (s, 1 H, OH). For $C_{15}H_{20}O$ (216·3) calculated: 83·28% C, 9·32% H; found: 83·50% C, 9·20% H.

TABLE I

(*s*-Hydrindacen-4-yl)alkanamides and (*s*-hydrindacen-4-yl)alkylamines

Compound (method/yield, %)	M.p., °C (solvent) or b.p., °C/kPa	Formula (mol.wt.)	Calculated/Found			
			% C	% H	% N	% Cl
XIIb	74—75	$C_{17}H_{23}NO$	79·33	9·01	5·44	—
(*A*/96)	(hexane)	(257·4)	79·76	8·95	5·22	—
XIIc	oil[a]	—	—	—	—	—
(*A*/93)		—	—	—	—	—
XIIIb	80—81	$C_{20}H_{28}N_2O$	76·89	9·03	8·96	—
(*A*[b]/84)	(hexane)	(312·4)	76·70	8·97	8·69	—
XIIIc	oil[a]	—	—	—	—	—
(*A*/85)		—	—	—	—	—
XIVb	118—119[c]	$C_{21}H_{30}N_2O_2$	73·64	8·83	8·18	—
(*A*/85)	(cyclohexane–benzene)	(342·5)	73·44	9·05	8·11	—
XIVc	oil[a]	—	—	—	—	—
(*A*/85)		—	—	—	—	—
IVc	152—153/0·13[d]	$C_{17}H_{25}N$	83·89	10·37	5·73	—
(*B*/99)		(243·4)	83·79	10·28	5·50	—
IVc-HCl	223—224	$C_{17}H_{26}ClN$	72·75	9·37	5·01	12·67
	(ethanol–ether)	(279·8)	72·67	9·45	4·95	12·81
IVd-HCl	196—197	$C_{18}H_{28}ClN$	73·55	9·61	4·77	12·07
(*B*/93)	(ethanol–ether)	(293·9)	73·33	9·71	4·70	11·73
Vc-2 HCl	257—258	$C_{20}H_{32}Cl_2N_2$	64·68	8·69	7·54	19·09
(*B*[b]/94)	(ethanol)	(371·4)	64·00	8·73	7·54	19·05
Vd-2 HCl	214—215[e]	$C_{21}H_{34}Cl_2N_2$	65·43	8·90	7·27	18·40
(*B*/96)	(ethanol)	(385·4)	65·42	9·03	6·91	18·05
VIc-2 HCl	235—236[f]	$C_{21}H_{34}Cl_2N_2O$	62·83	8·54	6·98	17·67
(*B*/97)	(aqueous ethanol)	(401·4)	62·53	8·57	6·97	17·63
VId-2 HCl	210—211[g]	$C_{22}H_{36}Cl_2N_2O$	63·59	8·74	6·74	17·08
(*B*/95)	(aqueous ethanol)	(415·4)	63·76	8·83	6·54	16·86

[a] The crude oily product was used to reduction without characterization. [b] See Experimental. [c] IR spectrum: 861 (solitary Ar—H), 1 019, 1 094 (C—O), 1 223, 3 160 (OH), 1 635 cm^{-1} ($CONR_2$); ^{1}H-NMR spectrum: δ 6·98 (s, 1 H, Ar—H), 3·63 (t, 4 H, $\begin{matrix}CH_2\\CH_2\end{matrix}\!\!>\!NCO$), 3·30 (t, 2 H, CH_2O), 2·80 (t, 8 H, 4 CH_2 in positions 1, 3, 5 and 7 of hydrindacene), 1·80—2·60 (m, 15 H, remaining 7 CH_2 and OH). [d] n_D^{22} 1·5390; ^{1}H-NMR spectrum: δ 6·90 (s, 1 H, Ar—H), 2·80 (t, 8 H, 4 CH_2 in positions 1, 3, 5 and 7 of hydrindacene), 1·50—2·60 (m, 10 H, remaining 5 CH_2), 2·16 (s, 6 H, 2 NCH_3). [e] Melts in a capillary at 229—231°C. [f] Melts in a capillary at 244—245°C. [g] IR spectrum: 859 (solitary Ar—H), 1 022, 1 075 (C—O) of CH_2OH), 2 445 (NH^+), 3 360 cm^{-1} (OH).

3-(*s*-Hydrindacen-4-yl)propyl Chloride (*VIIc*)

A suspension of 23 g *XVIc* in 50 ml chloroform was stirred and treated dropwise over 1 h with a solution of 50 g $SOCl_2$ in 50 ml chloroform, the mixture was stirred for 8 h at room temperature and refluxed for 3 h. Chloroform and excess of $SOCl_2$ were evaporated under reduced pressure, the residue was dissolved in benzene, the solution was washed with water and a saturated solution of $NaHCO_3$, dried and processed by distillation; 19·5 g (80%), b.p. 160°C/0·27 kPa, n_D^{23} 1·5590. For $C_{15}H_{19}Cl$ (234·8) calculated: 76·74% C, 8·16% H, 15·10% Cl; found: 77·39% C, 8·12% H, 14·78% Cl.

4-(*s*-Hydrindacen-4-yl)butyronitrile (*XVIIc*)

A suspension of 5·5 g NaCN in 28 ml dimethyl sulfoxide was heated to 90°C and treated under stirring over 7 h with 19·0 g *VIIc*, added dropwise. The mixture was stirred and heated to 120°C for 15 min and after partial cooling poured into 200 ml water. The separated product was filtered, washed with water and dried; 17·5 g (96%), m.p. 52—55°C. Analytical sample, m.p. 59—60°C (hexane). IR spectrum: 861 (solitary Ar—H), 2245 cm^{-1} (R—CN). ^{1}H-NMR spectrum: δ 6·95 (s, 1 H, Ar—H), 1·50—3·00 (m, 18 H, 9 CH_2). For $C_{16}H_{19}N$ (225·3) calculated: 85·28% C, 8·50% H, 6·22% N; found: 85·38% C, 8·59% H, 6·04% N.

4-(*s*-Hydrindacen-4-yl)butyric Acid (*Xc*)

A mixture of 17·3 g crude *XVIIc*, 15 ml acetic acid, 15 ml water and 15 ml H_2SO_4 was refluxed for 2 h (bath temperature 160—170°C). After cooling it was diluted with 160 ml water, allowed to stand overnight, the solid product filtered and washed with water. It was dissolved in a mixture of 40 ml 20% NaOH and 500 ml water, undissolved material was filtered off and the filtrate acidified with a mixture of 20 ml hydrochloric acid and 80 ml water. The separated product was filtered, dissolved in a mixture of 300 ml benzene and 100 ml ether, the solution was dried with Na_2SO_4, filtered with charcoal and evaporated; 14·7 g (79%) solid product, m.p. 124—127°C. Analytical sample, m.p. 134—135°C (cyclohexane). IR spectrum: 861 (solitary Ar—H), 948, 1 231, 1 311, 1 711, 2 660 cm^{-1} (COOH). For $C_{16}H_{20}O_2$ (244·3) calculated: 78·65% C, 8·25% H; found: 78·68% C, 8·21% H.

The acid chloride *XIc* (15·5 g oil, 100%) was prepared by refluxing a mixture of 14·4 g *Xc*, 80 ml benzene and 14 ml $SOCl_2$ for 80 min and by evaporation *in vacuo*. It was used in this crude form.

1-[3-(*s*-Hydrindacen-4-yl)propionyl]-4-methylpiperazine (*XIIIb*) (Method *A*)

A solution of 8·7 g crude *XIb* in 50 ml benzene was added over 20 min to a stirred and cooled solution of 7·0 g 1-methylpiperazine in 120 ml benzene, the mixture was stirred for 30 min without heating and for 1 h at 60°C. After cooling the solution was washed with water and the basic product was extracted with a mixture of 30 ml hydrochloric acid and 200 ml water. The aqueous layer was filtered, made alkaline with 70 ml 20% NaOH and the product extracted with benzene. The extract was dried and evaporated; 9·2 g (84%) oil which crystallized from hexane. m.p. 80—81°C. IR spectrum: 859 (solitary Ar—H), 1 641 ($CONR_2$), 2 755 cm^{-1} (NCH_3). ^{1}H-NMR spectrum: δ 6·95 (s, 1 H, Ar—H), 3·60 and 3·30 (2 t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·80 (t, 8 H, 4 $ArCH_2$ of the skeleton), 1·80—2·60 (m, 12 H, remaining 6 CH_2), 2·16 (s, 3 H, NCH_3). For analytical data, *cf.* Table I.

1-[3-(*s*-Hydrindacen-4-yl)propyl]-4-methylpiperazine (*Vc*) (Method *B*)

A solution of 8·0 g *XIIIb* in 40 ml benzene was slowly added to a stirred suspension of 3·5 g $LiAlH_4$ in 50 ml ether and the mixture was refluxed for 2 h. After cooling it was decomposed by addition of 14 ml 20% NaOH, the solid was filtered off and washed with benzene and the filtrate was evaporated *in vacuo*; 7·10 g (94%) oily *Vc*. It was dissolved in 20 ml ethanol, neutralized with an ethanolic solution of HCl and the mixture diluted with 70 ml ether; the precipitated dihydrochloride was filtered, washed with a mixture of ethanol and ether and dried; 8·4 g, m.p. 257—259°C. Analytical sample, m.p. 257—259°C (ethanol). For analytical data, *cf.* Table I.

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