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SYNTHESIS OF AN AMINO THIAZINE BY ACID CATALYZED CYCLIZATION OF AN ALLYLIC ISOTHIURONIUM SALT

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The isothiuronium salt 1 was synthesized by Wendler and co-workers[1] and shown to be useful in a total synthesis of estrone. Subsequently, related isothiuronium salts have been prepared and used as intermediates for the synthesis of thiasteroids[2], oxasteroids[3] and steroid analogs[4].

It occurred to us that allylic salts such as 1 should also be valuable intermediates for the synthesis of certain 2-amino-5,6-dihydro-4H-1,3-thiazines. We felt that protonation of the double bond in 1 should give rise to a benzylic carbonium ion 2 which could then react intramolecularly with a nitrogen atom of the isothiourea moiety. Neutralization of the resulting dication 3 should then afford the spirothiazinenaphthalene 4.

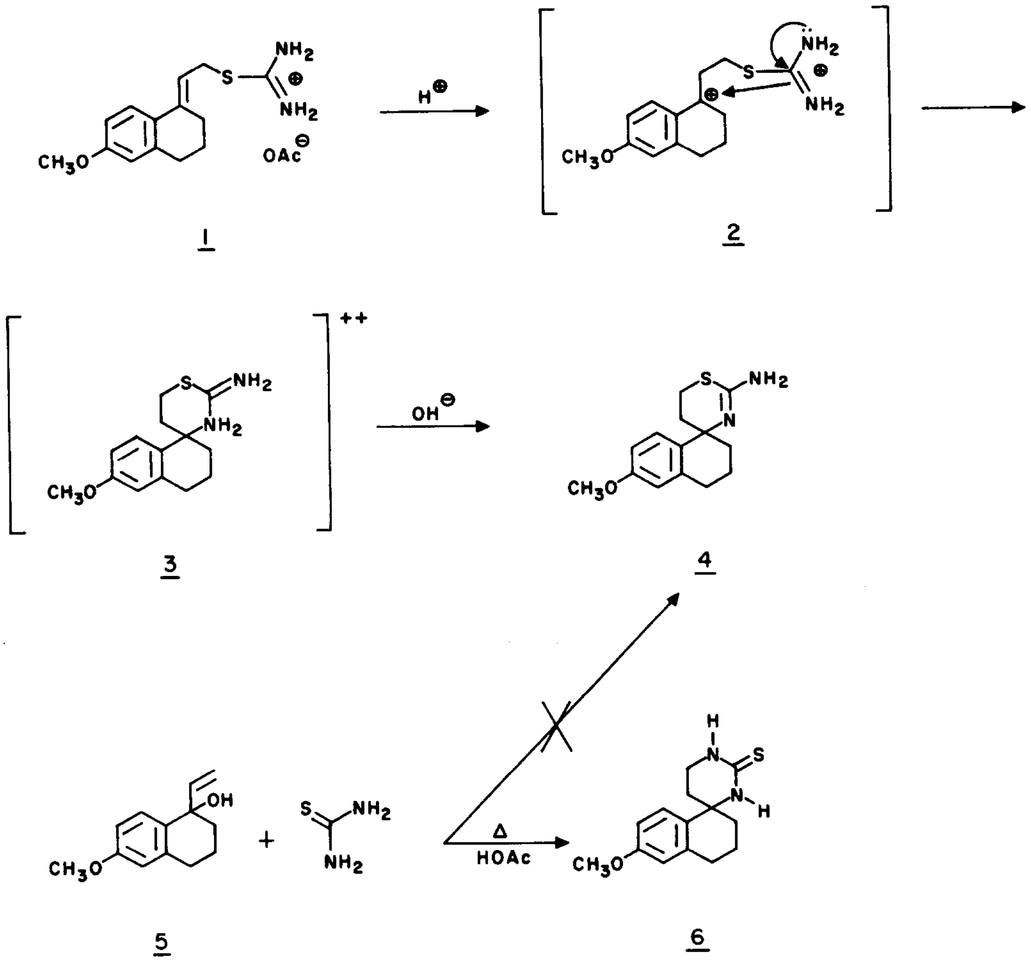
This transformation has been realized. On addition of salt 1 to trifluoroacetic acid at 23°, an intensely green solution resulted which furnished a colorless, crystalline product, m.p. 193-194°, in 40% yield, after quenching with alkali. That this product was indeed the thiazine 4 was indicated by the spectral and microanalytical properties: ir: $\nu_{\max}^{\mathrm{KBr}}$ 3430, 3300 (NH), 1650, 1610 (C=N) cm^{-1}; uv: $\lambda_{\max}^{\mathrm{EtOH}}$ 276 mμ (ε 1900), 284 (1810), $\lambda_{\mathrm{infl}}^{\mathrm{EtOH}}$ 220 (16100); nmr: $\delta_{\mathrm{TMS}}^{\mathrm{DMSO}}$ 6.33-7.00 (m, aromatic, 3), 5.16 (m, NH_2, 2), 3.64 (s, OCH_3, 3) ppm; Anal. calcd. for $C_{14}H_{18}N_2OS$: C, 64.10; H, 6.92; N, 10.68; S, 12.20; Found: C, 64.31; H, 6.81;

N, 10.54; S, 12.36. The mass spectrum showed the expected molecular ion at m/e 262 and a base peak at m/e 234 (M-28) corresponding to the loss of ethylene via a retro Diels-Alder process. This mode of fragmentation is characteristic of 2-amino-5,6-dihydro-4H-1,3-thiazines[5].

Wendler and co-workers[1] reported that reaction of vinyl tetralol 5 with thiourea in refluxing 2:1 xylene-acetic acid produced a $C_{14}H_{18}N_2OS$ compound, λ_{max} 244 mμ (ϵ 18500), m.p. 253-255°, to which they assigned structure 4. We have repeated this reaction and isolated in 10-20% yield a compound, m.p. 250-251° which showed spectral data essentially identical to those reported[1]. This material was also produced when the salt 1 was heated in refluxing 2:1 xylene-acetic acid . We also examined the pmr and mass spectra of the 250° compound (not reported previously[1]). The pmr spectrum in DMSO-d_6 was very similar to that of our 193° compound with one major difference. The NH multiplet (2 protons exchangeable by D_2O addition) was located relatively further downfield at δ 8.02. The mass spectrum of the 250° compound showed a molecular ion at m/e 262 but lacked completely the M-28 peak present in the spectrum of our 193° substance.

On the basis of this evidence, we prefer the spiropyrimidinenaphthalene structure 6 for the 250° compound. It should be noted that the intense UV absorbtion at 244 mμ exhibited by this substance is characteristic of thioureas[6]. Similarly, the location of the NH resonance at low field is compatible with a thiourea such as 6.

An examination of the scope and limitations of allylic isothiuronium salt cyclizations such as that described above for the synthesis of various 2-aminothiazines will be published elsewhere.


NH2
NH2
S
OAc
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H
NH2
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NH2
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N
S
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H
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1

2

3

4

5

6

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