ELECTROPHILIC AND NUCLEOPHILIC SUBSTITUTION IN OXAZOLO[3,2-f]XANTHINES

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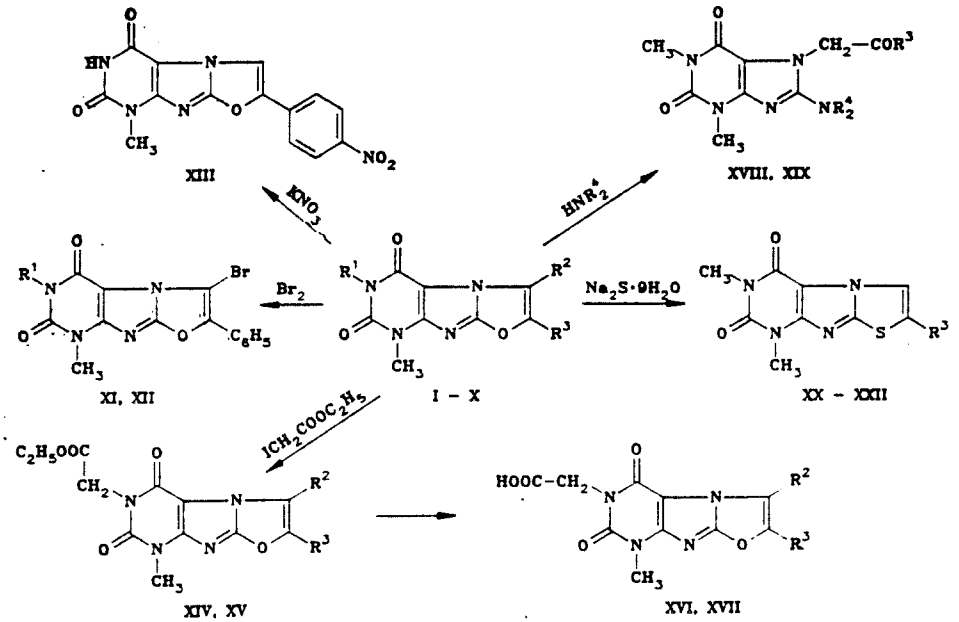
Bromination of 2-aryloxazolo[3,2-f]xanthines gives the 3-bromoderivatives whereas 8-methyl-2-phenyloxazolo[3,2-f]xanthine is nitrated in the para-position of the phenyl substituent. Alkylation of oxazolo[3,2-f]xanthines by ethylmonoiodoacetate gives the ethyl esters of oxazolo[3,2-f]xanthinyl-6-acetic acids. Reaction of oxazolo[3,2-f]xanthines with sodium sulfide gives thiazolo[3,2-f]xanthines whereas the reaction with secondary amines opens the oxazole ring.

Earlier [1, 2] we described the synthesis of oxazolo[3,2-f]xanthines and specific examples of their electrophilic (alkylation by methyl iodide) and nucleophilic (reaction with primary amines) substitution. In the present work the variation in reactions of oxazolo[3,2-f]xanthines with several electrophilic and nucleophilic agents is studied.



I, V—VIII, XI R^1=H, II—IV, IX, X, XII R^1=CH_3; I—IV, VII, VIII, X, XIV, XVI R^2=H, V, IX R^2=CH_3, VI, XV, XVII R^2=C_2H_5; I, II, V, VI, IX, XV, XVII—XX R^3=C_6H_5, III, XXII R^3=p-Br—C_6H_4, IV, XXI R^3=p-CH_3—C_6H_4, VII, XIV, XVI R^3=p-Cl—C_5H_4, VIII, X, R^3=p-F—C_6H_4, I NR_2^4= morpholino XIX NR_2^4= piperidino

Thus, the 3-bromoderivatives XI and XII are formed by reaction of bromine in glacial acetic acid with 2-phenyloxazolo[3,2-f]xanthines I and II [2]. A signal for the proton on $C_{(3)}$ is missing in the PMR spectrum of XII. Ions with m/z 362 and 360 (1:1) corresponding to M^+ with one Br are present in the mass spectrum. Loss of a fragment $[C_6H_5-C{\equiv}C-Br]^+$ with m/z 180 from the molecular ion confirms that bromination occurred at the 3-position. This is also evident by loss of halogen from M^+ [the ion with m/z 281 (29)] and subsequent loss of CO [the ion with m/z 253 (5)].

Nitration with KNO_3 of I in concentrated H_2SO_4 gives XIII with the phenyl substituted in the para-position [1].

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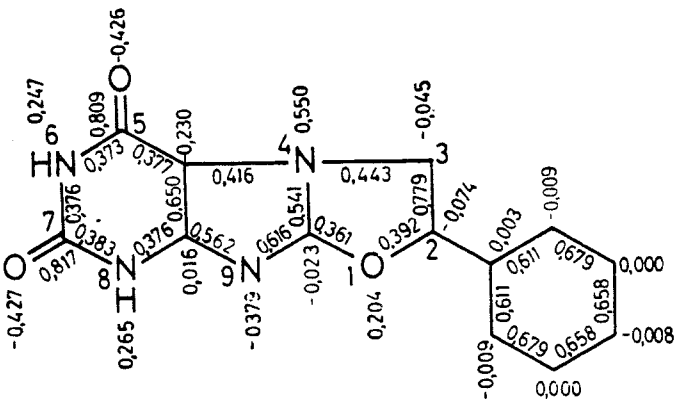

Fig. 1. 2-Phenyloxazolo[3,2-f]xanthine.

The different results for electrophilic bromination and nitration can be explained by facile protonation of the heterosystem in the second case (H_2SO_4 catalysis) that precludes attack at the 3-position and leads to sterically favorable nitration of only the phenyl ring.

Quantum-chemical Hückel calculations with standard parametrization [3] agree with the experimental data. Thus, the molecular structure of 2-phenyloxazolo[3,2-f]xanthine (Fig. 1) shows that the most probable sites of electrophilic attack are the 3-position of the heterocycle and the ortho- and para-positions of the phenyl ring. Protonation and alkylation of the heterocycle should be easiest at $N_{(9)}$. However, alkylation by methyl iodide is known to occur at $N_{(6)}$ [2].

Analogously, 6H-oxazolo[3,2-f]xanthines VI and VII are also alkylated at the NH group of the uracil fragment by ethylmonoiodoacetate in DMF in the presence of anhydrous K_2CO_3. This gives the ethyl esters of 2-p-chlorophenyl- and 2-phenyl-3-ethyl-8-methyloxazolo[3,2-f]xanthinyl-6-acetic acids (XIV and XV), which are easily hydrolyzed with base to the corresponding acids XVI and XVII. The oxazolo[3,2-f]xanthine may also be alkylated under the conditions described due to the presence of the basic catalyst K_2CO_3 in the reaction mixture.

Boiling 6,8-dimethyl-2-phenyloxazolo[3,2-f]xanthine II with secondary amines (morpholine and piperidine) in DMF opens the oxazole ring and forms the known 7-phenacyl-8-cycloalkyltheophyllines XVIII and XIX [4].

Prolonged heating of 2-aryloxazolo[3,2-f]xanthines II-IV with sodium sulfide nonahydrate in DMF gave the previously described 2-arylthiazolo[3,2-f]xanthines [5].

The structure of the synthesized compounds was confirmed by PMR (Table 1) and mass spectra (Table 2).

Peaks of the molecular ions have the greatest intensity in mass spectra of the oxasoloxanthine derivatives. The characteristic ions $[M-R^1NCO]^+$, $[M-CONR^1CO]^+$, $R^3-\underset{\backslash\,/}{\overset{}{C}}=C-R^2$ (O), $R^3-C{\equiv}C-R^2$, $R^3-C{\equiv}O^+$, and R^{3+} [1, 2, 6] are formed by fragmentation of the compounds due to electron impact. This is consistent with the structures of the compounds [2].

EXPERIMENTAL

PMR spectra were recorded on Tesla BS-467 and Bruker M-250 instruments in DMSO-D_6 and CF_3COOH solutions with TMS internal standard. Mass spectra were taken on a Varian MAT-311A spectrometer using a direct probe at 100-150°C vaporization temperature, 3 kV accelerating potential, 1 mA cathode emission current, and 70 eV ionizing electron energy.

Properties of the synthesized compounds are given in Tables 1 and 2. Elemental analyses for C, H, and N agreed with those calculated.

Oxazolo[3,2-f]xanthines I-X were prepared by the method of [2].

3-Bromo-2-phenyl-8-methyl- and 6,8-dimethyloxazolo[3,2-f]xanthines (XI and XII). To a boiling solution of 10 mmoles compound I or II in 100 ml glacial acetic acid were added dropwise 0.51 ml (0.01 moles) bromine in 20 ml acetic acid. The reaction mixture was boiled until colorless, cooled, and diluted with 300 ml water containing 20.0 g sodium acetate. The precipitate was filtered off, dried, and crystallized from DMF.

2-p-Nitrophenyl-8-methyloxazolo[3,2-f]xanthine (XIII). To a solution of 2.0 g (7 mmoles) compound I in 30 ml concentrated H_2SO_4 (d 1.85) at 0-5°C was added a solution of 0.7 g (7 mmoles) KNO_3 in 20 ml concentrated H_2SO_4. The mixture was left for 24 h at 20°C. Then, 100 ml water was added. The precipitate was filtered off and dried. Compound XIII was obtained in 92% yield [2].

TABLE 1. Properties of the Synthesized Compounds

Compound	Empirical formula	T_{mp}, °C	PMR spectrum δ, ppm (J, Hz)*					Yield, %
			ethyl-substituent		8-CH_3 (s, 3H)	R^3	CH_2 (s, 2H)	
			CH_3 (t, 3H)	CH_2 (q, 2H)				
V	$C_{15}H_{12}N_4O_3$	>300	—	—	3,56	7,24...7,52 (s, 5H)	—	87
VI	$C_{16}H_{14}N_4O_3$	314...316	1,03	2,87	3,30	7,13 (s, 5H)	—	92
VII	$C_{14}H_9ClN_4O_3$	>350	—	—	—	—	—	81
VIII	$C_{14}H_9FN_4O_3$	>300	—	—	—	—	—	92
IX	$C_{16}H_{14}N_4O_3$	240...241	—	—	3,13**	6,87...7,20 (s, 5H)	—	88
X	$C_{15}H_{11}FN_4O_3$	>300	—	—	—	—	—	89
XI	$C_{14}H_9BrN_4O_3$	>800	—	—	—	—	—	96
XII	$C_{15}H_{11}BrN_4O_3$	>300	—	—	3,37***	7,61...7,92 (s, 5H)	—	96
XIV	$C_{18}H_{15}ClN_4O_5$	237...239	0,93	3,93 (J=8,2)	3,30	7,23 (s, 4H	4,56	71
XV	$C_{20}H_{20}N_4O_5$	188...190	1,26	4,24 (J=8,2)	3,60	AB) 7,28...7,54 (s, 5H)	4,92	78
XVI	$C_{16}H_{11}ClN_4O_5$	308...310	—	—	—	—	—	67
XVII	$C_{18}H_{16}N_4O_5$	272...274	1,28	3,11 (J=8,2)	3,60	7,26...7,50 (s, 5H)	4,96	61

*V, 2.69 (3-CH_3, s, 3H); IX, 2.43 (3-CH_3, s, 3H); XIV, 7.07 ppm (3-H, s, 1H).

**Signal of the 6-CH_3 protons: 3.30 ppm (s, 3H).

***Signal of the 6-CH_3 protons: 3.37 ppm (s, 3H).

TABLE 2. Mass Spectra of the Synthesized Compounds

Compound	m/z (I, % of maximal)*
VI	42 (11), 43 (10), 44 (7), 50 (5), 51 (22), 52 (7), 53 (7), 54 (9), 55 (13), 56 (20), 57 (6), 59 (13), 63 (10), 65 (7), 66 (7), 67 (15), 68 (6), 69 (6), 70 (14), 72 (10), 75 (6), 76 (6), 77 (45), 78 (9), 80 (8), 81 (6), 82 (8), 83 (84), 84 (7), 89 (11), 91 (14), 102 (11), 103 (77), 104 (12), 105 (20), 115 (68), 116 (15), 117 (19), 118 (10), 127 (23), 128 (44), 129 (67), 130 (18), 139 (6), 140 (6), 142 (7), 154 (7), 155 (39), 156 (7), 162 (9), 177 (18), 182 (10), 183 (10), 184 (5), 185 (6), 193 (24), 198 (7), 199 (7), 206 (5), 210 (5), 212 (5), 226 (15), 238 (5), 240 (5), 252 (14), 253 (11), 254 (6), 267 (5), 281 (19), 295 (82), 296 (15), 309 (16), 310 (100), 311 (90), 312 (10)
VII	43 (11), 83 (23), 111 (20), 113 (7), 136 (11), 139 (6), 152 (7), 158 (5), 244 (23), 245 (16), 316 (100), 318 (35), 317 (18), 319 (7)
IX	43 (19), 44 (16), 45 (5), 51 (6), 55 (6), 56 (9), 67 (6), 75 (5), 77 (11), 83 (37), 89 (5), 104 (8), 105 (8), 111 (6), 115 (35), 116 (19), 129 (5), 148 (6), 149 (5), 155 (15), 212 (8), 224 (5), 240 (15), 281 (7), 309 (6), 310 (100), 311 (20)
X	57 (11), 83 (88), 95 (6), 119 (5), 120 (39), 123 (5), 136 (10), 157 (16), 228 (31), 229 (10), 257 (5), 313 (10), 314 (100), 315 (19)
XI	43 (16), 77 (43), 83 (61), 105 (80), 180 (5), 196 (6), 288 (5), 317 (5), 319 (5), 360 (100), 362 (98), 361 (20), 363 (18)

*Peaks of ions with intensity ≥5% are given.

Ethyl Esters of 2-p-Chlorophenyl-8-methyloxazolo[3,2-f]xanthinyl-6-acetic and 2-Phenyl-3-ethyl-8-methyloxazolo[3,2-f]xanthinyl-6-acetic Acids (XIV and XV). A mixture of 10 mmoles VII or VI, 1.2 ml (10 mmoles) ethylmonoiodoacetate, and 1.4 g (10 mmoles) anhydrous K_2CO_3 in 70 ml DMF was boiled for 1 h. The mixture was cooled and diluted with 250 ml water. The precipitate was filtered off, washed with water, dried, and crystallized from an alcohol–DMF mixture (1:1) or n-butanol.

2-p-Chlorophenyl-8-methyloxazolo[3,2-f]xanthinyl-6-acetic and 2-Phenyl-3-ethyl-8-methyloxazolo[3,2-f]xanthinyl-6-acetic Acids (XVI and XVII). A mixture of 10 mmoles of the ester of XIV or XV and 1.12 g (20 mmoles) KOH in 200 ml water was boiled for 20 min (until the starting compound dissolved), filtered, and acidified with concentrated HCl until slightly acidic. The precipitate was filtered off, washed with water, and reprecipitated from aqueous $NaHCO_3$. Compounds XVI and XVII were crystallized from ethanol or an ethanol–DMF mixture (2:1).

7-Phenacyl-8-N-morpholino- and 8-N-Piperidino-1,3-dimethylxanthines (XVIII and XIX). A mixture of 2.96 g (10 mmoles) II and 30 mmoles morpholine or piperidine in 40 ml DMF was boiled for 2.5 h and cooled. The precipitate was filtered off and dried. Compounds XVIII and XIX were obtained in 96 and 92% yields, respectively. The synthesized compounds did not depress the melting points of samples prepared by the method of [4].

2-Aryl-6,8-dimethylthiazolo[3,2-f]xanthines (XX-XXII). A mixture of 10 mmoles xanthines II-IV and 2.4 g (10 mmoles) sodium sulfide nonahydrate in 50 ml DMF was boiled for 5 h, cooled, diluted with 200 ml water, and treated with 1 ml concentrated H_2SO_4. The precipitate was filtered off. Compounds XX (92%), XXI (57%), and XXII (67%) were obtained. These did not depress the melting points of samples prepared by the method of [5].

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