GOULD–JACOBS REACTION OF 5- AND 6-AMINO-2-SUBSTITUTED BENZOXAZOLES. I. REACTION WITH DIETHYL ETHOXYMETHYLENEMALONATE

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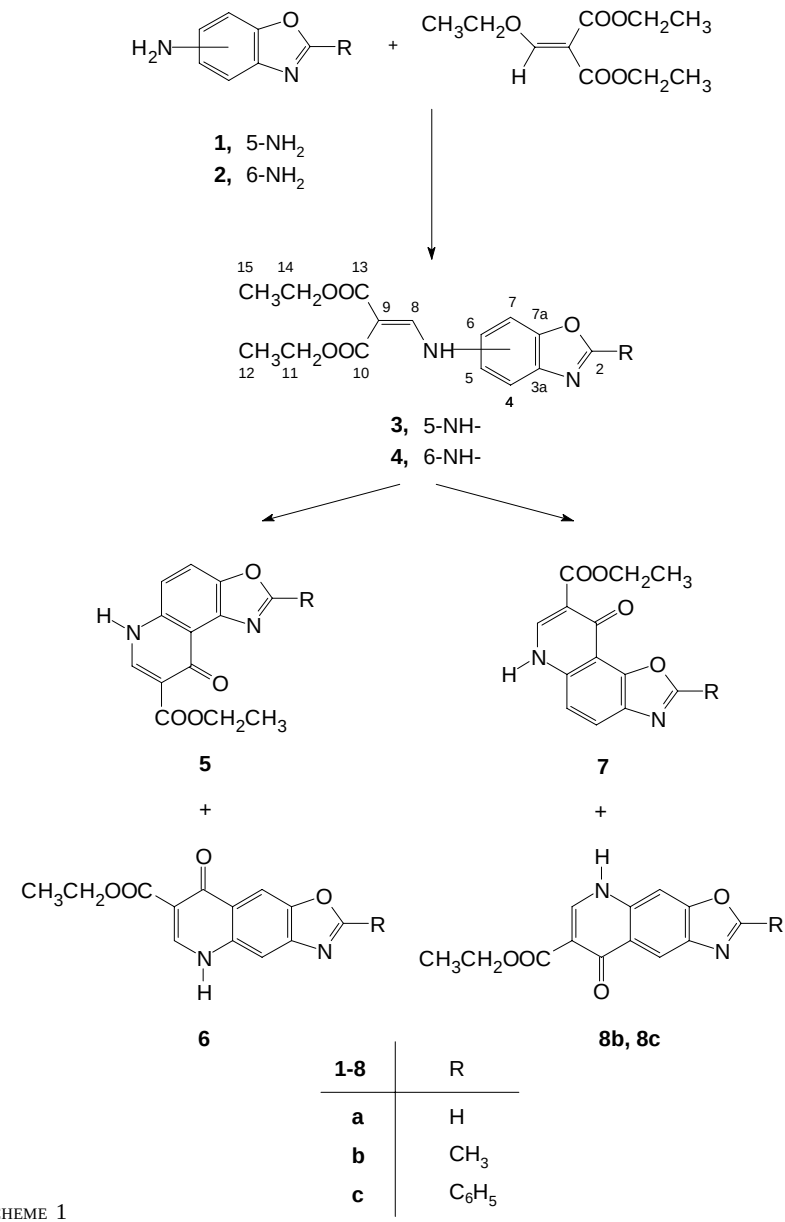
Reaction of 2-substituted 5- and 6-aminobenzoxazoles **1** and **2** with diethyl ethoxymethylenemalonate afforded the corresponding diethyl 3-*N*-(5- and 6-benzoxazolyl)aminomethylenemalonates **3** and **4**. Under conditions of the Gould–Jacobs reaction, the compounds **3** gave a mixture of angularly and linearly annelated oxazolo[4,5-*f*]quinolones **5** and oxazolo[5,4-*g*]quinolones **6**, and compounds **4** afforded a mixture of oxazolo[5,4-*f*]quinolones **7** and oxazolo[4,5-*g*]quinolones **8**.
Key words: Gould–Jacobs reaction; Oxazoloquinolones.

The Gould–Jacobs reaction, consisting in addition of a fused 4-pyridone ring to an aromatic structure, has received an increased attention since the discovery of antimicrobial properties of nalidixic acid[1] in 1962. In the aminobenzimidazole, aminobenzotriazole and aminobenzothiazole series, the cyclocondensation with derivatives of alkoxymethylenemalonic acid was studied in detail from the viewpoint of the structure of the resulting azoloquinolone[2–5] and of the interesting stereochemistry and spectral properties of the substitution products[6]. A similar reaction with aminobenzoxazole is mentioned in an only one Japanese patent[7]. All these papers report the exclusive formation of the angularly annelated azoloquinolone derivative.

In this study we describe the condensation of 2-substituted 5- and 6-aminobenzoxazoles **1a**–**1c** and **2a**–**2c** with diethyl ethoxymethylenemalonate (EMME) which leads to the respective substitution products **3a**–**3c** and **4a**–**4c**. Further we describe their thermal cyclization to oxazoloquinolone derivatives **5**–**8** and structural proof of the products (Scheme 1).

So far, no formation of linearly annelated heterocyclic derivative has been reported in the benzazole series (benzothiazoles, benzotriazoles). This communication describes for the first time the formation of mixtures of linearly and angularly annelated oxazoloquinolones. However, their structural similarity did not allow the isolation of the individual isomers and therefore we describe spectral characteristics and physicochemical data only for mixtures of both the isomers.

The substitution products **3** and **4** were obtained by refluxing a mixture of compound **1** or **2** with EMME in boiling toluene. The amino derivatives were prepared immediately before the reaction by catalytic reduction of the corresponding nitro derivative over 5% palladium on charcoal. The yields of the products are related to the starting nitrobenzo-



1-8	R
a	H
b	CH_3
c	C_6H_5

SCHEME 1

TABLE I
Physicochemical properties of compounds **3–8**

Compound or mixture	M.p., °C Yield, %	Formula M.w.	Calculated/Found		
			% C	% H	% N
3a	116–117	$C_{15}H_{16}N_2O_5$	59.20	5.30	9.21
	58	304.3	59.13	5.27	9.16
3b	106–107	$C_{16}H_{18}N_2O_5$	60.37	5.70	8.80
	56	318.3	60.28	5.63	8.75
3c	112–113	$C_{21}H_{20}N_2O_5$	66.30	5.30	7.37
	66	380.4	66.04	5.21	7.23
4a	116–117	$C_{15}H_{16}N_2O_5$	59.20	5.30	9.21
	35	304.3	59.03	5.21	9.15
4b	63–65	$C_{16}H_{18}N_2O_5$	60.37	5.70	8.80
	34	318.3	60.29	5.63	8.71
4c	84–85	$C_{21}H_{20}N_2O_5$	66.30	5.30	7.27
	73	380.4	66.22	5.23	7.41
5a[a]	–	$C_{13}H_{10}N_2O_4$	60.46	3.90	10.85
6a	79	258.2	60.39	3.65	10.48
5b[b]	–	$C_{14}H_{12}N_2O_4$	61.76	4.44	10.29
6b	76	272.3	61.29	4.12	9.97
5c[c]	–	$C_{19}H_{14}N_2O_4$	68.25	4.22	8.38
6c	93	334.3	68.01	4.08	8.11
7a	258–263	$C_{13}H_{10}N_2O_4$	60.46	3.90	10.85
	94	258.2	60.17	3.57	10.53
7b[d]	–	$C_{14}H_{12}N_2O_4$	61.76	4.44	10.29
8b	65	272.3	61.34	4.28	10.07
7c[e]	–	$C_{19}H_{14}N_2O_4$	68.29	4.22	8.38
8c	68	334.3	68.19	4.03	8.21

Ratio of isomers in mixture: [a] 4 : 1; [b] 4 : 3; [c] 2 : 1; [d] 2 : 1; [e] 2 : 1.

xazoles and are given in Table I. The proton NMR spectra of the products (Table II) show magnetic nonequivalency of the two ester groups (duplication of triplets and quadruplets of the ethoxy groups). The magnitude of interaction between the NH and the olefinic protons (J = 14 Hz) confirms their *anti*-arrangement in the –NH–CH= grouping. The spectrum also shows vicinal interaction of the *ortho*-protons, $^3J(6,7)$ = 9 Hz and $^3J(4,5)$ = 9 Hz, and long-range interactions of the *meta*-protons, $^4J(4,6) = {}^4J(5,7)$ = 2 Hz. The ^{13}C NMR spectral data of the products are summarized in Table III. The infrared spectra of compounds **3** and **4** (Table IV) contain two absorption bands of non-equivalent ester groups in the region 1 650–1 700 cm^{-1}, the lower-wavenumber band belonging to the group that forms a hydrogen bond with the NH group. The ultraviolet spectra (Table IV) show that introduction of the strongly polarized propene moiety into the molecule results in a bathochromic shift (18–50 nm) of the longest-wavelength band relative to that of the corresponding 2-substituted benzoxazole[8].

Compounds **3a**–**3c** and **4a**–**4c** were cyclized in the inert medium of Dowtherm (diphenyl ether–biphenyl mixture) at 250 °C. The isolation and purity of the products depended on the mutual ratio of the compound to Dowtherm and also on the reaction time. As optimal we found the ratio 40 ml of Dowtherm to 1 g of the compound; the optimum time was 15 min. Greater amounts of Dowtherm hindered its deposition from the solution whereas smaller amounts led to partial carbonization.

As seen from the proton NMR spectra of the cyclization products (Table V), the cyclization leads to a mixture of angularly and linearly annelated oxazoloquinolone derivatives **5**–**8** (Scheme 1). Because of their low solubility in the common solvents, their spectra were taken in CF_3COOD. Comparison of proton spectra of the cyclization products with those of structurally related angularly annelated azoloquinolones[4] allowed

TABLE II
^{1}H NMR data (δ, ppm; J, Hz[a]) for compounds **3** and **4**

Compound	H-4	H-5	H-6	H-7	H-8	NH	CH_2	CH_3	R
3a	7.81	–	7.46	7.76	8.61	11.04	4.24, 4.21	1.31, 1.24	8.33
3b	7.62	–	7.28	7.31	8.37	10.68	4.15, 4.05	1.27, 1.19	2.60
3c	7.66	–	7.37	7.40	8.41	10.76	4.22, 4.14	1.27, 1.23	–[b]
4a	7.75	7.14	–	7.52	8.52	10.97	4.19, 4.12	1.25, 1.23	8.08
4b	7.84	6.86	–	6.94	8.25	10.65	4.18, 4.10	1.26, 1.21	2.11
4c	7.80	7.39	–	7.74	8.44	10.84	4.21, 4.12	1.26, 1.19	–[c]

[a] $J(4,5)$ = 9, $J(4,6)$ = 2, $J(6,7)$ = 9, J(NH,8) = 14. [b] 8.06–8.21, 2 H (*o*-position); 7.37–7.53, 3 H (*m*- and *p*-positions). [c] 8.14–8.26, 2 H (*o*-position); 7.04–7.77, 3 H (*m*- and *p*-positions).

TABLE III
^{13}C NMR data (δ, ppm) for compounds **3** and **4**

Compound	C-2	C-3a	C-4	C-5	C-6	C-7	C-7a	C-8	C-9	C-10	C-11	C-12	C-13	C-14	C-15	R
3a	155.46	132.41	111.81	128.52	109.04	116.71	137.05	152.11	93.19	164.94	59.41	14.21	167.32	59.60	14.26	–
3b	165.95	141.94	110.55	136.31	107.84	114.97	147.49	151.46	93.19	164.06	58.94	13.72	165.00	59.19	14.51	13.38
3c	163.52	142.43	111.47	137.07	108.45	116.29	147.54	151.77	93.32	164.88	59.41	14.10	167.28	60.10	14.96	_[a]
4a	159.83	136.33	115.88	108.73	123.71	104.38	147.81	150.60	92.73	164.86	59.33	14.17	167.33	59.61	14.26	–
4b	165.04	131.20	116.08	113.97	127.37	111.38	144.99	151.71	91.64	167.58	59.30	14.26	169.18	59.51	14.33	23.82
4c	162.40	137.63	115.62	105.57	120.28	100.23	138.40	151.13	93.76	164.79	59.56	14.10	167.26	60.19	15.07	_[b]

[a] 126.16 (C-1′); 127.24 (C-2′,C-6′); 129.19 (C-3′,C-5′); 132.00 (C-4′). [b] 126.25 (C-1′); 127.04 (C-2′,C-6′); 129.25 (C-3′,C-5′); 131.80 (C-4′).

us to assign the signals of individual protons of both the isomers in the mixture. Compounds **3a**–**3c** afforded mixtures of oxazolo[4,5-*f*]quinolones **5a**–**5c** with characteristic doublet of benzene protons, J = 9 Hz and oxazolo[5,4-*g*]quinolones **6a**–**6c** with two singlets of benzene protons, corresponding to linear annelation. Compound **4a** cyclized to give solely the angularly annelated oxazolo[5,4-*f*]quinolone derivative **7a** whereas compounds **4b** and **4c** afforded again mixtures of angularly annelated oxazolo[5,4-*f*]-quinolones **7b** and **7c** and linearly annelated oxazolo[4,5-*g*]quinolones **8b** and **8c**. The ratios of the arising isomers were determined from the integrated intensities and are given in Table I. In the case of compounds **5b**, **6b** and **7b**, **8b** the presence of two isomers was confirmed by two methyl signals, in the case of derivatives **5a** and **6a** by two proton signals.

The low solubility and structural similarity of the compounds made them inseparable by fractional crystallization or by chromatography. The compounds **5**–**8** are thermally very stable: there was no opening of the oxazole ring during the cyclization as confirmed by two hours' heating of the benzoxazole derivative **7a** under the conditions of cyclization. Yields of the compounds **5**–**8** are given in Table I; the data relate to mixtures of both the structural isomers. Therefore, the IR and UV spectral data of these mixtures (Table IV) are given without detailed assignment of the bands to the individual isomers.

EXPERIMENTAL

The melting points were determined on a Kofler block and are uncorrected. Proton and ^{13}C NMR spectra were measured on a Varian VXR-300 instrument (300 MHz for ^{1}H, 75 MHz for ^{13}C) with tetramethylsilane as internal standard. IR spectra were taken on an M-80 (Zeiss, Jena) spectrometer (1 mg in 300 mg KBr). Electronic absorption spectra were measured on a UV-VIS M-40 spectrophotometer (Zeiss, Jena) in methanol, concentration 10^{-4} mol dm^{-3} or saturated solution for sparingly soluble compounds. The starting nitrobenzoxazoles were prepared by modified published procedures[8–11].

Preparation of 5- and 6-Aminobenzoxazoles **1** and **2**

A magnetically stirred suspension of the corresponding 2-substituted 5- or 6-nitrobenzoxazole (0.01 mol) and 5% Pd/C (0.5 g) in toluene (100 ml) was hydrogenated at 10 kPa of hydrogen until the consumption ceased (about 0.66 l, 0.03 mol H_2). After filtration, the toluene solution of the amine was immediately used in the next reaction.

Preparation of Diethyl 3-*N*-[5- or 6-(2-Substituted benzoxazolyl)]aminomethylenemalonates **3** and **4**

Diethyl ethoxymethylenepropanedioate (EMME; 3.5 g, 0.016 mol) was added to a stirred solution of the corresponding aminobenzoxazole **1** or **2** (0.01 mol) in toluene, the mixture was refluxed and the reaction was monitored by TLC. After cooling, the product was isolated by filtration or by concentration under diminished pressure. For physicochemical data of the products see Table I, for their ^{1}H NMR spectra Table II, for ^{13}C NMR spectra Table III and for UV and IR spectra Table IV.

TABLE IV
Characteristic IR bands (cm^{-1}) and UV maxima (λ_{max}, nm (log ε)) for compounds **3**–**8**

Compound or mixture	IR spectra		UV spectra
	$\tilde{\nu}$(C=O)	$\tilde{\nu}$(C=C), $\tilde{\nu}$(C=N)	
3a	1 650, 1 690	1 610, 1 640	207 (3.26), 227 (3.28), 298[a] (3.31), 318 (3.40)
3b	1 650, 1 690	1 595, 1 630	206 (3.38), 229 (3.41), 297[a] (3.39), 318 (3.51)
3c	1 650, 1 690	1 530, 1 560	202 (3.48), 223[a] (3.29), 260[a] (3.33), 328 (3.54)
4a	1 645, 1 690	1 595, 1 620	224 (3.26), 290[a] (3.06), 325 (3.54)
4b	1 650, 1 690	1 605, 1 625	225 (3.21), 291[a] (3.00), 326 (3.45)
4c	1 690, 1 725	1 590, 1 625	224 (3.34), 342 (3.65)
5a, **6a**	1 720	1 542, 1 590, 1 630	221, 256, 337[b]
5b, **6b**	1 715	1 540, 1 590, 1 630	227, 259, 349[b]
5c, **6c**	1 715	1 555, 1 590, 1 620	233, 287, 356[b]
7a	1 710	1 530, 1 590, 1 620	227, 261[a], 333[b]
7b, **8b**	1 710	1 530, 1 590, 1 630	227, 262[a], 335[b]
7c, **8c**	1 710	1 535, 1 585, 1 630	208[a], 263, 348[b]

[a] Shoulder. [b] Saturated solutions.

TABLE V
^{1}H NMR data (δ, ppm[a]) for compounds **5**–**8**

Compound	H-4	H-5	H-6	H-7	H-8	H-9	NH	CH_2	CH_3	R
5a	–	–	9.53	–	8.43	8.63	11.87	4.97	3.62	9.18
6a	9.08	–	9.53	–	–	9.08	11.87	4.97	3.62	9.18
5b	–	–	9.55	–	8.50	8.60	12.20	4.75	1.58	3.22
6b	8.91	–	9.46	–	–	8.95	12.20	4.75	1.58	3.04
5c	–	–	9.55	–	–[b]	8.69	11.81	4.76	1.60	–[b]
6c	9.01	–	9.48	–	–[b]	9.13	11.81	4.76	1.60	–[b]
7a	8.82	8.38	–	9.53	–	–	11.82	4.87	1.62	9.11
7b	8.65	8.35	–	9.47	–	–	11.95	4.72	1.57	3.12
8b	9.09	–	–	9.44	–	8.49	11.95	4.72	1.57	3.01
7c	8.82	–[c]	–	9.57	–	–	11.95	4.80	1.63	–[c]
8c	9.27	–[c]	–	9.53	–	8.67	11.95	4.80	1.63	–[c]

[a] J(8,9) = J(4,5) = 9 Hz. [b] 7.75–8.53 m, 6 H (H-8, arom.). [c] 7.77–8.53 m, 6 H (H-5, arom.).

Preparation of Mixtures of Oxazolo[4,5-*f*]quinolones **5a**–**5c** and Oxazolo[5,4-*g*]quinolones **6a**–**6c**, and Mixtures of Oxazolo[5,4-*f*]quinolones **7a**–**7c** and Oxazolo[4,5-*g*]quinolones **8b** and **8c**

Compound **3** or **4** (1.0 g) was added to hot Dowtherm (40 ml) and the solution was heated at reflux (250 °C) for 15 min. After cooling, the deposited compound was collected and washed with toluene and ether. The obtained product was dried at 120 °C in vacuo. The physicochemical data of the products are given in Table I, their ^{1}H NMR spectra in Table V, the IR and UV spectra in Table IV.

REFERENCES

1. Dietz W. H.: Antimicrob. Agents Chemother. *1964*, 583.
2. Renault J., Chaoui M., Renault S. G., Cavier R., Delage N.: Ann. Pharm. Fr. *40*, 81 (1982).
3. Spencer C. F., Snyder M. R., Alaimo R. J.: J. Heterocycl. Chem. *12*, 1319 (1975).
4. Milata V., Ilavsky D.: Collect. Czech. Chem. Commun. *52*, 2918 (1987).
5. Kadyoa S., Takamura I., Suzuki N., Dohmori R.: Chem. Pharm. Bull. *24*, 136 (1976).
6. Goljer I., Ilavsky D., Milata V.: Magn. Reson. Chem. *27*, 138 (1989).
7. Yanagisawa I., Murakami M., Nega I.: Japan. Kokai 7 472, 297; Chem. Abstr. *83*, 131573 (1975).
8. Passerini R.: J. Chem. Soc. *1954*, 2256.
9. Stephens F. F., Bower J. D.: J. Chem. Soc. *1949*, 2971.
10. Roussos M., Lecomte J.: Ger. Offen. 1 124 499; Chem. Abstr. *57*, 9858 (1962).
11. Garner R., Mullock E. B., Suschitzky H.: J. Chem. Soc. *1966*, 1980.