Chemical Reactions of Cycloalkanespirohydantoins. Part 3. Acid-Catalyzed Reaction of 4-Hydroxy-2-imidazolidinones. Preparation of Bis(1,3-diaza-2-oxospiro[4,5]decyl-4) ether (9)

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The use of *N*-carbamoyliminium ion initiated reactions for the generation of spiroimidazolidin-2-ones has been successfully exploited. N_3-Substituted-4-hydroxy-2-imidazolidinones have been treated under acid conditions to give the rearranged imidazolinones. Only in the case of N_3-dialkylaminomethyl-4-hydroxy-5-cyclohexanespiro-2-imidazolidinones upon treatment with trifluoroacetic anhydride/trifluoroacetic acid afforded a mixture containing bis(1,3-diaza-2-oxospiro[4,5]decyl-4) ether with the rearranged imidazolidinone.

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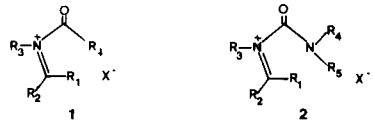
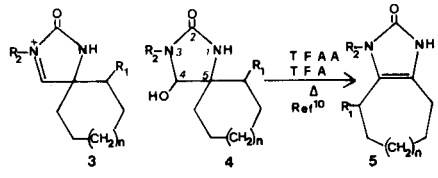
Recently, considerable attention has been devoted on *N*-acyliminium ions **1** have proven to be valuable intermediates in the synthesis of complex natural products [1-3]. However, little is known about the corresponding transformation beginning with *N*-carbamoyliminium ions **2** [4-10] (Scheme I).

Scheme I



We have recently described a convenient good-yield synthesis of the 2(3*H*)-imidazolinones **5** condensed on the d-side with C_6, C_7 and C_8 carbocycles from cycloalkanespirohydantoins by reaction of 4-hydroxy-2-imidazolidinones **4** with *p*-toluenesulfonic acid [10]. In the cases examined the group that underwent addition to the cationic center was attached to the iminium ring nitrogen atom. The intermediate *N*-amidolyminium ions **3** were prepared *in situ* from the corresponding 4-hydroxy-2-imidazolidinones **4** (R_2 = alkyl and aralkyl) (Scheme II).

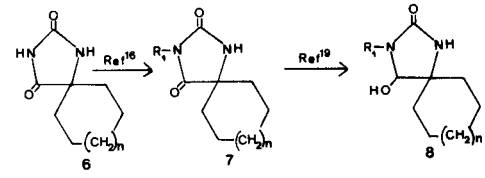
Scheme II



As an extention of our work of chemical reactions of cycloalkanespirohydantoins toward new heterocyclic compounds, in this paper, we describe the behavior of the 4-hydroxy-5-cycloalkanespiro-2-imidazolidinones Mannich bases on the N_3-nitrogen **8** under acid conditions and the influence of the ring effect is also discussed. These reactions formally extend the scope of intramolecular amidoalkylation transformations [11,12].

The desired starting materials for this study **8** were readily prepared in two stages from cycloalkanespirohydantoins **6** [13-15]. Condensation of **6** with formaldehyde and the appropriate amine [16-18] give the corresponding 3-substituted hydantoins **7a-e** in moderate to good yields (50-90%) [19-20]. Reduction of **7a-e** with excess lithium aluminum hydride in THF at room for 48 hours efficiently afforded the 4-hydroxy adducts **8a-e** in 53-91% [19] (Scheme III).

Scheme III



a; n = 0, R_1 = $CH_2N(CH_2C_6H_5)_2$
b; n = 0; R_1 = $CH_2N(CH_3)CH_2C_6H_5$
c; n = 1; R_1 = $CH_2N(CH_2C_6H_5)_2$
c; n = 1; R_1 = Piperidinomethyl
d; n = 1; R_1 = Morpholinomethyl

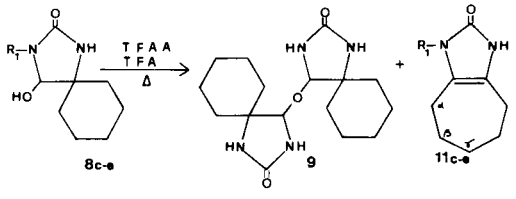
Treatment of **8c-e** with strong acid, trifluoroacetic acid and trifluoroacetic anhydride in dichloromethane at reflux for 48 hours to afford diastereomeric mixture of bis-(1,3-diaza-2-oxospiro[4,5]decyl-4) ether (**9**) in 20-27% yield with the rearranged imidazolinone **11c-e** in 50-55% yield.

In order to examine the ring effect at the 5-position of 4-hydroxy-2-imidazolidinones toward acid conditions, we investigated several 3-substituted-4-hydroxy-5-cycloal-

kanespiro-2-imidazolidinones. Treatment of **8a,b** under the same conditions did not lead to the desired product **9**, in this case only the rearranged imidazolinone **10a,b** in 64-71% yield was regioselectively recovered. These results show that the steric effect the ring at the 5-position control the attack of trifluoroacetic acid.

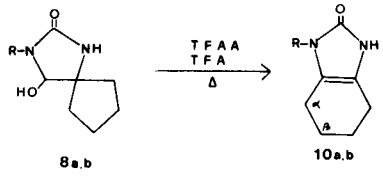
Subsequent treatment with trifluoroacetic acid of **8c** at room temperature for 24 hours or **8d** at reflux for 72 hours yields only the rearranged imidazolinones **11c** in 81% or **11d** in 72% yields respectively. However, the difference between acids conditions, trifluoroacetic acid and trifluoroacetic anhydride/trifluoroacetic acid in dichloromethane indicates that this effect is also involved in determining the relative rate of the competing reaction (Schemes IV and V).

Scheme IV



c; R_1 = $CH_2N(CH_2C_6H_5)_2$
d; R_1 = Piperidinomethyl
e; R_1 = Morpholinomethyl

Scheme V



a; R_1 = $CH_2N(CH_2C_6H_5)_2$
b; R_1 = $CH_2N(CH_3)CH_2C_6H_5$

The structure of a novel heterocyclic compound **9** was elucitated on the basis spectroscopic. Its ir spectrum gave two absorptions at 3220 and 3090 cm^{-1} indicating the existence of two N-H groups. The nmr spectrum of **9** in deuterium trifluoroacetic exhibits two broad resonance signals at δ 8.4 and 7.8 ppm due to the N-H protons which are distinguished by addition of deuterium oxide. The nmr observations provided evidence that the two products obtained in this reaction were a diastereomeric mixture **9**, along with the major product **11**. The proton chemical shifts for the carbon-4 hydrogen appeared at δ 6.1 and 5.5 ppm, indicating a characteristic structure of **9**.

The synthetic potential of *N*-carbamoyliminium ion initiated reactions for the generation of a wide range of new select 2-imidazolinones has been documented. These substrates have been of considerable recent interest due to their pronounced pharmacological activities [21].

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary melting apparatus and are uncorrected. The nmr spectra were recorded on a Hitachi R-24 spectrometer at 60 MHz as an internal standard. The ir spectra were recorded on a Perkin-Elmer 577 spectrometer. Infrared peak positions were recorded in cm^{-1} *vs.* the 1601 cm^{-1} band of polystyrene. The elemental analysis were determined with a Carlo Erba 1104 analyzer.

Mannich bases **7a-e** were prepared according to literature [16].

The reduction of **7a-e** to alcohols **8a-e** was carried out described in literature [19].

Bis(1,3-diazo-2-oxospiro[4,5]decyl-4) Ether (**9**).

The appropriate 4-hydroxy-5-spiro-2-imidazolidinone **8c-e** (15 mmoles) is refluxed in dichloromethane (150 ml) containing trifluoroacetic acid (29.6 g, 0.25 mole) and trifluoroacetic anhydride (4.2 g, 20 mmoles) during 48 hours. The reaction mixture is then diluted with dichloromethane (100 ml) and neutralized by 15% sodium hydroxide (70 ml). The organic extract is washed with water (2 × 25 ml) and dried with anhydrous magnesium sulphate. The solvent is evaporated under reduced pressure and

Table I

Analytical and Spectral Data of 2(3*H*)-Imidazolinones, **10a,b** and **11c-e**

Compound	Yield (%)	Mp °C [a]	Molecular Formula	Analysis % Calcd./(Found) C	H	N	IR, cm^{-1} (f) N-H	C=O	NMR (δ ppm)
10a	64	123-125 [b]	$C_{22}H_{25}N_3O_2$	76.05 (75.26)	7.25 (7.32)	12.09 (11.91)	3170	1680	9.5 (s, 1H, NH), 7.3 (m, 10H, aromatic), 4.5 (s, 2H, NCH_2N), 3.2 (s, 2H, NCH_2Ar), 2.1 (m, 4H, $CH_2\alpha$), 1.6 (m, 4H, $CH_2\beta$) [g]
10b	71	152-154 [b]	$C_{16}H_{21}N_3O$	70.81 (70.63)	7.79 (7.95)	15.48 (15.63)	3220	1685	10.1 (s, 1H, NH), 7.3 (m, 5H, aromatic), 4.2 (s, 2H, NCH_2N), 3.6 (s, 2H, NCH_2Ar), 2.5 (m, 4H, $CH_2\alpha$), 2.2 (s, 3H, CH_3), 1.7 (m, 4H, $CH_2\beta$) [h]
11c	52	109-111 [c]	$C_{23}H_{27}N_3O$	76.42 (76.22)	7.52 (7.34)	11.62 (11.37)	3180	1690	9.8 (s, 1H, NH), 7.3 (m, 10H, aromatic), 4.0 (s, 2H, NCH_2N), 3.6 (s, 2H, NCH_2Ar), 2.4 (m, 4H, $CH_2\alpha$), 1.6 (m, 6H, $CH_2\beta$ and $CH_2\beta$) [h]
11d	50	124-126 [d]	$C_{14}H_{23}N_3O$	67.42 (67.52)	9.29 (9.08)	16.85 (16.60)	3180	1690	10.2 (s, 1H, NH), 2.5 (m, 10H, NCH_2N, NCH_2C, $CH_2\alpha$), 1.5 (m, 12H, $NCCH_2CH_2CH_2$, $CH_2\alpha$ and $CH_2\beta$) [h]
11e	55	72-74 [e]	$C_{13}H_{21}N_3O$	62.12 (62.30)	8.42 (8.35)	16.72 (16.81)	3120	1700	9.8 (s, 1H, NH), 4.2 (s, 2H, NCH_2N), 3.6 (s, 4H, OCH_2C), 2.1 (m, 4H, $CH_2\alpha$), 1.6 (m, 6H, $CH_2\beta$ and $CH_2\alpha$) [h]

[a] Recrystallization solvents: [b] Methanol/ethanol 1:1. [c] Petroleum ether. [d] Acetonitrile/methanol 1:1. [e] Diethyl ether. [f] In potassium bromide. [g] In DMSO-d_6. [h] In deuteriochloroform.

the residue is treated with acetonitrile and filtered. The organic solution is evaporated and the products **11c-e** are obtained. The solid separated is purified by recrystallization from butanol affording 20-27% of an analytical sample **9**, mp 350°; ir (potassium bromide): 3220 (N_3-H), 3090 (N_1-H), 1710 (C = O) cm^{-1}; nmr (TFA-d_1): 8.4 (s, 2H, N_3H), 7.8 (s, 2H, N_1H), 6.1 (s, 1H, H4), 5.5 (s, 1H, H4), 1.7 (m, 20H, CH_2 of cycle) ppm.

Anal. Calcd. for $C_{16}H_{26}N_4O_3$: C, 59.60; H, 8.12; N, 17.37. Found: C, 59.35; H, 8.43; N, 16.99.

General Procedure for Preparation of 2(3*H*)-Imidazolinones **10a,b** and **11c-e**.

The appropriate 4-hydroxy-5-spiro-2-imidazolinone **8a-e** (15 mmoles) is refluxed in dichloromethane (150 ml) containing trifluoroacetic acid (29.6 g, 0.25 mole) and trifluoroacetic anhydride (4.2 g, 20 mmoles) during 48 hours. The reaction mixture is then diluted with dichloromethane (100 ml) and neutralized by 15% sodium hydroxide (70 ml). The organic extract is washed with water (2 × 25 ml) and dried with anhydrous magnesium sulphate. The solvent is evaporated under reduced pressure. The residue is treated with acetonitrile and filtered. The organic solution is evaporated under reduced pressure. The residue is purified by recrystallization, to give **10a,b** and **11c-e**. Physical properties of these compounds are given in Table I.

1-Dibenzylaminomethyl-4,5,6,7,8-pentahydrocyclohepta[d]-2(3*H*)imidazolinone (**11c**).

The N_3-dibenzylaminomethyl-4-hydroxy-5-cyclohexanespiro-2-imidazolinone (**8c**) (9.2 mmoles) containing trifluoroacetic acid (74 g, 0.64 mole) is stirred 24 hours at room temperature. The reaction mixture is then concentrated under reduced pressure and neutralized by 15% sodium hydroxyde (100 ml). The solution is extracted with chloroform (3 × 50 ml) and dried with anhydrous magnesium sulphate. The solvent is evaporated under reduced pressure and the residue is purified by recrystallization to give **11c**; the ir; nmr and mixture melting point indicated that this heterocycle was identical with **11c** obtained by the general procedure for preparation of 2(3*H*)-imidazolinones **10a,b** and **11c-e**, yield 81%.

1-Piperidinomethyl-4,5,6,7,8-pentahydrocyclohepta[d]-2(3*H*)-imidazolinone (**11d**).

The N_3-piperidinomethyl-4-hydroxy-5-cyclohexanespiro-2-imidazolinone (**8d**) (1.8 mmoles) containing trifluoroacetic acid (19 g, 0.25 mole) is refluxed 72 hours. The reaction mixture is then concentrated under reduced pressure and neutralized by 15% sodium hydroxide (50 ml). The solution is extracted with chloroform (2 × 25 ml) and dried with anhydrous magnesium sulphate. The solvent is evaporated under reduced pressure and the residue is purified by recrystallization, to give **11d** yield (73%); the ir, pmr and mixture melting point indicated that this heterocycle was identical with **11d** obtained by the general procedure for preparation of 2(3*H*)-imidazolinones **10a,b** and **11c-e**.

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