BENZOCYCLOHEPTENES AND HETEROCYCLIC ANALOGUES AS POTENTIAL DRUGS. VI.*

1-(6,7,8,9-TETRAHYDRO-5*H*-BENZOCYCLOHEPTEN-2-YL)-2-AMINOETHANOLS

Z.J.VEJDĚLEK, F.HRADIL and M.PROTIVA

Research Institute of Pharmacy and Biochemistry, Prague 3

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Reactions of 2-(bromoacetyl)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*II*) with 11 aliphatic, araliphatic and heterocyclic secondary amines yielded the amino ketones *III*—*XIII*. Ketones *III*—*VII* were reduced with sodium borohydride, the others were catalytically hydrogenated on platinum with simultaneous debenzylation to the N-substituted 1-(6,7,8,9-tetrahydro-5*H*-benzocycloheptен-2-yl)-2-aminoethanols *XIX*—*XXIX*. 2-Acetyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*I*) was processed in the usual way to prepare the amine *XXX* and the tertiary alcohol *XXXI*. Ritter's reaction of the alcohol *XXXI* with hydrogen cyanide and subsequent hydrolysis yielded only a minute amount of the amine *XXXIII*, together with the main product *XXXIV*. Aminoketone *VI* exhibited hypotensive, diuretic and spasmolytic activities, *XIII* was hypotensive, spasmolytic and considerably locally anaesthetic.

In the preceding communication of this series[1] we described the synthesis of 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl analogues of phenethylamine, amphetamine and phentermine as the main representatives of oxygen-free sympathomimetics, central stimulants and anorectics. In the present communication we describe the synthesis of a series of N-substituted 1-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl)-2-aminoethanols as analogues of adrenomimetics and adrenolytics of the phenylethanolamine series. Thus, *e.g.*, compound *XXIV* is an analogue of adrenaline with the two hydroxyl groups of its molecule replaced with a condensed seven-membered ring. Compound *XXV* is an analogue of the β-adrenomimetic "isoprenaline" as well as an analogue of the β-adrenolytic "pronethanol" in the molecule of which one benzene ring of the naphthalene system is replaced with a cycloheptene fragment[2].

The common starting compound was 2-acetyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene[3,4] (*I*), prepared by a Friedel–Crafts reaction from 6,7,8,9-tetrahydro-5*H*-benzocycloheptene[1]. Treatment with bromine in acetic acid[5] or, even better, bromination in ether in the presence of a small amount of aluminium chloride yielded the

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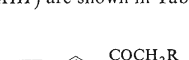
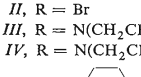
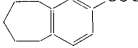
2-(bromoacetyl) derivative *II* which was used for the substitution reaction in boiling ether ("method C") with di(n-propyl)amine, diethanolamine, piperidine, 1-methylpiperazine, 1-ethoxycarbonylpiperazine[6], benzylmethylamine[7], benzylisopropylamine[8], benzylisobutylamine[9] (*XIVb*), benzylcyclohexylamine[10] (*XVb*), benzyl-2-furfurylamine[11,12] (*XVIb*) and benzyl-3-morpholinopropylamine[13,14] (*XVIIb*). The resulting amino ketones (*III*–*XIII*) are shown in Table I.



I, R = H
II, R = Br
III, R = $N(CH_2CH_2CH_3)_2$
IV, R = $N(CH_2CH_2OH)_2$



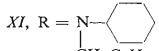
VII, R = 

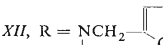
VIII, R = $NCH_2C_6H_5$ | CH_3

IX, R = $NCH_2C_6H_5$ | $CH(CH_3)_2$

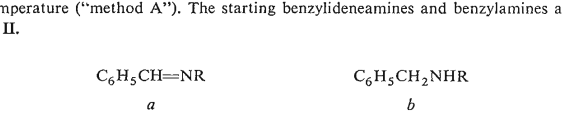
X, R = $NCH_2C_6H_5$ | $CH_2CH(CH_3)_2$

XI, R =

XII, R = 

XIII, R = 

Amines *XIVb*–*XVIIIb* were prepared by reduction of the corresponding benzylideneamines [*XIVa* (ref.[15]), *XVa* (ref.[16]), *XVIa* (ref.[12]), *XVIIa* (ref.[13,14]) and *XVIIIa*] with lithium aluminium hydride in ether ("method B"). The so far unknown N-benzylidene-2,3,3-trimethyl-2-butylamine (*XVIIIa*) was obtained by reaction of benzaldehyde with the primary amine[17] at room temperature ("method A"). The starting benzylideneamines and benzylamines are shown in Table II.



Amino ketones *III*–*VII* were reduced with sodium borohydride in aqueous methanol in the presence of sodium hydroxide ("method D") with the formation of the corresponding amino alcohols *XIX*–*XXIII*. Amino ketones *VIII*–*XIII* containing in their amino group the benzyl group as a substituent, were reduced in the form of hydrochlorides by catalytic hydrogenation on Adams' catalyst in ethanol at room temperature ("method E"). Besides reduction of the keto group, the hydro-

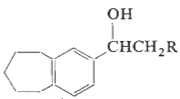
TABLE I

Amino Ketones *III*—*XIII* Prepared According to Method C

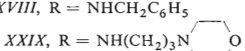
Compound	M.p., °C (solvent)	Formula (m. w.)	Calculated/Found			
			% C	% H	% N	% Cl
III-HM[a]	131—132 (ethyl acetate–ether)	$C_{23}H_{33}NO_5$ (403·5)	68·45 68·37	8·25 8·11	3·47 3·32	— —
IV	126—127[b] (benzene–hexane)	$C_{17}H_{25}NO_3$ (291·4)	70·06 70·06	8·65 8·71	4·81 4·59	— —
V-HM[a]	141—142[c]	$C_{22}H_{29}NO_5$ (387·5)	68·20 68·05	7·54 7·46	3·61 3·87	— —
VI	83—85[d] (light petroleum)	$C_{18}H_{26}N_2O$ (286·4)	75·47 75·62	9·16 9·19	9·78 9·75	— —
VI·2 HCl[e]	237—239 (ethanol)	$C_{18}H_{28}Cl_2N_2O$ . . 0·5 H_2O (368·3)	58·68 58·47	7·93 7·79	7·61 7·40	19·26 19·31
VII-HM[a]	142—143 (ethanol–ether)	$C_{24}H_{32}N_2O_7$ (460·5)	62·57 62·62	7·02 7·10	6·09 6·09	— —
VIII-HCl	187—189 (ethanol–ether)	$C_{21}H_{26}ClNO$ (343·9)	73·35 73·37	7·62 7·58	4·07 4·00	10·31 10·24
IX-HCl	155—156 (ethanol–ether)	$C_{23}H_{30}ClNO$ (371·9)	74·25 74·66	8·13 8·14	3·76 3·71	9·53 9·69
X-HCl	157—158[f] (ethanol–ether)	$C_{24}H_{32}ClNO$ (386·0)	74·67 74·10	8·36 8·26	3·63 3·42	9·19 9·15
XI[g]	84—85 (light petroleum)	$C_{26}H_{33}NO$ (375·5)	83·15 83·42	8·86 8·96	3·73 3·73	— —
XI-HCl	159—160 (ethanol–ether)	$C_{26}H_{34}ClNO$ (412·0)	75·80 75·92	8·32 8·39	3·40 3·16	8·60 8·53
XII-HCl	108—110 (ethyl acetate–ether)	$C_{25}H_{28}ClNO_2$ (409·9)	—	—	3·41 3·47	8·65 8·51
XIII·2 HCl[h]	191—193[i] (ethanol–ether)	$C_{27}H_{40}Cl_2N_2O_3$ (511·5)	63·39 63·88	7·89 7·91	5·48 5·59	13·86 13·73

[a] Hydrogen maleate. [b] Substitution reaction carried out in a mixture of ether and tetrahydrofuran; NMR spectrum: δ 6·90—7·80 (multiplet, 3 H of the benzene ring), 3·40—4·30 (multiplet, 4 H of the CH_2 of primary alcoholic groups), 4·01 (singlet, 2 H of OH groups), 2·00—3·05 (multiplet, 10 H of the CH_2 groups adjacent to the aromatic ring, to the CO group and the N atom), 1·80—2·00 (multiplet, 6 H of the other CH_2 groups of the seven-membered ring). [c] Ethyl acetate–ethanol–ether. [d] NMR spectrum: δ 7·75 (multiplet, 2 H of the aromatic protons in positions 1 and 3), 7·18 (doublet, 9 Hz, 1 H of the aromatic proton in position 4), 3·81 (singlet, 2 H of $COCH_2N$), 3·0—2·70 (multiplet, 8 H, of the piperazine CH_2 groups), 2·32 (singlet, 3 H of NCH_3), 2·0—1·45 (broad singlet, 6 H of the other CH_2 groups of the seven-membered ring). [e] Hemihydrate. [f] M.p. in a capillary. [g] See Experimental. [h] Monohydrate. [i] Melts first at 124 to 127°C and resolidifies.

genation carried out to complete cessation of hydrogen absorption was always accompanied by debenzylation so that the products were amino alcohols *XXIV*–*XXIX* with a secondary amino group. The only anomaly was represented by the hydrogenation of the benzyl-2-furfurylamino derivative *XII* when debenzylation did not take place but rather a hydrogenolytic cleavage of 2-furfuryl, the binding of which to the nitrogen atom is apparently even more labile than the binding of benzyl. The product was then the derivative *XXVIII*. Experimental data on the amino alcohols *XIX*–*XXIX* are contained in Table III.



XIX, R = $N(CH_2CH_2CH_3)_2$
XX, R = $N(CH_2CH_2OH)_2$
XXI, R = 
XXII, R = 
XXIII, R = 

XXIV, R = $NHCH_3$
XXV, R = $NHCH(CH_3)_2$
XXVI, R = $NHCH_2CH(CH_3)_2$
XXVII, R = 
XXVIII, R = $NHCH_2C_6H_5$
XXIX, R = 

The oxime of 2-acetyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene[4] was reduced with sodium and ethanol to 1-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl)ethylamine (*XXX*). Reaction of ketone *I* with methylmagnesium iodide yielded the tertiary alcohol *XXXI*. In an attempt to obtain the formamide derivative *XXXII* we subjected the alcohol *XXXI* to the action of sodium cyanide in a mixture of acetic acid and sulfuric acid[18,19]. The main reaction product obtained was a compound melting at 102–103°C and distilling without decomposition at 210–215°C/1 Torr. According to analysis it has a formula $C_{14}H_{18}$ but, judging from its boiling point, it might be a dimer $C_{28}H_{36}$. The same substance was obtained when attempting to dehydrate the tertiary alcohol *XXXI* by heating with a small amount of iodine. The primarily formed 2-isopropenyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene is apparently very unstable and readily dimerizes under the reaction conditions. By comparison with the literature we found that also isopropenylbenzene has a tendency to dimerize, especially on treatment with hot hydrochloric acid[20], by treatment with cold sulfuric acid[21] and also by treatment with stannic chloride[22]; the dimerization product was identified as 1,1,3-trimethyl-3-phenylindane[23]. By analogy, we derived the following formula for our compound: 1,1,3-trimethyl-3-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl)-1,2,3,5,6,7,8,9-octahydrocyclohept(*f*)indene (*XXXIV*). The correctness of the formula was confirmed by NMR spectra. The non-

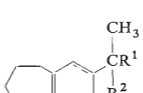
TABLE II

Benzylideneamines *XIVa*—*XVIIIa* and Benzylamines *XIVb*—*XVIIIb*

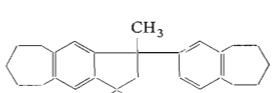
Compound[a] (method)	B.p., °C/Torr m.p., °C (solvent)	Formula (m. w.)	Calculated/Found			
			% C	% H	% N	% Cl
XIVa (A)	98—102/10[b]	—	—	—	—	—
XVa (A)	140—142/17[c]	—	—	—	—	—
XVIa (A)	144/10[d]	$C_{12}H_{11}NO$ (185·2)	77·81 77·51	5·99 6·09	7·56 7·58	— —
XVIIa (A)	144/0·6[e]	$C_{14}H_{20}N_2O$ (232·3)	72·38 72·80	8·68 8·65	12·06 11·71	— —
XVIIIa (A)[f]	138/15	$C_{14}H_{21}N$ (203·3)	82·70 82·99	10·41 10·58	6·89 6·82	— —
XIVb (B)[f]	96/12	—	—	—	—	—
XIVb-HCl	180—181 (ethanol–ether)	$C_{11}H_{18}ClN$ (199·7)	66·13 66·13	9·08 9·14	7·01 6·87	17·78 17·62
XVb (B)	118/2[g]	—	—	—	—	—
XVb-HCl	283—284[h] (ethanol–ether)	$C_{13}H_{20}ClN$ (225·8)	69·15 68·89	8·93 8·89	6·21 6·32	15·71 15·77
XVIb (B)	114/1[i]	—	—	—	—	—
XVIb-HCl	217—219[h] (ethanol)	$C_{12}H_{14}ClNO$ (223·7)	64·41 64·00	6·31 6·38	6·26 6·36	15·84 15·77
XVIIb (B)	154/1[j]	—	—	—	—	—
XVIIb-2 HCl[k]	225—227[h] (ethanol)	$C_{14}H_{26}Cl_2N_2O_2$ (325·3)	51·70 51·94	8·05 7·88	8·61 8·51	21·81 22·18
XVIIIb (B)[l]	104/1[m]	$C_{14}H_{23}N$ (205·3)	81·89 82·01	11·29 11·30	6·82 6·65	— —
XVIIIb-HCl	222—223[h] (ethanol–ether)	$C_{14}H_{24}ClN$ (241·8)	69·54 69·48	10·01 9·90	5·79 5·84	14·66 14·48

[a] Yields of method A varied between 86 and 97%, of method B between 91 and 97%. [b] n_D^{21} 1·5211; ref.[15] gives b.p. 208—210°C/744 Torr. [c] n_D^{22} 1·5506; ref.[16] gives b.p. 136°C/16 Torr. [d] n_D^{25} 1·5735; ref.[12] mentions the compound but does not characterize it. [e] n_D^{25} 1·5432; mentions in ref.[13,14] do not characterize the compound. [f] See Experimental. [g] n_D^{21} 1·5275; ref.[10] describes a different preparation procedure and reports a b.p. of 145—147°C/15 Torr for the base and a m.p. of 284°C for the hydrochloride. [h] In a capillary. [i] n_D^{21} 1·5480; ref.[11,12] describes the preparation by reduction with catalytic methods and reports for the base a b.p. of 115—124°C/4 Torr and for the hydrochloride a m.p. of 208—212°C, and 208—214°C, respectively. [j] n_D^{22} 1·5267; ref[13,14] describe a different preparation procedure and report only the b.p. of the base as 200 to 202°C/20 Torr. [k] Monohydrate. [l] Reduction done in boiling dibutyl ether. [m] n_D^{21} 1·5020.

crystallizing fractions of the mother liquors after this compound apparently contained small amounts of the desired formamide *XXXII* since alkaline hydrolysis resulted in a small amount of an oily amine which yielded a crystalline picrate. Analysis of the base and of the picrate, as well as the NMR spectrum of the base confirmed that we were dealing here with the desired 2-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl)-2-propylamine (*XXXIII*).



XXX, $R^1 = NH_2$, $R^2 = H$
XXXI, $R^1 = OH$, $R^2 = CH_3$
XXXII, $R^1 = NHCHO$, $R^2 = CH_3$
XXXIII, $R^1 = NH_2$, $R^2 = CH_3$



XXXIV

A systematic pharmacological testing was done with the salts of the following bases (Tables I–III show the nature of these salts). The way of administration, their acute toxicity in mice (LD_{50} in mg/kg) and the dose D in mg/kg which was applied in most *in vivo* tests are shown: *VI* (*i.v.*, 75, 15), *VII* (*i.v.*, 125, 25), *VIII* (*i.v.*, 67·5, 12), *IX* (*i.v.*, 100, 20), *X* (*p.o.*, > 2500, 300), *XI* (*p.o.*, > 2500, 300), *XII* (*p.o.*, > 2500, 300), *XIII* (*i.v.*, 50, 10), *XIVb* (*i.v.*, 50, 10), *XVb* (*i.v.*, 37·5, 7), *XVIb* (*i.v.*, 50, 10), *XVIIb* (*i.v.*, 137·5, 25), *XVIIIb* (*i.v.*, 35, 7), *XX* (*i.v.*, 60, 12), *XXIII* (*i.v.*, 100, 20). *XXVIII* (*p.o.*, 2000, 300), *XXX* (*i.v.*, 50, 10).

Of the amino ketones, the most interesting results were obtained with the methylpiperazine derivative *VI* which brings about in rats with normal tension pronounced and protracted depressions of blood pressure (it was not confirmed in rats with experimental hypertension), shows signs of adrenolytic activity, has a pronounced diuretic effect in mice, on the isolated rat intestine shows a myotropic spasmolytic activity (against barium chloride spasms), at a higher dose depresses heart inotropy and frequency, somewhat shortens the thiopental sleep in mice and causes motor disturbances in the rotating-rod test with mice. The ethoxycarbonylpiperazine derivative *VII*, on the other hand, has only a slight local anaesthetic effect and shows signs of antiarrhythmic activity (toward chloroform arrhythmia). The amino ketone *XIII* causes pronounced, short-term drops of blood pressure in rats with normal pressure and, similarly to *VI*, shows a myotropic spasmolytic effect of the papaverine type. In rabbit cornea it has a more powerful anaesthetic effect than cocaine.

Of the secondary benzylamine derivatives, compounds *XIVb* and *XVIIIb* bring about a short-term drop of blood pressure in rats. Compound *XVIIb* has a pronounced mydriatic effect on mouse pupil and shortens the thiopental sleep of mice. The amino alcohol *XX* has a slight central stimulatory effect (increases motility in mice), brings about a short-term drop of blood pressure and pronouncedly increases the blood sugar level. The amine *XXX* was of no special interest with the exception of a slight locally anaesthetic effect.

The other amino alcohols (acute toxicity in mice LD_{50} in mg/kg on intravenous application given) were studied in tests focussed on a possible adrenomimetic or adrenolytic activity: *XIX* (20), *XXI* (34), *XXII* (85), *XXIV* (38), *XXV* (33), *XXVI* (23), *XXVII* (17), *XXIX* (50). The following tests were performed: effect on the hypotensive reaction of narcotized cats following administration of 0·1 mg/kg isoprenaline *i.v.*, interaction of the compounds with isoprenaline in guinea pigs during histamine bronchospasm (test for β-adrenolytic activity), β-adrenomimetic effect

TABLE III

Amino Alcohols *XIX*—*XXIX*

Compound (method)	M.p., °C (solvent)	Formula (m. w.)	Calculated/Found			
			% C	% H	% N	% Cl
XIX-HM[a]	73—74[b]	$C_{23}H_{35}NO_5$	68·12	8·70	3·45	—
(D)		(405·5)	67·67	8·60	3·75	—
XX-HM[a,c]	114—115[d]	$C_{21}H_{33}NO_8$	59·00	7·77	3·29	—
(D)		(427·5)	59·24	7·44	3·30	—
XXI	95—96[e]	$C_{18}H_{27}NO$	79·07	9·95	5·12	—
(D)	(ether)	(273.4)	79·35	9·99	5·36	—
XXI—HM[a])	131—132[d]	$C_{22}H_{31}NO_5$	67·83	8·02	3·60	—
		(389·5)	67·57	8·03	3·52	—
XXII	89—90	$C_{18}H_{28}N_2O$	74·94	9·79	9·72	—
(D)[f]	(hexane)	(288·4)	74·72	9·93	9·71	—
XXII-2 HCl	218—220	$C_{18}H_{30}Cl_2N_2O$	59·82	8·37	7·76	19·62
	(ethanol)	(361·4)	59·62	8·57	7·92	19·30
XXIII	139—140[g]	$C_{20}H_{30}N_2O_3$	69·33	8·73	8·09	—
(D)	(ethyl acetate)	(346·5)	69·71	8·78	8·20	—
XXIII-HM[a,h]	83—84[b]	$C_{24}H_{34}N_2O_7 . 0{\cdot}5\ H_2O$	61·12	7·48	5·94	—
		(471·5)	61·19	7·55	6·11	—
XXIV-HCl	119—120	$C_{14}H_{22}ClNO$	65·74	8·67	5·47	13·86
(E)	(ethanol-ether)	(255·8)	65·78	8·75	5·30	13·62
XXV-HCl	168·5—170	$C_{16}H_{26}ClNO$	67·70	9·23	4·94	12·49
(E)[f]	(ethanol–ether)	(283·8)	67·59	9·13	4·79	12·47
XXVI-HCl	176—177	$C_{17}H_{28}ClNO$	—	—	4·70	11·92
(E)	(ethyl acetate)	(297·9)			4·68	11·93
XXVII-HCl	168—169[d]	$C_{19}H_{30}ClNO$	70·45	9·34	4·33	10·94
(E)		(323·9)	70·36	9·57	4·38	11·01
XXVIII-2 HCl	211—212	$C_{20}H_{26}ClNO$	72·39	7·90	4·21	10·69
(E)[i]	(ethanol)	(331·9)	72·27	7·88	4·37	11·01
XXIX-2 HCl	261—262	$C_{20}H_{34}Cl_2N_2O_2$	59·26	8·47	6·91	17·49
(E)	(ethanol)	(405·4)	58·93	8·31	7·32	17·25

[a] Hydrogen maleate. [b] Ethyl acetate–ether. [c] Monohydrate. [d] Ethyl acetate–ethanol–ether. [e] NMR spectrum: δ 7·07 (singlet, 3 H of the benzene ring), 4·65 (triplet, 1 H of the OH-bearing CH group), 3·90 (singlet, disappears after deuteration, 1 H of OH), 2·80 (multiplet, 4 H of the CH_2 groups vicinal to the benzene ring), 2·20—2·65 (multiplet, 6 H of the CH_2 groups vicinal to the N atom), 1·75 (multiplet, 6 H of the remaining CH_2 groups of the seven-membered ring), 1·55 (multiplet, 6 H of the remaining CH_2 groups of the piperidine ring). [f] See Experimental. [g] UV spectrum: λ_{max} 265·5 nm (log ε 3·61), 274 nm (3·58): IR spectrum: 819 and 889 (1,2,4-C_6H_3), 1090 and 1130 (CHOH), 1705 (NCOOR) and 3170 (OH) cm^{-1}. [h] Hemihydrate. [i] In this case, debenzylation was replaced by a cleavage of 2-furfuryl.

in a test with isolated trachea, inhibitory effect of the compounds toward adrenaline arrhythmia and changes of blood pressure after application of the compounds to monkeys with normal tension. In all the tests the compounds studied were found either ineffective or very little effective so that their affinity toward the adrenergic system is very low.

Some of the compounds showed inhibitory effects in *in vitro* tests toward growth of some microbial species. Compounds *VII*, *XII*, *XXVIII* and *XXX* at concentrations of 12·5—100 μg/ml showed antimicrobial activity of a rather wide spectrum (toward *Streptococcus β-haemolyticus, Staphylococcus pyogenes aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa, Escherichia coli, Salmonella typhi abdominalis, Proteus vulgaris*). Compounds *X*, *XI*, *XIX*, *XXVI* and *XXVII* at concentrations of 25—100 μg/ml were specifically active against *Mycobacterium tuberculosis* H 37 Rv; a similar activity was shown by compounds *XXVIII* and *XXX*. Finally, some compounds at concentrations of 62·5—125 μg/ml were active against *Trichophyton mentagrophytes*.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block; the samples were dried in the usual way. UV spectra (in methanol) were recorded in a Unicam SP 700 spectrophotometer, IR spectra (in Nujol) in a Unicam SP 200 G spectrophotometer and NMR spectra (in deuteriochloroform) in a ZKR 60 spectrometer (Zeiss, Jena).

2-Bromoacetyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*II*)

(A) *In acetic acid*: Bromine (8·0 g) was added dropwise over 15 min under stirring and cooling with water to a solution of 9·4 g 2-acetyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene[3,4] (*I*, b.p. 118—122°C/0·5 Torr) in 30 ml acetic acid. The mixture was stirred for 3 h and then combined with 150 ml ice-cold water. The separated oil was separated, washed with ice-cold water several times and dissolved in 50 ml benzene and 15 ml ether. After drying with Na_2SO_4 the solution was evaporated. The residue (12·5 g oil) crystallized in greater part on standing in the refrigerator. M.p. 58—59°C (ether–hexane). For $C_{13}H_{15}BrO$ (267·2) calculated: 58·44% C, 5·66% H, 29·91% Br; found: 58·42% C, 5·55% H, 29·75% Br. (B) *In ether*: Bromine (8·5 g) was added dropwise under stirring at 0—5°C to a solution of 9·9 g ketone *I* in 25 ml ether with 0·15 g anhydrous aluminium chloride. The mixture was stirred for another hour at the given temperature, left for 4 h at room temperature and evaporated to dryness at reduced pressure (25°C). The cooled residue was mixed with ice-cold water and some light petroleum, filtered and washed first with water and then with light petroleum; 12·5 g (89%), m.p. 58—60°C.

N-Benzylidene-2,3,3-trimethyl-2-butylamine (*XVIIIa*) (Method A)

A solution of 39 g 2,3,3-trimethyl-2-butylamine[17] in 30 ml benzene was slowly mixed with 35·3 g benzaldehyde; the solution warmed spontaneously. The mixture was stirred for 3 h and then left to stand overnight. The separated water was withdrawn and the benzene solution was distilled: 62·5 g (90%), b.p. 138°C/15 Torr, n_D^{25} 1·5185. Analytical data are shown in Table II. Benzylideneamines *XIVa*—*XVIIa* also shown in Table II were prepared analogously.

Benzylisobutylamine (*XIVb*) (Method B)

A solution of 125 g N-benzylideneisobutylamine in 200 ml ether was added dropwise over 1 h to a solution of 40 g lithium aluminium hydride in 200 ml ether and the mixture was refluxed for 1 h. After standing overnight it was decomposed by adding slowly 200 ml 20% sodium hydroxide, the precipitate was filtered and washed with ether. The ether filtrate was distilled:

139·5 g (97%), b.p. 96°C/12 Torr, n_D^{22} 1·4978. The hydrochloride melted at 180—181°C (ethanol–ether). Ref.[9] describes the reduction with sodium amalgam in ethanol and reports for the base a b.p. of 217—220°C and a m.p. for the hydrochloride of 175°C. Our analytical data are shown in Table II. In analogy, benzylamines *XVb*—*XVIIIb* shown also in Table II, were synthesized.

2-(N-Benzyl-N-cyclohexylaminoacetyl)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XI*) (Method C)

A solution of 18·8 g bromo ketone *II* in 140 ml ether was added over 10 min to 24·6 g benzylcyclohexylamine (*XVb*) in 50 ml ether. The mixture was stirred for 30 min at room temperature and refluxed for 2 h. After standing overnight the hydrobromide of the starting amine was filtered, the filtrate evaporated to dryness, the residue dissolved in 100 ml warm light petroleum, filtration was applied to remove another small amount of insoluble substance and the filtrate was evaporated. A total of 26 g crude base was obtained which was recrystallized before analysis from light petroleum, m.p. 84—85°C. UV spectrum: λ_{max} 261·5 nm (log ε 4·12). IR spectrum; 699 and 721 (C_6H_5), 821, 902 (1,2,4-C_6H_3), 1566 and 1601 (Ar), and 1699 cm^{-1} (Ar—CO). *Hydrochloride*, m.p. 159—160°C, in capillary 163—165°C (ethanol–ether). The analytical data are shown in Table I. Amino ketones *III*—*X*, *XII* and *XIII*, also shown in Table I, were prepared analogously.

1-(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-2-yl)-2-(4-methylpiperazino)ethanol (*XXII*) (Method D)

A solution of 10·0 g dihydrochloride (hemihydrate) of amino ketone *VI* in 20 ml water and 80 ml methanol was made alkaline with 12 ml 20% NaOH and, over 30 min, a solution of 3·0 g sodium borohydride in 50 ml water with 1 ml 20% NaOH was added. The mixture was heated for 1 h to 50—60°C, cooled to 20°C and decomposed by slowly adding 35 ml of dilute HCl (3 : 5), filtered and the filtrate was freed of methanol and some water by evaporation at reduced pressure. The residue was made alkaline with 20% NaOH and the product was isolated by extraction with a mixture of benzene and ether (1 : 1). A total of 7·2 g crude base was obtained which was recrystallized from hexane, m.p. 89—90°C. NMR spectrum: δ 7·08 (singlet, 3 H, aromatic protons), 4·68 (triplet, 8 Hz, 1 H of the hydroxyl-bearing CH group), 3·79 (singlet, 1 H, OH), 2·65 (multiplet, 4 H of the CH_2 groups adjacent to the benzene ring), 2·70—2·40 (multiplet, 8 H of the CH_2 groups of piperazine), 2·30 (singlet, 3 H of NCH_3), 1·40—2·00 (deformed singlet, 6 H of the remaining CH_2 groups of the seven-membered ring). Dihydrochloride, m.p. 218—220°C (ethanol). The analytical data are shown in Table III. Amino alcohols *XIX*—*XXI* and *XXIII* were prepared analogously (Table III).

1-(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-2-yl)-2-isopropylaminoethanol (*XXV*) (Method E)

Platinum dioxide (0·5 g) was added to a solution of 10·0 g hydrochloride of amino ketone *IX* in 140 ml ethanol and the mixture was shaken in an atmosphere of hydrogen at normal temperature until complete cessation of hydrogen absorption (8 h). The catalyst was filtered off and the filtrate evaporated to dryness. The residue was mixed with a small amount of ethyl acetate and ether and filtered. A total of 7·0 g (93%) hydrochloride of the product was obtained, m.p. 168·5-170°C (ethanol–ether). The analytical data are shown in Table III. Amino alcohols *XXIV* and *XXVI*—*XXIX* (Table III) were prepared analogously.

1-(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-2-yl)ethylamine (*XXX*)

A solution of 26 g oxime of 2-acetyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene[4] (m.p. 88–90°C) in 150 ml ethanol was added dropwise to 80 g sodium and the mixture was refluxed to dissolution (5 h), in the course of which further 550 ml of ethanol were gradually added. After cooling, it was decomposed by an addition of 200 ml water and the mixture was steam-distilled, the distillate receiver containing 25 ml of concentrated HCl in 120 ml water. The distillate (3 liters) was evaporated to dryness at reduced pressure. The remaining hydrochloride was recrystalized from a mixture of ethanol and ether; 19·0 g, m.p. 162–163°C. For $C_{13}H_{20}ClN$ (225·8) calculated: 69·16% C, 8·93% H, 15·71% Cl, 6·20% N; found: 69·15% C, 8·96% H, 15·69% Cl, 6·37% N. Decomposition of a sample of the hydrochloride with 20% NaOH and extraction with ether yielded a base, boiling at 146°C/10 Torr, n_D^{21} 1·5438. For $C_{13}H_{19}N$ (189·3) calculated: 82·48% C, 10·12% H, 7·40% N; found: 82·29% C, 10·53% H, 7·12% N.

2-(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-2-yl)-2-propanol (*XXXI*)

A solution of 40 g ketone *I* in 140 ml ether was added dropwise to a solution of methylmagnesium iodide (from 38 g methyl iodide and 6·2 g magnesium in 120 ml ether). The mixture was refluxed for 3 h, cooled, decomposed by adding 30 g ammonium chloride in 140 ml water and the ether phase after drying with $MgSO_4$ was evaporated. A total of 43 g residue was obtained. It crystallized on dissolving in 20 ml boiling hexane; m.p. 55–56°C. For $C_{14}H_{20}O$ (204·3) calculated: 82·30% C, 9·87% H; found: 82·27% C, 9·80% H.

1,1,3-Trimethyl-3-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl)-1,2,3,5,6,7,8,9-octahydrocyclohept(*f*)indene (*XXXIV*)

A) A cold mixture of 15 ml H_2SO_4 and 15 ml acetic acid was added to 42 g alcohol *XXXI* in 80 ml acetic acid and, under stirring, mixed with 28 g sodium cyanide, added gradually at less than 10°C. After 10 min of stirring, further 42 ml H_2SO_4 in 30 ml acetic acid was added, the mixture was stirred for 3 h and left for 48 h to stand at room temperature. It was then decomposed by pouring into 1·5 l cold water, neutralized with 20% NaOH, the precipitated solid was filtered and washed with water. It was dissolved in warm benzene, the solution was dried with Na_2SO_4 and evaporated. A part (3 g) of the residue (40 g) was crystallized from hexane to yield a compound melting at 102–103°C. Distillation of the remainder yielded 16 g of a compound boiling at 210–215°C/1 Torr which crystallized quantitatively, m.p. 102–103°C (hexane). NMR spectrum: δ 6·70–7·06 (multiplet, 5 H of the benzene ring protons), 2·72 (broad singlet, 8 H of the CH_2 groups adjacent to the benzene rings), 2·05 and 2·40 (doublet, J = 13 Hz, 2 H of the CH_2 group of the five-membered ring), c. 1·65 (multiplet, 12 H of the remaining CH_2 groups of the seven-membered rings), 1·65 (singlet, 3 H, C—CH_3), 1·03 and 1·30 (singlets, 6 H of CH_3—C—CH_3). For $C_{28}H_{36}$ (372·6) calculated: 90·26% C, 9·74% H; found: 90·11% C, 9·88% H. *B*) A mixture of 20·0 g alcohol *XXXI* and 80 mg iodine was heated gradually up to 200°C. After cooling, it was dissolved in a mixture of ether and benzene, the solution was washed with a solution of sodium bicarbonate and sodium thiosulfate, dried and evaporated. Distillation yielded 15 g product boiling at 208–214°C/1 Torr which crystallized on mixing with hexane. M.p. 102–103°C. The mixed melting point with the product prepared as under *A*) showed no depression.

2-(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-2-yl)-2-propylamine (*XXXIII*)

The mother liquor after crystallization of the hydrocarbon *XXXIV* obtained as under *A*) was examined by thin-layer chromatography on alumina and shown to contain a small amount

of another compound (formamide *XXXII*). The mother liquor was evaporated at reduced pressure to dryness and the residue refluxed for 48 h with excess aqueous-ethanolic solution of KOH. After cooling it was diluted with water and extracted with ether. Treatment of the extract yielded 0·60 g basic product boiling at 158°C/10 Torr, n_D^{20} 1·5516. The NMR spectrum: 9 7·10 (multiplet, 3 H of the benzene ring protons), 2·80 (doublet, 4H, CH_2 groups adjacent to the benzene ring), 1·72 (broad singlet, 6 H of the remaining CH_2 groups of the seven-membered ring), 1·56 (singlet, 2 H, NH_2), 1·45 (singlet, 6 H of CH_3—C—CH_3). For $C_{14}H_{21}N$ (203·3) calculated: 82·70% C, 10·41% H, 6·89% N; found: 83·17% C, 10·45% H, 6·42% N. *Picrate*, m.p. 252—254°C under decomposition (ethanol). For $C_{20}H_{24}N_4O_7$ (432·4) calculated: 55·55% C, 5·59% H, 12·96% N; found: 55·64 %C, 4·86% H, 12·86% N.

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