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REACTIONS OF METHYLQUINOXALINE DI-N-OXIDES WITH ALDEHYDES OF THE BENZENE AND FURAN SERIES

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UDC 615.281:547.863.11].074

We have shown previously [1, 2] that the ability of 2-methyl- and 2,3-dimethylquinoxalinedi-N-oxides to react with aromatic aldehydes in the presence of acidic catalysts is lower than that of the corresponding bases which are not oxidized at the heterocyclic nitrogen, but in the presence of bases it is much higher. We have obtained arylvinyl and hydroxyaralkyl derivatives.

Other workers have since described [3, 4] the preparation under similar conditions of arylvinyl derivatives only.

The object of the present investigation was to synthesize quinoxaline di-N-oxides with possible antibacterial activity, and to study the factors influencing the formation of either hydroxyaralkyl or vinyl derivatives of quinoxaline di-N-oxides in the reactions of 2-methyl, 2-methyl-6-chloro-, and 2,3-dimethyl-6-chloroquinoxaline di-N-oxides (Ia, Ib, and V) with aldehydes of the benzene and furan series (IIa-g).



The effects of the following factors were examined: the structure of the aldehydes and quinoxaline di-N-oxides, their proportions, the amount of base, and the nature of the solvent.

The reactions were all carried out at the same temperature (20-25°C), and were followed by chromatography on Silufol UV-254 plates using the solvent system benzene-alcohol (9:1). The bases used were NaOH or KOH. The reactions were carried out in the presence of

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 16, No. 9. pp. 1063-1067, September, 1982. Original article submitted December 24, 1981.

inoxal- e reac- nt	dehyde	nount of e, moles 1 mole (Ia), (Ib), (V)	nount of lehyde, les per nole of ', (Ib),	Yie1	d, %	Notes
tai Ou	A1	An bas per of or	An alo	or vY	Iva-n	
Ia Ia	IIa IIa	0,12 7,1	1,2 2,8	a, 34 —	a, 19 a, 65	Reaction accompanied by resinification
Ia	Пъ	0,12	1,2	b, 85		Small amount of (IVb) pre- sent in the mother liquors
Ia	Пр	0,12	2,8		b, 22, 9	Mixture of (IIIb) and (IVb) in the mother liquors
Ia	IIb	7,1	2,8		b,43,5	Mixture of (IIIb) and (IVb)
Ia	IIc	0,12	1,2	c,90,2		Very small amount of (IVc) in the mother liquors
Ia Ia Ia Ia Ia Ib	IIC IIC IId IId IId IIa	7,1 7,1 0,12 7,1 7,1 0,48	1,2 2,8 1,2 1,2 2,8 2,8	d, 90 d	e c, 92, 6 d d, 94 e, 39	<pre>(~1:1) Very small amount of (IVd) present in the mother liquors (IVd) predominant</pre>
Ib Ib Ia Ia Ia Ia Ia Ia V	II c IId IIe IIe IIf IIf IIg IIg IIg	$\begin{array}{c} 0,12\\ 0,12\\ 7,1\\ 0,3\\ 0,3\\ 0,24\\ 0,24\\ 0,12\\ \end{array}$	1,2 1,2 2,8 1,2 1,2 1,2 1,2 1,2 1,2 5,6	e, 95, 7 f, 93, 7 g, 95* g, 98, 8† IV, 59	g, 44, 5* g, 98 † h, 86* h, 98, 5†	Unreacted (V) in the mother
v	IIa	0,48-7,1	5,6			Considerable resinification

*Reaction carried out in DMF †Reaction carried out in alcohol.

a catalytic amount of base (0.12 mole per mole of quinoxaline di-N-oxide), aqueous solutions of NaOH or solid KOH being used (no significant differences were noted). When the reactions were carried out in the presence of larger amounts of base, only solid KOH was used. The solvents employed were alcohols (methyl or ethyl, depending on the solubilities of the reactants) or DMF. Ratios of reagents, and results obtained, are shown in Table 1.

Reaction of the dioxide (la) with benzaldehydes (IIa-d) in the presence of catalytic amounts of base [1 mole of Ia:1.2 mole of IIa-d:0.12 mole Na(K)OH] afforded mainly the addition products, and depending on the structure of the aldehyde component, nearly quantitative yields of (IIIb-d) or mixtures of the arylvinyl and hydroxyaralkyl derivatives with the latter predominating, were obtained. When larger amounts of alkali were used, there was a tendency to the formation of arylvinyl derivatives (Table 1).

The course of the reaction was also considerably influenced by the proportions of the dioxide and aldehyde reagents. Thus, with a ratio of 1 mole (Ia):1.2 mole (IIc), a mixture of approximately equal amounts of (IIIc) and (IVc) was obtained, even in the presence of a large excess of base [7.1 moles of KOH per mole of (Ia)], whereas when the same amount of base was used, but in the presence of an excess of the aldehyde [2.8 mole per mole of (Ia)], (IVc) only was obtained, in nearly quantitative yield.

Similar behavior was observed in the reactions of (Ia) with the other benzaldehydes.

Introduction of chlorine into 2-methyl- and 2,3-dimethylquinoline N-oxides considerably increased their sensitivity to bases. For this reason, the amount of base used in the reactions of the dioxide (Ib) with aldehydes (IIa,c,d), and of dioxide (V) with aldehyde (IIa), must not exceed 0.6 mole per mole of N-oxide reagent, otherwise considerable resinification occurs. Under these conditions, the dioxide (Ib) afforded high yields of the hydroxyaralkyl derivatives (IIIe, f) or mixtures in which these compounds predominated, and only in the reaction of (Ib) with unsubstituted benzaldehyde (with a reagent ratio of 1 mole of Ib:2.8 mole of IIa:0.48 mole of KOH) was the arylvinyl derivative (IVe) obtained. The dioxide (V) (1

			Found				Calculated		
Compound	Mp, °C (from acetic acid)	U	11	z	formula	υ	Ξ	z	Spectral data
di I i	205-206	58,7	4,2	12,6	C ₁₆ H ₁₃ N ₃ O ₅	58,7	4,0	12,8	
IIIc	215,5-216,5 (decomp.)	60,8	4,1	8,9	C ₁₆ H ₁₃ CIN ₂ O ₃	60,7	4,1	8,8	
PIII	206,5-207,5	54,8	3,6	7,5	$C_{1 6}H_{12}Cl_2N_2O_3$	54,8	3,4	8,0	
IIIe	204,5—205 (from 80% CH ₃ COOH)	54,6	3,4	7,6	$C_{16}H_{12}Cl_{2}N_{2}O_{3}$	54,8	3,4	8,0	IR spectrum: $u3200-3300$
IIIf	210-211 (decomp.)	50,0	2,9	7,3	$C_{1.6}H_{11}Cl_3N_2O_3$	49,8	2,9	7,3	CHI (DI, 4350C, OII)
IIIg	214—215 (decomp.)	61,4	3,6	10,5	C ₂₀ H ₁₅ N ₃ O ₆	61,2	3,8	10,6	
VI	196—197	65,9	4,7	6,3	$C_{17}H_{15}CIN_{2}O_{4}$	66,0	4,8	6,4	
IVb	256,5-257	61,8	3,4	13,5	$C_{1,6}H_{11}N_3O_4$	62,2	3,2	13,6	
IVc	226—227 (decomp., from 80%) CH ₃ COOH)	64,5	3,7	9,4	$C_{1.6}H_{11}CIN_{2}O_{2}$	64,3	3,7	9,4	IR spectrum: ν 3200-3300 cm ⁻¹ (no bands for assoc. OH)
٩	238239	57,2	3,1	8,1	$C_{1 \ 6}H_{1 \ 0}Cl_2N_2O_2$	57,6	3,1	8,4	
IVe	231-232 (decomp.)	64,4	3,6	9,3	$C_{16}H_{11}ClN_2O_2$	64,3	3,7	9,4	
IVf	239-240 (decomp., from DMF)	64,1	3,4	11,0	$C_{20}H_{13}N_{3}O_{5}$	64,1	3,5	11,2	IR spectrum: $u3200-3300 \text{ cm}^{-1}$
IVg	207-208 (from 80% CH ₃ COOH)	65,7	3,4	7,4	C20H13CIN2O3	. 65,8	3,6	7,7	
lVh	227228	69,0	4,4	6,7	$C_{23}H_{1R}N_{2}O_{5}$	68,6	4,5	7,0	
		_					_		

TABLE 2. Properties of the Compounds Obtained

mole of V and 0.12 mole of KOH) gave the dihydroxyaralkyl compound (VI), unreacted (V) being found in the reaction solution.

It has been shown [5, 6] that the reaction of (Ia) with 5-(p-nitro-,p-chloro-, and pethoxycarbonylphenyl)furfurals (IIe-g) is much less dependent on the amount of base and the aldehyde reactant, the products being determined mainly by the nature of the substituents in the benzene ring. Thus (Ia) reacts with (IIe) to give the hydroxyaralkyl derivative (IIIg) only, even under conditions which are most favorable for the formation of vinyl derivatives (2.8 moles of IIe and 7.1 moles of KOH per 1 mole of Ia). If, however, the substituent in the p-position of the benzene ring is chlorine or the ethoxycarbonyl group, the vinyl derivatives (IVg, h) are formed even with minimal amounts of base and aldehyde [0.24-0.3 mole of Na(K)OH and 1.2 mole of the aldehyde]. A comparison of the two types of solvent (DMF and alcohol) shows that the nature of the solvent has little effect on the course of the reaction of the dioxide (Ia) with the aldehyde (IIe), but in the reaction of the same dioxide with aldehydes (IIf, g) the yields of the vinyl derivatives (IVg, h) were higher in alcohol than in DMF, and were nearly quantitative.

The hydroxyalkyl compounds can be converted into the corresponding vinyl derivatives by heating in sulfuric acid in the presence of hydroquinone, or by keeping for extended periods in trifluoroacetic acid at room temperature. In those instances in which the hydroxyaralkyl compounds are not resinified by bases [for instance, (IIIc)] they are converted into the corresponding arylvinyl compounds (IVc-d) by prolonged standing in alcoholic NaOH or KOH.

The PMR spectra of the arylvinyl derivatives (IVc, g) were examined. From the values of $J_{H\alpha H\beta}$ (16.3 and 16.8 Hz respectively), it was concluded that these compounds possessed the transconfiguration.

The compounds obtained were examined for antibacterial activity against Salmonella, Escherichia, Staphylcoccus, Pseudomonas aeruginosa in vitro (by twofold serial dilution in meatpeptone broth, inoculation dose $1\cdot10^6$ cells per ml), and in vivo in 950 white mice infected by intraperitoneal inoculation with S. typhi, Staph. aureus, Ps. aeruginosa (the infecting dose caused the deaths of 80-100% of control, untreated animals within 24-48 h of infection). The minimum inhibitory concentrations in vivo were greater than 500 µg/ml for all the compounds. In the in vivo experiments, administration of the compounds per os 30 min after infection in doses up to 400 mg/kg showed the compounds to be inactive, the treated animals having the same death rate as the controls. Under these experimental conditions, the drug dioxidine [2,3-bis(hydroxymethyl)quinoxaline di-N-oxide] ensured the survival of more than 90% of the treated animals.

EXPERIMENTAL

IR spectra were obtained on a Perkin-Elmer-457 spectrophotometer (Sweden) in vaseline oil, and PMR spectra on an XL-100A spectrometer, solvent DMF, internal standard TMS.

 $\frac{2-[\beta-(o-Chlorophenyl)vinyl]quinoxaline Di-N-oxide (IVc). A mixture of 1 g (3.2 mmole) of (IIIc) and 13 ml of 10% KOH in methanol (23 mmole of KOH) was kept for 96 h at 20-22°C. The solid was filtered off to give 0.7 g (74.3%) of (IVc), identical from its R_f and IR spectrum with (IVc) obtained from (Ia) and (IIc).$

 $\frac{2-[\beta-[5-(p-nitropheny1)fury1]viny1]quinoxaline Di-N-oxide (IVf).}{(IIIg), 2 ml of 63\% H_2SO_4, and 0.04 g of hydroquinone was stirred at 85-90°C for 1 h, poured on to ice, neutralized to pH 7.0-8.0 with NaHCO_3 solution, and the solid filtered off to give 0.32 g (83.8\%) of (IVf) (see Table 2).$

 $\frac{2-[\beta-(2,4-\text{Dichlorophenyl})\text{vinyl}]\text{quinoxaline Di-N-oxide (IVd)}.$ A mixture of 0.5 g of (IIId) and 5 ml of CF₃COOH was kept at 22-25°C for 6 days, poured into water, the solid filtered off, and washed with water to give 0.3 g (63.4%) of (IVd), identical from its mp, Rf, and IR spectrum with (IVd) obtained from (Ia) and (IId).

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