MORPHOLINE DERIVATIVES.

IV.* REACTION OF METHYL IODIDE AND HYDROHALIC ACIDS WITH OXACYCLOBUTANE DERIVATIVES CONTAINING MORPHOLINOMETHYL SUBSTITUENTS

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The β-oxide ring of 3-alkyl-3-(N-morpholinomethyl)oxacyclobutanes is opened to give methiodides or hydrohalide salts, respectively, of 2-alkyl-2-(N-morpholinomethyl)-3-halopropanol when they are heated with methyl iodide in methanol under pressure or heated with hydrohalic acids. When two morpholinomethyl groups are present in the 3 position of the oxacyclobutane ring, it is not opened.

It has been established [1] that, depending on the reaction conditions, different products are obtained in the reaction of 3-methyl-3-(N-morpholinomethyl)oxacyclobutane (I) with methyl iodide; a substance in which the oxide ring is retained is obtained under mild conditions, but when the reaction is carried out under pressure in methanol at 100°C, a substance in which this ring is apparently destroyed is obtained. In order to establish its structure, we studied the iodomethylation and reaction with hydrohalic acids of 3-methyl- and 3-ethyl-3-(N-morpholinomethyl)- (Ia, b) and 3,3-bis(N-morpholinomethyl)oxacyclobutanes (VIII).

It is known [2, 3] that the CO bond is cleaved when oxacyclobutane is heated with triphenylbromomethane, and 1-triphenylmethoxy-3-bromopropane is formed. At 150-160° the reaction between methyl iodide and α-oxides [4], tetrahydrofuran, 1,4-dioxane, and hexamethylene oxide [5] leads to ring opening. 2-Phenyloxacyclobutane derivatives react with methanol in the presence of dioxane in acidic media to give 3-methoxy-3-phenyl-1-propanol derivatives [6]. Ring cleavage is also observed in the reaction of oxacyclobutane derivatives with hydrohalic acids [7-9]. Quantitative opening of the β-oxide ring occurs when oxacyclobutane derivatives are heated with excess pyridinium chloride in pyridine [10].

When the iodomethylation is carried out in acetone, Ia, b form methiodides (IIa, b) of 3-alkyl-3-(N-morpholinomethyl)oxacyclobutanes. However, if the reaction with methyl iodide is carried out in methanol under pressure, the oxacyclobutane ring opens, and methiodides (IIIa, b) of 2-alkyl-2-(N-morpholinomethyl)-3-iodopropanol are formed. It was found that methiodides II can be converted to methiodides III if they are heated under pressure in methanol with methyl iodide or hydriodic acid and also with aqueous hydriodic acid.

The absence of a β-oxide ring in IIIa is confirmed by comparison of the NMR spectra of Ia, IIa, and IIIa (also see [11]). The quartet peculiar to the ring in Ia and

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*See [1] for Communication III.

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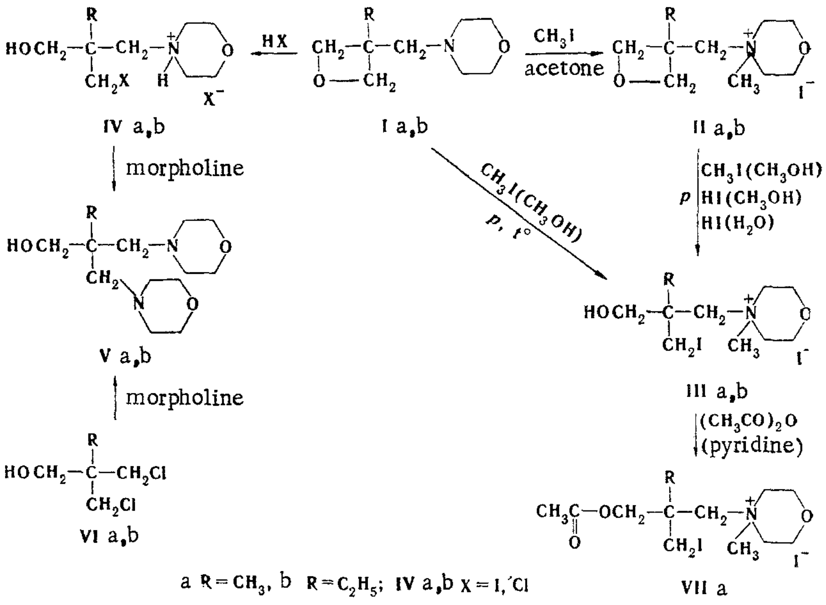
IIa (lines at 5.62-5.79 ppm) vanishes for IIIa.



The signals of the protons of the N–CH₂, N–CH₃, and CH₂ groups are simultaneously shifted somewhat to weak field; this is due to the positive charge on the nitrogen atom.

The products of opening of 3-alkyl-3-(N-morpholinomethyl)oxacyclobutanes I — 3-iodopropanols IVa, b (X = I) — were obtained by heating Ia, b with hydriodic acid. Compound Ia undergoes a similar transformation when it is refluxed with concentrated hydrochloric acid. It should be noted that, in contrast to Ia, Ib undergoes only partial opening. Heating 2-alkyl-2-(N-morpholinomethyl)-3-iodopropanols IV with morpholine gives 2,2-bis(N-morpholinomethyl)propanol (Va) and butanol Vb, which were obtained by alternative synthesis by condensation of 2,2-bischloromethylpropanol (VIa) and butanol (VIb) with morpholine.

The presence of an absorption band at 3200-3400 cm^{-1} in the IR spectra of III, IVa, and Va indicates that they have labile hydrogen atoms bonded to oxygen. Deuteration led to a shift in these bands to the low-frequency region, and the ν_H/ν_D ratio of 1.33-1.34 is close to the literature data [12]. This and the acetylation [13] of IIIa to 1-acetoxy-2-methyl-2-(N-morpholinomethyl)-3-iodopropanol methiodide (VIIa) constitute evidence for the presence of an OH group.

It is interesting to note that the opening of the oxacyclobutane ring that we observed occurs when there is only one morpholinomethyl residue in the 3 position. The ring is retained when a second morpholinomethyl residue is introduced. Depending on the conditions, monomethiodides or dimethiodides are formed in the iodomethylation of 3,3-bis(N-morpholinomethyl)oxacyclobutane (VIII) [1]; dihydrohalides of starting base VIII are obtained by refluxing with hydrohalic acids. This fact can be explained by the shielding action with respect to the oxide oxygen of two bulky morpholinomethyl substituents.

EXPERIMENTAL

The IR spectra of mineral-oil pastes of the substances were measured with an IKS-14 spectrometer. The NMR spectra* of saturated solutions of the compounds in o-dichlorobenzene (Ia) and D_2O (IIa and (IIIa) were obtained with a JNM-3 spectrometer (40 MHz) with tetramethylsilane as the internal standard.

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Compounds Ia, IIa, and IIIa were described in [1].

3-Ethyl-3-(N-morpholinomethyl)oxacyclobutane (Ib). A mixture of 0.13 mole of 3-ethyl-3-chloromethyloxacyclobutane and 0.26 mole of morpholine was heated at 140° for 4 h. It was then cooled and diluted with ether, and the morpholine hydrochloride (22 g, mp 173-174°) was removed by filtration. The ether solution was dried with Na_2SO_4 and distilled to give 17 g of Ib. Hydrochloride: a 1-g sample of Ib was dissolved in benzene, and a stream of dry hydrogen chloride was passed through the solution; 1.16 g of a product with mp 108° precipitated (the melting point increased to 132° when the substance was allowed to stand in air). Dissolving of Ib in concentrated HCl and evaporation of the solution also gave a precipitate with mp 132°. Hydroiodide: a 1-g sample of Ib was mixed with 1 ml of 45% HI with cooling. Workup gave 0.4 g of product.

3-Ethyl-3-(N-morpholinomethyl)oxacyclobutane Methiodide (IIb). The method in [1] was used to obtain 3.9 g of IIb from 0.02 mole of Ib.

2-Methyl-2-(N-morpholinomethyl)-3-iodopropanol Methiodide (IIIa). A) The method in [1] was used to obtain IIIa from Ia.

B) A 2.5-mmole sample of methiodide IIa was heated with 7 mmole of methyl iodide and 1 ml of methanol in a sealed ampule at 100° for 11 h. Crystallization of the product from water with the addition of charcoal and one drop of sodium bisulfite solution gave 0.56 g of IIIa.

C) A mixture of 3 mmole of methiodide IIa, 1 ml of 45% HI, and 1 ml of methanol was heated at 100° in a sealed ampule for 5 h. A quantitative yield of methiodide IIIa with mp 176-178° was obtained. Crystallization from water gave 0.86 g of a product with mp 178-179°. The reaction with concentrated HI without the addition of methanol proceeded similarly.

2-Ethyl-2-(N-morpholinomethyl)-3-iodopropanol Methiodide (IIIb). A) Under the conditions described for IIIa [1], IIIb was obtained from 0.01 mole of Ib as an oil that crystallized slowly. The yield of product with mp 143-145° was 2.39 g; two crystallizations from water raised the melting point to 157°.

B) In analogy with the conversion of IIa to IIIa, methiodide IIb was converted to IIIb in 48% yield under the influence of methyl iodide and was obtained in 75% yield by the action of HI.

1-Acetoxy-2-methyl-2-(N-morpholinomethyl)-3-iodopropanol Methiodide (VIIa). A mixture of 3 mmole of methiodide IIIa and 4 ml of pyridine–acetic anhydride (15:2) was heated at 100° for 5 h, after which it was evaporated to dryness. The residual oil was heated twice with 3 ml of absolute alcohol and stored in a refrigerator for crystallization. Workup gave 0.92 g of a product with an indistinct melting point (148-162°).

Salts IV and VIII. A 0.02-mole sample of base I or VIII was heated at 100° with a fivefold excess of concentrated HI or HCl for 10 h. The mixture was then vacuum evaporated to dryness. The hydriodides were recrystallized from dry acetone, and the hydrochlorides were recrystallized from alcohol. When Ib was heated with concentrated HI, hydriodide Ib (~6%), with mp 165-166° always precipitated from the reaction mixture.

Compounds V. A) A 10-mmole sample of hydrohalide IV was heated with 36 mmole of morpholine at 140° for 5 h, after which it was treated repeatedly with ether. The residue was the morpholine salt, while the ether contained base Va or Vb. The ether was removed by distillation, and the residue was crystallized from petroleum ether. Hydriodide Va: a 0.65-g sample of base Va in 2 ml of absolute alcohol was added to 2 ml of 45% HI and 10 ml of ether. The resulting oil was treated three times with absolute ether and crystallized (0.78 g).

B) A mixture of 0.05 mole of VIa or VIb and 0.2 mole of morpholine was heated in a sealed ampule at 180-200° for 4 h. The melt was treated repeatedly with ether, and the ether extract was dried with Na_2SO_4. The ether and the unchanged morpholine were removed by distillation and the residue was crystallized. No melting-point depression was

TABLE 1. Characteristics of the Compounds Obtained

Compound	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
			C	H	I	N	C	H	I	N	
Ib base	142—143[a]	$C_{10}H_{19}NO_2$	64,8	9,9	—	7,7	65,2	10,3	—	7,6	50
hydrochloride	132	$C_{10}H_{19}NO_2 \cdot HCl \cdot 2H_2O$	46,9	8,7	13,9b	5,6	46,6	9,3	13,8b	5,4	98
hydriodide	166c	$C_{10}H_{19}NO_2 \cdot HI$	38,2	3,7	40,4	4,5	38,3	3,2	40,5	4,5	24
picrate	174d	$C_{10}H_{19}NO_2 \cdot C_6H_3N_3O_7$	—	—	—	13,8	—	—	—	13,8	95
IIb	227—228e	$C_{11}H_{22}INO_2$	—	—	38,8	4,3	—	—	38,8	4,3	60
IIIa	173—176f	$C_{10}H_{21}I_2NO_2$	27,6	4,9	28,9g 57,4h	3,2	27,2	4,8	28,8g 57,5h	3,2	see [1].
IIIb	157f	$C_{11}H_{23}I_2NO_2$	—	—	27,8g 55,9h	3,5	—	—	27,8g 55,8h	3,1	53
IVa hydrochloride X=Cl	166—168d	$C_9H_{18}ClNO_2 \cdot HCl$	—	—	14,5b 28,7i	5,8	—	—	14,5b 29,0i	5,7	68
IVa hydrochloride X=I	151—153	$C_9H_{18}INO_2 \cdot HI$	25,8	4,0	59,4h	3,3	25,3	4,5	59,4h	3,3	77
IVb, X=I	121e	$C_{10}H_{20}INO_2 \cdot HI$	27,5	5,1	56,0h	3,2	27,2	4,8	57,5h	3,2	51
Va base	68—71j	$C_{13}H_{26}N_2O_3$	60,4	10,1	—	10,8	60,4	10,1	—	10,8	44k, 57l
hydriodide	188—190	$C_{13}H_{26}N_2O_3 \cdot 2HI$	—	—	49,2	5,4	—	—	49,4	5,4	61
Vb	65j	$C_{14}H_{28}N_2O_3$	61,9	10,5	—	10,3	61,7	10,4	—	10,3	57
VIIa	160—162m	$C_{12}H_{23}I_2NO_3$	—	—	52,5	3,1	—	—	52,6	2,9	64
VIII dihydriodide	207—208d,n	$C_{13}H_{24}N_2O_3 \cdot 2HI$	—	—	49,5	5,5	—	—	49,6	5,5	75

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a — Boiling point at 14 mm; d_4^{20} 1.028, n_D^{20} 1.4750; b — ionic chlorine; c — from absolute alcohol; d — from alcohol; e — from acetone; f — from water; g — ionic iodine; h — total iodine; i — total chlorine; j — from petroleum ether; k — from IVa, X = Cl; l — from IVa, X = I; m — from benzene—alcohol (2:1); n — with decomposition.

observed for a mixture of this product with samples obtained from IVa and IVb. Data on the compounds are presented in Table 1.

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