SYNTHESIS OF 5-METHYL-2*H*-1,3-OXAZINE-2,4(3*H*)-DIONE*

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Received April 26th, 1978

The title compound (*II*) was prepared by acid-catalysed hydrolysis of N,N-disubstituted β-methoxy-α-methylacryloylureas *V*—*VIII*. This reaction is accompanied by the parallel cleavage of the amide bond in the compounds *V*—*VII* leading to N,N-disubstituted ureas and α-formylpropionic acid.

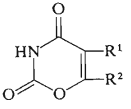
The recently published[1] synthesis of the nucleoside antibiotic oxazinomycin[2-4] (*I*) prompted us to publish our previous studies leading to the synthesis of 5-methyl-2*H*-1,3-oxazine-2,4(3*H*)-dione (*II*), which served as a model compound for the planned synthesis of the above-mentioned antibiotic *I*.

Whereas neither 2*H*-1,3-oxazine-2,4(3*H*)-dione (*III*) nor its 5-methyl derivative *II* have hitherto been described, numerous derivatives of the compound *III*, carrying alkyl or aryl groups in the positions 6 or 5, 6, are known. 6-Methyl-2*H*-1,3-oxazine-2,4(3*H*)-dione (*IV*) and some of its N-substituted derivatives were prepared by reaction of diketene with cyanic acid[5-7] or with N-substituted derivatives of urea[5,6] (see also ref.[8-10]). A more general synthetic approach[11] to derivatives of the compound *III* is represented by the reaction of β-oxocarboxylates with N,N-disubstituted ureas or with ethyl carbamate. Other syntheses of the mentioned type of oxazine derivatives[12-14] are not generally applicable. We synthesized the compound *II* using the procedure described by Shaw and coworkers[11] for preparation of the compound *IV*. This method is based on the acid-catalysed cyclisation of N′-acetoacetyl-N,N-dimethylurea. Analogically, we expected that N′-(α-formylpropionyl)-N,N-disubstituted ureas — and therefore also N′-(β-methoxy-α-methylacryloyl)-N,N-disubstituted ureas — would undergo cyclisation in an acidic medium to the compound *II*.

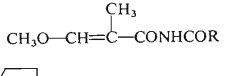
As starting compound for synthesis of the oxazine derivative *II* we used the N′-(β-methoxy-α-methylacryloyl)-N,N-disubstituted ureas *V*—*VIII*, prepared by reaction of β-methoxy-α-methylacryloyl isocyanate with pyrrolidine, dimethylamine, morpholine and diisopropylamine, respectively. Reaction of the compounds *V*—*VII* with 0·1M-HCl at 95°C afforded the compound *II* in the respective yields 45·7%, 27·4%

* Part CXCV in the series Nucleic Acids Components and Their Analogues; Part CXCIV: *43*, 2054 (1978).

and 18·9%. On the contrary, the compound *VIII* did not afford even traces of the oxazine derivative *II*. Cyclisation of the compound *V* was accomplished also at lower temperature (65–70°C) using Dowex 50 (H^+) ion exchange resin; however, the yield of *II* was substantially lower (19·7%). From the reaction mixture we isolated N-carbamoylpyrrolidine, propionaldehyde being detected as the volatile side-product.



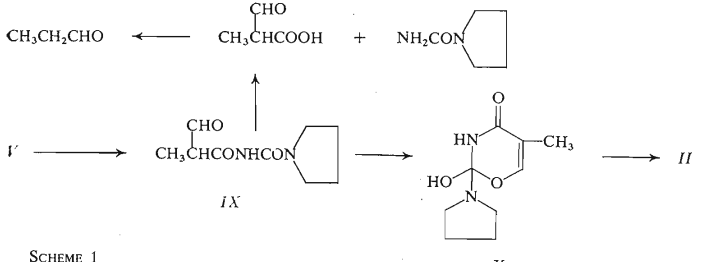
I; R^1 = β-D-ribofuranosyl, R^2 = H
II; R^1 = CH_3, R^2 = H
III; R^1 = R^2 = H
IV; R^1 = H, R^2 = CH_3



V R = 
VI: R = $N(CH_3)_2$

VII; R = 
VIII; R = $N(iso\text{-}C_3H_7)_2$

The first step in the transformation of the compound *V* probably consists in the hydrolytic fission of the vinyl ether bond leading to the α-formylpropionic acid derivative *IX* which affords the compound *II* *via* the cyclic intermediate *X* (Scheme 1).



SCHEME 1

Parallel to this cyclisation, acryloyl amide bond in the compound *IX* is hydrolysed to give α-formylpropionic acid and N-carbamoylpyrrolidine. (The formation of intermediates of the type *X* in the synthesis of oxazine derivatives is assumed also by other authors[6,11].) The significantly different yields of the cyclisation of the compounds *V*—*VIII* are probably caused by the steric effect of substituent in the ureido part of the molecule which influences to a different extent both the mentioned reaction pathways.

Stability of the compound *II* in aqueous solutions was investigated spectrophotometrically in the UV region. It is stable in 0·05M-HCl at room temperature whereas at elevated temperature (95°C) it decomposes slowly as indicated by the drop in its UV absorption maximum. In a borate buffer (pH 9·2) and at room temperature, the UV spectrum of *II* remains unchanged for several hours. After heating to 95°C for 3 hours the spectrum displays a new absorption maximum at 268 nm whose intensity increases with increasing pH of the solution, whereas in an acidic medium this maximum at 268 nm disappears completely. This spectral behaviour is characteristic for enolates of β-oxocarboxylic acids and it shows therefore that alkaline hydrolysis of the compound *II* could lead to a salt of N-(α-formylpropionyl)carbamic acid or α-formylpropionamide.

Heating of the compound *II* in aqueous ammonia affords thymine in low yield. Also oxazinomycin[2] (*I*), as well as derivatives of the compound *III* (ref.[11]) substituted in positions 6 or 5, 6 with alkyl or aryl groups, afford by reaction with ammonia the corresponding substituted uracil.

EXPERIMENTAL

Analytical samples were dried at 25°C/0·05 Torr. The melting points were determined on a Kofler block. The UV spectra were measured on a Specord UV spectrophotometer (Zeiss, Jena, GDR). The ^{1}H-NMR spectra were taken at 60 MHz (Tesla BS 467 instrument) and at 100 MHz (Varian HA 100 instrument), using hexamethyldisiloxane as standard. Thin-layer chromatography was performed on Silufol plates (Kavalier, Sázava, Czechoslovakia) in the systems: S_1, benzene–ethyl acetate (1 : 1); S_2, ethyl acetate, the spots being detected by UV light and by spraying with 0·1% potassium permanganate solution.

N′-(β-Methoxy-α-methylacryloyl)-N,N-disubstituted Ureas (*V*—*VIII*)

A solution of β-methoxy-α-methylacryloyl chloride[15] (2·69 g; 0·02 mol) in benzene (10 ml) was added dropwise at 25°C in the course of 10 min to a stirred suspension of silver cyanate (3·3 g; 0·22 mol; dried at 80°C/0·05 Torr for 8 h) in benzene (30 ml). The mixture was then stirred for 1 h, filtered and the silver salts on the filter washed with benzene (2 × 20 ml) under exclusion of moisture. To the clear filtrate a solution of the secondary amine (0·02 mol) in benzene (10 ml) was added dropwise at room temperature over 20 min with stirring. The mixture was set aside for 1 h at room temperature and then taken down in vacuo at 35°C. The residue was mixed with ether, the solid product filtered and purified by crystallisation. The yields, elemental analyses and physical constants of the compounds *V*—*VIII* are given in Table I and II. Their respective R_F values are: 0·05, 0·05, 0·07 and 0·20 in the system S_1; 0·25, 0·20, 0·36 and 0·58 in the system S_2.

5-Methyl-2*H*-1,3-oxazine-2,4(3*H*)-dione(*II*)

A) *Using* 0·1M-HCl. The compound *V* (0·212 g; 1 mmol) was heated in 0·1M-HCl (20 ml) to 95°C for 2 h. The mixture was taken down *in vacuo* and the solid residue was extracted with ethyl acetate (about 50 ml) at 50°C. The extract was dried over sodium sulfate and taken down. Crystallisation of the residue from benzene–light petroleum afforded 57·8 mg (45·7%) of the compound *II*,

TABLE I

Melting Points and Analyses of N′-(β-Methoxy-α-methylacryloyl)-N,N-disubstituted Ureas *V*– *VIII*

Compound Yield, %	M.p., °C (solvent)	Formula (mol.w.)	Calculated/Found		
			% C	% H	% N
V	123–124·5	$C_{10}H_{16}N_2O_3$	56·59	7·60	13·20
34·9	ethanol	(212·3)	56·32	7·69	13·22
VI	82–83	$C_8H_{14}N_2O_3$	51·60	7·58	15·04
44·2	diisopropyl ether	(186·2)	51·51	7·54	14·89
VII	119–121	$C_{10}H_{16}N_2O_4$	52·62	7·07	12·27
45·5	ethyl acetate–ether	(228·5)	52·38	6·88	12·17
VIII	102–104	$C_{12}H_{22}N_2O_3$	59·48	9·15	11·56
39·2	diisopropyl ether	(242·3)	59·68	9·23	11·67

TABLE II

Spectra of N′-(β-Methoxy-α-methylacryloyl)-N,N-disubstituted Ureas *V*– *VIII*

Compound	UV spectra in methanol		1 H-NMR spectra (60 MHz) in $CDCl_3$ δ, ppm (*J*, Hz)		
	λ_{max}, nm	log ε	CH_3	CH	CH_3O
V	252·5	4·121	1·74 d (1·5)	7·29 q (1·5)	3·81[a]
VI	251·0	4·105	1·75 s	7·32 s	3·81[b]
VII	252·0	4·135	1·72 d	7·28 q	3·77[c]
VIII	251·0	4·114	1·73 d (1·5)	7·28 q (1·5)	3·77[d]

[a] 1·82 (m, 4 H, CH_2—CH_2), 3·43 (m, 4 H, CH_2NCH_2). [b] 2·97 (s, 6 H, $N(CH_3)_2$. [c] 3·57 (m, 8 H, $2(CH_2$—$CH_2)$. [d] 1·25 (d, 12 H, 4 CH_3; $J = 7$ Hz); 3·77 (m, 2 H, 2 $CH(CH_3)_2$).

m.p. 152—153°C (benzene). The analytical sample was purified by sublimation at 100°C/0·07 Torr. For $C_5H_5NO_3$ (127·0) calculated: 47·25% C, 3·97% H, 11·02% N; found: 47·39% C, 3·93% H, 11·04% N. ^{1}H-NMR spectrum at 100 MHz in hexadeuteriodimethyl sulfoxide (1% $CDCl_3$), δ in ppm: 1·72 (d, 3 H, $J_{5',6}$ = 2 Hz, CH_3); 7·58 (q, 1 H, $J_{6,5'}$ = 2 Hz, H—6). UV spectrum in 0·05M-HCl: λ_{max} 209 nm and 233 nm (log ε 3·761 and 3·731); in 0·05M sodium tetraborate: λ_{max} 233 nm (log ε 3·924). IR spectrum in chloroform, cm^{-1}: 1 803 (m), 1 774 (s) ($C_{(2)}$=O); 1 721 ($C_{(4)}$=O); 1 661 (C=C); 3 395 (NH). ^{1}H-NMR spectrum at 100 MHz of compound *IV* in hexadeuteriodimethyl sulfoxide containing 1% $CDCl_3$ (measured for comparison), δ in ppm: 2·11 (s, 3 H, CH_3); 5·76 (s, 1 H, H—5). R_F of *II*: 0·65 (S_1), 0·82 (S_2; R_F of *IV* (comparison sample): 0·49 (S_1), 0·79 (S_2).

Cyclisation of the compounds *VI* and *VII* under the above-mentioned conditions afforded the compound *II* in the yield 27·4% and 18·9%, respectively. Attempts to cyclise *VIII* under the same conditions afforded neither the starting compound *VIII* nor the oxazine derivative *II*.

B) *Using Dowex* 50 (H^+) *ion exchange resin.* Moist Dowex 50 (H^+) (3 g) was added to a solution of the compound V (1 g; 4·72 mmol) in water (25 ml) and the mixture was stirred at 65—70°C until the starting compound disappeared (2 h). A gentle stream of nitrogen was introduced into the mixture during the reaction. The nitrogen, leaving the reaction flask, contained volatile reaction products and was passed into 0·1% solution of 2,4-dinitrophenylhydrazine in 5% hydrochloric acid (100 ml). After the reaction had been complete, the ion exchange resin was filtered and washed with water (20 ml). The combined filtrates were evaporated *in vacuo* and the solid residue was extracted with ethyl acetate (25 ml) at 50°C. The extract was taken down *in vacuo* and the residue crystallised from a mixture of ethyl acetate and benzene, yielding 0·118 g (19·7%) of the compound *II*, m.p. 152—153°C, no depression in m.p. on admixture with a sample of *II*, prepared by the method *A*. The insoluble portion from the extraction of the crude reaction mixture with ethyl acetate was crystallized from water, affording a compound (0·194 g), m.p. 212—213°C, which showed no depression in melting point when mixed with an authentic sample of N-carbamoylpyrrolidine[16].

In the course of the reaction the solution of 2,4-dinitrophenylhydrazine deposited a voluminous precipitate which after the end of the reaction was filtered, washed with water, dried and crystallized from ethyl acetate. The obtained red needles (55 mg) had m.p. 150°C, undepressed on admixture with an authentic sample of propionaldehyde 2,4-dinitrophenylhydrazone[17].

A solution of the compound *VIII* (90·3 mg) in dioxane (2 ml) was mixed with moist Dowex 50 (H^+) (200 mg) and heated to 60—70°C for 2 h under stirring. The mixture was filtered, the ion exchange resin washed with methanol (25 ml), the filtrate evaporated *in vacuo* and the residue chromatographed on a loose layer (10 cm × 25 cm) of silica gel (Silpearl, Kavalier, Votice Czechoslovakia) in the solvent system S_1. The absorbing band, corresponding to the compound *II*, was eluted with methanol. The yield of *II* (3·7%) was determined spectrophotometrically in methanol at 233 nm. The chromatogram showed the presence of neither the starting compound nor N,N-diisopropylurea.

Reaction of the Compound *II* with Water and Ammonia

A 10^{-4}M solution of the compound *II* in 0·05M-HCl was heated to 95°C; after 1 h the decrease in absorptivity (at λ_{max} 233 nm) was 3·75%.

A $3 . 10^{-3}$M solution of *II* in 0·05M sodium tetraborate was heated to 95°C for 3 h. After cooling, the reaction mixture was divided into two parts. One part (25 ml) was mixed with the same volume of 0·05M sodium tetraborate: λ_{max} 203 nm and 268 nm (log ε 3·312 and 3·540, respectively). To the other part (25 ml) the same volume of 0·01M-NaOH was added: λ_{max} 210 nm

and 268 nm (log ε 3·965 and 4·025, respectively). After acidification of this alkaline solution with 0·5M-HCl to pH 3, no absorption maximum in the region 220—350 nm was detectable.

The compound *II* (30·7 mg) was heated in a sealed tube with 10% aqueous ammonia (2 ml) to 95°C for 2 h. The mixture was taken down *in vacuo* and the residue was crystallized from water to give 4·8 mg of a compound, which was shown to be thymine by UV-spectrum and paper chromatography (in the system 1-butanol–ethanol–water 40 : 11 : 19).

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Translated by M. Tichý.