THERMAL CYCLOCONDENSATIONS OF 3-N(4- AND 5-BENZIMIDAZOLYL AND BENZTRIAZOLYL)AMINO DERIVATIVES OF 2-PROPENOIC ACID

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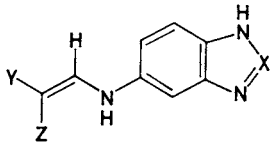
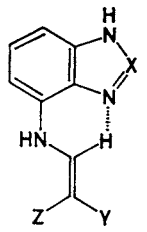
Dedicated to Prof. J. Kováč on the occasion of his 60th birthday.

The cyclization of 3-N-(4- and 5-benzimidazolyl and benztriazolyl)amino-2-cyano- and 2-ethoxycarbonyl-2-propenoate esters *Ia, b—IVa, b* under the conditions of the Gould–Jacobs reaction leads to angularly ring-fused substituted imidazo or triazolo[4,5-*f*] (*V, VI*) and [4,5-*h*] (*VII, VIII*) quinolines, respectively. The esters *Vb—VIIIb* have been transformed into the corresponding chloroderivatives *Vc—VIIIc*. 3-N(5-Benzimidazolyl and 5-benztriazolyl)amino-2-cyano-2--propenenitriles are cyclized in the presence of aluminium(III) chloride to give the aminoquinolines *Vd, VId*. The structure of the products has been characterized by their ^{1}H, ^{13}C NMR, IR, and UV spectra.

A modification of the Gould–Jacobs reaction is used for the condensation of the 4-oxopyridine-3-carboxylic acid skeleton onto the starting amine[1]. If benzocondensed heterocyclic amines with amino group in the benzene ring are used, then angularly ring-fused derivatives of quinoline are formed[2–5]. The present communication deals with the conditions and direction of the cyclocondensation reaction of 4- (*III, IV*) and 5-substituted (*I, II*) benzimidazole (*I, III*) and benztriazole (*II, IV*) derivatives of 2-propenoic acid (the preparation and structure of these derivatives was described in ref.[6]).



Ia–Ic, X = CH
IIa–IIc, X = N

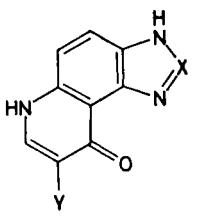


IIIa–IIIc, X = CH
IVa–IVc, X = N

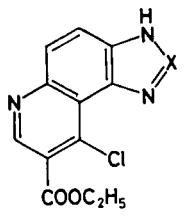
In formulae *I–IV*: *a*, Y = CN; Z = $COOCH_3$ *b*, Y = Z = $COOC_2H_5$
c, Y = Z = CN

The cyclization takes place in the inert medium of Dowtherm (a mixture of diphenyl ether and biphenyl) at 250°C. The formation of products and their isolation are affected by the reaction time and by dilution: The optimum lies at 15–20 min and the dilution of 1 g *per* 20 ml Dowtherm (compounds *Ib–IVb*) or 80 ml Dowtherm (compounds *Ia–IVa*). At lower concentrations the products do not separate from the reaction mixture, whereas at higher concentrations the product undergoes carbonization. The 2-cyano-2-propenenitriles with a substituent at the 5 position of the corresponding heterocycle (*Ic*, *IIc*) are cyclized in chlorobenzene with the catalysis of anhydrous aluminium(III) chloride[7]. Under other conditions (thermal cyclization or acid catalyzed cyclization) the products were not obtained, the same being true of the 4-substituted derivatives.

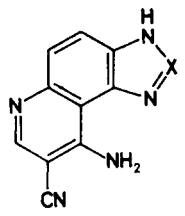
From the proton spectra it follows that in the case of 4- and 5-substituted benzazole derivatives *I–IV* the angularly ring-fused substituted azolo[4,5-*h*] (*VII*, *VIII*) and [4,5-*f*]quinolines (*V*, *VI*), respectively, are formed: Two doublets of benzene protons with the coupling constant of 9 Hz, characteristical of their mutual ortho position, are present[2–4]. The angular ring fusion is confirmed by the IR spectra containing the deformation out-of-plane vibrations in the region of 800 cm^{-1}, which is characteristical of 1,2,3,4-tetrasubstituted benzene derivatives, and by the shifts of carbon atoms in the ^{13}C NMR spectra of compounds *Vb–VIIIb*, *Vd*, and *VId*.



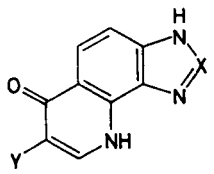
Va, X = CH; Y = CN
Vb, X = CH; Y = $COOC_2H_5$
VIa, X = N; Y = CN
VIb, X = N; Y = $COOC_2H_5$



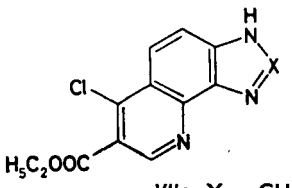
Vc, X = CH
VIc, X = N



Vd, X = CH
VId, X = N



VIIa, X = CH; Y = CN
VIIb, X = CH; Y = $COOC_2H_5$
VIIIa, X = N; Y = CN
VIIIb, X = N; Y = $COOC_2H_5$



VIIc, X = CH
VIIIc, X = N

The cyclization products (Table I) exhibit low solubilities in organic solvents. For the spectral measurements to be possible, the corresponding more soluble

TABLE I
Azoloquinolines *V*—*VIII*

Compound	Formula (mol. mass)	M.p., °C yield, %	Calculated/found			
			% C	% H	% N	% Cl
Va	$C_{11}H_6N_4O$ (210·2)	<400[a] 96[a]	62·86 63·03	2·88 2·73	26·65 25·32	—
Vb	$C_{13}H_{11}N_3O_3$ (257·3)	314—315 96	60·70 61·12	4·31 4·34	16·33 16·21	—
Vc	$C_{13}H_{10}ClN_3O_2$ (275·7)	<400 76	56·64 57·02	3·66 3·82	15·24 15·18	12·86 12·91
Vd	$C_{11}H_7N_5$ (209·2)	380—383[b] 93	63·15 63·36	3·37 3·31	33·48 33·12	—
VIa	$C_{10}H_5N_5O$ (211·2)	<400 77	56·88 56·66	2·39 2·28	33·16 32·94	—
VIb	$C_{12}H_{10}N_4O_3$ (258·2)	282—285 94	55·81 55·62	3·90 3·72	21·70 21·56	—
VIc	$C_{12}H_9ClN_4O_2$ (276·7)	215—217[c] 36	52·09 51·93	3·28 3·42	20·25 20·12	12·82 12·64
VId	$C_{10}H_6N_6$ (210·2)	282—290[b] 72	57·14 57·38	2·88 2·83	39·98 40·09	—
VIIa	$C_{11}H_6N_4O$ (210·2)	<400 43	62·86 63·01	2·88 2·86	26·65 26·70	
VIIb	$C_{13}H_{11}N_3O_3$ (257·3)	306—308 65	60·70 60·98	4·31 4·26	16·33 16·33	—
VIIc	$C_{13}H_{10}ClN_3O_2$ (275·7)	280—288 53	56·64 56·82	3·66 3·82	15·24 15·41	12·86 12·34
VIIIa	$C_{10}H_5H_5O$ (211·2)	<400 98	56·88 57·02	2·39 2·39	33·16 33·51	—
VIIIb	$C_{12}H_{10}N_4O_3$ (258·2)	314—317 98	55·81 55·68	3·90 3·93	21·70 21·96	—
VIIIc	$C_{12}H_9ClN_4O_2$ (276·7)	255—258 90	52·09 51·96	3·28 3·21	20·25 20·41	12·82 12·58

[a] Ref.[2] 315—316°C, 52%; [b] sublimes at 250°C; [c] sublimes below m.p.

6-(or 9)-chloroazoloquinolines *Vc – VIIIc* were prepared by the reaction of *Vb – VIIIb* with phosphoryl trichloride and dimethylformamide[2].

TABLE II
IR and UV spectra of compounds *V – VIII*

Compound	IR, ν_{max}, cm^{-1}				UV, λ_{max}, nm (log ε, m^2 mol^{-1})			
	ν(C=O)	ν(C≡N)	ν(CH, NH)	γ(CH)				
Va	1 620	2 225	2 630 3 325	810	—	—	—	—
Vb	1 640	—	2 650 3 350	825	—	—	—	—
Vc[a]	1 725	—	3 070 3 425	835	222 (3·23)	263 (3·60)	—	322 (2·90)
Vd	—	2 235	2 630 3 100	815	—	—	—	—
VIa	1 630	2 235	3 050 3 440	805	—	—	—	—
VIb	1 630 1 700	—	2 975 3 415	820	—	—	—	—
VIc	1 740	—	2 980 3 430	840	230 (3·15)	264 (3·61)	—	311 (2·93)
VId	—	2 220	2 610 3 050	805	—	—	—	—
VIIa	1 630	2 230	3 050 3 440	795	—	—	—	—
VIIb	1 630 1 725	—	2 110 3 425	805	—	—	—	—
VIIc	1 705	—	2 970 3 410	790	226 (3·04)	264 (3·27)	276 (3·27)	332 (2·52)
VIIIa	1 625	2 225	2 855 3 450	815	—	—	—	—
VIIIb	1 635 1 725	—	2 900 3 450	805	—	—	—	—
VIIIc	1 730	—	2 915 3 440	805	228 (3·30)	257 (3·46)	—	306 (2·80)

[a] *Vb* ref.[3]: ν(C=O) 1 640 and 1 700 cm^{-1}, ν(NH and CH) 2 700 and 3 350 cm^{-1}.

The IR spectra of compounds *V*–*VIII* show the valence vibrations of the ester carbonyl group in the region of 1 700–1 740 cm^{-1} and those of carbonyl in pyridine ring in the region of 1 620–1 640 cm^{-1} (Table II). The presence of carbonyl group vibration confirms the presumption that the compounds *Va,b*–*VIIIa,b* exist in the form of 4-pyridone and not as 4-hydroxyquinolines[3], whereas *Vd*, *VId* are present in their amino forms and not in imino forms. Valence vibrations of the cyano group lie in the region of 2 220–2 235 cm^{-1}.

The proton spectra of the compounds synthesized (Table III) show the proton coupling constants of the benzene nucleus 9 Hz, whereas in the case of *VIIIc* the doublets coalesce into a single signal of double intensity.The introduction of chlorine atom causes a down-field shift of the pyridine proton by as much as 0·5 ppm. In the [4,5-*f*] condensed derivatives *V* the signal of the imidazole proton shifts by 0·20 ppm upfield as compared with the [4,5-*h*] condensed derivatives *VII*.

In the ^{13}C NMR spectra (Table IV) the signals of carbon atoms of the cyclic products were assigned with the use of the carbon–hydrogen interactions as well as comparison with the chemical shifts of carbon atoms in benzimidazole[8] and benzotriazole[9] with quinoline[10] and thienopyridines[11], respectively. The signal values of carbon atoms in 4-amino-3-cyanopyridine derivatives *Vd*, *VId* were calculated from the substituent increments of substituted pyridines[12]. The addition (condensa-

TABLE III

The ^1H NMR chemical shifts δ (in ppm) and multiplicity of the compounds *V*–*VIII*

Compound	H-2	H-4[a]	H-5[a]	H-7(8)	—O—CH_2—CH_3
Va	8·20 s	7·42 d	8·04 d	8·68 s	—
Vb[b]	8·13 s	7·38 d	7·94 d	8·48 s	4·19 q, 1·24 t
Vc	8·43 s	7·88 d	8·19 d	9·01 s	4·38 q, 1·33 t
Vd	9·21 s	7·93 d	8·26 d	8·63 s	—
VIa	—	7·54 d	8·34 d	8·82 s	—
VIb	—	7·59 d	8·28 d	8·66 s	4·23 q, 1·26 t
VIc	—	7·83 d	8·48 d	8·79 s	4·40 q, 1·43 t
VId	—	7·84 d	8·16 d	8·43 s	—
VIIa	8·43 s	7·51 d	7·95 d	8·49 s	—
VIIb	8·36 s	7·58 d	7·97 d	8·38 s	4·13 q, 1·16 t
VIIc	8·63 s	7·67 d	7·87 d	9·26 s	4·49 q, 1·42 t
VIIIa	—	7·69 d	8·08 d	8·66 s	—
VIIIb	—	7·65 d	8·13 d	8·41 s	4·19 q, 1·24 t
VIIIc	—	8·19 s	8·19 s	9·19 s	4·40 q, 1·33 t

[a] $^3J(4, 5) = 9$ Hz. [b] Ref.[3] for *Vb*: hexadeuteriodimethyl sulphoxide: 8·20 s (H-2); 7·40 d (H-4); 8·00 d (H-4, $J(4, 5) = 9$); 4·20 q, 2 H (OCH_3); 1·20 t, 3 H (CH_3); 12·60 and 13·10 s (NH).

TABLE IV

^{13}C NMR spectra of selected azoloquinolines

Compound	C-2	C-3a	C-4	C-5	C-5a	C-7	C-8	C-6(9)	C-9a	C-9b	OCH_2	CH_3	CO, CN
Vb[a]	141·90	129·29	124·36	135·53	141·90	143·33	109·93	171·54	112·01	139·43	59·38 58·86	14·16	164·77
Vb	143·95	127·37	122·99	127·77	142·39	148·92	110·41	174·16	112·36	132·64	68·51	15·00	169·78
VIb[a]	—	129·56	115·82	123·81	141·55	144·28	112·02	172·45	113·48	138·92	59·87	14·26	164·65
VIb	—	132·35	123·09	128·84	143·85	148·14	109·40	173·58	110·60	140·34	67·92	14·52	169·29
VIIb	146·24	140·30	121·19	128·41	133·28	111·45	150·63	178·11	133·85	143·03	69·73	16·62	171·68
VIIIb[a]	—	134·89	108·64	124·36	122·54	112·66	143·46	172·44	131·12	136·45	59·65 58·87	14·03	164·38
Vd[a]	143·46	130·47	115·26	120·98	137·36	145·54	85·51	156·72	107·34	135·80	—	—	114·35
Vd	144·25	127·81	123·89	127·35	141·68	149·00	93·24	159·75	109·15	133·37	—	—	113·90
VId	—	126·70	124·36	125·92	140·73	148·43	91·90	159·93	109·90	136·44	—	—	113·70

[a] The spectra were measured in hexadeuteriodimethyl sulphoxide, the other ones in CF_3COOD.

tion) of pyridine nucleus causes changes in chemical shifts of carbon atoms of the 2-propane residue[6]: The signal of the ester carbonyl group and that of the carbon atom carrying the two ester groups show downfield shifts, whereas the tertiary carbon atom adjacent to the nitrogen atom shows an upfield shift.

EXPERIMENTAL

The melting points were determined on a Kofler apparatus and are uncorrected. The IR spectra were measured in KBr disc with a Specord IR 75 apparatus (Zeiss Jena), the UV spectra were measured in ethanol with a Specord UV-VIS (Zeiss Jena). The ^{1}H NMR spectra were measured with a Tesla BS 487C apparatus (80 MHz operation frequence), the ^{13}C NMR spectra with a JEOL FX-60 and FX-100 apparatus (operation frequences 15·036 and 25·047 MHz, respectively) in hexadeuteriodimethyl sulphoxide or trifluoroacetic acid. The internal standard for the ^{1}H NMR spectra was hexamethyldisiloxane (HMDS), the indirect internal standard for the ^{13}C NMR spectra was the central signal of the solvent (for dimethyl sulphoxide at 39·5 ppm; for carbonyl of CF_3COOD at 164·2 ppm).

Thermal Cyclization of Ethyl Esters of 3-N-Benzazolylamino Derivatives of 2-Ethoxycarbonyl-2-propenoic Acid

A mixture of 60 ml Dowtherm and 3 g (10 mmol) ethyl 2-ethoxycarbonyl-2-propenoate *Ib—IVb* was refluxed at 250°C 15 min. The product separated on cooling was collected by suction, washed with 2 × 50 ml toluene, 2 × 50 ml hexane, and 2 × 50 ml diethyl ether, and dried under reduced pressure at 110°C for 5 h. For analyses the samples were recrystallized (without pre-drying) from aqueous dimethyl sulphoxide and dried. The yields and melting points are given in Table I.

Thermal Cyclization of Methyl Esters of 3-N-Benzazolylamino Derivatives of 2-Cyano-2--2-propenoic Acid

A mixture of 80 ml Dowtherm and 1 g (4 mmol) methyl 2-cyano-2-propenoate *Ia—IVa* was rapidly heated to boiling and refluxed 15 min. The product separated on cooling was collected by suction, washed and dried as in the previous case. For analyses the samples were recrystallized from dimethyl sulphoxide and washed with water. The yields and melting points are given in Table I.

Cyclizations of 2-Cyano-2-propenenitriles

A mixture of 20 ml chlorobenzene, 0·5 g (2·4 mmol) nitrile *Ic*, *IIc*, and 1·5 g resublimed aluminium chloride was refluxed 6 h. After cooling, the mixture was poured onto 50 ml water, treated with 2 ml concentrated hydrochloric acid, and left to stand 15 h. The precipitate was crushed and collected by suction, washed with 2 × 50 ml water, 2 × 50 ml ethanol, and dried under reduced pressure at 110°C 3 h. For analyses the samples were recrystallized from trifluoroacetic acid. The yields and melting points are given in Table I.

Chloroazoloquinolines *Vc— VIIIc*

Dimethylformamide (5 ml) was added drop by drop to a mixture of 1·03 g (4 mmol) *Vb— VIIIb* and 5 ml phosphoryl trichloride with stirring , which caused the temperature increase to 80—100°C. The mixture was cooled and stirred overnight, poured onto 300 ml ice water, boiled with

charcoal, and filtered. The filtrate was cooled and neutralized with 20% aqueous sodium hydroxide. After cooling, the precipitate was collected by suction, washed with 2 × 50 ml water, and dried under reduced pressure at 60°C 6 h. The products *VIc*, *VIIIc* were recrystallized from ethanol, the products *Vc*, *VIIc* from aqueous dimethylformamide. The yields and melting points are given in Table I.

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