FUSED IMIDAZO-, PYRIMIDO- AND 1,3-DIAZEPINO[1,2-*c*]PTERIDINES FROM *o*-AMINOPYRAZINECARBONITRILES

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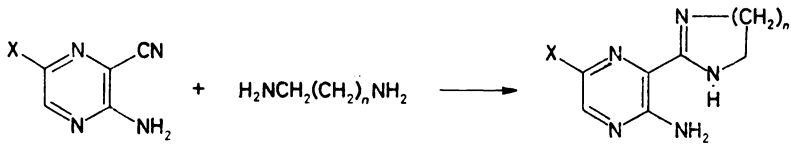
Dedicated to Dr Miroslav Protiva with best wishes for his 70th birthday.

A series of partially hydrogenated imidazo[1,2-*c*]pteridines *IXa*—*IXc*, *XIa*—*XIf* and *XVa*—*XVc*, pyrimido[1,2-*c*]pteridines *XIIa*—*XIId* and *XVIa*—*XVIc*, and 1,3-diazepino[1,2-*c*]pteridines *XIIIa*—*XIIIc* and *XVII* have been prepared from 2-amino-3-cyanopyrazines *I* via reactions of *I* with alkanediamines *II*—*IV* and subsequent condensation of the resulting intermediates *V*—*VII* with orthoesters *VIII*, aldehydes *X* and ketones *XIV*.

In continuation of our recent work on *o*-aminonitriles and dinitriles[1,2], we have prepared the novel 2-amino-3-(4,5-dihydro-1*H*-imidazol-2-yl)pyrazines *V*, 2--amino-3-(1,4,5,6-tetrahydropyrimidin-2-yl)pyrazine *VI*, and 2-(3-aminopyrazin-2-yl)--4,5,6,7-tetrahydro-1*H*-1,3-diazepine *VII* as starting materials for further syntheses by a known method[3] utilizing catalytic amounts of P_4S_{10} at moderate temperature from 2-amino-3-cyanopyrazines *I* and aliphatic diamines *II*—*IV* (Scheme 1).



Ia, X = H
Ib, X = Br

II, *n* = 1
III, *n* = 2
IV, *n* = 3

	n	X
Va	1	H
Vb	1	Br
VI	2	H
VII	3	H

SCHEME 1

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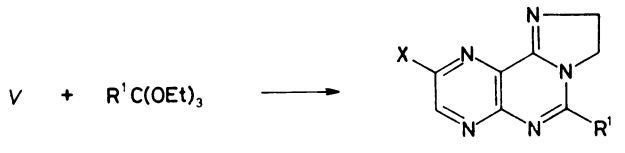
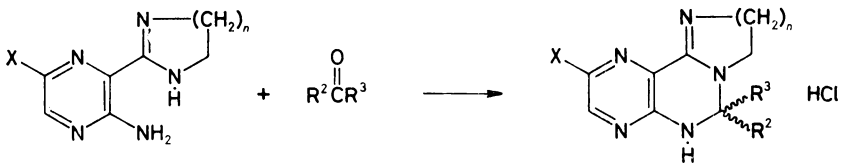
Reactions of intermediates *V*–*VII* with orthoesters *VIII*, aliphatic or aromatic aldehydes *X* and ketones *XIV* in the presence of catalytic or stoichiometric amounts of acid resulted in the formation of (partially hydrogenated) imidazo[1,2-*c*]pteridines



	X	R^1
IX a	H	H
IX b	H	Me
IX c	Br	H

SCHEME 2



XI, *XV*, *n* = 1
XII, *XVI*, *n* = 2
XIII, *XVII*, *n* = 3

	X	R^2 (R^3= H)
XI a, *XII a*, *XIII a*	H	Me
XI b, *XII b*, *XIII b*	H	Et
XI c, *XII c*, *XIII c*	H	Ph
XI d, *XII d*	H	4-$NO_2C_6H_4$
XI e	Br	Me
XI f	Br	Ph

	X	R^2	R^3
XV a, *XVI a*, *XVII*	H	Me	Me
XV b, *XVI b*	H	Me	Et
XV c, *XVI c*	H	$CH_2(CH_2)_3CH_2$	
XV d	H	Me	Ph
XV e	Br	Me	Me
XV f	Br	Me	Et
XV g	Br	$CH_2(CH_2)_3CH_2$	
XV h	Br	Me	Ph

SCHEME 3

IX, *XI* and *XV*, pyrimido[1,2-*c*]pteridines *XII* and *XVI*, and 1,3-diazepino[1,2-*c*]-pteridines *XIII* and *XVII*, which were usually isolated as their hydrochlorides upon addition of the reaction mixture into a large excess of ether (Schemes 1–3, Table I). All structures were confirmed by microanalytical and spectroscopic methods (IR,

TABLE I

Characteristics of prepared compounds

Product	Reaction time, h	Yield %	M.p., °C (solvent)	Formula (M.w.)	Calculated/Found		
					% C	% H	% N
Va	18	82	121–123 (EtOH–H_2O)	$C_7H_9N_5$ (163·2)	51·52 51·65	5·56 5·61	42·91 42·65
Vb	20	74	155–156 (EtOH–H_2O)	$C_7H_8N_5Br$ (242·1)	34·73 34·98	3·33 3·33	28·93 28·72
VI	24	74	95–96 (EtOH–H_2O)	$C_8H_{11}N_5$ (177·2)	54·22 54·14	6·26 6·25	39·52 39·31
VII	24	69	106–108 (i-PrOH–H_2O)	$C_9H_{13}N_5$ (191·2)	56·53 56·40	6·85 6·90	36·62 36·60
IXa	3·5	69	266–268[a] (MeOH)	$C_8H_7N_5$ (173·2)	55·48 55·50	4·07 4·10	40·44 40·30
IXb	4	66	238–240[a] (EtOAc–MeOH)	$C_9H_9N_5$ (187·2)	57·74 57·70	4·85 4·80	37·41 37·20
IXc	4	72	dec. >209 (MeOH)	$C_8H_6N_5Br$ (252·1)	38·12 38·41	2·40 2·36	27·78 27·58
XIa	1[b]	90	262–264[a] (EtOH–ether)	$C_9H_{10}N_5$.HCl (224·7)	47·90 47·83	5·36 5·42	31·03 30·80
XIb	2[b]	89	245–247[a] (EtOH–ether)	$C_{10}H_{13}N_5$.HCl (239·7)	50·11 49·88	5·89 5·93	29·22 28·96
XIc	1[b]	90	246–247[a] (EtOH–ether)	$C_{14}H_{13}N_5$.HCl (287·8)	58·44 58·14	4·90 5·00	24·34 24·17
XId	4[b]	84	258–261[a] (EtOH–ether)	$C_{14}H_{12}N_6O_2$.HCl .H_2O (350·8)	47·94 47·66	4·31 4·59	23·96 24·17
XIe	1[b]	92	227–228[a] (EtOH–ether)	$C_9H_{10}N_5Br$.HCl .2/3 H_2O (316·6)	34·16 34·29	3·92 4·08	22·13 21·93
XIf	2[b]	79	dec. >178 (EtOH–ether)	$C_{14}H_{12}N_5Br$.HCl (366·7)	45·86 45·80	3·57 3·57	19·10 18·95
XIIa	2[b]	87	dec. >235 (EtOH–ether)	$C_{10}H_{13}N_5$.2 HCl .1/2 H_2O (285·2)	42·11 42·12	5·66 5·85	24·56 24·37
XIIb	3[b]	65	232–235[a] (EtOH–ether)	$C_{11}H_{15}N_5$.HCl (253·7)	52·07 51·83	6·36 6·58	27·60 27·32

TABLE I
(*Continued*)

Product	Reaction time, h	Yield %	M.p., °C (solvent)	Formula (M.w.)	Calculated/Found		
					% C	% H	% N
XIIc	2[b]	94	265–267[a] (EtOH–ether)	$C_{15}H_{15}N_5$.HCl .3/2 H_2O (301·8)	54·79 54·64	5·82 5·77	21·30 21·25
XIId	5[b]	23	153–155 (EtOAc–MeOH–aq.NH_3)	$C_{15}H_{14}N_6O_2$ (310·3)	54·87 54·72	4·91 4·74	25·60 25·39
XIIIa	2[b]	37	203–205[a] (EtOH–ether)	$C_{11}H_{15}N_5$.HCl .1/3 H_2O (259·7)	50·87 50·93	6·47 6·38	26·96 26·81
XIIIb	2[b]	68	dec. >180 (EtOH–ether)	$C_{12}H_{17}N_5$.HCl.H_2O (285·8)	50·43 50·51	7·05 7·26	24·51 24·24
XIIIc	2[b]	92	252–254 (EtOH–ether)	$C_{16}H_{17}N_5$.HCl (315·8)	60·85 60·75	5·75 5·87	22·18 21·89
XVa	2[b]	95	262–263 (EtOH–ether)	$C_{10}H_{13}N_5$.HCl .1/3 H_2O (245·7)	48·88 48·96	6·02 6·28	28·50 28·36
XVb	3[b]	80	248–250[a] (EtOH–ether)	$C_{11}H_{15}N_5$.HCl .1/4 H_2O (258·2)	51·16 51·21	6·44 6·36	27·12 27·29
XVc	3[b]	95	dec. >230 (EtOH–ether)	$C_{13}H_{17}N_5$.2 HCl .3/4 H_2O (329·7)	47·35 47·35	6·27 6·21	21·24 21·25
XVd	5[b]	83	dec. >191 (EtOH–ether)	$C_{15}H_{15}N_5$.HCl .3/4 H_2O (315·3)	56·80 56·78	6·11 6·31	20·70 20·67
XVe	1[b]	85	245[a] (EtOH–ether)	$C_{10}H_{12}N_5Br$.HCl (318·6)	37·70 37·44	4·11 4·32	21·98 21·71
XVf	2[b]	79	dec. >173 (EtOH–ether)	$C_{11}H_{14}N_5Br$.HCl .1/3 H_2O (338·6)	39·01 38·99	4·66 4·80	20·68 20·75
XVg	2[b]	82	dec. >165 (EtOH–ether)	$C_{13}H_{16}N_5Br$.HCl .1/3 H_2O (364·7)	42·82 42·83	4·88 5·13	19·20 18·94
XVh	5[b]	27	dec. >215 (EtOAc–MeOH)	$C_{15}H_{14}N_5Br.H_2O$ (362·2)	49·74 49·52	4·45 4·19	19·33 19·07

TABLE I
(*Continued*)

Product	Reaction time, h	Yield %	M.p., °C (solvent)	Formula (M.w.)	Calculated/Found		
					% C	% H	% N
XVIa	2[b]	76	286–288[a] (EtOH–ether)	$C_{11}H_{15}N_5.HCl$ (253·4)	52·07 51·85	6·36 6·52	27·60 27·46
XVIb	3[b]	38	263–265[a] (EtOH–ether)	$C_{12}H_{17}N_5.HCl$ (267·8)	53·83 53·57	6·78 6·77	26·16 25·95
XVIc	3[b]	34	162–165[a] (EtOH–ether)	$C_{14}H_{19}N_5.1·5\ HCl$ $.2/3\ H_2O$ (324·0)	51·89 52·00	6·79 6·80	29·61 21·42
XVII	3[b]	68	dec. >170 (EtOH–ether)	$C_{12}H_{17}N_5.HCl.H_2O$ (285·8)	50·43 50·30	7·05 7·07	24·51 24·51

[a] Decomposition; [b] in days.

TABLE II
Spectral data of the prepared compounds

Product	IR ν, cm^{-1}	^1H NMR δ, J, Hz
Va	3 325 s (NH); 3 260, 3 140 s–m (NH_2); 3 030 sh (CH arom); 2 950–2 860 m (CH_2); 1 620 sh, 1 600 s, br (C=N, C=C); 1 560 m (arom.); 1 490, 1 465, 1 430 s (CH)	3·34 t, 2 H (CH_2, J = 10); 3·92 t, 2 H (CH_2, J = 10); 7·01 s, 1 H (NH); 7·1 bs, 1 H (NH_2); 7·8 d, 1 H (arom., J = 2·6); 8·06 d, 1 H (arom., J = 2·6); 8·7 bs, 1 H (NH_2)
Vb	3 380 m (NH); 3 290, 3 120 s–m (NH_2); 3 040 sh (CH arom); 2 960–2 850 m (CH_2); 1 615, 1 590 s (C=N, C=C); 1 540 m (arom); 1 490 m, 1 465 s, 1 435 m (CH)	3·35 t, 2 H (CH_2, J = 9·8); 3·93 t, 2 H (CH_2, J = 9·8); 6·93 s, 1 H (NH); 7·45 bs, 1 H (NH_2); 8·19 s, 1 H (arom.); 8·75 bs, 1 H (NH_2)

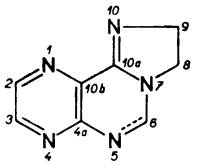
TABLE II
(*Continued*)

Product	IR ν, cm^{-1}	^1H NMR δ, J, Hz
VI	3 400 s (NH); 3 270 s, 3 130 m (NH_2); 3 030 sh (CH arom); 2 980–2 840 m (CH_2); 1 620 s, 1 600 sh (C=N, C=C); 1 550 w (arom); 1 500, 1 470, 1 430 m (CH)	1·71 m, 2 H (CH_2, J = 6); 3·35 t, 2 H (CH_2, J = 6); 3·5 t, 2 H (CH_2, J = 6); 6·9 bs, 1 H (NH); 7·28 s, 1 H (NH); 7·72 d, 1 H (CH arom., J = 2·6) 8·01 d, 1 H (CH arom., J = 2·6); 9·52 bs, 1 H (NH)
VII	3 350 m (NH); 3 300 s, 3 130 s (NH_2); 3 050 w (CH arom); 2 940–2 830 m (CH_2); 1 630, 1 620, 1 595 s (C=N, C=C, N–H); 1 550 w (arom); 1 520 s, 1 505 sh, 1 440 s (CH)	1·71 s, 4 H, 3·20 s, 2 H; 3·62 s, 2 H (4 × CH_2); 7·0 bs, 1 H (NH_2); 7·28 s, 1 H (NH); 7·69 d, 1 H (CH arom., J = 2·6); 8·01 d, 1 H (CH arom., J = 2·6); 9·58 bs, 1 H (NH_2)
IXa	3 080, 3 040 w (CH arom); 3 000–2 880 m–w (CH_2); 1 640, 1 575 s (C=N, C=C); 1 470 m, 1 420 s (CH_2); 1 370 s, 1 350 s, 1 215 s	3·95–4·25 m, 4 H (2 × CH_2); 8·1 s, 1 H (CH); 8·51 d, 1 H (CH arom., J = 2·4); 8·68 d, 1 H (CH arom., J = 2·4)
XIa	3 450, 3 370 s–m (NH); 3 250–2 800 br (NR_4^+); 1 625, 1 600 s (C=N, C=C); 1 440 m, 1 430 sh (CH); 1 375 w (CH_3), 1 275 m, 1 255 m, 1 190 s	1·54 d, 3 H (CH_3, J = 5·9); 3·8–4·1 m, 4 H (2 × CH_2); 5·4 q, 1 H (CH, J = 5·9); 8·05 d, 1 H (CH arom., J = 2·4); 8·41 d, 1 H (CH arom., J = 2·4); 8·76 s, 1 H (NH); 11·12 bs, 1 H (NH)
XIIb	3 400 br (NH); 3 250–2 700 br (NR_4^+); 2 980–2 840 w (CH aliph.); 1 650 s, 1 575 s (C=N, C=C); 1 540 m (CH arom); 1 450, 1 430 m (CH); 1 360, 1 320 m; 1 230, 1 205, 1 190 s–m	0·87 t, 3 H (CH_3, J = 7·3); 1·8 m, 2 H (CH_2, J = 7·3, J' = 3); 2·03 m, 2 H (CH_2); 3·5–3·7 m, 4 H (2 × CH_2); 5·08 m, 1 H (CH); 8·04 d, 1 H (CH arom., J = 2·4); 8·4 d, 1 H (CH arom., J = 2·4); 9·0 d, 1 H (NH, J' = 3); 10·1 s, 1 H (NH)

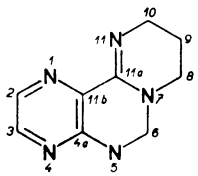
TABLE II
(*Continued*)

Product	IR ν, cm^{-1}	^1H NMR δ, J, Hz
XIIIc	3 430 br (NH); 3 300—2 700 br (NR_4^+); 2 980—2 820 w (CH_2); 1 635 s, 1 570 s (C=N, C=C); 1 440 m, 1 420 (CH); 1 540 m (arom.); 1 360, 1 205, 1 190 s; 760, 730 m, 705 s	1·9 m, 4 H (2 × CH_2); 3·8 m, 2 H (CH_2); 4·2 m, 2 H (CH_2); 6·4 d, 1 H (CH, J = 3); 7·4 m, 5 H (phenyl); 8·05 d, 1 H (CH arom., J = 2·4); 8·44 d, 1 H (CH arom., J = 2·4); 9·7 d, 1 H (NH, J = 3); 10·1 bs, 1 H (NH)
XVa	3 440 s, 3 360 m (NH); 3 250—2 700 br (NR_4^+); 2 980 sh, 2 920 sh (CH); 1 630, 1 600 s (C=N, C=C); 1 560 m (arom); 1 430 s, 1 375 (CH_2, CH_3); 1 300 s, 1 255, 1 235 s; 1 105, 1 060	1·64 s, 6 H (2 × CH_3); 4·02 m, 4 H (2 × CH_2); 8·09 d, 1 H (CH arom., J = 2·3); 8·44 d, 1 H (CH arom., J = 2·3); 8·9 s, 1 H (NH); 11·0 s, 1 H (NH)
XVIa	3 440, 3 360 s—m (NH); 3 200 br, s (NR_4^+); 2 980—2 800 w (CH_2, CH_3); 1 655, 1 580 s (C=N, C=C); 1 530 m (arom.); 1 440 s, 1 375 w (CH_2, CH_3); 1 320 s, 1 310 m, 1 230 s, 905 m, 850 m, 805 m	1·65 s, 6 H (2 × CH_3); 2·0 t, 2 H (CH_2); 3·4 bs, 2 H (CH_2); 3·7 t, 2 H (CH_2); 8·1 d, 1 H (CH, J = 2·4); 8·5 d, 1 H (CH, J = 2·4); 8·8 s, 1 H (NH); 10·6 bs, 1 H (NH)
XVII	3 460, 3 380 s (NH); 3 180 br, s (NR_4^+); 2 980—2 860 w (CH_2, CH_3); 1 630, 1 570 s (C=N, C=C); 1 530 (arom.); 1 490 m, 1 475 w, 1 435 s, 1 420 m (CH_2, CH_3); 1 375 m (CH_3); 1 235 s, 870, 840 m	1·66 s, 6 H (2 × CH_3); 1·95—2·15 m, 4 H (CH_2); 3·8 m, 2 H (CH_2); 3·98—4·2 m, 2 H (CH_2); 8·1 d, 1 H (CH arom., J = 2·4); 8·4 d, 1 H (CH arom., J = 2·4); 8·9 s, 1 H (NH); 9·8 s, 1 H (NH)

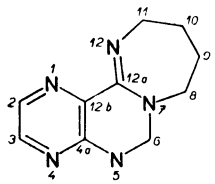
^{1}H and ^{13}C NMR are given in Table II). For numeration of the respective heterocyclic rings see Scheme 4.



8,9-Dihydro-imidazo[1,2-*c*]pteridines



5,6,9,10-Tetrahydro-8*H*-pyrimido[1,2-*c*]pteridines



5,6,8,9,10,11-Hexahydro-1,3-diazepino[1,2-*c*]pteridines

SCHEME 4

It should be noted that a number of structurally related tricyclic heterocycles have recently attracted attention due to their interesting pharmacological (mainly CNS-active and antipsychotic) properties[4,5].

EXPERIMENTAL

Melting points (uncorrected) were measured on an Elektrothermal 6304 or Gallenkamp MFB-595 Apparatus. IR spectra (KBr) were recorded on a Perkin Elmer 398 spectrophotometer. ^{1}H and ^{13}C NMR data were obtained on Varian XL 200 or VXR 300 instruments in hexadeuteriodimethylsulfoxide with TMS as internal standard. Microanalyses were performed on a Heraeus CHN-Rapid elemental analyzer.

2-Amino-3-(4,5-dihydro-1*H*-imidazol-2-yl)pyrazines (*Va*—*Vb*),
2-Amino-3-(1,4,5,6-tetrahydro-pyrimidin-2-yl)pyrazine (*VI*), and
2-(3-Aminopyrazin-2-yl)-4,5,6,7-tetrahydro-1*H*-1,3-diazepine (*VII*). General Procedure

2-Amino-3-cyanopyrazine *I* (20 mmol) is slowly added to an excess of the appropriate diaminoalkane *II*, *III* or *IV* (100 mmol) in small (10 mg) portions with stirring and the resulting solution is warmed to 40°C. A catalytic amount of P_4S_{10} (44 mg, 0·1 mmol) is added and the temperature slowly raised to 80—90°C. The mixture is kept at this temperature until no more ammonia is evolved (18—25 h), and concentrated on a rotary evaporator under reduced pressure. The oily residue is dissolved in hot ethanol (30—50 ml), filtered, and to the filtrate is added an equal amount of water. Upon cooling, the product is collected by filtration, washed with water and recrystallized from ethanol–water or isopropylalcohol–water.

^{13}C NMR data of compound *Vb* (δ): 42·3; 54·4 (C5′, C4′ imidazoline); 120·8; 124·3; 145·1 (C6, C2, C5 pyrazine); 152·6 (C2′ imidazoline); 162·3 (C3 pyrazine).

8,9-Dihydro-imidazo[1,2-*c*]pteridines (*IXa*—*IXc*). General Procedure

To a suspension of 2-amino-3-(4,5-dihydro-1*H*-imidazol-2-yl)pyrazine *V* (1 mmol) in the appropriate ortho ester *VIII* (2 ml) is added a small amount of formic or acetic acid (0·05 ml) and the mixture is heated at reflux for 4 h. After cooling to room temperature, the product is collected by filtration, washed with ether and dried. Pure products are obtained by column chromatography on silica gel (7·5 g, column size 20 × 1·5 cm) with methanol or ethyl acetate/methanol 4 : 1 as eluent. ^{13}C NMR data of product *IXa* (δ): 46·3 (C8); 54·3 (C9); 142·5 (C6); 148·1 (C2); 148·4 (C3). The three quaternary C-atoms (C4a, C10a, C10b) were not resolved.

5,6,8,9-Tetrahydro-imidazo[1,2-*c*]pteridines (*XI*, *XV*),
5,8,9,10-Tetrahydro-6*H*-pyrimido[1,2-*c*]pteridines (*XII*, *XVI*), and
5,6,8,9,10,11-Hexahydro-1,3-diazepino[1,2-*c*]pteridines (*XIII*, *XVII*). General Procedure

To a solution of the diamine *V*, *VI* or *VII* (1 mmol) and the appropriate aldehyde *X* (3 mmol) or ketone *XIV* (5 mmol) in absolute ethanol (5—10 ml) is added concentrated HCl (0·15—0·2 ml, 1·5—2 mmol), and the mixture is stirred at 50—60°C in a well stoppered round bottom flask for the time indicated in Table I. The products are conveniently isolated as their hydrochlorides by slow addition of the resulting solution into a large excess of ether (60—100 ml), collected by filtration, washed with ether, and dried. Purified products are obtained by reprecipitation from absolute ethanol–ether.

In some instances the products were isolated as free bases by column chromatography on silica gel with ethyl acetate–methanol–25% aq. NH_3 (6 : 3 : 1) as eluent.

^{13}C NMR data of product *XIIb* (δ): 7·9 (CH_3 ethyl); 18·3 (C9); 26·9 (CH_2 ethyl); 44·5 (C8); 44·7 (C10); 70·5 (C6); 120·2 (C11b); 134 (C2); 150 (C3); 150·9 (C4a); 151·1 (C11a).

^{13}C NMR data of product *XVa* (δ): 26·3 (2× CH_3); 43·8 (C8); 45·4 (C9); 71·4 (C6); 117·2 (C10b); 135·1 (C2); 151·3 (C3); 152·5 (C4a); 157·3 (C10a).

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