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A NOVEL TRANSFORMATION OF THIAZOLIUM SALTS TO 2,3-DIHYDRO-1,4-THIAZINES

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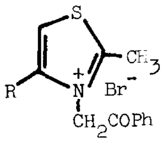
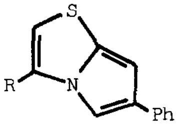
2,4-Dimethyl-3-phenacylthiazolium bromide (Ia) condenses intramolecularly in the presence of hot sodium carbonate to yield (IIa), (1). It is stated in the literature (2), however, that similar treatment of the salt (Ib) with base gives a low molecular weight polymer, containing only traces of (IIb). In our hands, treatment of (Ib) with various aqueous bases yields a new compound, 4-acetyl-2,3-dihydro-2-hydroxy-2-phenyl-4H-1,4-thiazine* (IIIa), m.p. 125-126° (55%). Similarly, 2-methyl-3-p-bromophenacylthiazolium bromide gives (IIIb), m.p. 116-118°, (65%). The reaction is best carried out by treatment of an aqueous solution of the quaternary compound with an excess of 5% aqueous sodium hydrogen carbonate solution. The reaction mixture is then allowed to stand at room temperature overnight and the product filtered off and recrystallised from ethyl acetate.



Ia R = CH_3
Ib R = H



IIa R = CH_3
IIb R = H

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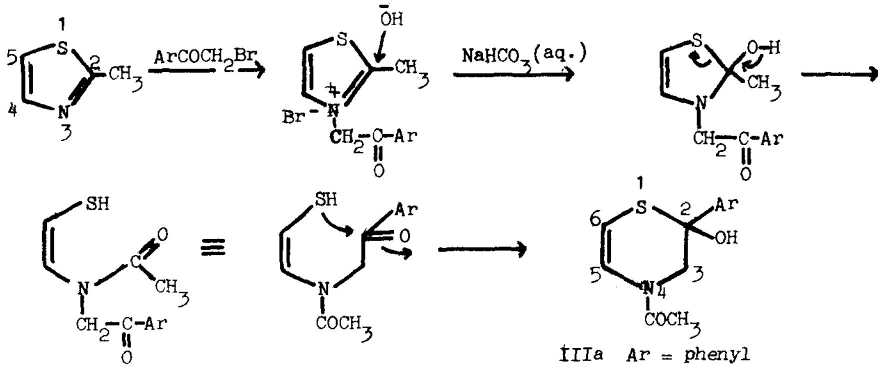
* Satisfactory elementary analyses have been obtained for all new compounds.

The overall reaction can be represented by the scheme shown below.$^{+}$



IIIa Ar = phenyl

IIIb Ar = p-bromophenyl

Structure assignment of the dihydro-1,4-thiazine derivatives has been mainly limited to that for (IIIa). The mass spectrum shows a molecular ion peak $^m/_e$ 235. The infra-red spectrum ($CHCl_3$) exhibits significant absorption bands at 3580 and 3340 [ν(OH) (free) and ν(OH) (bonded) respectively], 1656 (C=O) and 1616 (C=C)cm.$^{-1}$. Dilution studies show the hydroxyl group to form an intermolecular hydrogen bond.

The n.m.r. spectrum (Fig. 1) is of interest due to the presence of two rotamers (IV) and (V) resulting from hindered rotation about the amide bond. Furthermore, we propose the thiazine ring exists predominantly in the two conformations shown.

FIG. 1

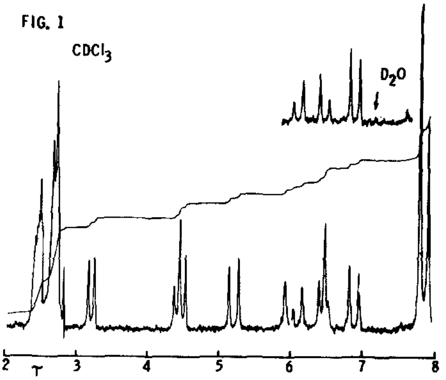
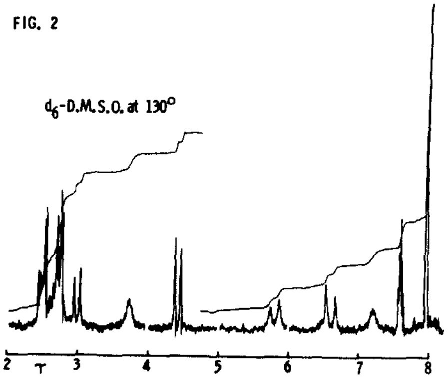
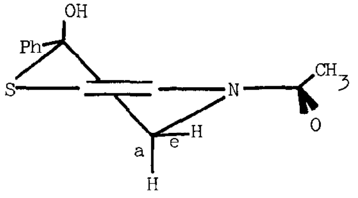


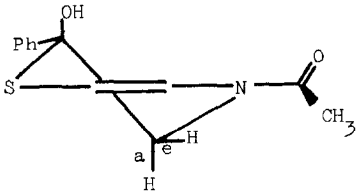
FIG. 2



[+] Takamizawa (3) has reported rather different thiazole-thiazine transformations also involving attack at C_2 of thiazolium salts.



(IV) exo-



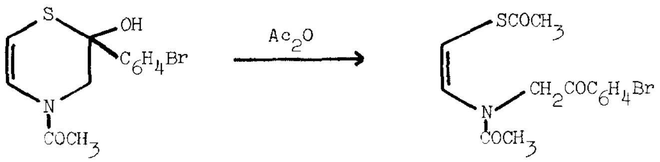
(V) endo-

Thus the spectrum ($CDCl_3$, T.M.S.) shows the presence of two methylene groups (τ 6.27, Δ_{AB} = 37.5Hz, J_{AB} = 14Hz and τ6.05, Δ_{AB} = 170Hz, J_{AB} = 14Hz) and two sets of ethylenic protons (τ 3.85, Δ_{AB} = 128Hz, J_{AB} = 8Hz, and τ~3.5, Δ_{AB} ~ 170Hz, J_{AB} = 8Hz), two methyl resonances at τ7.83 and τ7.94 and two hydroxyl resonances at τ 6.48 and τ5.93.

The occurence of the two AB quartets for the methylene protons in (IIIa) is of particular interest. In both rotamers (IV) and (V) the downfield section of each AB quartet is assigned to the equatorial protons H_e, the lower field signal being ascribed to H_e in (IV) due to the deshielding effect of the adjacent carbonyl group. Monro and Sewell (4) have described similar effects with N-acetylpiperidines.

In both deuteriochloroform and d_6-dimethylsulphoxide solutions the ratio of exo:endo is approximately 2:1. With increasing temperature the spectrum (d_6-D.M.S.O., T.M.S.; see Fig. 2) reveals the expected broadening of the spectral lines resulting from rapid inter-conversion of the rotamers. At 130° the spectrum is considerably simplified due to fast interconversion of both exo- and endo- forms. Thus, the resonance of the C_3 methylene protons and the ethylenic protons at C_5 and C_6 are reduced to simple AB quartets (τ6.19, Δ_{AB} = 80Hz, J_{AB} = 14Hz and τ3.7, Δ_{AB} = 144Hz, J_{AB} = 8Hz respectively). The amide methyl protons are seen as a sharp singlet (τ7.97) and the hydroxyl proton as a broad singlet (τ3.7).

Treatment of (IIIb) with acetic anhydride at 60° results in ring opening and S-acetylation giving a low yield of cis-1-(N-acetyl-N-p-bromophenacyl)amino-2-acetylmercaptoethylene (VI) m.p. 105-106°C; $\nu_{max.}$(nujol) 1700 (C=O) (Ph), 1682 $[\nu$(C=O) (N and S)$]$ and 1622 (C=C)cm.$^{-1}$., N.m.r. (d_6-D.M.S.O., T.M.S.) τ 2.67, Δ_{AB} = 21Hz, J_{AB} = 8Hz (aromatic AB quartets), τ 3.50, Δ_{AB} = 84Hz, J_{AB} = 8Hz, (ethylenic AB quartet), τ 5.02 (singlet, methylene protons), τ 7.71 (singlet, ester methyl) and τ 7.9 (singlet, amide methyl).



IIIb VI

A more detailed study of both the generality of the reaction and the interpretation of the n.m.r. spectra has been carried out and will be published elsewhere.

The n.m.r. spectra quoted for the above compounds were determined on a Varian HR 100MHz spectrometer.

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