MANNICH AND GRIGNARD REACTION OF SOME N-(2-PROPYNYL) AZAHETEROCYCLES

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1,4-Disubstituted butynes *IV*—*VII* were prepared by Mannich reaction of N-(2-propynyl) derivatives of 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline, piperidine and azacycloheptane with polyoxymethylene and another heterocyclic amines. Reaction of 3-(1-piperidinyl)-1-propynylmagnesium bromide or 3-(1-azacycloheptyl)-1-propynylmagnesium bromide afforded alcohols *X*—*XIII*.

Compounds of the general formulae *I* and *IIa,b* have been the subject of many studies. Both free bases and quaternary salts of these acetylenic derivatives exhibit fungicidal, bactericidal[1-4], hypotensive[5] or hypnotic[6] effects; some of them are corrosion inhibitors[7]. Parkinsonic, cholinergic and halucinogenic effects of tremorine and its homologues have been investigated[8,9]. Preparation and testing of other propynylamines are the result of the interest in new psychotropic compounds[10]. In this communication we describe the preparation of further compounds of the type *IIa* and *IIb*.

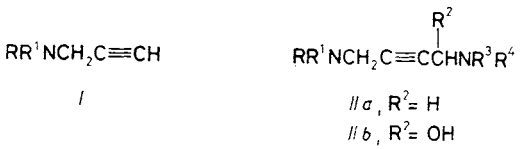
The so far described symmetrically substituted 1,4-bis(N-azaheterocyclic) 2-butyne derivatives *IIa* were synthesized starting from 1,4-diiodo-2-butyne or 1,4-dichloro-2-butyne[11-13]; the best approach to unsymmetrically substituted derivatives was Mannich condensation of substituted propynes with polyoxymethylene and secondary amines (see e.g. refs[14-16]). The latter reaction was also employed by us in the preparation of compounds *IV*—*VII*. We started from 1-(2-propynyl)piperidine, 1-(2-propynyl)azacycloheptane, 1-(2-propynyl)-1,2,3,4-tetrahydroquinoline or 2-(2-propynyl)-1,2,3,4-tetrahydroisoquinoline, which on heating with an excess of polyoxymethylene and secondary amines (diethylamine, piperidine, pyrrolidine, morpholine, azacycloheptane, 1-methylpiperazine, 1,2,3,6-tetrahydropyridine, 1,2,3,4-tetrahydroisoquinoline) and with copper (*II*) acetate as catalyst in dioxane afforded butyne derivatives *IV*—*VII*, listed in Table I. Compounds *IVa*—*c* were also prepared without a catalyst or using only the stoichiometric ratio of the reactants. In both cases the yields were substantially lower. We also tried to prepare the Mannich bases *IVd* and *Vd* in the reversed manner, i.e. from 1-propynylazacycloheptane and 1,2,3,4-tetrahydroisoqui-

TABLE I

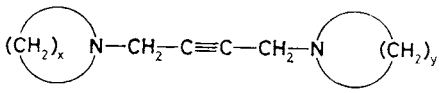
Physical and analytical data of compounds *IV*—*VII*

Product Secondary amine	B.p., °C/Pa Yield %	Formula (M.w.)	Calculated/Found		
			% C	% H	% N
IVa[a]	130—133/130	$C_{17}H_{24}N_2$	79·64	9·44	10·92
diethylamine	80	(256·4)	79·63	9·47	11·17
IVb[b]	130—140/133	$C_{17}H_{22}N_2$	80·27	8·72	11·01
pyrrolidine	93	(254·4)	80·31	8·86	11·09
IVc[c]	115—135/130	$C_{18}H_{24}N_2$	80·55	9·01	10·44
piperidine	60	(268·4)	80·38	8·95	10·58
IVd	165—172/27	$C_{19}H_{26}N_2$	80·80	9·28	9·92
azacycloheptane	59	(282·4)	80·39	9·52	9·99
IVe	160—170/40	$C_{17}H_{22}N_2O$	75·52	8·20	10·36
morpholine	39	(270·9)	75·88	8·49	10·38
IVf[d]	150—160/40	$C_{18}H_{25}N_3$	76·28	8·89	14·82
1-methylpiperazine	60	(283·4)	76·51	8·91	14·60
Va	130—136/40	$C_{17}H_{24}N_2$	79·64	9·44	10·92
diethylamine	71	(256·4)	79·80	9·43	10·78
Vb	160—175/40	$C_{17}H_{22}N_2$	80·27	8·72	11·01
pyrrolidine	57	(254·4)	80·18	9·00	11·26
Vc	160—165/40	$C_{18}H_{24}N_2$	80·55	9·01	10·44
piperidine	73	(268·4)	80·32	9·15	10·17
Vd	172—173/20	$C_{19}H_{26}N_2$	80·80	9·28	9·92
azacycloheptane	84	(282·4)	80·80	9·25	10·10
Ve	160—178/40	$C_{17}H_{22}N_2O$	75·52	8·20	10·36
morpholine	65	(270·4)	75·32	8·44	10·34
Vf	170—180/40	$C_{18}H_{25}N_3$	76·28	8·89	14·82
1-methylpiperazine	71	(283·4)	76·34	9·16	14·71
VIa	115—118/40	$C_{14}H_{22}N_2$	77·01	10·16	12·83
1,2,3,6-tetrahydropyridine	37	(218·3)	76·78	10·49	12·83
VIb	122—123/13	$C_{15}H_{26}N_2$	76·87	11·18	11·95
azacycloheptane	73	(234·4)	76·95	11·31	12·24
VIIa	137—139/120	$C_{15}H_{24}N_2$	77·53	10·41	12·06
1,2,3,6-tetrahydropyridine	52	(232·4)	77·64	10·71	11·79
VIIb	140—146/110	$C_{15}H_{27}N_3$	72·24	10·91	16·85
1-methylpiperazine	32	(249·4)	72·26	10·94	16·99
IVg	220/40[e]	$C_{22}H_{24}N_2$[f]			
1,2,3,4-tetrahydroisoquinoline	65	(316·4)			

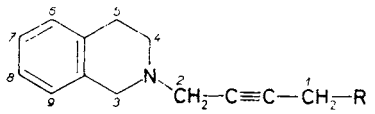
noline or 1,2,3,4-tetrahydroquinoline; however, these reactions led to more complex mixtures of bases. With 1,2,3,6-tetrahydropyridine, the general method of preparation of 1-(2-propynyl)azaheterocycles from the corresponding amine and 3-bromopropyne



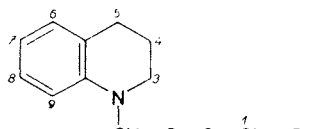
I *IIa*, R^2 = H; *IIb*, R^2 = OH



III

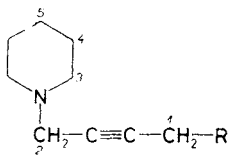


IV

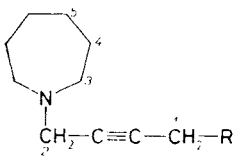


V

In formulae *IV* and *V*: *a*, R = diethylamino *b*, R = 1-pyrrolidinyl *c*, R = 1-piperidinyl *d*, R = 1-azacycloheptyl *e*, R = 4-morpholinyl *f*, R = 1-(4-methylpiperazinyl) *g*, R = 2-(1,2,3,4-tetrahydroisoquinolinyl)



VIa, R = 1-(1,2,3,6-tetrahydropyridinyl) *VIb*, R = 1-azacycloheptyl



VIIa, R = 1-(1,2,3,6-tetrahydropyridinyl) *VIIb*, R = 1-(4-methylpiperazinyl)

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[a] *IVa*. 2 CH_3I, m.p. 115–117°C (2-propanol; for $C_{19}H_{30}I_2N_2$ (540·2) calculated: 46·98% I, 5·19% N; found: 46·73% I, 5·08% N; [b] *Vb*. 2 CH_3I, m.p. 209·5–210·5°C (2-propanol), for $C_{19}H_{28}I_2N_2$ (538·3) calculated: 47·15% I, 5·20% N; found: 47·07% I, 5·22% N; [c] *IVc*. 2 CH_3I, m.p. 210–211°C (2-propanol), for $C_{20}H_{30}I_2N_2$ (552·3) calculated: 45·95% I, 5·07% N; found: 46·07% I, 5·08% N; [d] *Vf*. 2 CH_3I, m.p. 123–125°C (2-propanol), for $C_{20}H_{31}I_2N_3$ (567·3) calculated: 44·74% I, 7·07% N; found: 44·86% I, 7·15% N; [e] bath temperature, m.p. 55°C; [f] mass spectrum (*m/z*, % r.i.) 317 (M^+ + 1) (19), 211 (60), 183 (68), 132 (95), 104 (100), 78 (50), 53 (65), 42 (50).

did not give the tertiary amine but instead directly the quaternary salt, 1,1-di(2-propynyl)-1,2,3,6-tetrahydropyridinium bromide (*VIII*). Thus, even in this case it was not possible to prepare the bases *VIa* and *VIIa* in the reversed manner.

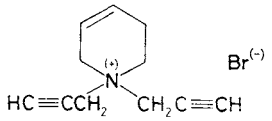
Some authors investigated the preparation of amino alcohols *IIb* (RR'N = piperidinyl). Reaction of acetylenes with ketones or aldehydes gave first alkynols or their esters which in Mannich reaction with polyoxymethylene and piperidine in the presence of copper(II) acetate afforded alcohols *IIb*, usually in good yields[17–20]. Another approach to these alcohols consists in reaction of substituted propynylmagnesium bromides with carbonyl compounds. In the series of N-azaheterocyclic compounds, the reaction of 3-(1-azacycloheptyl)propynylmagnesium bromide with ethyl orthoformate[21] or of 3-(1-azacycloheptyl)propynylmagnesium bromide with polyoxymethylene[22] has been described. Hennion and Campbell[23] prepared acetylenic 1,4-amino alcohols from substituted acetylenic amines by treatment with lithium or sodium amide in ammonia or with ethylmagnesium bromide in ether, followed by reaction with carbonyl compounds, the yields varying considerably. However, no reaction with heterocyclic amines has been carried out as yet.

Whereas we did not succeed in isolation of products when the conversion of acetylenes into acetylides was carried out with alkyllithium compounds (ethyllithium, butyllithium), reactions performed with ethylmagnesium bromide in tetrahydrofuran gave the desired products. We carried out the reaction of 3-(1-piperidinyl)-1-propynylmagnesium bromide with several aldehydes. Reaction with butanal afforded the liquid alcohol *Xa*; with benzaldehyde, 4-dimethylaminobenzaldehyde, 2-furaldehyde, 2- and 3-thiophenecarbaldehyde and 3-pyridinecarbaldehyde we obtained colourless crystalline alcohols *Xb–g*, along with some polymeric material which (according to NMR spectra) did not contain any aromatic protons. The reactions were carried out in tetrahydrofuran. With ether as solvent, the formation of polymeric compounds was also observed; in the case of reaction with benzaldehyde in ether we did not succeed to separate the product from the unreacted components. Alcohol *Xb* was converted into its acetyl derivative *Xh* by treatment with acetic anhydride in pyridine under catalysis with 4-dimethylaminopyridine. Without this catalyst the reaction proceeded only very sluggishly.

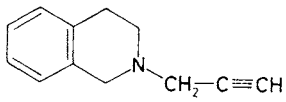
Under the same conditions, reaction of 3-(1-piperidinyl)-1-propynylmagnesium bromide with ketones gave complex mixtures of products as shown by GLC and TLC analyses. Alcohol *XIa*, obtained by reaction with acetone, was isolated by fractionation in vacuo, alcohol *XIb* from the reaction with cyclopentanone was purified by column chromatography. Since the oily residue could not be obtained free of the solvent under mild conditions, the alcohol *XIb* was converted into its crystalline methiodide.

Similarly, from azacycloheptane we prepared 3-(1-azacycloheptyl)-1-propynylmagnesium bromide which on reaction with butanal and cyclopentanone afforded

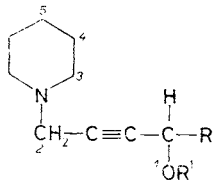
the respective alcohols *XIIa* and *XIIb*. Analogously to its piperidine derivative, the alcohol *XIIb* was isolated, after chromatography, as the methiodide.

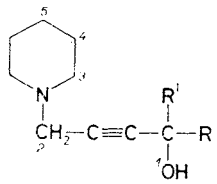


VIII



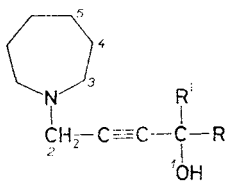
IX



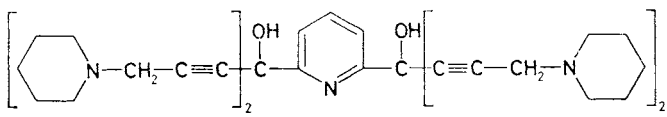


Xa, R = propyl ; R^1 = H
Xb, R = phenyl ; R^1 = H
Xc, R = 4-dimethylaminophenyl ; R^1 = H
Xd, R = 2-furyl ; R^1 = H
Xe, R = 2-thienyl ; R^1 = H
Xf, R = 3-thienyl ; R^1 = H
Xg, R = 3-pyridinyl ; R^1 = H
Xh, R = phenyl ; R^1 = acetyl

XIa, R = R^1 = methyl
XIb, R, R^1 = tetramethylene
XIc, R = 3-pyridinyl ; R^1 = 3-(1-piperidinyl)-1-propyn-1-yl
XId, R = 4-pyridinyl ; R^1 = 3-(1-piperidinyl)-1-propyn-1-yl
XIe, R = H ; R^1 = 3-(1-piperidinyl)-1-propyn-1-yl



XIIa, R^1 = H ; R = propyl
XIIb, R^1, R = tetramethylene



XIII

3-(1-Piperidinyl)-1-propynylmagnesium bromide also reacted with some esters. Reaction with ethyl 3-pyridinecarboxylate, ethyl 4-pyridinecarboxylate and diethyl

TABLE II

Physical and analytical data of compounds *X*—*XIII*

Product Yield %	M.p., °C (b.p., °C/Pa) (solvent)	Formula (M.w.)	Calculated/Found		
			% C	% H	% N
Xa	(120/27)	$C_{12}H_{21}NO$	73·80	10·84	7·17
44		(195·3)	73·77	11·09	7·24
Xb	112·5—113	$C_{15}H_{19}NO$	78·56	8·35	6·11
33	(cyclohexane)	(229·3)	78·67	8·38	5·91
Xc	95—98	$C_{17}H_{24}N_2O$	74·96	8·88	10·28
6	(cyclohexane)	(272·4)	74·98	8·94	10·05
Xd	99·5—100·5	$C_{13}H_{17}NO_2$	70·98	7·76	6·31
38	(cyclohexane)	(219·3)	70·90	7·74	6·29
Xe	122	$C_{13}H_{17}NOS$	66·34	7·28	5·95[a]
54	(benzene)	(235·3)	66·10	7·27	5·77
Xf	124—125	$C_{13}H_{17}NOS$	66·34	7·28	5·95[b]
36	(cyclohexane)	(235·3)	66·49	7·27	5·93
Xg	98—99	$C_{14}H_{18}N_2O$	73·01	7·88	12·16
41	(cyclohexane)	(230·3)	72·95	7·88	12·08
Xh	(140/6·7)[c]	$C_{17}H_{21}NO_2$	75·25	7·80	5·16
46		(271·4)	75·06	7·85	5·18
XIIa	(120—122/67)	$C_{13}H_{23}NO$	74·59	11·08	6·69
52		(209·3)	74·58	11·12	6·78
XIb	156—158[d]	$C_{14}H_{24}INO$	48·15	6·93	4·01
41	(2-propanol–ethyl acetate)	(349·2)	48·12	6·86	3·71
XIc	205—207[e]	$C_{25}H_{38}I_3N_3O$	38·63	4·93	5·41
34	(ethanol–water)	(777·3)	38·08	4·88	5·28
XId	146	$C_{22}H_{29}N_3O$	75·18	8·32	11·95
85	(cyclohexane–ethyl acetate)	(351·5)	74·80	8·29	11·80
XIe	170[f]	$C_{19}H_{32}I_2N_2O$	40·88	5·78	5·02
24	(methanol)	(558·3)	41·02	5·74	4·90
XIa	(120—123/530)[g]				
XIIb	179·5[h]	$C_{15}H_{26}INO$	49·59	7·21	3·86
40	(2-propanol–ethyl acetate)	(363·3)	49·68	7·18	3·58
XIII	110—112	$C_{39}H_{53}N_5O_2$	75·08	8·56	11·23
24		(623·9)	73·96	8·33	10·90
XIII[i]	180—190	$C_{43}H_{65}I_4N_5O_2$	42·06	5·62	5·70
	(ethanol)	(1 192)	42·40	5·42	5·78

[a] For *Xe* calculated: 13·62% S, found: 13·56% S; [b] for *Xf* calculated: 13·62% S, found: 13·80% S; [c] bath temperature; [d] methiodide of *XIb*; [e] trimethiodide of *XIc*; [f] dimethiodide of *XIe*; [g] reported[18] b.p. 120°C/600 Pa; [h] methiodide of *XIIb*; [i] tetramethiodide of *XIII*.2 H_2O.

2,6-pyridinedicarboxylate afforded alcohols *XIc, d* and *XIII*; analogously, ethyl formate gave alcohol *XIe*. Except the alcohol *XId* which was obtained in the crystalline state directly from the crude reaction mixture, the other products were again isolated by column chromatography and then converted into the corresponding methiodide.

The structure of all the new compounds has been confirmed by ^{1}H NMR spectra (Tables III and IV) in which the signals were distributed over a wide range and were easily assigned. For structurally similar compounds, the chemical shifts of the corresponding types of protons agreed well. 2-(2-Propynyl)-1,2,3,4-tetrahydroisoquinoline (*IX*) was prepared by reaction of 1,2,3,4-tetrahydroisoquinoline with 3-bromopropyne in the presence of potassium carbonate in butanone or by reduction of 2-(2-propynyl)isoquinolinium bromide with sodium borohydride; reduction of the latter compound with potassium formate in formic acid led to a complex mixture of products. For the preparation of 1-(2-propynyl)piperidine we also used the more accessible 3-chloropropyne.

EXPERIMENTAL

^{1}H NMR spectra were measured on a Bruker AM 400 (400·133 MHz) instrument in deuterochloroform or perdeuteromethanol with tetramethylsilane as internal standard. IR spectra were recorded on a Perkin–Elmer 325 spectrophotometer in chloroform, mass spectra on a Jeol DX 303/DA 5 000 spectrometer. Gas–liquid chromatography (GLC) was carried out on a Chrom 5 chromatograph (flame-ionization detector) on 2 500 × 3 mm columns packed with 3% OV 225 on Chromaton N-AW-DMCS, carrier gas nitrogen. Thin-layer chromatography (TLC) was performed on Silufol UV 254 foils in benzene–ethanol (9 : 1) or chloroform–ethanol (9 : 1).

1-(2-Propynyl)piperidine (*I*, RR'N = piperidinyl)

1-(2-Propynyl) chloride (74·5 g; 1 mol) was added dropwise to a stirred solution of piperidine (170 g; 2 mol) in dry diethyl ether (480 ml). After refluxing for 10 h, the separated piperidine hydrochloride (98·2 g; 81%) was filtered off. Most of the ether was distilled off through a column and another portion of piperidine hydrochloride (7·6 g; 6%) was removed by filtration. The remaining liquid residue was distilled as rapidly as possible at 1·5 kPa. The obtained distillate was then redistilled through a column. The principal fraction, boiling at 51°C/1·5 kPa (61·8 g; 50%), was shown by GLC to be completely pure 1-(2-propynyl)piperidine; a lower-boiling fraction was collected (8 g; 6%) which contained the product with less than 2% of piperidine. (The rapid distillation separates the product from the dissolved piperidine hydrochloride which decomposes on longer heating of the crude mixture and the distillate then contains piperidine even in the higher-boiling fractions).

2-(4-(1-Piperidinyl)-2-butynyl)-1,2,3,4-tetrahydroisoquinoline (*IVc*)

A mixture of base *IX* (3·0 g; 17·5 mmol), polyoxymethylene (5·3 g; 175 mmol), piperidine (3·0 g; 35 mmol), copper(II) acetate monohydrate (25 mg) and dioxane (10 ml) was gently refluxed for 16 h. The reaction mixture was decomposed with water (100 ml) and extracted three times with ether (50–60 ml portions). After drying over sodium sulfate, the solvent was evaporated and

TABLE III

^{1}H NMR spectra of compounds *IV*–*VII* (δ, $CDCl_3$)

	H-1	H-2	H-3	H-4	H-5	H-6	H-7,8,9	Other signals
IVa	3·46 s 2 H	3·51 s 2 H	3·74 s 2 H	2·93 t 2 H $J(4,5) = 6$	2·81 t 2 H $J(5,4) = 6$	6·95–7·08 m 1 H	7·01–7·15 m 3 H	2·54 q, 4 H ($J = 7{\cdot}2$, 22 × $\mathbf{CH_2CH_3}$); 1·06 t, 6 H ($J = 7{\cdot}2$, 2 × $\mathbf{CH_3CH_2}$)
IVb	3·45 s 2 H	2·54 s 2 H	3·78 s 2 H	2·96 t 2 H $J(4,5) = 6$	2·86 t 2 H $J(5,4) = 6$	6·97–7·09 m 1 H	7·00–7·18 m 3 H	2·52–2·69 m, 4 H ($NCH_2\mathbf{CH_2}$–); 1·68–1·88 m, 4 H ($NCH_2\mathbf{CH_2}$–)
IVc	3·32 t 2 H $J = 2$	3·53 t 2 H $J = 2$	3·75 s 2 H	2·92 t 2 H $J(4,5) = 6$	2·83 t 2 H $J(5,4) = 6$	6·97–7·05 m 1 H	7·05–7·19 m 3 H	2·37–2·60 m, 4 H ($NCH_2\mathbf{CH_2}$); 1·48–1·65 m, 4 H ($NCH_2\mathbf{CH_2}$); 1·34–1·50 m, 2 H ($NCH_2\mathbf{CH_2}CH_2$)
IVd	3·42 s 2 H	3·55 t 2 H $J = 1{\cdot}9$	3·78 s 2 H	2·96 t 2 H $J(4,5) = 5{\cdot}8$	2·85 t 2 H $J(5,4) = 5{\cdot}8$	7·02–7·05 m 1 H	7·03–7·11 m 3 H	2·71 t, 4 H ($NCH_2\mathbf{CH_2}$, $J = 5{\cdot}6$); 1·64–1·75 m, 4 H ($NCH_2\mathbf{CH_2}$); 1·56–1·67 m, 4 H ($NCH_2\mathbf{CH_2}CH_2$)
IVe	3·31 t 2 H $J = 2$	3·52 t 2 H $J = 2$	3·74 s 2 H	2·93 t 2 H $J(4,5) = 5{\cdot}9$	2·82 t 2 H $J(5,4) = 5{\cdot}9$	6·95–7·04 m 1 H	7·04–7·18 m 3 H	2·55 t, 4 H (N–$\mathbf{CH_2}CH_2$, $J = 4{\cdot}5$); 3·65–3·72 m, 4 H (O–$\mathbf{CH_2}CH_2$)
IVf	3·38 s 2 H	3·53 s 2 H	3·65 s 2 H	2·95 t 2 H $J(4,5) = 6$	2·83 t 2 H $J(5,4) = 6$	6·95–7·03 m 1 H	7·00–7·18 m 3 H	2·32 s, 3 H (N–CH_3); 2·35–2·78 m, 8 H ($NCH_2\mathbf{CH_2}N$)
IVg		3·55 s 4 H	3·78 s 4 H	2·95 t 4 H $J(4,5) = 6$	2·85 t 4 H $J(5,4) = 6$	7·00–7·09 m 2 H	7·07–7·20 m 6 H	

Va	3·35 t 2 H $J = 1·9$	4·00 t 2 H $J = 1·9$	3·26 t 2 H $J = 5·7$	1·99 m 2 H	2·75 t 2 H $J = 6·5$	6·72 d 1 H $J = 8·2$	6·64 t $J = 7·7$ 7·04 t $J = 7·8$ 6·94 d $J = 8·2$	0·99 t, 6 H (CH_3CH_2N, $J = 7·2$), 2·43 q, 4 H (CH_3CH_2N, $J = 7·2$)
Vb	3·36 t 2 H $J = 1·9$	4·02 t 2 H $J = 1·9$	3·28 t 2 H $J = 5·7$	2·00 m 2 H	2·75 t 2 H $J = 6·5$	6·73 d 1 H $J = 8·1$	6·65 t $J = 7·7$ 7·06 t $J = 8·5$ 6·96 d $J = 7·3$	2·47–2·60 m, 4 H (NCH_2CH_2), 1·69–1·82 m, 4 H (NCH_2CH_2)
Vc	3·32 t 2 H $J = 1·9$	4·07 t 2 H $J = 1·9$	3·25 t 2 H $J = 6·5$	2·03 m 2 H	2·80 t 2 H $J = 6·5$	6·78 d 1 H $J = 8·1$	6·70 t $J = 7·3$ 7·13 t $J = 8·5$ 7·00 d $J = 7·4$	1·35–1·52 m, 2 H ($N(CH_2)_2CH_2$), 1·56–1·71 m, 4 H (NCH_2CH_2) 2·35–2·55 m, 4 H (NCH_2CH_2)
Vd	3·28 t 2 H $J = 2$	3·99 t 2 H $J = 2$	3·25 t 2 H $J = 5·8$	1·99 m 2 H	2·73 t 2 H $J = 6·5$	6·73 d 1 H $J = 8·2$	6·64 m $J = 8·2$ 7·06 m 6·95 d $J = 7·5$	1·50–1·58 m, 4 H ($NCH_2CH_2CH_2$) 1·53–1·68 m, 4 H (NCH_2CH_2), 2·55 t, 4 H (NCH_2, $J = 5$)
Ve	3·23 t 2 H $J = 1·9$	4·03 t 2 H $J = 1·8$	3·28 t 2 H $J = 5·7$	1·99 m 2 H	2·76 t 2 H $J = 6·5$	6·72 d 1 H $J = 7·3$	6·66 t $J = 7·3$ 7·08 t $J = 8·2$ 6·97 d $J = 7·3$	2·48 t, 4 H (NCH_2CH_2O, $J = 4·5$) 3·69 t, 4 H (OCH_2, $J = 4·6$)
Vf	3·24 t 2 H $J = 1·8$	4·02 t 2 H $J = 1·8$	3·27 t 2 H $J = 5·7$	1·99 m 2 H	2·75 t 2 H $J = 6·5$	6·72 d 1 H $J = 8·3$	6·65 t $J = 7·4$ 7·08 t $J = 8·3$ 6·96 d $J = 7·3$	2·35–2·65 m, 8 H (NCH_2CH_2N) 2·28 s (NCH_3)
VIa	3·41 t 2 H $J = 1·9$	3·14 t 2 H $J = 1·9$	2·48 m 4 H	1·58–1·67 m 4 H	1·42 m 2 H			2·18–2·25 m, 2 H ($NCH_2CH_2CH{=}$) 2·65 t, 2 H ($J = 5·7$) $NCH_2CH_2CH{=}$); 3·06–3·13 m ($NCH_2C{=}$); 5·71 m (CH=CH)
VIb	3·38 s 2 H	3·28 s 2 H	2·49 m 4 H	1·53–1·65 m	1·41 m 2 H			1·53–1·65 m, 8 H ($NCH_2CH_2CH_2$— and H-4) 1·65–1·74 m, 4 H ($NCH_2CH_2CH_2$) 2·64–2·74 m, 4 H (NCH_2CH_2)

TABLE III
(*Continued*)

	H-1	H-2	H-3	H-4	H-5	H-6	H-7,8,9	Other signals
VIIa	3·41 t 2 H $J = 1·9$	3·39 t 2 H $J = 1·9$	2·64– 2·74 m	1·65–1·73 4 H	1·56–1·67 m 4 H			2·64–2·74 m, 6 H (H-3 and $NCH_2CH_2CH=$); 2·18–2·26 m 2 H ($NCH_2CH_2CH=$); 3·07–3·12 m, 2 H ($NCH_2CH=$); 5·70 m (CH=CH)
VIIb	3·32 t 2 H $J = 1·9$	3·37 t 2 H $J = 1·9$	2·65– 2·73 m 4 H	1·65–1·73 m 4 H	1·56–1·67 m 4 H			2·28 s, 3 H (NCH_3); 2·40–2·66 m 8 H (NCH_2CH_2N)

the residue fractionated in vacuo, the distillate being analyzed by GLC. Fraction of b.p. 115 to 135°C/130 Pa (2·8 g; 60%) consisted of the pure base *IVc* (for data see Tables I and III). Analogously were prepared the amines *IVa, b, d—g, Va—f, VIa, b, VIIa, b.*

1,1-Di(2-propynyl)-1,2,3,6-tetrahydropyridinium Bromide (*VIII*)

A mixture of 3-bromopropyne (4·6 g; 39 mmol), 1,2,3,6-tetrahydropyridine (5·8 g; 70 mmol) and butanone (30 ml) was refluxed for 6 h. The separated yellow crystals were collected and washed with butanone and ether. Two crystallizations from 2-propanol afforded 4·1 g (88%) of colourless crystals of quaternary salt *VIII*, m.p. 179—180°C. For $C_{11}H_{14}BrN$ (240·1) calculated: 55·02% C, 5·88% H, 5·83% N; found: 55·13% C, 5·89% H, 5·77% N. ^{1}H NMR spectrum (δ, $(CD_3)_2SO$): 2·50 t, 2 H (J = 2·4, C≡CH); 3·75 t, 2 H (J = 6·2, N—CH_2CH_2CH=); 4·14 to 4·22 m, 2 H (N—CH_2CH=); 4·47—4·62 m, 4 H ($NCH_2C{\equiv}C$); 5·76 d, 1 H (J = 10·5, NCH_2CH=); 6·03 d, 1 H (J = 10·5, $NCH_2CH{=}CH$).

2-(2-Propynyl)-1,2,3,4-tetrahydroisoquinoline (*IX*)

A) A solution of 3-bromopropyne (4·4 g; 38 mmol) in butanone (10 ml) was added dropwise to a stirred mixture of 1,2,3,4-tetrahydroisoquinoline (5·0 g; 38 mmol) in butanone (20 ml) and potassium carbonate (5·7 g; 41 mmol). The mixture was refluxed for 5 h, the solid was filtered and washed with butanone. The butanone was distilled off in vacuo and then the residue (8·9 g) was distilled, affording 5·1 g (80%) of colourless liquid, b.p. 99—105°C/130 Pa, identical with the pure product prepared according to procedure *B*).

B) A mixture of isoquinoline (150 g; 1·15 mol), 3-bromopropyne (140·0 g; 1·20 mol) and benzene (500 ml) was allowed to stand at room temperature for 8 days. The solid was filtered, washed with benzene and acetone to give crude quaternary salt (250·0 g; 87%), m.p. 171—173°C after crystallization from 2-propanol.

To a cooled solution of this quaternary salt (100 g; 0·40 mol) in ethanol (1 000 ml) was gradually added at 5°C a suspension of sodium borohydride (45·6 g; 1·20 mol) in ethanol (500 ml). After addition of the whole amount of the hydride, the reaction mixture was stirred at 15°C for 7 h. Part of the ethanol (1 000 ml) was then distilled off, the residue was mixed with water (500 ml) and the mixture was extracted with ether (3 × 400 ml). The combined ethereal layers were dried over magnesium sulfate, the solvent was evaporated and the residue was distilled in vacuo to give 37·0 g (54%) of the base which was not homogenous (GLC). It was purified via hydrochloride, m.p. 194—195°C (after washing with 2-propanol). After liberation and drying, the base was obtained as a colourless liquid, b.p. 100—110°C/130 Pa; yield 29·1 g (42%). For $C_{12}H_{13}N$ (171·2) calculated: 84·16% C, 7·65% H, 8·18% N; found: 84·20% C, 7·61% H, 8·29% N. ^{1}H NMR spectrum (δ, $CDCl_3$): 2·31 t, 1 H (J = 2, C≡CH); 2·87 t, 2 H (J = 6, NCH_2CH_2); 2·98 t, 2 H (J = 2, NCH_2CH_2); 3·55 t, 2 H ($NCH_2C{\equiv}C$); 3·77 s (NCH_2); 7·00—7·08 m, 1 H (H-5) and 7·05—7·20 m, 3 H (H-6, H-7, H-8 aromat.). IR spectrum ($CHCl_3$): 3 300 cm^{-1} (s) for C≡C.

2-Methyl-2-(2-propynyl)-1,2,3,4-tetrahydroisoquinolinium iodide, m.p. 159—160°C (2-propanol). For $C_{13}H_{16}IN$ (313·2) calculated: 49·86% C, 5·13% H, 40·52% I, 4·47% N; found: 49·47% C, 5·13% H, 40·41% I, 4·27% N.

2-Methyl-2-(2-propynyl)-1,2,3,4-tetrahydroisoquinolinium bromide, m.p. 188—189°C (benzene–ethanol 4 : 1). For $C_{13}H_{16}BrN$ (266·2) calculated: 58·66% C, 6·06% H, 30·02% Br, 5·26% N; found: 58·72% C, 6·04% H, 29·86% Br, 5·16% N.

2-(2-Propynyl)-1,2,3,4-tetrahydroisoquinoline picrate, m.p. 151—152°C (ethanol). For $C_{18}H_{16}$·$.N_4O_7$ (400·4) calculated: 54·00% C, 4·03% H, 14·00% N; found: 53·85% C, 4·12% H, 13·70% N.

TABLE IV

^{1}H NMR spectra of alcohol[a] *X*–*XIII* (δ, $CDCl_3$)

Compound	H-1	H-2	H-3	H-4	H-5	Other signal[a]
Xa	4·49 m	3·39 d	2·49 t	1·53–1·62 m	1·70–1·83 m	1·70–1·83 m, 10 H (H-5 and $CH_2CH_2CH_3$);
		J = 1·7	J = 5·4			1·05 t, 3 H (J = 7·3, CH_3CH_2)
	1 H	2 H	4 H	4 H		
Xb	5·49 m	3·29 d	2·48 m	1·58–1·62 m	1·41–1·43 m	7·26–7·38 m, 3 H (arom. β, γ);
		J = 1·7				7·53–7·55 m, 2 H (arom. α)
	1 H	2 H	4 H	4 H	2 H	
Xc	5·41 s	3·36 s	2·52 t	1·59–1·65 m	1·41–1·46 m	7·39–7·42 m, 2 H (arom. H-α); 6·70–6·73 m
			J = 5·4			2 H (arom. H-β); 2·90–3·01 m, 6 H (CH_3N)
	1 H	2 H	4 H	4 H	2 H	
Xd	5·48 m	3·33 d	2·51 t	1·59–1·64 m	1·41–1·44 m	7·38–7·39 d, 1 H (J = 2, OCH=CH);
		J = 1·8	J = 5·4			6·32–6·44 m, 1 H (OCH=CH); 6·43 d, 1 H
	1 H	2 H	4 H	4 H	2 H	(J = 3·2, OCH=CH)
Xe	5·68 s	3·30 d	2·51 m	1·58–1·63 m	1·41–1·42 m	7·26–7·27 m, 1 H (SCH=CH); 6·95–6·97 m, 1 H
		J = 1·7				(SCH=CH); 7·15–7·16 m, 1 H (SCR=CH)
	1 H	2 H	4 H	4 H	2 H	
Xf	5·52 m	3·32 d	2·50 t	1·59–1·64 m	1·41–1·45 m	7·40 m, 1 H (SCH=C); 7·30 dd, 1 H
		J = 1·7	J = 5·4			(J = 3, J = 5, SCH=CH); 7·20 dd, 1 H
	1 H	2 H	4 H	4 H	2 H	(J = 5, J = 1, SCH=CH)
Xg	5·55 m	3·30 d	2·49 t	1·58–1·63 m	1·40–1·44 m	8·78 d, 1 H (J = 2·2, NCH=C); 8·50 dd (J = 4·9,
		J = 1·8	J = 5·3			J = 1·9, NCH=CH); 7·78–7·90 m, 1 H
	1 H	2 H	4 H	4 H	2 H	(NCH=CH); 7·26–7·29 m, 1 H
						(H-γ of pyridine ring).
Xh	6·50 s	3·36 s	2·49 s	1·58–1·64 m	1·42–1·43 m	2·09 s, 3 H ($OCOCH_3$); 7·52–7·54 m, 2 H
	1 H	2 H	4 H	4 H	2 H	(arom. H-α); 7·35–7·40 m, 3 H (H-β and H-γ
						arom.).

XIa		3·25 s	2·48 t	1·58—1·66 m	1·38—1·48 m	1·52 s, 6 H (2 × CH_3)
			$J = 6$			
		2 H	2 H	4 H	2 H	
XIb[a]	4·85 s	4·41 s	3·45—3·47 m	1·65—2·00 m		1·65—2·00 m, 14 H ($(CH_2)_4$ and H-4, H-5);
		2 H	4 H			3·19 s, 3 H (CH_3N^+)
XIc		3·34 s	2·48 s	1·56—1·60 m	1·38 m	7·29—7·34 m, 1 H (H-β); 8·12—8·15 m, 1 H
		4 H	8 H	8 H	4 H	(H-α); 8·51—8·53 m, 1 H (H-γ); 9·05 d,
						1 H (H-α′) of pyridine ring
XIc[b]		4·67 s	3·55 m	1·96 m	1·68—1·80 m	3·24 s, 6 H (N^+CH_3 piperidine rings); 4·52 s,
		4 H	8 H	8 H	4 N	3 H (N^+CH_3 pyridine ring); 8·21 dd, 1 H
						($J = 8·1$, $J = 6$, H-β); 8·96 d, 1 H ($J = 6$, H-γ);
						9·02 d, 1 H ($J = 8·1$, H-α); 9·41 s, 1 H
						(H-α′ pyridine ring)
XId		3·37 s	2·52 t	1·60—1·65 m	1·41—1·43 m	7·66—7·68 m, 2 H (H-β); 8·61—8·63 m, 2 H
		4 H	8 H	8 H	4 H	(H-α pyridine ring)
			$J = 5·4$			
XIe	5·2 t	3·31 s	2·52 m	1·60—1·66 m	1·43 m	
	$J = 1·8$					
	1 H	4 H	8 H	8 H	4 H	
XIIa	4·40 t	3·39 d	2·68 t	1·65—1·75 m	1·55—1·65 m	1·65—1·75 m, 6 H (H-2 and $CH_2CH_2CH_3$);
	$J = 6·6$	$J = 5·6$				1·45—1·55 m, 2 H ($CH_2CH_2CH_3$); 0·95 t, 3 H
	1 H	2 H	4 H		4 H	($CH_2CH_2CH_3$, $J = 3·6$)
XIIb[a]		4·36 s	3·49—3·64	1·74—1·98 m		3·16 s, 3 H (CH_3N^+); 1·74—1·98 m, 16 H
		2 H	4 H			($(CH_2)_4$, H-4, H-5);
XIII[c]		3·34 s	2·51 s	1·58—1·64 m	1·40—1·43 m	7·81—7·89 m, 3 H (H-β, H-γ pyridine
		8 H	16 H	16 H	8 H	ring)

[a] methiodide, in CD_3OD; [b] trimethiodide, in CD_3OD; [c] in CD_3OD

4-(1-Piperidinyl)-1-(3-pyridinyl)-2-butyn-1-ol (*Xg*)

Ethylmagnesium bromide was prepared from magnesium (2·4 g; 100 mmol) and ethyl bromide (6·0 g; 55 mmol) in tetrahydrofuran (70 ml). After gentle reflux for 30 min, 1-(2-propynyl)piperidine (6·15 g; 50 mmol) in tetrahydrofuran (20 ml) was added dropwise and the reflux was continued for 1·5 h. Then a solution of 3-pyridinecarbaldehyde (5·35 g; 50 mmol) in tetrahydrofuran (20 ml) was added dropwise and the mixture was refluxed for 3 h. The reaction was performed in an atmosphere of dry nitrogen. The tetrahydrofuran was evaporated in vacuo, the reaction mixture was decomposed with saturated ammonium chloride solution and extracted with ether. The ethereal layer was dried over sodium sulfate, and the solvent was evaporated. The residue, which turned into a semicrystalline mass on standing overnight, was spread on a porous tile (this removed the sirupy component better than filtration through a sintered glass), affording 4·8 g (41%) of slightly brownish crystals. Several crystallizations from cyclohexane (charcoal) afforded colourless crystals, m.p. 98—99°C (Tables II and IV). Alcohols *Xa—f* were prepared analogously. In the case of alcohol *Xf*, the reaction mixture was not heated and was worked up after stirring at room temperature for 1·5 h. In the preparation of alcohols *XIc—e* the molar ratio ester: Grignard reagent was 1 : 2, for *XIII* this ratio was 1 : 4. Compounds *XIc* and *XIe* had to be purified by column chromatography on silica gel (benzene, benzene–ethanol), compounds *XIb* and *XIII* were chromatographed on alumina (chloroform).

1-Acetoxy-1-phenyl-(4-(1-piperidinyl))-2-butyne (*Xh*)

Acetic anhydride (0·37 ml; 4·2 mmol) was added to a solution of alcohol *Xb* (229 mg; 1 mmol) in pyridine (0·6 ml) and the mixture was allowed to stand at room temperature for 2 days. Since considerable amount of the starting alcohol was still present (TLC), 4-dimethylaminopyridine (30 mg) was added and the mixture was set aside for 12 h. After this time no starting alcohol was found. Pyridine was distilled off and the residue was filtered through a column of alumina (chloroform). Yield 126 mg (46%) of pure compound *Xh* (Tables II and IV).

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