REDUCTION OF SPIROHYDANTOINS WITH LITHIUM ALUMINIUM HYDRIDE: SYNTHESIS OF SPIROIMIDAZOLIDIN-2'-ONES AND SPIROIMIDAZOLIDINES

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Abstract - The behaviour of some spirohydantoins against reduction with lithium aluminium hydride as well as the influence of the N_3-substituent on this reaction are analized. N_3-Unsubstituted spirohydantoins yielded the corresponding spiroimidazolidin-2'-ones, while N_3-substituted spirohydantoins originated the spiroimidazolidines. Isomeric (α and β) spiroimidazolidin- 2'-ones can be prepared by reduction of the suitable epimeric (α and β) spirohydantoins.

Scanty and contradictory results have been published in relation to the reduction of hydantoins with lithium aluminium hydride (LAH). While Wilk et al.[1] reported a complete reduction of hydantoins to imidazolidines, Marshall[2] assumed that only one carbonyl group is reduced in this process. The aim of the present paper is to clarify these conflictive results showing the influence not only of the N_3-substituent but of the overall molecular structure on the hydride attack on some spirohydantoins.

As a general procedure, the spirohydantoins were slowly added into a dried ethereal solution of LAH under reflux with vigorous stirring. After 48 hours, LAH was decomposed according to the Mićović-Mihalović method[3]. In the case of N_3-unsubstituted spirohydantoins I-III the insoluble residue in ether was filtered and extracted with absolute ethanol, yielding the spiroimidazolidin-2'-ones IX-XI. When N_3-substituted spirohydantoins were used the spiroimidazolidines XII-XVI were isolated from the ethereal solution by distillation under vacuum (see Table I).

Ir and ^{1}H nmr data of spiroimidazolidin-2'-ones[4-6] are in agreement with those reported in the literature for compounds IX and X[12,13].

Ir spectra of spiroimidazolidines XII-XVI showed the absence of CO groups at the 1700 cm^{-1} region, and two new methylene groups appeared, in the ^{1}H nmr spectra, as two singlets at δ = 2.40-2.15 ppm and δ = 2.10-2.00 ppm for all compounds[7-11].

Monoreduction of N_3-unsubstituted spirohydantoins could be explained as a consequence of the lower reactivity of the intermediate salt formed from the acidic N_1- and N_3- hydrogens of hydantoin ring (Figure 1).

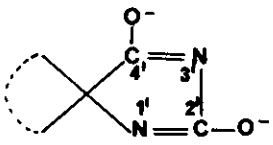


Figure 1

In this salt the 4'-carbonyl group can readily be attacked by the hydride anion. This fact cannot be accomplished on 2'-carbonyl group because of its low electrophilic character, due to the resonance anionic N_1-C_2-N_3 system (Figure 2).

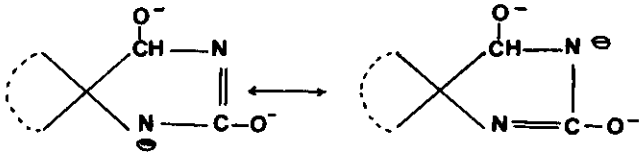


Figure 2

This low electrophilic character of 2'-carbonyl group was again noticed when the purified cyclopentane-4'-imidazolidin-2'-one (monoreduced compound) was treated with excess LAH in the same conditions as above, the starting material being recovered. This result is in accordance with that reported by Ried et al.[14] in relation to the reduction of NN'-disubstituted ureas, which only underwent reduction when stronger conditions (higher temperature) were used[15,16].

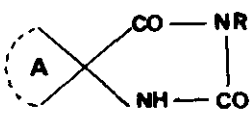
The electrophilic character of the 2'-carbonyl group can be increased if the N_3- is substituted and the intermediate salt can be reduced easier yielding the spiroimidazolidines.

Looking at the yields (see Table 1) we can deduce that in the case of N_3-unsubstituted spirohydantoins the carbocycle size is not very decisive. But in N_3-substituted spirohydantoins, reduction of the two carbonyl groups depends on the carbocycle size as well as the nature of the substituent. Thus, for the same substituent (benzyl) only 28% of spiroimidazolidine XVI was obtained from the more hindered N_3-benzyl-bicyclo [3.2.1] octan-3-spiro-5'-hydantoin VIII. When different substituents (benzyl, n-butyl and methyl) were placed on the same spirohydantoin (cyclohexanespirohydantoin) the yields were 60, 27 and 40%, respectively. This fact revealed that not only the size but the spacial disposition of the N_3-substituent affect the reduction process.

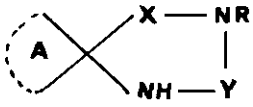
From a synthetic point of view, reduction of N_3-unsubstituted spirohydantoins with LAH could be a good method to prepare spiroimidazolidin-2'-ones. This way would be easier than that proposed by Granger et al.[12] and Hardy et al.[17] from cycloketones. It would be also the only method to obtain pure isomeric spiroimidazolidin-2'-ones when α and β-spirohydantoins, obtained by Bucherer and Read[18,19], were used as starting material.

Table I Results obtained in the reduction of spirohydantoins with LAH

Starting spirohydantoin



Reaction products



Compd. No.	A	R	M.R.[d]	Compd. No.	X	Y	Yield %	mp	bp (mmHg)
I		H[a]	1:4	IX	CH_2	CO	63	210-211°	
II		H[a]	1:4	X	CH_2	CO	52	220-221°	
III		H[a]	1:4	XI	CH_2	CO	52	193-195°	
IV		$CH_2C_6H_5$[b]	1:4	XII	CH_2	CH_2	58		80-84°(0.3)
V		$CH_2C_6H_5$[b]	1:4	XIII	CH_2	CH_2	60		100-105°(0.5)
VI		n-$(CH_2)_3CH_3$[b]	1:4	XIV	CH_2	CH_2	27		85-90°(0.5)
VII		CH_3[c]	1:4	XV	CH_2	CH_2	40		58-60°(0.2)
VIII		$CH_2C_6H_5$[b]	1:4	XVI	CH_2	CH_2	28		80-83°(0.2)

a:Prepared by Bucherer synthesis, ref. 18; b:Prepared following a general procedure of N_3-substitution of hydantoins, ref. 20; c:Prepared according to ref. 21; d:Molar ratio of spirohydantoin to LAH.

References and Notes

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4. (IX): $ir\nu_{max}^{KBr}$ cm^{-1} : 3240, 3200 (NH); 1717 (C=O); nmr ($CDCl_3$) δ 5.75 (1H,s,N_3-H), 3.17 (1H,s, N_1-H), 3.30 (2H,s,C_5-H_2), 1.70 (8H,s).

5. (X): $ir\nu_{max}^{KBr}$ cm^{-1}: 3250 (NH), 1697 (C=O); nmr ($CDCl_3$) δ 5.60 (1H,s,N_3-H), 5.15 (1H,s,N_1-H)

3.17 (2H,s,C_5-H_2), 1.50 (10H,s).

6. (XI): ir ν_{max}^{KBr} cm^{-1}: 3350, 3200 (NH), 1700 (C=O); nmr ($CDCl_3$) δ 5.40 (2H,s,N_1-H, N_3-H), 3.20 (2H,s,C_5-H_2), 2.30 (2H,m, w $\frac{1}{2}$ 16Hz), 2.00-1.50 (10H,m).

7. (XII): ir ν_{max}^{Film} cm^{-1} : 3320 (NH); nmr (CCl_4) δ 7.10 (5H,s,$C_6\underline{H}_5$), 3.65 (2H,s,$\underline{CH}_2C_6H_5$), 2.40 (2H,s,C_2-H_2), 2.10 (2H,s,C_5-H_2), 1.60 (1H,s,NH), 1.45 (8H,s).

8. (XIII): ir ν_{max}^{Film} cm^{-1} : 3320 (NH); nmr (CCl_4) δ 7.17 (5H,s,$C_6\underline{H}_5$), 3.67 (2H,s, $\underline{CH}_2C_6H_5$), 2.35 (2H,s,C_2-H_2), 2.05 (2H,s,C_5-H_2), 1.60 (1H,s,NH), 1.35 (10H,s).

9. (XIV): ir ν_{max}^{Film} cm^{-1}: 3320 (NH); nmr (CCl_4) δ 2.59 (2H,t, J=4Hz, $NC\underline{H}_2$), 2.30 (2H,s,C_2-H_2), 2.15 (2H,s,C_5-H_2), 1.40 (10H,s), 1.22 (1H,s,NH), 1.25-0.85 (7H,m,$C\underline{H}_2C\underline{H}_2C\underline{H}_3$).

10. (XV): ir ν_{max}^{Film} cm^{-1} : 3320 (NH); nmr (CCl_4) δ 2.29 (3H,s,$NC\underline{H}_3$), 2.21 (2H,s,C_2-H_2), 2.00 (2H, s,C_5-H_2), 1.29 (10H,s), 1.00 (1H,s,NH).

11. (XVI): ir ν_{max}^{Film} cm^{-1}: 3320 (NH); nmr (CCl_4) δ 7.50 (5H,s,$C_6\underline{H}_5$), 3.58 (2H,s,$\underline{CH}_2C_6H_5$), 2.15 (2H,s,C_2-H_2), 2.05 (2H,s,C_5-H_2), 2.10 (2H,m, $C_{1(5)}H$), 1.63 (10H,m), 1.15 (1H,s,NH).

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