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REACTION BETWEEN 4-HYDROXY- AND 4-METHOXY-HEXAHYDROPYRIMIDINE-2-THIONES AND SECONDARY AND TERTIARY ARYLAMINES

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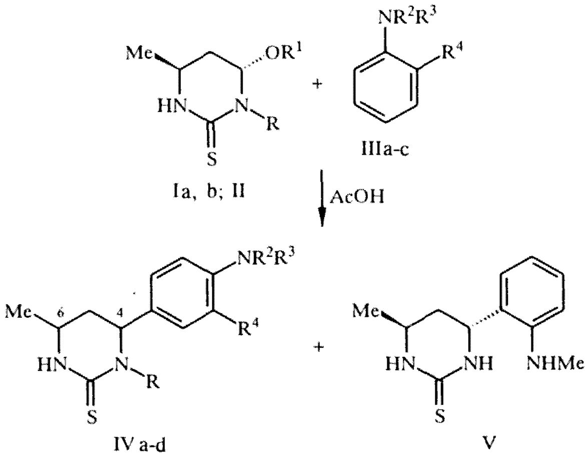
It is shown that the reaction between both 4-hydroxy- and 4-methoxyhexahydropyrimidine-2-thiones and N,N-dimethylaniline, N-methylaniline and N-methylanthranilic acid in 50% acetic acid proceeds regio- and stereoselectively, resulting in the formation of the corresponding 4-aryl-substituted hexahydropyrimidine-2-thiones.

In a previous report [1] we demonstrated that in the presence of an acidic or basic catalyst both 4-hydroxy- and 4-alkoxyhexahydropyrimidine-2-thiones and 1,2,3,6-tetrahydropyrimidine-2-thiones react with primary arylamines to produce 4-arylaminohexahydropyrimidine-2-thiones. However, in this stereo- and regioselective reaction, no amidoalkylation products are formed at the primary arylamine carbon atoms. In continuing our research into the use of the amidoalkylation reaction for synthesis purposes in heterocyclic chemistry [2-5] it was thought worthwhile to examine the reaction between these amidoalkylating systems and secondary and tertiary arylamines. This would have the added benefit of enabling us to study the effect of steric factors on the reaction development course. In the current communication we have set out the results obtained from investigating the reaction between both trans-4-hydroxy-6-methylhexahydropyrimidine-2-thiones (Ia, Ib) and trans-6-methyl-4-methoxyhexahydropyrimidine-2-thione (II) and N,N-dimethylaniline (IIIa), N-methylaniline (IIIb) and N-methylanthranilic acid (IIIc) when the reagents were allowed to stand in 50% acetic acid on a boiling water bath.



I R^1 = H, a R = H, b R = Me; II R = H, R^1 = Me; III a R^2 = R^3 = Me, R^4 = H; b R^2 = R^4 = H, R^3 = Me; c R^2 = H, R^3 = Me, R^4 = COOH; IV a R = R^4 = H, R^2 = R^3 = Me; b R = R^2 = R^3 = Me, R^4 = H; c R = R^2 = R^4 = H, R^3 = Me; d R = R^2 = H, R^3 = Me, R^4 = COOH

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It was found that under these conditions 4-hydroxyhexahydropyrimidine Ia reacted readily with N,N-dimethylaniline IIIa. As a result, trans-6-methyl-4-(4-dimethylaminophenyl)hexahydropyrimidine-2-thione (trans-IVa) was afforded in 64% yield after 2-2.5 h with complete stereo- and regioselectivity. The reaction between 3-methyl-4-hydroxyhexahydropyrimidine Ib and N,N-dimethylaniline proceeded at a much slower rate: after 10 h the corresponding amidoalkylation product, namely 3,6-dimethyl-4-(4-dimethylaminophenyl)hexahydropyrimidine-2-thione (IVb), was obtained in a yield of just 42%. It must be pointed out that in the latter case, while fully regioselective, the reaction was stereoselective to a lesser extent, resulting in a mixture (70:30) of trans- and cis-isomers of compound IVb.

We took as an example the reaction between methoxyhexahydropyrimidine II and N,N-dimethylaniline to show that it is possible to use 4-alkoxylhexahydropyrimidine-2-thiones instead of their 4-hydroxy- analogues to obtain type IV products. After 2 h the reaction had produced the trans-IVa thione in 53% yield.

It was found that when compounds Ia or II reacted with N-methylaniline, amidoalkylation proceeded exclusively at the methylaniline aromatic ring, unlike their reaction with the primary arylamines [1]. The result was a mixture (41:59) of methylaniline substitution products at the o- and p- positions, namely trans-6-methyl-4-(4-methylaminophenyl)- (trans-IVc) and trans-6-methyl-4-(2-methylaminophenyl)hexahydropyrimidine-2-thione (V). It is important to emphasize that this reaction was highly diastereoselective, with only trans-isomers of compound IVc being formed.

As in the case of dimethylaniline IIIa, the reaction between hydroxypyrimidine Ia and N-methylanthranilic acid was regio- and stereoselective, resulting in the formation of trans-6-methyl-4-(3-carboxy-4-methylaminophenyl)hexahydropyrimidine-2-thione (trans-IVd) in 72.8% yield. The high amidoalkylation regioselectivity in this case is probably due to steric factors.

The structure of the synthesized compounds was corroborated by PMR and IR spectral data. For example, the IR spectra of products IVa, IVb and IVd and a mixture of products IVc and V revealed broad absorption bands for NH group valency vibrations at 3164-3398 cm^{-1}, while either one or a number of strong "thioamide-II" bands caused by thioureide moiety vibrations [6] appeared at 1511-1570 cm^{-1}. In addition the compounds displayed characteristic absorption bands indicating the presence of an aryl substituent at the $C_{(4)}$ carbon atom (see Experimental section). The substitution type was deduced by analyzing absorption in the 650-1000 cm^{-1} region, where extraplanar deformational vibrations of the aromatic ring CH bonds [7] are manifested. So, for example, an intense absorption band typical of the p-substituted benzene ring [7] was observed at 803-816 cm^{-1} in the IR spectra of compounds IVa and IVb.

The substitution type of the reaction products was also demonstrated using PMR spectroscopy. Thus, in the PMR spectra of compounds IVa-c two doublets appeared in the aromatic proton resonance region with centers at 6.50-6.70 and 6.89-7.04 ppm and a distance of 8.5-8.8 Hz between the doublet lines, indicating 1,4-substitution in the benzene ring. The spectrum of acid IVd had three aromatic proton signal groups at 7.62 (d), 7.22 (d.d) and 6.70 ppm (d). The splitting type and the spin-spin coupling constant values (see Experimental section) provide unambiguous confirmation of 1,2,4-substitution. In a similar way, by analyzing the aromatic proton signals in V (four multiplets) 1,2-substitution in the benzene ring was inferred for this compound.

From the values of the coupling constant between the 5-Ha proton and the protons at the $C_{(4)}$ and $C_{(6)}$ carbon atoms in the PMR spectra of compounds trans-IVa-d and V ($J_{4,\,5a} = 4.5\text{-}5.2$, $J_{5a,\,6} = 9.5\text{-}11.2$ Hz) it was concluded that the aryl substituent and the 6-Me group had axial and equatorial orientations respectively in the molecules of these compounds. The axial orientation preference of the fairly large aryl substituent [8] at atom $C_{(4)}$ is probably caused by the anomeric effect, which we established for other 4-substituted hexahydropyrimidine-2-thiones in previous works [1-4, 9, 10]. In compound cis-IVb molecules both these substituents occupy an equatorial position ($J_{4,\,5a} = 11.3$, $J_{5a,\,6} = 10.6$ Hz).

EXPERIMENTAL

IR spectra were recorded on a Shimadzu IR-435 instrument (vaseline oil suspensions or KBr tablets). Electronic spectra in the 200-400 nm region were obtained on a Specord UV-Vis spectrophotometer for methanol solutions ($5 \cdot 10^{-5}$ moles/l concentration). PMR spectra were registered on on a Bruker MSL-200 spectrometer (200 MHz) for solutions of samples in $CDCl_3$, DMSO-D_6 or a mixture of DMSO-D_6 + D_2O, internal standard HMDS. Reaction course and product purity were monitored using TLC on Kieselgel 60 F254 plates (Merck) in a 9:1 chloroform−methanol system, with iodine vapor development.

The compounds Ia, Ib and II used initially were obtained using the technique described in a previous communication [9].

Elemental analysis data with respect to C, H, N, and S was in line with calculated values for compounds IVa, IVb and IVd, and for a mixture of IVc and V.

trans-6-Methyl-4-(4-dimethylaminophenyl)hexahydropyrimidine-2-thione (trans-IVa, $C_{13}H_{19}N_3S$). A mixture of 2.813 g (19.24 mmoles) of hydroxyhexahydropyrimidine Ia, 2.448 g (20.20 mmoles) N,N-dimethylaniline, 5 ml acetic acid and 5 ml water was allowed to stand on a boiling water bath for 2 h (the reaction product began to separate from the resultant solution after 30 min). The mixture was cooled to −5°C, the precipitate was filtered off, washed on the filter with ice-cold water and hexane, then dried to yield 3.087 g (64.3%) of compound trans-IVa, which was recrystallized from methanol, mp 234-235°C (decomp.). IR spectrum (vaseline oil): 3167 (ν NH), 3073 (ν CH_{Ar}), 1624 (ν C=C), 1552, 1525 (thioamide-II), 803 (δ CH_{Ar}), 1303, 1210 cm^{-1}. PMR spectra (DMSO-D_6): 8.25 (1H, Broad, d, $N_{(3)}$-H, $J_{NH,\,4e}$ = 3.5 Hz), 8.00 (1H, broad s, $N_{(1)}$-H, $J_{NH,\,6a}$ = 0 Hz), 6.99 (2H, d, 2'-H, 6'-H), 6.70 (2H, d, 3'-H, 5'H, $J_{2',\,3'}$ = $J_{5',\,6'}$ = 8.7 Hz), 4.42 (1H, m, 4-H_e, $J_{4e,\,5a}$ = 4.9, $J_{4e,\,5e}$ = 3.1 Hz), 3.03 (1H, m, 6-H_a, $J_{5e,\,6a}$ = 4.0, $J_{5a,\,6a}$ = 9.9 Hz), 2.86 (6H, s, $(CH_3)_2N$), 1.82 (1H, d.t, 5-H_e, $J_{5e,\,5a}$ = 13.2 Hz), 1.64 (1H, d.d.d, 5-H_a), 1.07 ppm (3H, d, 6-CH_3, J = 6.4 Hz).

The trans-IVa compound was obtained in a similar way in 52.7% yield by reacting 4-methoxyhexahydropyrimidine II with N,N-dimethylaniline IIIa.

3,6-Dimethyl-4-(4-dimethylaminophenyl)hexahydropyrimidine-2-thione (IVb, $C_{14}H_{21}N_3S$). Using the technique outlined above 2.669 g (16.65 mmoles) of hydroxyhexahydropyrimidine Ib and 2.217 g (18.29 mmoles) N,N-dimethylaniline afforded after 10 h 1.825 g (41.6%) of compound IVb in the form of a mixture (70:30) of trans- and cis-diastereomers, mp 179.5-180.5°C (4:3 hexane−ethanol). IR spectrum (in vaseline oil): 3183 (ν NH), 1615 (ν C=C), 1513 (thioamide-II), 816 (δ CH_{Ar}), 1288 cm^{-1}. PMR spectrum of trans-diastereomer ($CDCl_3$): 6.95 (2H, d, 2'-H, 6'-H), 6.67 (2H, d, 3'-H, 5'-H, $J_{2',\,3'}$ = $J_{5',\,6'}$ = 8.8 Hz), 6.31 (1H, broad s, $N_{(1)}$-H, $J_{NH,\,6a}$ = 0 Hz), 4.49 (1H, t, 4-H_e, $J_{4e,\,5a}$ + $J_{4e,\,5e}$ = 6.9 Hz), 3.32 (3H, s, $N_{(3)}$-CH_3), 3.23-3.41 (1H, m, 6-H_a) 2.91 (6H, s, $(CH_3)_2N$), 1.86-2.02 (2H, m, 5-H_e and 5-H_a, $J_{5e,\,5a}$ = 12.8 Hz), 1.10 ppm (3H, d, 6-CH_3, J = 6.6 Hz). PMR spectrum of cis-diastereomer ($CDCl_3$): 7.04 (2H, d, 2'-H, 6'-H), 6.67 (2H, d, 3'-H, 5'-H, $J_{2',\,3'}$ = $J_{5',\,6'}$ = 8.8 Hz), ~6.35 (1H, broad s, $N_{(1)}$-H, $J_{NH,\,6a}$ = 0 Hz), 4.34 (1H, d.d, 4-H_a, $J_{4a,\,5a}$ = 11.3, $J_{4a,\,5e}$ = 5.1 Hz), 3.55 (1H, m, 6-H_a, $J_{5a,\,6a}$ = 10.6, $J_{5e,\,6a}$ = 3.3 Hz), 3.05 (3H, s, $N_{(3)}$-CH_3), 2.92 (6H, s, $(CH_3)_2N$), 2.17 (1H, m, 5-H_e, $J_{5e,\,5a}$ = 13.5, $J_{NH,\,5e}$ = 1.8 Hz), 1.83 (1H, d.d.d, 5-H_a), 1.14 ppm (3H, d, 6-CH_3, J = 6.6 Hz).

trans-6-Methyl-4-(4-methylaminophenyl)hexahydropyrimidine-2-thione (trans-IVc, $C_{12}H_{17}N_3S$) and trans-6-Methyl-4-(2-methylaminophenyl)hexahydropyrimidine-2-thione (V, $C_{12}H_{17}N_3S$). A mixture of compounds trans-IVc and V was obtained similarly to compound IVa by reacting hydroxyhexahydropyrimidine Ia or methoxyhexahydropyrimidine II with N-methylaniline (in 97.7 and 55.0% yields respectively). The product precipitated from the reaction mixture comprised a mixture (41:59) of compounds trans-IVc and V, which were purified by recrystallization from glacial acetic acid, mp 261-262°C (decomp.). IR spectrum (in vaseline oil): 3363, 3163 (ν NH), 3078 (ν CH_{Ar}), 1606 (ν C=C), 1570, 1544, 1525, 1511 (thioamide-II), 742 (δ CH_{Ar}), 1302, 1208 cm^{-1}. PMR spectrum of compound IVc (DMSO-D_6): 8.16 (1H, broad s, $N_{(3)}$-H, $J_{NH,\,4e}$ > 0 Hz), 8.02 (1H, broad s, $N_{(1)}$-H, $J_{NH,\,6a}$ = 0 Hz), 6.89 (1H, d, 2'-H, 6'-H, J = 8.5 Hz), 6.50 (1H, d, 3'-H, 5'-H), 4.36 (1H, m, 4-H_e, $J_{4e,\,5a}$ = 4.8 Hz), 3.09 (1H, m, 6-H_a), 1.61 (1H, d.d.d, 5-H_a, $J_{5a,\,6a}$ = 9.7 Hz), 1.07 ppm (3H, d, 6-CH_3, J = 6.4 Hz). PMR spectrum of compound V (DMSO-D_6): 8.22 (1H, broad s, $N_{(3)}$-H, $J_{NH,\,4e}$ > 0 Hz), 7.99 (1H, broad s, $N_{(1)}$-H, $J_{NH,\,6a}$ = 0 Hz), 7.10 (1H, d.d.d, 4'-H, $J_{3',\,4'}$ = 7.5, $J_{4',\,5'}$ = 7.9, $J_{4',\,6'}$ = 1.6 Hz), 6.79 (1H, d.d, 6'-H, $J_{5',\,6'}$ = 7.5 Hz), 6.60 (1H, d.d.d, 5'-H, $J_{3',\,5'}$ = 1.2 Hz), 6.51 (1H, d.d, 3'-H), 5.29 (1H, broad q, NH, J ~ 4.4 Hz), 4.61 (1H, m, 4-H_e, $J_{4e,\,5a}$ = 5.2 Hz), 2.96 (1H, m, 6-H_a), 2.70 (3H, d, NCH_3), 1.75-1.90 (1H, m, 5-H_e), 1.52 (1H, d.d.d, 5-H_a, $J_{5a,\,6a}$ = 11.2, $J_{5e,\,5a}$ = 13.3 Hz), 1.05 ppm (3H, d, 6-CH_3, J = 6.5 Hz).

trans-4-(3-Carboxy-4-methylaminophenyl)-6-methylhexahydropyrimidine-2-thione (trans-IVd, $C_{13}H_{17}N_3O_2S$. The compound was obtained in a similar way to IVa in 72.8% yield by reacting hydroxypyrimidine Ia with N-methylanthranilic acid. The compound was purified by washing away impurities with boiling acetone, mp 269-269.5°C (decomp.). IR spectrum (KBr): 3398, 3200 (ν NH), 3086 (ν CH_{Ar}), 2746, 2650, 2570 (ν OH), 1659 (ν C=O), 1564, 1530 (thioamide-II), 806 (δ CH_{Ar}), 1242 cm^{-1}. UV spectrum, λ_{max} (log ε): 227 (4.44), 252 (4.39), 357 nm (3.79). PMR spectrum (DMSO-D_6): 8.31 (1H, broad d, $N_{(3)}$-H, $J_{NH,\,4e}$ = 3.0 Hz), 8.06 (1H, broad s, $N_{(1)}$-H, $J_{NH,\,6a}$ = 0 Hz), 7.62 (1H, d, 2'-H, $J_{2',\,6'}$ = 2.0 Hz), 7.22 (1H, d.d, 6'-H, $J_{5',\,6'}$ = 8.7 Hz), 6.70 (1H, d, 5'-H), 4.43 (1H, m, 4-H_e, $J_{4e,\,5a}$ = 4.5, $J_{4e,\,5e}$ = 2.9 Hz), 3.06 (1H, m, 6-H_a, $J_{5e,\,6a}$ = 4.5, $J_{5a,\,6a}$ = 9.5 Hz), 2.84 (3H, s, N-CH_3), 1.82 (1H, d.t, 5-H_e, $J_{5e,\,5a}$ = 13.3 Hz), 1.66 (1H, d.d.d, 5-H_a), 1.08 ppm (3H, d, 6-CH_3, J = 6.5 Hz).

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