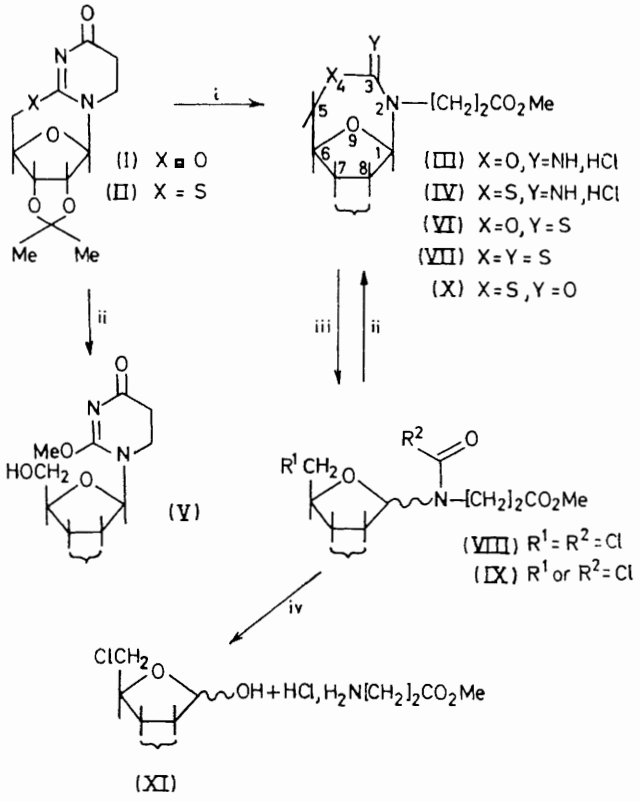
Novel Azabicyclo[4,2,1]nonanes from Anhydrodihydronucleosides

By VINKO ŠKARIĆ* and MARIJAN HOHNJEC
(*Institute 'Rudjer Bošković', Zagreb, Croatia, Yugoslavia*)

Summary The selectivity of opening of the dihydropyrimidine ring in 2,5′-anhydro-5,6-dihydrouridine (I) and its 2-thio-analogue (II) into 4,9-dioxa-2-aza- and 4-thia-9-oxa-2-azabicyclo[4,2,1]nonanes has been shown to be dependent upon the reaction media.

THERE have been few reports dealing with the chemistry of anhydrodihydronucleosides.[1] The cyclization of 5′-deoxy-5′-iodo-2′,3′-*O*-isopropylidene-5,6-dihydrouridine[2] into the anhydrodihydrouridine (I) appeared to involve several transformations.

We now report that the anhydrodihydronucleoside (I) and its 2-thio-analogue (II) in acidic media are readily transformed into very reactive 3-imino-derivatives of hitherto unknown 2-azabicyclo[4,2,1]nonanes. Thus, ring



Reagents: i, a, HCl–MeOH; b, H_2S–$HCONMe_2$–Et_3N; ii, NaOMe–MeOH; iii, $SOCl_2$; iv, H_2O.

cleavage of (I) at the 3,4-position in methanolic HCl afforded the hydrochloride of the dioxa-azabicyclononane (III), m.p. 136—138° (51%). The n.m.r. spectrum of (III) in CD_3OD showed clearly a sharp singlet at τ 4·69 and two quartets centred at 5·28 and 5·65 (J 14·0 Hz), signals characteristic of the anomeric 1′- and geminal 5′-protons of anhydronucleosides[3] and similar cyclic compounds.[4]

The thiouracil (II), m.p. 208–210°, in methanolic hydrochloric acid was shown to generate the hydrochloride of the thiaoxa-azabicyclononane (IV), m.p. 187—189° (81%), τ (D_2O) 4·49 (s, 1-H), 6·49 (q), and 6·86 (ABq, $J_{A,B}$ 14·7 Hz, 5-H).

The transformation of the anhydro-compound (I), conveniently studied in Na–MeOH, proceeded to the dihydrouridine (V), m.p. 128—130°, in quantitative yield, τ 6·05 (OMe), $\lambda_{max.}$ 244 nm (ϵ 11,355), indicating nucleophilic attack of the methoxide ion at position 2.

The structures of the azabicyclononanes (III) and (IV) were verified by reaction with H_2S which gave the corresponding thiones (VI), m.p. 148—149° (73%), τ ($CDCl_3$) (4·78) (s, 1-H), 5·62 (d), and 6·01 (ABq, $J_{A,B}$ 12·5 Hz, 5-H), and (VII), m.p. 166—168° (52%), τ ($CDCl_3$) 4·53 (s, 1-H), 6·47 (q), and 7·50 (ABq, $J_{A,B}$ 14·5 Hz, 5-H).

Treatment of the dioxa-azabicyclononane (VI) with thionyl chloride led to cleavage of the seven-membered ring and the formation of oily ribofuranosylamine derivatives. Thus, the amino-compound (VIII), $[\alpha]_D$ −26·2° (27%), and a sulphur- and chlorine-containing derivative (IX), $[\alpha]_D$ −19·5° (60%), were isolated.

The tentative structure (IX) remained to be decided. However, this compound, which may be a mixture of two anomers, recyclised in Na–MeOH into the thia-oxa-azabicyclononane (X), m.p. 114—115° (36%), τ ($CDCl_3$) 4·80 (s, 1-H), 6·56 (q), and 7·46 (ABq, $J_{A,B}$ 14·5 Hz, 5-H).

The ease of hydrolysis of the dichlorofuranosylamine (VIII) into the deoxy-ribofuranose (XI), m.p. 61—66° $[\alpha]_D$ − 41° (96%) and the hydrochloride of methyl β-aminopropionate further substantiated the foregoing azabicyclo[4,2,1]nonane and ribofuranosylamine structures as well as the routes for several transformations and degradation sequences in the handling of dihydronucleosides.

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