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THE THERMAL REARRANGEMENT OF 6-ETHOXY-4-THIOURACILS AND RELATED COMPOUNDS. AN O,S-ALKYL MIGRATION IN THE PYRIMIDINE SERIES.

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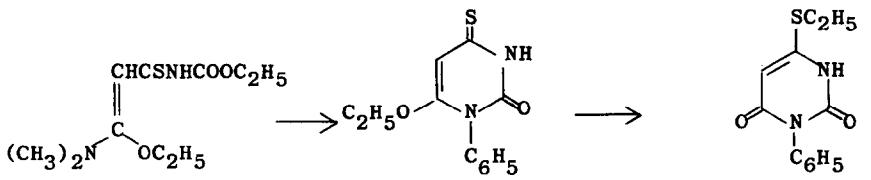
During the course of preparing 4-thiouracils from tertiary enamine-ethoxycarbonyl isothiocyanate adducts (1), a 30% yield of 6-ethoxy-1-phenyl-4-thiouracil (II) was obtained by heating the ketene O,N-acetal adduct (I) with aniline in ethanol. The 4-thiouracil (II), uv max 326 mμ (ϵ 33,900);

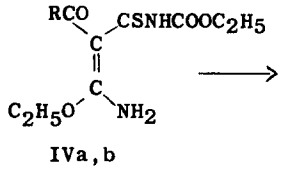


I II III

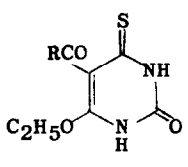
nmr δ 4.14 (q, 2H, $C\underline{H}_2$-O), 6.12 (s, 1H, C-5 proton), showed melting characteristics suggesting a thermally induced reaction (209-212°, solidification and remelting at 234-237°, from ethanol).* Fusion of II (225° bath) afforded the isomeric 6-ethylthio-3-phenyluracil (III) in 81% yield, mp 237-239° (from ethanol, uv max 276 mμ (ϵ16,000); nmr δ 3.02 (q, 2H, $C\underline{H}_2$-S), 5.64 (s, 1H, C-5 proton).

*The melting points are uncorrected; uv spectra were determined in ethanol and only the longer-wavelength maxima are given. The nmr spectra mentioned in the text were determined in DMSO-d_6. Only significant $C\underline{H}_2$-O or -S proton signals (and ring $\underline{C}H$ where applicable are shown. All new compounds (and Va) gave satisfactory analytical values.

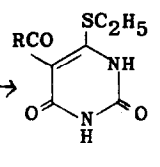
Synthesis of analogous 4-thiouracils was achieved in good yield by modification of the procedures of Goerdeler and Keuser(2). Thus, ethoxycarbonyl isothiocyanate combined readily with ethyl ß-amino-ß-ethoxyacrylate(3) and ß-amino-ß-ethoxyacrylophenone(4) in ether to produce the adducts IVa, mp 93-94° (from chloroform-ligroin) and IVb, mp 116-117° (from acetone-ligroin).* Treatment of IVa with 25% aqueous or methanolic trimethylamine gave 5-carbethoxy-6-ethoxy-4-thiouracil (Va), uv max 321 mμ (ε 22,200); nmr δ 4.12 and 4.28 (overlapping quartets, 4H, $2C\underline{H}_2$-O). The product, in our hands, had an ill-defined melting point (ca. 195-203°, from ethanol, lit.(2) mp 240°dec). Fusion of Va (210° bath) or boiling in tetralin caused isomerization to 5-ethoxycarbonyl-6-ethylthiouracil (VIa) in 64-69% yield, mp 203-204° (sintering at 201°, from ethanol), uv max 291 mμ (ε 11,700); nmr δ 3.16 (q, 2H, $C\underline{H}_2$-S). Treatment



IVa,b



Va,b



VIa,b

(a) R = OC_2H_5

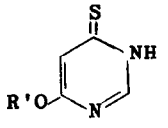
(b) R = C_6H_5

of VIa with hot, dilute alkali afforded directly the decarbethoxylation product 6-ethylthiouracil, mp 230-233° (from ethanol), uv max 276 mμ (ε 13,500), nmr δ 5.40 (s, 1H, C-5 proton), which, on acid hydrolysis, gave barbituric acid. The cyclization of IVb was effected with aqueous trimethylamine to produce the 4-thiouracil Vb, mp 265-273°dec (from DMF-H_2O), which rearranged in boiling tetralin to 5-benzoyl-6-ethylthiouracil (VIb), mp 278-280°dec (from ethanol).

The simplest pyrimidine analogue of the 6-ethoxy-4-thiouraciles, i.e., 6-methoxy-4(3H)-pyrimidinethione (VIIa), was prepared after the method of Brown and Teitei(5). Our sample, by nmr, appeared to contain a small amount of the rearranged material (VIII) and had mp 185-190° (from methanol, lit.(5) 193-194°). Fusion of VIIa (190° bath) produced 6-methylthio-4-(3H)-pyrimidinone

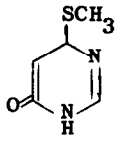
*The nmr spectrum ($CDCl_3$) of IVb contained one methyl triplet centered at δ 0.56, the second at δ 1.26. The abnormal shielding represented by the former value implies a cis orientation of the benzoyl and ß-ethoxy functions, as illustrated.

(VIII) in 72% yield, mp 229-234° (from methanol, lit.(6) 233-234°). Identical



R' =

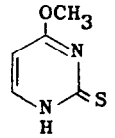
VII (a) CH_3
(b) C_2H_5
(c) n-C_3H_7



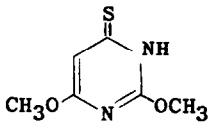
VIII

material was obtained by repeating the procedures of Isbecque et al(6). The homologous 6-alkoxy derivatives (VII b,c), mp 196-199° and 160-162°, respectively (from ethanol), uv max 297 mμ (ε 21,000), did not give isolable amounts of rearrangement product under conditions used to isomerize VIIa.

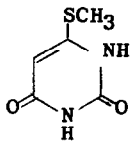
Heating 4-methoxy-2(1H)-pyrimidinethione (IX), mp >250°dec (sintering at 187-190°, from methanol) and 2,6-dimethoxy-4(3H)-pyrimidinethione (X)(7) at 190° led to the isolation of dealkylation products. Thus, IX produced 2-thiouracil (33% yield) and X afforded the rearrangement-dealkylation product XI in 44% yield, mp 328-330°dec (from ethanol). The latter product was



IX



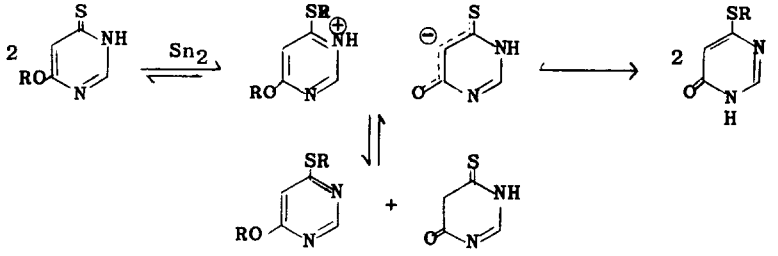
X



XI

identified by spectra and by acid hydrolysis to barbituric acid. The fate of the lost alkyl group has not been determined (see below).

A plausible mechanism for the O,S-rearrangement is given in the following sequence:



This scheme implies that the rearrangement is dependent on the size of R (cf. VIIa with apparently unreactive VIIb,c)*, the lability of the R-O bond (cf. II and Va,b with VIIb) and the acidity of the neutral dealkylated form (cf. principal product from VIIa with those from IX and X)‡.

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*The susceptibility of 2-alkoxypyrimidines to thermal O,N-rearrangement is dependent on the size of the alkyl group. Reactions of this type probably involve bimolecular ion-pairs. See reference 8.

‡The implied presence of dialkylated forms has not as yet been established.