A NEW METHOD FOR PREPARATION OF 1-(4-SUBSTITUTED PHENYL)-6-PHENYL-2-THIOURACILS *via* CYCLIZATION OF N-(4-SUBSTITUTED PHENYL)-N'-3-PHENYLPROPENOYL-THIOUREAS AND DIMROTH REARRANGEMENT OF 2-(4-SUBSTITUTED PHENYLIMINO)-6-PHENYL-5,6-DIHYDRO-*4H*-1,3-THIAZIN-4-ONES

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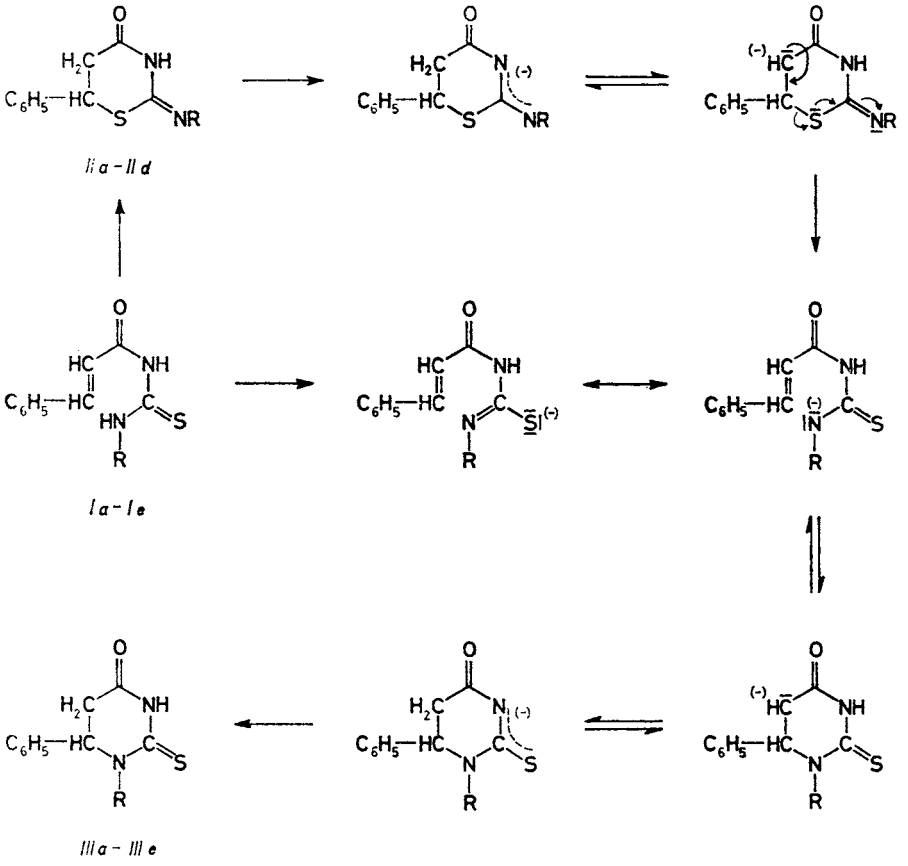
N-(4-Substituted phenyl)-N'-3-phenylpropenoylthioureas treated with lithium hydride afforded 1-(4-substituted phenyl)-6-phenyl-2-thiouracils; these could also be obtained by Dimroth rearrangement of 2-(4-substituted phenylimino)-6-phenyl-5,6-dihydro-4*H*-1,3-thiazin-4-ones under the same reaction conditions. 2-(4-Substituted phenylimino)-6-phenyl-5,6-dihydro-4*H*-1,3-thiazin-4-ones were synthesized from the corresponding thioureas under catalysis of boron trifluoride in chloroform.

As shown in our preceding papers[1-6], the ambident character of thiocarbamoyl group of thioureas, synthesized from 3-phenylpropenyl isothiocyanate, directed the ring closure exclusively through sulfur to form five- or six-membered heterocycles depending on the conditions. Action of bromine on the N-substituted N'-3-phenylpropenoylthioureas resulted in formation of sulfenyl bromide and closure of the ring to β-carbon of the double bond to afford either thiazolines or benzothiazoles; this depends on the character of the amine involved[1,2]. Upon heating of the respective thioureas or by boron trifluoride catalysis a nucleophilic attack of sulfur to β-carbon of the polarized double bond took place to furnish 1,3-thiazines[3,4]. Thioureas prepared from 2-cyano-3-phenylpropenoyl isothiocyanate and 2-cyanocyclohexylideneacetyl isothiocyanate cyclized to β-carbon through sulfur in a neutral, or through nitrogen in an alkaline medium[5,6].

This paper concerns a new and simple method for preparation of 1-(4-substituted phenyl)-6-phenyl-2-thiouracils (Scheme 1, compounds *IIIa*–*IIIc* from N-(4-substituted phenyl)-N'-3-phenylpropenoylthioureas *Ia*–*Ie*, or 2-(4-substituted phenylimino)-6-phenyl-5,6-dihydro-4*H*-1,3-thiazin-4-ones *IIa*–*IId* by Dimroth rearrangement. Compounds *Ia*–*Ie* lost hydrogen when treated with lithium hydride and form an ambident ion which could cyclize either through sulfur or nitrogen. Similar systems are known to favour cyclization through the more basic atom of the ambident ion[7,8], and accordingly, N-cyclization took place with our compounds after addition

of a proton to yield the corresponding 2-thiouracil derivatives (Scheme 1, compounds *IIIa–IIIe*). This reaction proceeded at room temperature during several days as follows: Thioureas *Ia*, *Id* required 3 days, *Ic*, *Ie* and *Ib* 4 and 10 days, respectively. The reaction course was monitored by thin-layer chromatography.



In formulae *I*, *II*, *III*: *a*, R = C_6H_5, *b*, R = 4-BrC_6H_4, *c*, R = 4-$CH_3C_6H_4$, *d*, R = 4-$CH_3OC_6H_4$, *e*, R = 4-$(CH_3)_2NC_6H_4$

SCHEME 1

2-(4-Substituted phenylimino)-6-phenyl-5,6-dihydro-4*H*-1,3-thiazin-4-ones *IIa–IId* were obtained from the respective thioureas *Ia–Id* in chloroform under catalysis of boron trifluoride[4]. This reation involves an acid catalyzed intramolecular cyclization, where the attack was favoured by the nucleophilic sulfur. The reaction time

needed for preparation of 1,3-thiazines depended on tbe solubility of the respective thiourea in chloroform; thus *Ib* required 30 days, *Ia*, *Ic* and *Id* 30 min and 5 h, respectively. Nevertheless, an attempt to obtain 2-(4-N,N-dimethylaminophenylimino)-6-phenyl-5,6-dihydro-4*H*-1,3-thiazin-4-one failed even when a 4-molar excess of boron trifluoride *per* thiourea *Ia* was applied. We suggest that the complex of boron trifluoride with the dimethylamino grouping lowered the nucleophility of sulfur and consequently, no cyclization could take place; after neutralization with sodium hydrogen carbonate the starting *Ie* was recovered.

As known, N-substituted thiazoles[9], thiadiazoles[10], and 1,3-thiazines[11] undergo the Dimroth rearrangement when heated in acid or alkaline medium[12,13]. We attempted to rearrange 2-(4-substituted phenylimino)-6-phenyl-5,6-dihydro-4*H*-1,3-thiazin-4-ones *IIa*–*IId* in alkaline medium. In ethanolic sodium hydroxide solution a decomposition at an ambient temperature occured to produce 3-phenylpropenoic acid and the corresponding thiourea. Therefore, the Dimroth rearrangement was proceeded in an aprotic solvent (dimethylformamide) in the presence of lithium hydride under the same conditions as with preparation of 2-thiouracils from thioureas. For the Dimroth rearrangement of 1,3-thiazines we suggest the following course: The carbanion originating at the α-carbon facilitated the C—S bond cleavage in the thiazine ring to yield the ambident ion, which in turn cyclized to the respective 2-thiouracil derivatives (Scheme 1, compounds *IIIa*–*IIId*).

These results evidence the cyclization in an alkaline medium to proceed throug the nitrogen atom, whereas formation of thiazine was not observed. For this reaction the Baldwin cyclization rules[14] could be applied; accordingly both the 5-Exo-Trig and the 6-Endo-Trig processes are advantageous for a nucleophilic addition to double bond. The preference of a 6-Endo-Trig process could be in our case explained by a polarization of the double bond and as a consequence, formation of an electron gap at the β-carbon of the propenoyl moiety appeared.

Structure of the synthesized 1,3-thiazines *IIa*–*IId* and 2-thiouracils *IIIa*–*IIIe* was backed by spectral methods. Thus, the IR spectra showed the presence of stretching vibrations associated with carbonyl groups; for 2-(4-substituted phenylimino)-6-phenyl-5,6-dihydro-4*H*-1,3-thiazin-4-ones *IIa*–*IId*, occuring in an imine form[15,16], the ν(CO) appeared at 1 690 cm^{-1}. The 1-(4-substituted phenyl)-6--phenyl-2-thiouracils had this band noticeably shifted to higher wavelength values (1 708–1 725 cm^{-1}). The ^{13}C NMR spectra of thiazine derivatives *IIa*–*IId* and thiouracils *IIIa*–*IIIe* were characteristic of resonance signals of carbonyl carbons at δ = 170 and 165, respectively. Both types of compounds could well be distinguished by the resonance signal due to δ(C=N) of thiazines *IIa*–*IId* at δ = 151, which absented in thiouracils *IIIa*–*IIIe*. On the other hand, compounds *IIIa*–*IIIe* revealed resonance signals of thiocarbonyl carbons at δ = 179, the appearance of which corroborated the cyclization to have occured through nitrogen atom in line with[6].

EXPERIMENTAL

N-Phenyl-N′-3-phenylpropenoylthiourea[17] (*Ia*), N-(4-bromophenyl)-3-phenylpropenoylthiourea[2] (*Ib*), N-(4-methoxyphenyl)-N′-3-phenylpropenoylthiourea[18] (*Id*), and 2-phenylimino-6-phenyl--5,6-dihydro-4*H*-1,3-thiazin-4-one[4] (*IIa*) were prepared according to the indicated literature.

The IR spectra were recorded with Specord IR-75 (Zeiss, Jena), the ^{1}H and ^{13}C NMR spectra with Tesla BS 487A (80 MHz) and Tesla BS 567 (25·15 MHz) apparatuses, respectively, tetramethylsilane being the internal reference. The chemical shift values (ppm) refer to δ scale. The reaction course was monitored by thin-layer chromatography on Silufol (Kavalier) sheets.

N-(4-N,N-Dimethylaminophenyl)-N′-3-phenylpropenoylthiourea (*Ie*)

N,N-Dimethylaniline (1·36 g; 10 mmol) in benzene (20 ml) was dropwise added to the stirred solution of 3-phenylpropenoyl isothiocyanate (1·89 g, 10 mmol) in benzene (10 ml). The immediately forming precipitate was filtered off after 30 min and crystallized from ethanol. Yield 3·06 g (94%), m.p. 200—202°C. For $C_{18}H_{19}N_3OS$ (325·4) calculated: 66·44% C, 5·89% H, 12·91% N; found: 66·35% C, 5·92% H, 12·84% N. IR (KBr, cm^{-1}): 1 678 (C=O), 1 616 (C=C). ^{1}H NMR (C^2HCl_3–(C^2H_3)$_2$SO): 2·94 s, 6 H ($N(CH_3)_2$); 6·89 and 7·73 d, (2 H, CH=CH, J_{AB} = 16 Hz); 7·10 m, 9 H (C_6H_5, C_6H_4); 11·23 s, 1 H (NH).

2-(4-Substituted phenylimino)-6-phenyl-5,6-dihydro-4*H*-1,3-thiazin-4-ones (*IIb—IId*)

These compounds were prepared according to procedure given for *IIa* (ref.[4]).

2-(4-*Bromophenylimino*)-6-*phenyl*-5,6-*dihydro*-4*H*-1,3-*thiazin*-4-*one* (IIb). Yield 73%, m.p. 186 to 187°C (chloroform–light petroleum). For $C_{16}H_{17}BrN_2OS$ (361·3) calculated: 53·19% C, 4·74% H, 7·76% N; found: 53·29% C, 4·81% H, 7·85% N. IR ($CHCl_3$, cm^{-1}): 3 360 (NH), 1 694 (C=O), 1 610 (C=N). ^{1}H NMR (C^2HCl_3–C^2H_3)$_2$SO): 3·10 m, 2 H (CH_2); 4·64 m, 1 H (CH); 7·19 m, 9 H (C_6H_5, C_6H_4); 10·93 s, 1 H (NH). ^{13}C NMR ((C^2H_3)$_2$SO): 39·79 t (CH_2); 41·04 d (CH); 151·03 s (C=N); 169·90 s (C=O).

2-(4-*Methylphenylimino*)-6-*phenyl*-5,6-*dihydro*-4*H*-1,3-*thiazin*-4-*one* (IIc). Yield 88%, m.p. 156—157°C (ethanol). For $C_{17}H_{16}N_2OS$ (296·4) calculated: 68·89% C, 5·44% H, 9·45% N; found: 68·96% C, 5·49% H, 9·58% N. IR ($CHCl_3$, cm^{-1}): 3 378 (NH), 1 690 (C=O), 1 620 (C=N). ^{1}H NMR (C^2HCl_3): 2·28 s, 3 H (CH_3); 3·10 m, 2 H (CH_2); 4·55 m, 1 H (CH); 7·13 m, 9 H, (C_6H_5, C_6H_4); 9·63 s, 1 H (NH). ^{13}C NMR (C^2HCl_3): 20·90 q (CH_3); 41·13 t (CH_2); 42·63 d (CH); 151·03 s (C=N); 170·05 s (C=O).

2-(4-*Methoxyphenylimino*)-6-*phenyl*-5,6-*dihydro*-4*H*-1,3-*thiazin*-4-*one* (IId). Yield 90%, m.p. 103—104°C (tetrachloromethane). For $C_{17}H_{16}N_2O_2S$ (312·4) calculated. 65·36% C, 5·16% H, 8·97% N; found: 65·47% C, 5·20% H, 9·05% N. IR ($CHCl_3$, cm^{-1}): 3 365 (NH), 1 698 (C=O), 1 618 (C=N). ^{1}H NMR (C^2HCl_3): 3·08 m, 2 H, (CH_2); 3·73 s, 3 H (CH_3); 4·54 m, 1 H (CH); 7·03 m, 9 H (C_6H_5, C_6H_4). ^{13}C NMR (C^2HCl_3): 41·21 t (CH_2); 42·70 d (CH); 55·39 q (CH_3); 156·60 s (C=N); 169·99 s (C=O).

1-(4-Substituted phenyl)-6-phenyl-2-thiouracils (*IIIa—IIIe*)

To the respective thiourea *Ia—Ie* (5 mmol), or 1,3-thiazine *IIa—IId* dissolved in a minimum amount of dimethylformamide (10—15 ml) lithium hydride (10 mmol) was added. The mixture was left at room temperature for 3 to 10 days (*Ia, Id, IIa, IId* — 3 days, *Ic, Ie, IIc* — 4 days, *Ib, IIb* — 10 days). The same amount of water with respect to dimethylformamide was added, the mixture was neutralized with 2M-HCl, and the filtered precipitate was crystallized from ethanol.

1,6-*Diphenyl-2-thiouracil* (IIIa). Yield 92%, m.p. 195—196°C. For $C_{16}H_{14}N_2OS$ (282·4) calculated: 68·05% C, 5·00% H, 9·92% N; found: 68·16% C, 5·08% H, 9·98% N. IR ($CHCl_3$, cm^{-1}): 3 392 (NH), 1 718 (C=O). ^1H NMR (C^2HCl_3–$(C^2H_3)_2SO$): 3·08 m, 2 H (CH_2); 5·14 m, 1 H, (CH); 7·40 m, 10 H, (C_6H_5, C_6H_5). ^{13}C NMR ($(C^2H_3)_2SO$): 38·60 t (CH_2); 63·53 d (CH); 164·99 s (C=O); 179·62 s (C=S).

1-(4-*Bromophenyl*)-6-*phenyl*-2-*thiouracil* (IIIb). Yield 90%, m.p. 212—213°C. For $C_{16}H_{13}BrN_2OS$ (361·3) calculated: 53·19% C, 4·74% H, 7·76% N; found: 53·26% C, 4·85% H, 7·87% N. IR ($CHCl_3$, cm^{-1}): 3 375 (NH), 1 720 (C=O). ^1H NMR (C^2HCl_3–$(C^2H_3)_2SO$): 3·05 m, 2 H (CH_2); 5·05 m, 1 H (CH); 7·39 m, 9 H (C_6H_5, C_6H_4); 11·06 s, 1 H (NH). ^{13}C NMR ($(C^2H_3)_2SO$): 38·27 t (CH_2), 62·24 d (CH); 165·56 s (C=O); 179·52 s (C=S).

1-(4-*Methylphenyl*)-6-*phenyl*-2-*thiouracil* (IIIc). Yield 91%, m.p. 201—202°C. For $C_{17}H_{16}N_2OS$ (296·4): calculated: 68·89% C, 5·44% H, 9·45% N; found: 68·93% C, 5·56% H, 9·60% N. IR ($CHCl_3$, cm^{-1}): 3 386 (NH), 1 722 (C=O). ^1H NMR (C^2HCl_3): 2·29 s, 3 H (CH_3); 3·16 m, 2 H (CH_2); 5·06 m, 1 H (CH); 7·16 m, 9 H, (C_6H_5, C_6H_4). ^{13}C NMR (C^2HCl_3): 21·13 q (CH_3); 38·52 t (CH_2); 63·98 d (CH); 164·76 s (C=O); 179·17 s (C=S).

1-(4-*Methoxyphenyl*)-6-*phenyl*-2-*thiouracil* (IIId). Yield 89%, m.p. 209—210°C. For $C_{17}H_{16}N_2O_2S$ (312·4) calculated: 65·36% C, 5·16% H, 8·97% N; found: 65·49% C, 5·28% H, 9·12% N. IR ($CHCl_3$, cm^{-1}): 3 395 (NH), 1 725 (C=O). ^1H NMR (C^2HCl_3–$(C^2H_3)_2SO$): 3·05 m, 2 H (CH_2); 3·73 s, 3 H (CH_3); 5·10 m, 1 H (CH); 7·13 m, 9 H (C_6H_5, C_6H_4). ^{13}C NMR ($(C^2H_3)_2SO$): 38·57 t (CH_2); 55·15 q (CH_3); 62·84 d (CH); 165·64 s (C=O); 179·60 s (C=S).

1-(4-N,N-*Dimethylaminophenyl*)-6-*phenyl*-2-*thiouracil* (IIIe). Yield 83%, m.p. 225—226°C. For $C_{18}H_{19}N_3OS$ (325·4) calculated: 66·44% C, 5·89% H, 12·91% N; found: 66·57% C, 5·98% H, 12·98% N. IR ($CHCl_3$, cm^{-1}): 3 375 (NH), 1 708 (C=O). ^1H NMR (C^2HCl_3): 2·83 s, 6 H ($N(CH_3)_2$); 3·11 m, 2 H (CH_2); 5·05 m, 1 H (CH); 6·93 m, 9 H (C_6H_5, C_6H_4); 9·00 s, 1 H (NH).

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