CYCLIC AMIDINES DERIVED FROM BENZ[*c*,*d*]INDOLE AND 4,5-DIHYDRO-3*H*-1-BENZAZEPINE INCLUDING SOME RELATED COMPOUNDS: SYNTHESIS AND PHARMACOLOGICAL SCREENING

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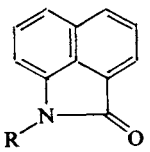
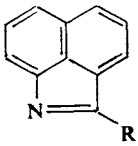
Received December 7th, 1984

Reactions of naphthostyril (*I*) with primary and secondary amines and titanium tetrachloride afforded cyclic amidines *III*—*IX*. Hydrogenation of *I* on Pd—C resulted in the 6,7,8,8a-tetrahydro derivative *X* which gave by treatment with sodium amide and 3-dimethylaminopropyl chloride the N-(aminoalkyl) compound *XI*. Reduction of *I* and its N-methyl derivative *II* with sodium amalgam in aqueous sodium hydroxide gave the 2a,3,4,5-tetrahydro derivatives *XII* and *XIII*. Reaction of *XIII* with sodium amide and 3-dimethylaminopropyl chloride afforded the 2a-(aminoalkyl) compound *XIV*. 1,3,4,5-Tetrahydro-1-benzazepin-2-one (*XV*) treated with primary amines and titanium tetrachloride gave the amidines *XVI*—*XVIII*. 3-Methyl-7,8,9,9a-tetrahydro-1*H*-benz[*d*,*e*]isoquinoline (*XIX*) was reduced with sodium borohydride to compound *XX* which was alkylated with propargyl bromide to 1-methyl-2-propargyl-2,3,3a,4,5,6-hexahydro-1*H*-benz[*d*,*e*]isoquinoline (*XXI*). An attempt to prepare the 2-(2-phenylethyl) analogue by treatment of compound *XX* with phenylacetyl chloride and by the following reduction with lithium aluminium hydride resulted in the open-chain amine *XXII*. The lactams *I*, *II*, *X*, and *XIII* showed some discoordinating, hypothermic, peripheral vasodilating, hyperglycaemic, diuretic and antiinflammatory effects. The amidines *III*—*IX* and *XVI*—*XVIII* had local anaesthetic, slight hypotensive, antiarrhythmic, peripheral myorelaxant, papaverine-like spasmolytic and thiopental potentiating effects.

A longer time ago our group investigated aminoalkyl derivatives of 1,3,4,5-tetrahydrobenz[*c*,*d*]indole and naphthostyril (*I*) as potential psychotropic agents[1]. In the present communication we come back to this topic and describe the synthesis of some further compounds containing in their molecules this *peri*-condensed tricyclic system. By the reaction of naphthostyril (*I*) (ref.[2,3]) with isobutylamine, benzylamine, 2-phenylethylamine, 2-diethylaminoethylamine, 2-morpholinoethylamine, 3-morpholinopropylamine and 1-methylpiperazine in the presence of titanium tetrachloride in a boiling mixture of tetrahydrofuran and benzene (for analogy, *cf.*[4]) there were prepared the cyclic amidines *III*—*IX*. In most cases the products were isolated and characterized as pure amidine bases which were then transformed to hydrochlorides. In some cases the bases were oily and it was necessary to purify them after transformation to hydrochlorides. In the Experimental only the preparation of the amidine *VIII* is being described. The other compounds, prepared by this

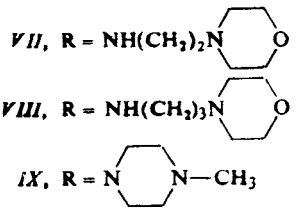
general method (method *A*), are assembled in Table I with the usual experimental data.





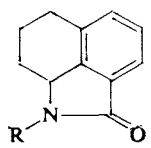
I, R = H
II, R = CH_3

III, R = $NHCH_2CH(CH_3)_2$
IV, R = $NHCH_2C_6H_5$
V, R = $NHCH_2CH_2C_6H_5$
VI, R = $NH(CH_2)_2N(C_2H_5)_2$



VII, R = $NH(CH_2)_2$N O
VIII, R = $NH(CH_2)_3$N O
IX, R = N N—CH_3

Literature[5] described the pressure catalytic hydrogenation of naphthostyril (*I*) on nickel; a mixture of two tetrahydro derivatives was obtained which was separated to the higher melting and minor 6,7,8,8a-tetrahydro derivative *X* and to the prevailing lower melting 2a,3,4,5-tetrahydro derivative *XII*. Now we have carried out the catalytic hydrogenation of naphthostyril (*I*) in acetic acid on palladium–carbon at 98°C under pressure and obtained *X* in a yield of 71%. Its alkylation with 3-dimethylaminopropyl chloride in a mixture of toluene and dimethylformamide in the presence of sodium hydride afforded in a low yield an oily base whose ^{1}H NMR spectrum confirmed the structure *XI*. Neutralization with fumaric acid resulted in a hygroscopic hydrogen fumarate whose analysis indicated that it was a monohydrate.



X, R = H
XI, R = $(CH_2)_3N(CH_3)_2$

Reduction of naphthostyril (*I*) with sodium amalgam in a boiling aqueous solution of sodium hydroxide gave in a yield of 55% the lower melting 2a,3,4,5-tetrahydro derivative *XII*. Its alkylation with 3-dimethylaminopropyl chloride in the presence of sodium amide in a mixture of toluene and dimethylformamide afforded product consisting mainly of two components (TLC); in addition to N-alkylation the alkylation on $C_{(2a)}$ takes probably simultaneously place. For this reason naphthostyril (*I*) was transformed by a modification of the described procedure[6,7] to 1-methylnaphthostyril (*II*). The modification consisted in methylation of naphthostyril

TABLE I

Cyclic amidines *III*—*IX*, *XVI*—*XVIII* and their hydrochlorides (prepared by method *A*)

Compound (% yield)	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found			
			% C	% H	% Cl	% N
III[a]	158—160	$C_{15}H_{16}N_2$	80·32	7·19	—	12·49
(70)	(benzene–light petroleum)	(224·3)	80·09	7·40	—	12·72
III-HCl	222—225	$C_{15}H_{17}ClN_2$	—	—	13·60	10·74
	(ethanol–ether)	(260·8)	—	—	13·53	10·53
IV[b]	179—181	$C_{18}H_{14}N_2$	83·69	5·46	—	10·84
(53)	(ethanol)	(258·3)	83·75	5·57	—	10·57
IV-HCl	257—258	$C_{18}H_{15}ClN_2$	73·34	5·13	12·03	9·50
	(ethanol)	(294·8)	73·30	5·19	12·12	9·52
V-HCl	256—260	$C_{19}H_{17}ClN_2$	73·89	5·55	11·48	9·07
(80)	(ethanol)	(308·8)	73·65	5·51	11·56	8·91
VI[c]	127—128	$C_{17}H_{21}N_3$	76·36	7·91	—	15·72
(83)	(benzene–light petroleum)	(267·4)	76·19	8·09	—	15·80
VI-2 HCl[d]	237—240	$C_{17}H_{23}Cl_2N_3$ · 2·5 H_2O	53·05	7·20	18·42	10·92
	(aqueous ethanol)	(384·8)	53·29	7·28	18·29	10·89
VII-2 HCl	292—294	$C_{17}H_{21}Cl_2N_3O$	57·63	5·97		11·86
(66)	(aqueous ethanol)	(354·3)	57·83	6·11		11·72
VIII[e]	116—118	$C_{18}H_{21}N_3O$	73·19	7·16	—	14·23
(58)	(benzene–light petroleum)	(295·4)	72·96	7·32	—	14·32
VIII-2 HCl[f]	290—292	$C_{18}H_{23}Cl_2N_3O$ · H_2O	55·96	6·52	18·36	10·88
	(aqueous ethanol)	(386·3)	56·34	6·57	18·33	10·95
IX-2 HCl[g,h]	297—300	$C_{16}H_{19}Cl_2N_3$ · 0·5 H_2O	57·66	6·05	21·28	12·61
(72)	(aqueous ethanol)	(333·3)	57·78	5·97	21·77	12·61
XVI-HCl	206—207	$C_{13}H_{19}ClN_2$	65·39	8·02	14·85	11·73
(93)	(ethanol–ether)	(238·8)	65·63	7·99	14·71	11·60
XVII-HCl	178—179	$C_{14}H_{21}ClN_2$	66·52	8·37	14·03	11·08
(45)	(ethanol–ether)	(252·8)	66·59	8·48	13·78	10·98
XVIII-HCl[i]	202—203	$C_{14}H_{21}ClN_2$	66·52	8·37	14·03	11·08
(78)	(ethanol–ether)	(252·8)	66·54	8·56	14·22	10·96

[a] UV spectrum: λ_{max} 258 nm (log ε 4·24), 327 nm (3·56), 343 nm (3·77), 380 nm (3·69), inflexes 263 nm (4·10), 286·5 nm (3·70); IR spectrum: 760, 770 (3 adjacent Ar—H), 1 060, 1 149, 1 221, 1 230 (C—N), 1 355, 1 370 (C—H in gem CH_3), 1 570, 1 605 (Ar), 1 630 (C=N), 3 200 cm^{-1} (NH); ^1H NMR spectrum: δ 6·80—8·10 (m, 6 H, ArH), 355 (d, J = 8·0 Hz, 2 H, CH_2N), 2·05

TABLE I
(*Continued*)

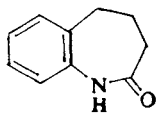
(m, 1 H, CH), *c.* 1·00 (1 H, NH), 0·96 (d, J = 3·0 Hz, 6 H, 2 CH_3). [b] UV spectrum: λ_{max} 255 nm (log ε 4·28), 290 nm (3·77), 303·5 nm (3·69), 331 nm (3·68), 347 nm (3·81), 386 nm (3·75), infl. 264 nm (4·21); IR spectrum: 700, 728, 757, 780 (5 and 3 adjacent Ar—H), 1 062, 1 223, 1 236 (C—N), 1 342, 1 356 (Ar—N), 1 568, 1 602 (Ar), 1 625 (C=N), 2 780 (CH_2—N), 3 120 cm^{-1} (NH); ^{1}H NMR spectrum: δ 7·00—8·00 (m, 11 H, ArH), 6·28 (bs, 1 H, NH), 4·75 (s, 2 H, $ArCH_2N$).[c] UV spectrum: λ_{max} 253 nm (log ε 4·23), 288 nm (3·69), 300 nm (3·62), 313·5 nm (3·26), 328 nm (3·59), 337 nm (3·47), 344·5 nm (3·73), 389 nm (3·63), infl. 262 nm (4·13); IR spectrum: 771 (3 adjacent Ar—H), 1 070, 1 177, 1 225 (C—N), 1 370 (Ar—N), 1 456, 1 523, 1 576, 1 602 (Ar), 1 622 (C=N), 2 800, 2 860, 2 920, 2 950 (CH_2, CH_3), 3 200 cm^{-1} (NH); ^{1}H NMR spectrum: δ 7·00—8·00 (m, 6 H, ArH), 6·75 (bs, 1 H, NH), 3·72 (t, J = 6·0 Hz, 2 H, CH_2 adjacent to ArN), 2·72 (t, J = 6·0 Hz, 2 H, CH_2 adjacent to diethylamine N), 2·55 (q, J = 7·0 Hz, 4 H, CH_2NCH_2 of diethylamino), 1·03 (*t*, J = 7·0 Hz, 6 H, 2 CH_3 of diethylamino). [d] Solvate with 2·5 H_2O. [e] See Experimental. [f] Monohydrate. [g] Hemihydrate. [h] UV spectrum λ_{max} 255 nm (log ε 4·48), 285·5 nm (3·80), 296 nm (3·78), 351 nm (3·96), 389 nm (3·94), infl. 249·5 nm (4·42); IR spectrum: 757, 790 (3 adjacent Ar—H), 1 070 (C—N), 1 590 (Ar), 1 625 (C=N), 2 440, 2 555, 2 670 (NH^+), 3 380, 3 470 cm^{-1} (O—H of H_2O). [i] ^{1}H NMR spectrum: δ 11·35 (bs, 1 H, NH), 10·60 (bs, 1 H, $=NH^+$—), 7·05—7·70 (m, 4 H, ArH), 3·56 (t, J = 7·0 Hz, after ^2H_2O d, J = 7·0 Hz, 2 H, CH_2N), 1·70—2·85 (m, 7 H, remaining 3 CH_2 and CH), 1·00 (d, J = 7·0 Hz, 6 H, 2 CH_3).

with dimethyl sulfate in toluene in the presence of sodium amide. Reduction of compound *II* thus obtained with sodium amalgam gave 1-methyl-2a,3,4,5-tetrahydro derivative *XIII* in a yield of 59% (the procedure included the cyclization of the partially formed amino acid by heating in acid solution to 100°C). Alkylation of compound *XIII* with 3-dimethylaminopropyl chloride in the presence of sodium hydride proceeded then in the only way possible, *i.e.* on $C_{(2a)}$. The base, released from the pure fumarate, was used for recording the ^{1}H NMR spectrum which confirmed the structure *XIV*.

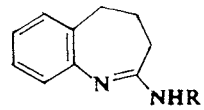
XII, R = R¹ = H
XIII, R = CH_3, R¹ = H
XIV, R = CH_3, R¹ = $(CH_2)_3N(CH_3)_2$

1,3,4,5-Tetrahydro-1-benzazepin-2-one (*XV*) (ref.[8,9]) was transformed by method *A* and by using propylamine, butylamine and isobutylamine to the cyclic amidines *XVI*–*XVIII*. These compounds were isolated as hydrochlorides and are included in Table I.

1*H*-Benz[*d*,*e*]isoquinoline is a homologue of benz[*c*,*d*]indole. 3-Methyl-7,8,9,9a-tetrahydro-1*H*-benz[*d*,*e*]isoquinoline (*XIX*), which was prepared by the Bischler–

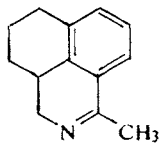


XV

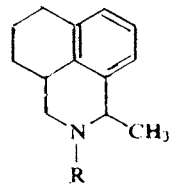


XVI, R = $(CH_2)_2CH_3$
XVII, R = $(CH_2)_3CH_3$
XVIII, R = $CH_2CH(CH_3)_2$

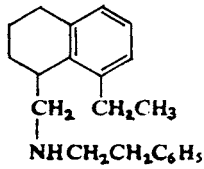
-Napieralski reaction of 1-(acetamidomethyl)-1,2,3,4-tetrahydronaphthalene according to the literature[10], was reduced with sodium borohydride in methanol to 1-methyl-2,3,3a,4,5,6-hexahydro-1*H*-benz[*d*,*e*] isoquinoline (*XX*). The molecule of this compound contains two asymmetrical centers and the oily base obtained is apparently the mixture of both racemates. One of them probably prevails because this base afforded in a relatively high yield a hydrochloride which is evidently homogeneous. Alkylation of the oily base *XX* with propargyl bromide in boiling 1-butanol in the presence of potassium carbonate gave the oily *XXI* which was characterized only as the picrate. With the aim at preparing the 2-(2-phenylethyl) derivative the oily base *XX* was subjected to treatment with phenylacetyl chloride in benzene and the neutral product obtained was reduced with lithium aluminiun hydride in ether. An oily base was obtained which distilled *in vacuo* without decomposition and afforded a crystalline hydrogen maleate. The ^{1}H NMR spectrum showed the presence



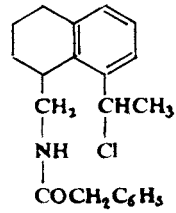
XIX



XX, R = H
XXI, R = $CH_2C{\equiv}CH$



XXII



XXIII

of 27 protons, *i.e.* by two more than expected. It is necessary to assume the opening of the nitrogen-containing ring during the reaction sequence; the reaction with phenylacetyl chloride is apparently connected with the intermolecular N-dealkylation. The primarily formed substituted benzyl chloride *XXIII* was then transformed by treatment with lithium aluminium hydride in two ways: it was dehalogenated by hydrogenolysis, and it was reduced in the amide group. The structure of 8-ethyl--1-(2-phenylethylamino)methyl-1,2,3,4-tetrahydronaphthalene (*XXII*) was assigned to the product.

The compounds prepared were evaluated by methods of the general pharmacological screening as such or in the form of salts described in the Experimental or in Table I; oral or intravenous administration was used in the *in vivo* tests. The acute toxicity was estimated in mice (LD_{50} values in mg/kg and the way of administration given) doses (D in mg/kg) used in the scrreening are also given: *I*, 1 000, *p.o.*, 200; *II*, 1 500, *p.o.*, 300; *III*, 12, *i.v.*, 2; *IV*, 500, *p.o.*, 100; *V*, 1 500, *p.o.*, 300; *VI*, 30, *i.v.*, 6; *VII*, 50, *i.v.*, 10; *VIII*, 42·5, *i.v.*, 8·5; *IX*, 40, *i.v.*, 8; *X*, 375, *p.o.*, 100; *XIII*, 2 000, *p.o.*, 300; *XIV*, 60, *i.v.*, 12; *XVI*, 18, *i.v.*, 3·5; *XVII*, 15, *i.v.*, 3; *XVIII*, 15, *i.v.*, 3; *XX*, 30, *i.v.*, 6; *XXII*, 50, *i.v.*, 10. In doses higher than D compounds *III*, *XVI*, *XVII* and *XVIII* had central stimulating effects. Some typical effects manifested in doses D or in lower doses: Significant inhibition of the spontaneous motoric activity in mice by compound *II*. In the rotarod test in mice ataxia was brought about by compounds *I*, *II*, *X* and *XIII*. Hypothermic effect in rats (reduction of the rectal temperature by 1°C or more): *I* (1·1–2·0°C), *II* (1·5–2·0°C), *III* (mild effect), *XIII* (2·0–2·3°C). Thiopental sleeping time in mice was prolonged to 200% of the control value or more by compounds *IV* and *IX*. Local anaesthetic effect on the rabbit's eye cornea (weaker than that of cocaine): *III*, *XVII*, *XVIII*. Local anaesthetic effect in the test of infiltration anaesthesia in guinea-pigs: *XVII*, *XVIII*, *XX* (concentration of 0·5–1·0%). Myotropic spasmolytic effect towards barium chloride contractions of the isolated rat's duodenum (intensity like with papaverine): *III*, *VI*. Indication of parasympathomimetic effect manifested by miosis of the mouse eye: *IX*, *XVIII*. A long-lasting myorelaxant effect on the gastrocnemius muscle in rats was shown by compound *XVIII*, administered in a dose of 30 mg/kg *i.v.* (*i.e.* 2 LD_{50}; the animals were connected to a respiratory pump). Compound *XIV* had some antagonistic effect towards catalepsy brought about by perphenazine in rats (anticataleptic action). Most of the compounds had mild and brief hypotensive effect in normotensive rats in the dose D (or lower): *III* (1 mg/kg *i.v.*), *VI* (3 mg/kg *i.v.*), *VII* (5 mg/kg *i.v.*), *VIII* (4·25 mg/kg *i.v.*), *IX*, *XIV* (a longer lasting effect), *XVI*, *XVII*, *XX* (a longer lasting effect; an oral dose of 120 mg/kg decreased the blood pressure by 20% in 2 h after the administration, after 4 h the decrease was still 10% in comparison with the starting value), *XXII* (the drops of the pressure were followed by a pressoric phase lasting for 25–180 min). Peripheral vasodilating activity in guinea-pigs evaluated by the increase of temperature of the ear by 1°C: *I*, *II*, *IX*, *X*. Mild antiarrhythmic

effect in mice (protection of less than 50% of mice from the occurrence of ventricular fibrillations elicited by inhalation of chloroform): *IV*, *VII*, *VIII*, *XVI*. Antiarrhythmic effect in rats towards calcium chloride fibrillation: *XIV*, *XXII*. Diuretic effect in mice (diuresis increased by 100% as compared with the control): *I*, *II*, *X*. Hypoglycaemic effect in rats (decrease of the blood sugar level by 20%): *XIV*, *XXII*. Hyperglycaemic effect in rats (increase of the blood sugar level by 20%): *I*, *II*, *V*, *VI*, *IX*, *X*, *XIII*, *XIV*. Antiinflammatory effect in rats (a significant inhibition of the development of rat hind limb oedema elicited by subplantar administration of 0·1 ml 10% kaolin suspension): *II*, *X*, *XIII*. In general, two subgroups can be differentiated among the substances prepared and tested. The first is formed by the nonbasic lactams (*I*, *II*, *X*, *XIII*) which are little toxic and showed some discoordinating, hypothermic, peripheral vasodilating, diuretic, antiinflammatory and hyperglycaemic effects. The second subgroup are the rather toxic cyclic amidines (*III*–*IX*, *XVI*–*XVIII*) having local anaesthetic, slight hypotensive, antiarrhythmic, papaverine-line spasmolytic and thiopental potentiating effects.

The compounds were also tested for antimicrobial activity *in vitro* (species, compound and the minimum inhibitory concentration in μg/ml are given unless they exceed 125 μg/ml): *Streptococcus β-haemolyticus*, *IV* 50, *V* 25, *XXII* 100; *Staphylococcus pyogenes aureus*, *IV* 50, *V* 25; *Mycobacterium tuberculosis* H37Rv, *I* 50, *III* 100, *IV* 50, *V* 25, *XXII* 50; *Saccharomyces pasterianus*, *II* 125, *XIII* 125; *Trichophyton mentagrophytes*, *I* 125, *II* 125, *XIII* 125, *XXII* 125.

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 60 Pa over P_2O_5 at room temperature or at 77°C. UV spectra (in methanol) were recorded with a Unicam SP 700 spectrophotometer, IR spectra (in Nujol unless stated otherwise) with a Unicam SP 200G spectrophotometer and ^1H NMR spectra (in C^2HCl_3) with a ZKR-60 (Zeiss, Jena) spectrometer. The homogeneity of the compounds was tested by thin-layer chromatography on silica gel (Silufol).

2-(3-Morpholinopropylamino)benz[*c*,*d*]indole (*VIII*) (Method *A*)

A mixture of 8·45 g *I* (ref.[2,3]) and 150 ml tetrahydrofuran was stirred and treated first with 36·0 g 4-(3-aminopropyl)morpholine and then over 10 min with a solution of 8·6 g $TiCl_4$ in 20 ml benzene, it was refluxed for 16 h, cooled and decomposed by addition of 12 ml water. The solid was filtered off and washed with 25 ml tetrahydrofuran. The filtrate was evaporated *in vacuo*, the residue was dissolved in chloroform, the solution was washed with dilute aqueous ammonia and water, dried with $MgSO_4$ and filtered with charcoal. The filtrate was evaporated, the residue was dissolved in 150 ml ether and the base was extracted into 1 : 3 dilute hydrochloric acid. The aqueous acid layer was combined with the solid hydrochloride, the base was released with NH_4OH and extracted with benzene. The extract was washed with water, dried ($MgSO_4$) and evaporated; 8·7 g (58%) *VIII*, m.p. 116–118°C (benzene–light petroleum). UV spectrum: λ_{max} 252·5 nm (log ε 4·26), 262 nm (4·05), 286·5 nm (3·64), 299 nm (3·47), 328 nm (3·54), 344 nm (3·76), 384 nm (3·70), infl. 246 nm (4·18). IR spectrum (KBr): 767, 786 (3 adjacent Ar—H), 1 111 (C—O—C), 1 456, 1 525, 1 573, 1 601 (Ar), 1 625 (C=N), 2 770, 2 800 (CH_2—N), 3 200

cm^{-1} (NH). ^1H NMR spectrum: δ 7·00—8·00 (m, 6 H, ArH), *c.* 3·75 (m, 6 H, CH_2OCH_2 and 2-NCH_2), 3·65 (s, 1 H, NH), *c.* 2·40 (m, 6 H, remaining 3 CH_2N), 1·90 (m, 2 H, CH_2 in the middle of the propane chain).

The yellow hydrochloride was prepared by neutralization of the ethanolic solution of the base with a solution of HCl in ether, m.p. 290—292°C (ethanol). The analysis (*cf.* Table I) identified it to be the dihydrochloride monohydrate.

6,7,8,8a-Tetrahydrobenz[*c*,*d*]indol-2(1*H*)-one (*X*)

A solution of 250 g *I* (ref.[2,3]) in 1·5 l acetic acid containing the Pd catalyst, prepared from 4·0 g $PdCl_2$ and 20 g charcoal, was hydrogenated at 98°C and an initial pressure of 815 MPa H_2; the calculated consumption of 66 l H_2 took place over 4 h. After cooling the mixture was filtered and the catalyst was washed with 150 ml hot acetic acid. The filtrate was evaporated *in vacuo* and the residue crystallized on standing. The product was filtered, washed with benzene and light petroleum, and dried; 150 g, m.p. 163—164°C. Processing of the mother liquor gave 41·5 g of a second product which was recrystallized from 270 ml benzene; 33·3 g, m.p. 163—164°C. The total yield was 183 g (71%). Lit.[5], m.p. 165°C.

1-(3-Dimethylaminopropyl)-6,7,8,8a-tetrahydrobenz[*c*,*d*]indol-2(1*H*)-one (*XI*)

A mixture of 8·65 g *X*, 50 ml toluene and 3·0 g 50% NaH (dispersion in oil) was stirred and refluxed for 30 min under nitrogen. After cooling it was treated with a solution of 7·6 g 3-dimethylaminopropyl chloride in 20 ml dimethylformamide and the mixture was refluxed for 6 h. After cooling the mixture was decomposed with water and extracted with benzene. The extract was washed with water and the base was transferred by shaking into 25 ml 1·25M-H_2SO_4. The aqueous layer was made alkaline with 5M-NaOH and the released base was extracted with ether. The extract was washed with water, dried with K_2CO_3 and filtered with charcoal. Evaporation of the filtrate gave 4·0 g inhomogeneous base which was purified by crystallization of the hydrochloride from a mixture of ethanol and ether. Decomposition of the hydrochloride with NH_4OH and extraction with ether gave 1·55 g (12%) almost homogeneous base which was neutralized with 0·70 g fumaric acid in 4 ml ethanol; 1·05 g hydrogen fumarate monohydrate, m.p. 141—142°C (ethanol). For $C_{20}H_{26}N_2O_5 + H_2O$ (392·4) calculated: 61·21% C, 7·19% H; found: 61·21% C, 6·67% H. The released oily base was used for recording the ^1H NMR spectrum: δ 7·25—7·70 (m, 3 H, ArH), 4·10—4·37 (q, 1 H, 8a-H), 3·60 (t, 2 H, $ArCH_2$), 2·21 (s, 6 H, CH_3NCH_3), 1·00—3·00 (m, 10 H, remaining 5 CH_2).

1-Methylbenz[*c*,*d*]indol-2(1*H*)-one (*II*)

A mixture of 33·8 g *I* (ref.[2,3]), 240 ml toluene and 11·7 g powdered (under toluene) $NaNH_2$ was stirred and refluxed for 45 min. At 90°C it was treated with a solution of 37·8 g dimethyl sulfate in 40 ml toluene over 20 min. When the exothermic reaction was over, the mixture was stirred and refluxed for 6 h. After cooling it was decomposed with 120 ml water and 40 ml 5M-NaOH, it was stirred for 30 min, the organic layer was separated and washed repeatedly with water and 2·5M-NaOH. After drying with K_2CO_3 and filtration with charcoal the filtrate was evaporated *in vacuo*. The residue (36·7 g) is the crude product (m.p. 69—71°C) containing some starting *I*. It was heated for 15 min with 200 ml 5M-NaOH to 100°C, after cooling to 70°C extracted with benzene, the extract was repeatedly washed with warm 5M-NaOH, finally with water, dried and evaporated; 28·5 g (76%), m.p. 77—79°C. Crystallization from a mixture of benzene and light petroleum gave a pure product melting at 78—80°C. Lit.[6,7], m.p. 77—79°C, and 79·4 to 80·8°C, respectively.

2a,3,4,5-Tetrahydrobenz[*c,d*]indol-2(1*H*)-one (*XII*)

A stirred solution of 30·0 g *I* (ref.[2,3]) in 600 ml hot 2M-NaOH was treated under nitrogen with 500 g 10% sodium amalgam, added over 6 h (reflux condenser, bath temperature 155–160°C). The mixture was heated for 10 h under reflux, allowed to stand overnight at room temperature, the separated solid was dissolved by heating on a water bath, mercury was separated, the filtrate was diluted with water, acidified to pH 3–4 with hydrochloric acid and the solution heated for 2 h in a water bath to 90°C. It was cooled and the crude product was filtered. It was extracted with chloroform, the extract was evaporated and the residue was crystallized from benzene giving 17·0 g (55%) *XII*, m.p. 156–158°C. Lit.[5], m.p. 157°C.

1-Methyl-2a,3,4,5-tetrahydrobenz[*c,d*] indol-2(1*H*)-one (*XIII*)

A refluxing mixture of 28·5 g *II*, 440 ml 2M-NaOH and 200 ml ethanol was stirred and treated under nitrogen over 4 h with 360 g 10% sodium amalgam. The mixture was refluxed for further 7 h with stirring, ethanol was distilled off and mercury was separated. The mixture was diluted with 150 ml water, acidified to a pH of 3·5–4 and stirred and heated for 2 h to 95–100°C. After cooling the product was extracted with ether, the extract was dried ($MgSO_4$), filtered with charcoal and distilled; 17·2 g (59%) *XIII*, b.p. 128–130°C/40 Pa. The product solidified and melted at 58–60°C. UV spectrum: λ_{max} 259 nm (log ε 3·89). IR spectrum: 758, 774 (3 adjacent Ar—H), 1 608 (Ar), 1 728 cm^{-1} (CO—N in the five-membered ring). For $C_{12}H_{13}NO$ (187·2) calculated: 76·97% C, 7·00% H, 7·48% N; found: 76·52% C, 6·79% H, 7·44% N.

1-Methyl-2a-(3-dimethylaminopropyl)-2a,3,4,5-tetrahydrobenz[*c,d*] indol-2(1*H*)-one (*XIV*)

A suspension of 4·25 g 50% NaH (dispersion in oil) in 120 ml toluene was stirred and slowly treated with 15·0 g *XIII* and the mixture was heated for 15 min to 110°C. 3-Dimethylaminopropyl chloride (10·7 g) was then slowly added and the mixture was heated with stirring for 3 h to 110°C, allowed to stand for 3 days at room temperature and diluted with 400 ml ether. The bases were extracted with 140 ml 1·25M-H_2SO_4, the acid solution was washed with ether, made alkaline with K_2CO_3 and the bases were extracted with ether. The extract was washed with water, dried with K_2CO_3, filtered with charcoal and evaporated. The residue (14·15 g) was neutralized with 6·05 g fumaric acid in 25 ml boiling ethanol and the solution was diluted with ether. Crystallization gave 15·9 g (51%) hydrogen fumarate, m.p. 110–120°C. Analytical sample, m.p. 123 to 124°C (ethanol–acetone–water). For $C_{21}H_{28}N_2O_5$ (388·5) calculated: 64·93% C, 7·27% H, 7·21% N; found: 64·57% C, 7·26% H, 7·13% N.

A sample of the fumarate was treated with NH_4OH, the pure oily *XIV* was isolated by extraction with ether and used for recording the ^1H NMR spectrum: δ 6·54–7·20 (m, 3 H, ArH), 3·15 (s, 3 H, $CONCH_3$), 2·50–2·92 (def. t, 2 H, $ArCH_2$), 1·00–2·50 (m, 10 H, remaining 5 CH_2), 2·12 (s, 6 H, CH_3NCH_3).

1-Methyl-2,3,3a,4,5,6-hexahydro-1*H*-benz[*d,e*]isoquinoline (*XX*)

A stirred solution of 16·2 g *XIX* (ref.[10]) in 150 ml methanol was slowly treated with 6·4 g $NaBH_4$, heated for 1 h to 60°C and evaporated *in vacuo*. The residue was distributed between water and benzene, the benzene solution was dried with K_2CO_3 and evaporated; 16·3 g crude base *XX*. It was dissolved in 20 ml acetone and the solution was neutralized with a solution of HCl in ether; 16·2 g (83%) hydrochloride melting at 173–177°C. Two crystallizations from a mixture of ethanol and ether gave 13·9 g of needles, m.p. 183–185°C. For $C_{13}H_{18}ClN$ (223·7) calculated: 69·78% C, 8·10% H, 15·85% Cl, 6·26% N; found: 69·82% C, 7·92% H, 15·85% Cl, 6·17% N.

The pure hydrochloride (13·9 g) was treated with 10% NaOH, the base was extracted with ether and distilled; 11·4 g oil, b.p. 125—127°C/0·21 kPa. IR spectrum: 747, 773, 786 (3 adjacent Ar—H), 1 021, 1 033, 1 070, 1 145 (C—N), 1 584 (Ar), 3 270 cm^{-1} (NH). For $C_{13}H_{17}N$ (187·3) calculated: 83·37% C, 9·15% H, 7·48% N; found: 83·16% C, 9·14% H, 7·41% N.

1-Methyl-2-propargyl-2,3,3a,4,5,6-hexahydro-1*H*-benz[*d*,*e*]isoquinoline (*XXI*)

A mixture of 5·5 g *XX*, 4·8 g K_2CO_3, 4·22 g propargyl bromide and 100 ml 1-butanol was stirred and refluxed for 12 h. After cooling the salts were filtered off, the filtrate was evaporated and the residue was chromatographed on a column of 100 g neutral Al_2O_3 (activity II). Benzene eluted 5·0 g product which was distilled; 3·0 g (45%) oily *XXI*, b.p. 158—166°C/0·4 kPa. Picrate, m.p. 183—185°C (acetone–ethanol). For $C_{22}H_{22}N_4O_7$ (454·4) calculated: 58·14% C, 4·88% H, 12·33% N; found: 57·98% C, 4·89% H, 12·29% N.

8-Ethyl-1-(2-phenylethylamino)methyl-1,2,3,4-tetrahydronaphthalene (*XXII*)

A solution of 6·35 g *XX* in 25 ml benzene was stirred and treated dropwise with a solution of 8·0 g phenylacetyl chloride in 5 ml benzene, the mixture was allowed to stand overnight at room temperature and then refluxed for 8 h. After cooling the reaction mixture was washed with 25% K_2CO_3, 10% NaOH, 10% hydrochloric acid and water, the benzene solution was dried with K_2CO_3 and evaporated *in vacuo*. The residue (10·3 g) was dissolved in 50 ml ether and the solution was added to a stirred suspension of 1·5 g $LiAlH_4$ in 50 ml ether. The mixture was stirred for 1 h at 20°C, refluxed for 8 h, cooled and decomposed under stirring by addition of 1·5 ml water, 1·5 ml 15% NaOH and 4·5 ml water. After 30 min stirring the precipitate was filtered off, washed with ether and the filtrate was extracted into 450 ml 15% hydrochloric acid (in three portions). The aqueous layer of the hydrochloride was made alkaline with 20% NaOH and the base was isolated by extraction with benzene. Processing of the extract gave 7·7 g crude base which was distilled; 4·5 g (45%), b.p. 195—198°C/0·16 kPa. ^{1}H NMR spectrum: δ 7·21 (s, 5 H, C_6H_5), 6·75—7·45 (m, 3 H, remaining ArH), 3·50—4·30 (m, 3 H, $ArCH_2$ and ArCH), 1·50—3·40 (m, 13 H, remaining 6 CH_2 and NH), 1·34 (t, 3 H, CH_3 of ethyl). For $C_{21}H_{27}N$ (293·4) calculated: 85·95% C, 9·27% H, 4·77% N; found: 86·35% C, 8·99% H, 4·32% N.

Hydrogen maleate (5·5 g) was prepared by neutralization of 4·5 g base with 2·2 g maleic acid in 120 ml ether; needles melting at 138—139°C (acetone–ether). For $C_{25}H_{31}NO_4$ (409·5) calculated: 73·32% C, 7·63% H, 3·42% N; found: 73·69% C, 7·23% H, 3·36% N.

Compounds XI *and* XIV *were prepared by Dr K. Pelz and compounds* XX—XXII *by Dr V. Seidlová in this laboratory. The authors thank their colleagues from the respective departments of this institute for their contributions: Mrs J. Komancová, Mrs A. Slavíková, Mr K. Havel* (†), *Mrs V. Šmídová, Mrs J. Kropáčová (elemental analyses) and Dr A. Šimek* (†) *(microbiological screening).*

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Translated by the author (M. P.).