THERMAL CYCLOCONDENSATION OF ETHYL (1-METHYL-5- AND 6-BENZIMIDAZOLYL/BENZOTRIAZOLYL)-AMINOMETHYLENEPROPANEDIOATES

Viktor MILATA[a], Dusan ILAVSKY[a], Igor GOLJER[b] and Lubomir ZALIBERA[c]

[a] *Department of Organic Chemistry, Slovak Technical University, 812 37 Bratislava, The Slovak Republic*
[b] *Central Laboratory of Chemical Techniques, Slovak Technical University, 812 37 Bratislava, The Slovak Republic*
[c] *Department of Physical Chemistry, Slovak Technical University, 812 37 Bratislava, The Slovak Republic*

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Dedicated to Professor J. Kuthan on the occasion of his 60th birthday.

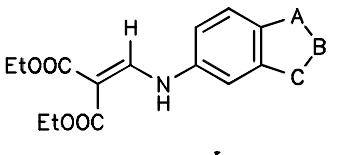
Thermal cyclocondensation of starting ethyl (1-methyl-5- and 6-benzimidazolyl/benzotriazolyl)-aminomethylenepropanedioates (*Ia – Ie*) in aprotic medium gives angularly condensed ethyl azolo[4,5-*f*]quinolonecarboxylates *IIa*, *IIc*, *IIe* and azolo[5,4-*f*]quinolonecarboxylates *IIb*, *IId*, respectively, which are hydrolyzed to the corresponding carboxylic acid *III* in acid medium. The structure of reaction products has been confirmed by ^{1}H and ^{13}C NMR, IR, and UV spectroscopy.

5-Substituted benzimidazole and benzotriazole derivatives of 2-propenoic acid undergo thermal cyclization in aprotic medium to give angularly condensed azolo[4,5-*f*]quinolones[1 – 8]. The same cyclization of diethyl (1-methylbenzimidazolyl)aminomethylenepropanedioate (*Ia*) or its 1-methyl- (*Ic*) or 2-methyl- (*Ie*) benzotriazole analogues also gives exclusively angularly condensed heterocycles[5 – 8]. Intensive research activity in the field of imidazo[4,5-*f*]quinoline derivatives was started by the finding of strong cancerogenic effect of the 2-amino-3-methyl analogue[9] and also of immunomodulation[10], antibacterial[11], and antiparasitic effects of imidazoquinolines[12,13].

The present study concerns the effect of N–CH_3 group in azole nucleus upon the cyclization direction, the cyclization reactions being carried out at the same conditions with all the *N*-methyl derivatives *Ia – Ie*. The preparation of starting compounds is described elsewhere[14]. Steric repulsion can be expected in the derivatives *Ib* and *Id* during formation of angularly annulated heterocycle. The linear annulation was not observed in any of the cyclocondensation mixtures given in spite of the considerable electron repulsion between carbonyl oxygen atom and methyl group (Scheme 1).

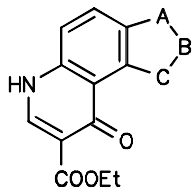
Also with the substitution derivatives *Ia*, *Ic*, *Ie* the only isolated reaction products were angularly annelated imidazo- or triazoloquinolones in all the cases. These conclusions are surprising with the cyclizates *IIb* and *IId* mainly because there are cases described in literature where an alkyl substituent[15,16] or halogen atom[16 – 20] is used to change the annulation of the heterocycle formed.

Italian authors described the preparation of tautomers with 4-oxo- (refs[7,8]) and 4-hydroxypyridone[8] skeleton depending on the reaction conditions (thermal cyclization in Dowtherm, diphenyl ether, or cyclization in polyphosphoric acid or its ethyl ester).

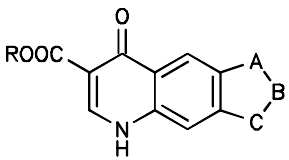


I

250 °C

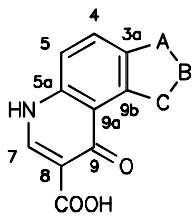


II



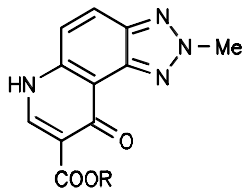
IVa, R = H
IVb, R = Et

HCl, NaOH



III

III	A B C
a	–NMe–CH=N–
b	–N=CH–NMe–
c	–NMe–N=N–
d	–N=N–NMe–



IIe, R = Et
IIIe, R = H

SCHEME 1

The cyclization products at the conditions of acid hydrolysis (concentrated hydrochloric acid) involve the acids *III* (Scheme 1, Table I) which can be considered nonalkylated analogues of nalidixic acid at the pyridone nitrogen atom. The basic hydrolysis does not lead to free acids, the hydrolysis being probably prevented by low solubility of the starting esters in the aqueous medium of sodium hydroxide, although such a hydrolysis of nonmethylated benzimidazole and benzotriazole derivatives has been described[1 – 5,14].

TABLE I
Yields and physico-chemical properties of compounds *II* and *III*

Compound	M.p., °C Yield, %	Formula M.w.	Calculated/Found		
			% C	% H	% N
IIa	313 – 314[a]	$C_{14}H_{13}N_3O_3$	61.97	4.83	15.50
	89	271.1	–	–	–
IIb	292 – 294	$C_{14}H_{13}N_3O_3$	61.97	4.83	15.50
	93	271.1	62.03	4.62	15.37
IIc	286 – 289	$C_{13}H_{12}N_4O_3$	57.33	4.44	20.59
	78	272.1	57.30	4.38	20.40
IId	272 – 275	$C_{13}H_{12}N_4O_3$	57.33	4.44	20.59
	81	272.1	57.13	4.28	20.42
IIe	292 – 293	$C_{13}H_{12}N_4O_3$	57.33	4.44	20.59
	56	272.1	57.28	4.22	20.32
IIIa	368 – 370[b]	$C_{12}H_9N_3O_3$	59.24	3.73	17.29
	76	243.1	–	–	–
IIIb	283 – 285	$C_{12}H_9N_3O_3$	59.24	3.73	17.29
	86	243.1	59.14	3.53	17.09
IIIc	>360	$C_{11}H_8N_4O_3$	54.08	3.30	22.95
	76	244.1	54.00	3.13	22.76
IIId	284 – 288	$C_{11}H_8N_4O_3$	54.08	3.30	22.95
	74	244.1	53.96	3.31	22.69
IIIe	320 – 328	$C_{11}H_8N_4O_3$	54.08	3.30	22.95
	62	244.1	53.92	3.27	23.09

[a] Ref.[5]: *IIa* m.p. 313 – 315 °C. [b] Ref.[5]: *IIIa* m.p. 368 – 372 °C.

Both the benzimidazole[21] and benzotriazole derivatives[7,8] are known to exist as hydrates although thermal cyclization above 200 °C and subsequent reactions with exclusion of water make their existence little likely, especially so if the melting points given[7,8] are above 200 °C.

The position of methyl group has no effect on IR and UV spectra of esters and acids *III* (Table II). The typical bands in the region of 1 700 – 1 735 cm^{-1} can be ascribed to the vibrations of carbonyl of ester group and those in the region of 1 610 – 1 635 cm^{-1} to the pyridone carbonyl group. They are often overlapped by C=C, NH–C=C vibrations[22]. The absorption band of compounds *IIe*, *IIIe* about 290 nm can be ascribed to the 2-methylbenzotriazole skeleton[23,24].

The proton spectra of all the compounds studied (Table III) unambiguously confirm the regioselectivity of thermal cyclocondensation reaction. The value of coupling constant $^3J(4,5)$ (about 9 – 9.5 Hz) can only be ascribed to mutual *ortho*-position of protons and the therefrom following angular annulation of all the cyclization products[1,5 – 8,20]. The distinctly higher shifts of the signals of methyls at the azole nucleus are observed particularly in the case of sterically hindered methyl groups (*IIb*, *IId*, *IIIb*, *IIId*), the respective shift being even higher with the triazole derivatives[14] *IId*, *IIId*. This shift can be expected when comparing the 2- with the 1-methylbenzotriazole derivatives[23,25].

The carbon signals of the ^{13}C NMR spectra (Table IV) were assigned on the basis of different intensities of signals of quaternary and tertiary carbons, using the APT

TABLE II
IR and UV spectra of compounds *II* and *III*

Compound[a]	IR spectrum ν(C=O), cm^{-1}	UV spectrum[b] λ_{max}, nm
IIa	1 715, 1 620	263, 272, 310 i, 326, 341
IIb	1 710, 1 630, 1 615	260, 270, 312 i, 326, 339
IIc	1 715, 1 615	260, 269, 290, 326, 341
IId	1 715, 1 630, 1 615	258, 273, 307 i, 321, 328
IIe	1 715, 1 635, 1 610	262, 272, 289, 298, 326, 339
IIIa	1 725, 1 630	250, 257, 304, 317, 333
IIIb	1 710, 1 630	251, 258, 270 i, 322, 333
IIIc	1 725, 1 620	259, 267, 295, 322, 337
IIId	1 735, 1 620	258, 273 i, 305 i, 319, 333
IIIe	1 700, 1 635	252, 262, 273, 291, 321, 335

[a] Ref.[5]: *IIa* 1 640, 1 710 ν(C=O), *IIIa* 1 630, 1 720 ν(C=O); ref.[7]: *IIc* 1 710, 1 630 (Nujol), *IId* 1 740, 1 710, 1 630, 1 610 (Nujol); ref.[8]: *IIe* 1 720, 1 710, 1 620, 1 590 (Nujol); UV data of saturated solutions in refs[5,7,8] are the same as in Table II. [b] i Inflex.

method, as well as by comparing the measured and calculated values. The calculated values were obtained by superposition of signals of 4-oxo-1,4-dihydroquinoline-3-carboxylic acid or its ethyl ester (*IVa*, *IVb*; Table V; measured in deuteriotrifluoroacetic acid[26]) with those of 2-methylbenzotriazole (Fig. 1; measured in the same solvent) referred to benzene ($\delta(C_6H_6)$ = 128.5 ppm). The measured and calculated values are compared in Table V. The greatest deviation is observed with the signals of C-4 carbons whereas the other calculated values agree relatively well with those measured, the sequence of chemical shifts being the same (confirmed by APT method).

TABLE III
^{1}H NMR spectra of compounds *II* and *III*

Compound	Solvent	H-2	H-4	H-5	H-7	N–Me	OC_2H_5		^3J(4,5)
IIa[a]	DMSO	8.30 s	7.58 d	7.93 d	8.58 s	3.92 s	4.27 q	1.26 t	9.0
	TFA	9.13 s[b]	8.06 d	8.25 d	9.13 s[b]	4.01 s	4.29 q	1.10 t	9.5
IIb	DMSO	8.08 s	7.36 d	7.76 d	8.34 s	4.25 s	4.19 q	1.23 t	9.0
	TFA	9.03 s	8.03 d	8.27 d	9.10 s	4.35 s	4.33 q	1.13 t	9.5
IIc	TFA	–	8.14 d	8.32 d	9.16 s	4.38 s	4.33 q	1.13 t	9.5
IId	TFA	–	7.94 d	8.44 d	9.11 s	4.66 s	4.33 q	1.13 t	9.5
IIe	DMSO	–	7.62 d	8.03 d	8.53 s	4.45 s	4.23 q	1.25 t	9.0
	TFA	–	7.73 d	8.28 d	8.99 s	4.35 s	4.29 q	1.11 t	9.5
IIIa[a]									
IIIb	DMSO	8.86 s	7.84 d	8.09 d	8.96 s	4.18 s	–		9.0
IIIc	TFA	–	8.03 d	8.23 d	9.03 s	4.38 s	–		9.5
IIId	TFA	–	7.90 d	8.35 d	9.04 s	4.70 s	–		9.5
IIIe	TFA	–	7.75 d	8.31 d	9.06 s	4.38 s	–		9.5

[a] Ref.[5]: *IIa* (hexadeuteriodimethyl sulfoxide + trifluoroacetic acid) 1.3 t, 3 H (CH_3CH_2); 4.15 s, 3 H (NCH_3); 4.3 q, 2 H (CH_2); 7.8 d, 1 H (H-4); 8.25 d, 1 H (H-5); ^3J(4,5) = 9 Hz; 8.7 s, 1 H (H-7); 9.7 s, 1 H (H-2); *IIIa* (hexadeuteriodimethyl sulfoxide + trifluoroacetic acid) 4.3 s, 3 H (NCH_3); 7.85 d, 1 H (H-4); 8.3 d, 1 H (H-5); ^3J(4,5) = 9 Hz; 8.85 s, 1 H (H-7), 9.7 s, 1 H (H-2). [b] Unresolved.

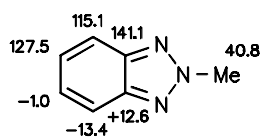


FIG. 1
^{13}C NMR chemical shifts of 2-methylbenzotriazole and relative chemical shifts due to substituent (SCS) of 2-methyltriazole ring (in deuteriotrifluoroacetic acid)

TABLE IV
^{13}C NMR spectra of compounds *II* and *III*

Compound	N–Me	C-2	C-4	C-5	C-7	C-8	C-9	C-3a	C-5a	C-9a	C-9b	COO	–OCH_2–	–CH_3
IIa	36.7	142.7[a]	123.0	120.8	146.6	108.0	171.8	141.5[a]	139.9[a]	110.0	131.7	167.3	66.7	13.3
IIb	44.5	148.1[a]	127.7	124.1	147.2[a]	109.9	173.8	143.7	135.4	114.1	129.9	170.9	68.0	16.2
IIc	37.2	–	124.0	122.0	146.8	109.6	171.6	141.8	134.3	110.2	132.6	167.0	66.6	13.2
IId	45.8	–	131.9	123.1	148.5	110.8	174.7	145.9	139.0	115.5	132.5	171.3	68.7	16.8
IIe	43.5	–	130.0	120.6	144.9[a]	109.0	171.8	143.4[a]	143.0[a]	112.4	137.8	167.9	65.9	13.9
IIIa	34.2	143.7[a]	125.6	122.8	146.2	107.8	172.9	138.9[a]	140.0[a]	109.0	133.7	169.4	–	
IIIb	42.8	144.7	125.5	122.0	146.3	107.4	172.8	132.5	141.2	112.3	127.7	170.1	–	
IIIc	37.4	–	124.0	120.5	147.2	110.4	174.5	133.8[a]	141.9	111.2	132.3[a]	169.4	–	
IIId	45.6	–	124.1	120.0	145.7	108.7	174.6	132.5	140.9	112.4	131.2[a]	171.0	–	
IIIe	43.6	–	130.4	120.5	145.7	108.4	172.1	143.4[a]	143.5[a]	112.5	138.0	170.0	–	

[a] Unresolved.

TABLE V
Calculated and found ^{13}C NMR signals of *IIe* and *IIIe*

Compound	Solvent	R	A	B	C	C(3a)–C(9b)	C-4	C-5	C-7	C-8	C-9	C-3a	C-5a	C-9a	C-9b
IVa[a]	TFA	H	H	–	H	C=C	133.9	119.6	145.1	107.6	178.3	126.1	139.9	124.4	125.0
IIe	Calc.	H	=N–	NMe–	N=	C–C	120.5	118.6	–	–	–	138.7	138.9	111.0	137.6
IIe	TFA	H	=N–	NMe–	N=	C–C	130.4	120.5	145.7	108.4	172.1	143.5[b]	143.4[b]	112.5	138.0
IVb[a]	TFA	Et	H	–	H	C=C	131.6	118.2	143.7	109.0	172.8	125.2	135.6	126.9	123.9
IIIe	Calc.	Et	=N–	NMe–	N=	C–C	118.2	117.2	–	–	–	137.8	137.6	113.5	138.0
IIIe	TFA	Et	=N–	NMe–	N=	C–C	130.0	120.6	144.9	109.0	171.8	143.4[b]	143.0[b]	112.4	137.8

[a] See text and Fig. 1. [b] Unresolved.

The shift values of methyl group in azole nucleus increase in the order: 1-methylbenzimidazole, 1-methylbenzotriazole, 2-methylbenzotriazole. In compounds exhibiting repulsion between methyl and carbonyl groups – azolo[5,4-*f*]quinolones *IIb*, *IId*, *IIIb*, *IIId* – we can see a downfield shift by about 8 ppm. The same can be observed in the case of the acids and esters also with the shifts of carbonyls of carboxy/ethoxycarbonyl group (for esters even also OCH_2 group).

From the results obtained it follows that only the angularly annulated azolo[4,5-*f*] and [5,4-*f*]quinolones are produced by applying the Gould–Jacobs reaction to diethyl (1-methyl-5- and 6-benzimidazolyl/benzotriazolyl)aminomethylenepropanedioates in all the cases (even in those sterically hindered).

EXPERIMENTAL

The melting points were measured on a Kofler apparatus. The IR spectra (0.5 mg substance per 300 mg KBr) and the UV spectra (saturated solutions in methanol, cell width 2 mm) were recorded with an FTIR PU 9802 (Philips) and a Specord (Zeiss, Jena) spectrophotometers, respectively. The ^1H and ^{13}C NMR spectra of deuteriotrifluoroacetic acid solutions run with a Varian VXR-300 instrument at 298 K relative to hexamethyldisiloxane (internal reference for ^1H NMR). Saturated solutions were measured in a 5 mm multinuclear probe. The ^1H NMR spectra were recorded at the spectral width of 4 kHz, number of points 16 000. The ^{13}C NMR spectra were measured at 75 MHz operating frequency, spectral width of 16 kHz and 64 000 words of datapoints per spectrum. The number of accumulations of proton-decoupled ^{13}C NMR spectra varied within 250 and 5 000. The pulse repetition time 3 s, flip angle 45°.

Thermal Cyclocondensation of Diethyl Esters *I*

A mixture of diethyl ester *I* (3.2 g, 10 mmol) and Dowtherm (60 ml) was heated at 250 – 260 °C 30 min. The precipitate formed after cooling was collected by suction and washed with toluene (50 ml), heptane (50 ml) and diethyl ether (50 ml). If no or gel precipitates formed after cooling, the solution was treated with heptane (200 ml) at 100 °C and left to stand overnight. The mixture was stirred, the separated solid was collected by suction on a Büchner funnel and washed as above. The cyclizate was recrystallized from dimethyl sulfoxide with addition of charcoal and, as the case may be, water. The collected and washed precipitate was dried in vacuum at 80 °C 4 h. The yields of reactions and physico-chemical data of the synthesized azoloquinolones *II* are listed in Table I.

Hydrolysis of Ethyl Quinolonecarboxylates *II*

A mixture of ethyl ester *II* (0.5 g) and 5% hydrochloric acid (5 ml) was refluxed with stirring 8 h. During the reaction, greater part of the ethyl ester dissolved and, after a certain time, the acid formed began to separate. It was collected by suction and dried in vacuum at 80 °C 12 h. If the acid did not precipitate after 8 h, the reaction mixture was cooled and neutralized with 20% sodium hydroxide and cooled again. The separated acid was isolated as above. The samples for analyses were prepared by reprecipitation from a solution in 10% sodium hydroxide with addition of charcoal if necessary. The reaction yields and physico-chemical properties of the quinolonecarboxylic acids *III* synthesized are summarized in Table I.

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