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DIAZAPOLYCYCLIC COMPOUNDS. XV.
OPENING OF THE EPOXIDE RINGS IN DIAZAQUINONE ADDUCTS: A NEW CONDENSED 1,4-OXAZEPINE DERIVATIVE.

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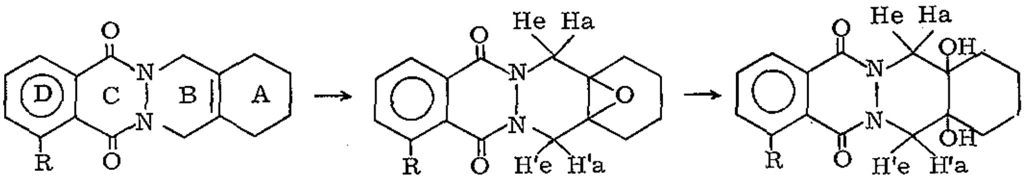
Epoxidation by m-chloroperbenzoic acid of adducts of 5-hydroxy and 5-chlorophthalazin-1,4-dione and 1,2-dimethylencyclohexane, respectively, is reported. Compounds IIa and IIb, 4a,14a-epoxide derivatives, were transformed into the 1,2-diols IIIa and IIIb by treatment with a mixture of aqueous sulfuric acid and acetone in high yields. Reaction of IIa in an alkaline solution resulted in opening of the ring C of pyridazinedione, yielding an intermediate sodium carboxylate IV which, in acidic medium, led to the formation of V, this compound being isolated in another different crystalline form VI. All structures have been determined by analytical and ir, pmr and mass spectroscopic evidences. The structure of V and VI was unambigously established by X-ray analysis.

Previously we have described [1] the synthesis of diazatetracyclic adducts of type I. The present communication reports the epoxidation of these adducts and the solvolytic opening of the oxirane ring in order to modify their biological behaviour by introducing a 1,2-diol group at an angular position between rings A and B. These solvolytic reactions were carried out alternatively in acid and alkaline aqueous media.

Oxidation of 8-hydroxy and 8-chloro derivatives Ia and Ib with m-chloroperbenzoic acid in chloroform under reflux for 2 hr, afforded epoxides IIa and IIb in 85% and 92% yields, mp 204-205°C and 209-211°C respectively (from ethanol).



Ia, R = OH
Ib, R = Cl

IIa, R = OH
IIb, R = Cl

IIIa, R = OH
IIIb, R = Cl

The ir spectra exhibit two absorption bands at 1275 and 870 cm^{-1} corresponding to the oxirane ring in both cases. In the pmr spectra of both IIa and IIb (table I), the signals of the four protons (Ha, He, H'a, H'e) attributable to the two methylenic groups next to the nitrogens appear as two pairs of doublets, forming AB and A'B' systems ($J_{HaHe} = J_{H'aH'e} = 15$ Hz). For compound IIa, the differences in the chemical shifts of protons He and H'e and Ha and H'a are close to 4 Hz and are 2 and 3 Hz, respectively, for compound IIb.

TABLE I. PMR (δ) ppm

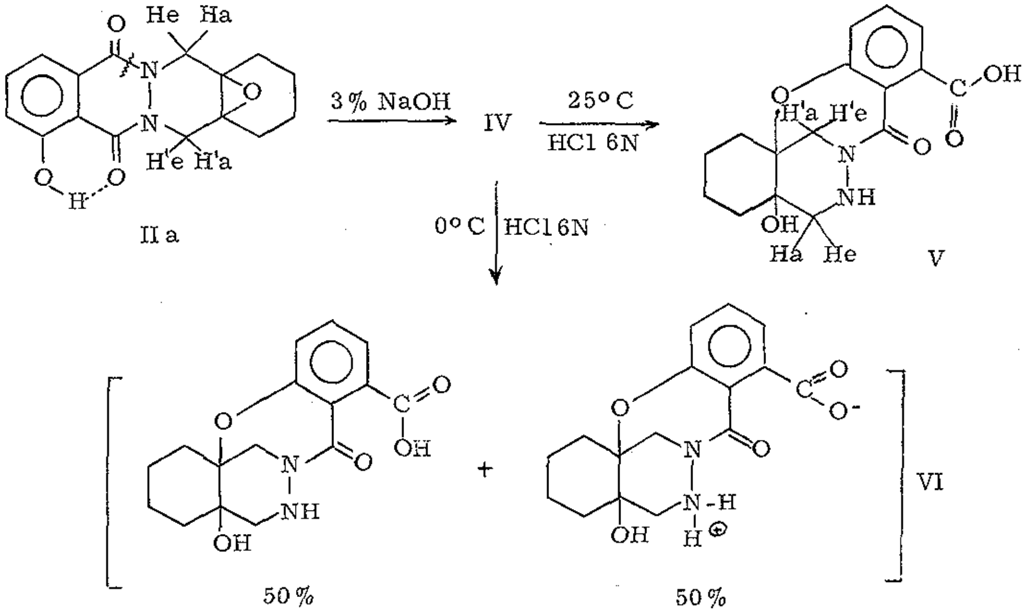
Compound	Solvent	$N-CH_2-C$ He-H'e	 Ha-H'a	$C-CH_2-C-O$	$C-CH_2-C$	OH	OH
II a	$CDCl_3$	5.05 dd 2H	3.80 dd 2H	1.70 - 2.50 m 4H	1.20 - 1.70 m 4H		
II b	$CDCl_3$	5.03 d 2H	3.85 d 2H	1.70 - 2.20 m 4H	1.30 - 1.75 m 4H		
III a	DMSO-d_6	4.40 d 2H	3.50 dd 2H	1.10 - 2.0 m 8 H		5.04 d 1H	3.27 s 1H
III b	DMSO-d_6	4.22 dd 2H	3.50 dd 2H	1.20 - 2.0 m 8H		5.0 s 1H	3.50 m 1H

The solvolytic opening of the oxirane ring of IIa and IIb, in an aqueous medium acid, was performed by refluxing in a mixture of aqueous sulfuric acid and acetone for about 2-4 hr. The diol derivatives IIIa and IIIb were isolated in good yields (80%), (IIa, mp 325°C (dec); IIb, mp 330° C (dec) from AcOH). In the ir spectrum of IIIa, the 1,2-diol group shows a double hydroxyl absorption band at 3480 and 3430 cm^{-1}. Similarly in IIIb the same group appears at 3490 and 3430 cm^{-1}. These two hydroxylic protons have in both compounds a large difference between their chemical shifts (1.7 and 1.5 ppm, respectively). On the other hand the two methylenic groups next to the nitrogens of IIIa and IIIb show the same features as those explained above for compounds IIa and IIb. The geminal coupling between Ha and He (or H'a and H'e) is 13 Hz. It is interesting to remark that in both IIa and IIIa, the phenol group, is intramolecularly hydrogen bonded to the neighbouring amidocarbonyl group, and appears at δ=13 ppm as a characteristic singlet.

Attempts to obtain the diol derivatives mentioned above, starting from epoxides IIa and IIb in an alkaline aqueous medium, have been unsuccessful. However, in this medium, the results obtained from the 8-hydroxy derivative, were very interesting. When IIa was treated with 3% sodium hydroxide and refluxed for about 1 hr, and the resulting basic solution concentrated, an intermediate sodium salt IV (mp > 345° C) was obtained. On dissolving this salt in water and neutralizing it at room temperature with 6N hydrochloric acid, compound V (mp 278-281° C) was obtained in 40% yield. If this same sodium salt IV previously dissolved in water was cooled to 0° C and then carefully neutralized with 6N hydrochloric acid, a different solid VI could be isolated. The analytical data of compound VI are identical to those of V, but remarkable differences were observed in its ir spectrum.

The structures of V and VI were established according to their analytical [2] nmr, mass spectrometric data and, specially, by single crystal X-ray diffraction techniques [3,4] (Scheme I). Compound VI is not an isomer of V but a different crystalline form, and both V and VI are namely 4-carboxy-8,8a,9,10,11,12-hexahydro-5H,12H,12bH-8a-hydroxy-5-oxo pthalazin[8a,2-bc] benzo[f][1,4] oxazepine.

Comparing the ir (KBr) spectra of both compounds, a large degree



SCHEME I

of association of VI in relation to V can be observed. At λ_{max} 3520 and 3320 cm^{-1} compound V shows two sharp bands due to OH and NH groups whilst in VI the same groups appear as a single broad band at 3450. Similarly the acidic group in V shows two bands at 1730 and 1710 whilst in VI this same group exhibits a broad band at a lower frequency (1700 cm^{-1}). The amidic group appears at 1630 cm^{-1} in compound V and at 1600 in VI. Finally, the absorption band of the ether group appears at 1045 cm^{-1} in both cases.

The chemical shifts obtained from the nmr spectrum for V, in two different solvents, and their differences ($\delta_1 - \delta_2$) are shown in Table II.

From these data, it can be deduced that there is a single amidic group, since the two methylenic groups next to the nitrogens form two AB and A'B' systems with remarkably different chemical shifts. The assignment of the signals of the proton Ha, He and H'a, H'e has been confirmed by double resonance experiments. These demonstrated that the two protons Ha and He close to the NH group are shielded 0.82 and 0.58 ppm with respect to H'a and H'e which are close to the neighbouring C=O amidic group (J_{HaHe} = 13 Hz),

TABLE II. PMR (δ) ppm

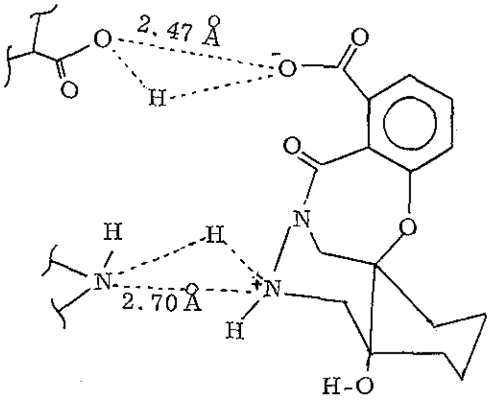
V	C-CH$_2$-N				C-CH$_2$-C	H-Ar	OH hydrox.	HO-Ar -NH
	H'e	He	H'a	Ha				
DMSO-d$_6$ δ_1	3.83 d 1H	3.25 d 1H	3.20 d 1H	2.38 d 1H	0.8-2.10 m 8H	7.0-7.8 n 3H	5.0 m 1H	6.0-6.9 m 2H
C_5D_5N δ_2	4.19 d 1H	3.85 d 1H	3.52 d 1H	2.17 d 1H	1.0-2.40 m 8H			
δ_1-δ_2	0.36	0.60	0.32	0.33	0.2-0.3			

$J_{H'a\,H'e}$ = 15 Hz. The differences found in the chemical shifts when the spectra are registered in pyridine and dimethyl sulfoxide can be explained on the basis of the hydroxylic group attached to the carbon atom which is situated at β position to the NH group. This is due to the well known fact [5] that the above mentioned OH group forms a complex with a molecule of DMSO thus exerting a special deshielding effect on the neighbouring equatorial proton He (δ_1-δ_2 = 0.6 ppm).

In the mass spectra, according to the aromatic character of the ring to which the carboxylic group is linked, the molecular ion M^+318 was found with an intensity of 80%. Besides, the simultaneous breaking of the molecule V through both amidic and ether linkages gives rise to the ions at m/e 165 and 154. The former is the base peak and contains the rest of the aromatic ring while the latter has an intensity of 87% and corresponds to the rest of perhydrophthalazine.

From the X-ray diffraction analysis of V and VI, the following data were obtained. The main difference between compound V and VI is the orientation which the carboxylic groups adopt in both cases. As we have noted that VI clearly softens at 234-241° C and melts definitely at 279-281° C, it can be through that by heating over 234-241° C the carboxylic group can absorb enough rotation energy so as to turn 180° C, around its axis, thus adopting a position identical to that of V.

In compound VI, 50% of the molecules are ionized forming "zwitter ions" whilst the rest have no charge. In both compounds V and VI, the 1,4-oxazepinone ring and the two perhydrophthalazine rings adopt, respectively, the twisted boat and chair-chair in trans disposition conformations, being the OH in an axial disposition. The two nitrogen atoms N(6) and N(7) are pyramidal for both crystalline forms (bond angles 116.5 and 108.5 for V and 115.5 and 112.4 for VI). Another remarkable feature is the existence of intermolecular hydrogen interactions. In compound V there is an interaction between the OH of the acidic group and the C=O of the amidic group of a neighbouring molecule, which can be considered within the limit of a strong hydrogen bond, (O–O : 2.634 Å). However in VI there are two strong hydrogen interactions between a molecule disposed in the zwitterion form, and other uncharged molecules, as shown in Scheme II.



SCHEME II

Finally, in relation to the intermediate sodium salt IV, its ir spectrum showed two strong absorption bands of carboxylate group at λ_{max} 1580 and 1390 cm^{-1}. It also exhibits two bands at 3600 - 2200 and 3280 cm^{-1} corresponding to associated OH and NH groups. In spite of the fact that from its analysis and pmr data a definite structure could not be assigned, we believe that IV could be the sodium salt of V (or VI). Formation from IIa could be explained [6] by means of an ionic mechanism through the nucleophilic attack of the phenoxide anion in the alkaline medium.

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