Unexpected Substitution of the Acyl group in Isothiazole-ring Formation. Attempted Conversion of 1-Acyl-2,2-diaminoethylenes into 2-Acyl-3,3-diaminoacrylonitriles

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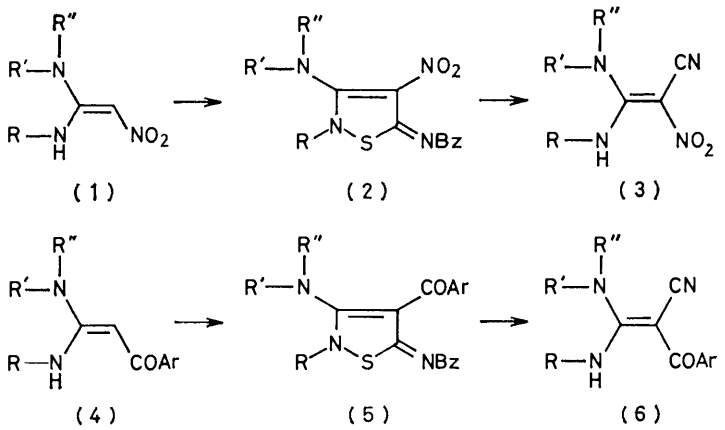
2-(Acylmethylene)hexahydropyrimidines (7) have been converted into the corresponding benzoyl isothiocyanate adducts (8), treatment of which with sulphuryl chloride gave the 3-chloroisothiazolo[2,3-*a*]pyrimidine (10) instead of the expected 3-acyl compound (9). Oxidation of the adduct (8c) by bromine gave the isothiazolo[2,3-*a*]-pyrimidine (9c) in low yield; this failed to undergo base-catalysed fragmentation to the nitrile (13c). Finally, the α-acyl-α-cyanomethylenehexahydropyrimidines (13) were prepared from the phenacyl- and 2-thenoylmethyl-cyanides (11) by condensation with 1-methyl-2-methylthio-1,4,5,6-tetrahydropyrimidine (12).

OLEFINS with two electron-donating amino-groups at one end of the double-bond and two electron-withdrawing groups at the other have attracted recent theoretical attention.[1] Earlier we reported a novel synthesis of one such system [2] in which the 1,1-diamino-2-nitroethylenes (1) were converted into 3,3-diamino-2-nitroacrylonitriles (3); this conversion involved the preparation of the isothiazoline derivative (2) from compound (1) and its



(1) (2) (3)

(4) (5) (6)

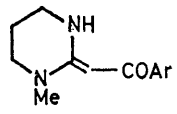
base-catalysed fragmentation into compound (3). We ascribed the ease of fragmentation of the isothiazoline (2) to the presence of the nitro-group.

We report herein work in which the nitro-group has been replaced by a carbonyl group. The projected synthesis involved the transformation of the 1-acyl-2,2-diaminoethylenes (4) into the isothiazolines (5) and the fragmentation of the latter with base to give the 2-acyl-3,3-diaminoacrylonitriles (6). While success eluded us, a more conventional route led to the required 2-acyl-3,3-diaminoacrylonitriles (6). We also report the unexpected displacement of the acyl group by chlorine during the sulphuryl chloride oxidative formation of the isothiazoline (5).

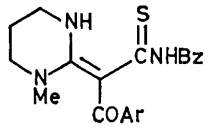
As substrates for the isothiazoline fragmentation we chose the hexahydropyrimidine derivatives (7) which were easily accessible by known routes.[3] Reaction of compounds (7) with benzoyl isothiocyanate gave compounds (8) which we planned to oxidise to the isothiazolo-[2,3-*a*]pyrimidines (9). Treatment of compound (8a) with sulphuryl chloride gave two products in poor yields; the more soluble one, isolated after chromatography and crystallization, was shown to be the required isothiazolo[2,3-*a*]pyrimidine (9a). The mass spectrum and analytical values of the insoluble product obtained from the reaction supported the assignment of structure (10) to it, in which the acyl group of (9a) is displaced by a chlorine atom. The same compound was the sole product obtained from the reaction of sulphuryl chloride with compounds (8b) and (8c); the corresponding isothiazolo[2,3-*a*]pyrimidines (9b) and (9c) were not obtained in this reaction. A possible explanation for the formation of compound (10) is shown in Scheme 1 in which the action of sulphuryl chloride on compound (8) results both in the expected *S*-chlorination and chlorination of the enanime system, to give the intermediate (A). Ring-closure then gives the pyrimidinium ion (B) which, after removal of the acyl group during the basic work-up ($NaHCO_3$), gives the 3-chloroisothiazolo[2,3-*a*]pyrimidine (10). A referee has pointed out that the two steps could also take place in a concerted manner from the intermediate (A) to give compound (10) directly.

Oxidative cyclization of compound (8c) to the isothiazolo[2,3-*a*]pyrimidine (9c) with bromine did occur, but

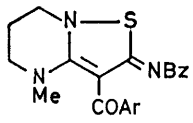
the yield was low. In spite of this, compound (9c) was chosen for an attempted fragmentation, but was recovered unchanged after being refluxed with methanolic sodium methoxide, conditions under which the nitro-compounds (2) were fragmented. This reinforced our earlier theory [2] that the contribution of amidinium-nitro-



(7)



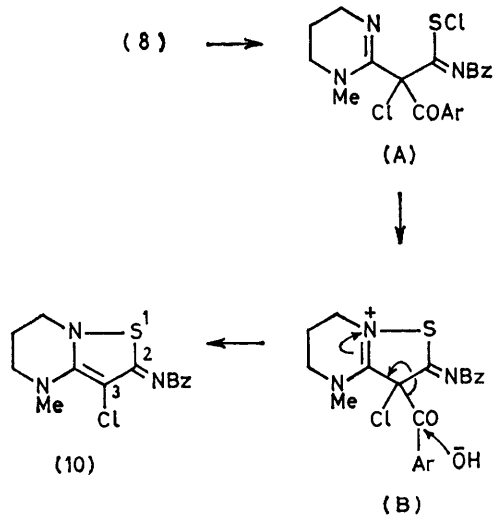
(8)



(9)

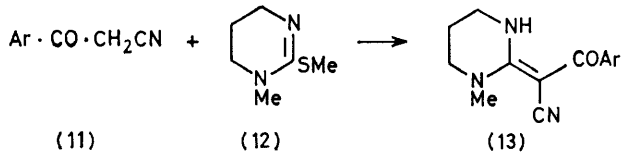
a; Ar = $C_6H_4NO_2$-*p*
b; Ar = Ph
c; Ar = C_6H_4Cl-*p*

nate structures to (2) was responsible for their ease of fragmentation. Evidently equivalent charged structures are not significant contributors to (5). Alkaline hydrogen peroxide [2] similarly failed to convert the adduct (8c) into the nitrile (13c).



SCHEME 1

Finally, we prepared the nitriles (13) by the conventional route shown in Scheme 2, which involved the condensation of the phenacyl- and thenoylmethyl-cyanides (11) with 1-methyl-2-methylthio-1,4,5,6-tetrahydropyrimidine (12). A further route has been reported for the preparation of 2-acyl-3,3-diaminoacrylonitriles.[4]



(11) (12) (13)

a; Ar = Ph
b; Ar = C_6H_4Me-*p*
c; Ar = C_6H_4Cl-*p*
d; Ar = 1-Thienyl
e; Ar = 5-Cl-1-Thienyl

SCHEME 2

EXPERIMENTAL

^{1}H n.m.r. spectra were recorded on a Varian A-60 or a Bruker WH 90 spectrometer. Chemical shifts are quoted as δ values downfield from Me_4Si. Mass spectra were determined on a Varian Mat CH-7 instrument at 70 eV utilising direct insertion.

The Benzoylaminothiocarbonyl Compounds (8).—The hexahydropyrimidines (7) [3] were treated with benzoyl isothiocyanate in acetonitrile at 30 °C and the respective products were separated off, filtered, and washed with acetonitrile to give yields of the following compounds in the range 75—85%: 2-[α-*benzoylaminothiocarbonyl*-α-(p-*nitrobenzoyl*)-*methylene*]-1-*methylhexahydropyrimidine* (8a), m.p. 166—169 °C (from chloroform–hexane) (Found: C, 59.1; H, 5.1; N, 13.5. $C_{21}H_{20}N_4O_4S$ requires C, 59.4; H, 4.75; N, 13.2%); 2-(α-*benzoyl*-α-*benzoylaminothiocarbonylmethylene*)-1-*methylhexahydropyrimidine* (8b), m.p. 169—170 °C (from chloroform–hexane) (Found: C, 66.5; H, 5.7; N, 11.2. $C_{21}H_{21}N_3O_2S$ requires C, 66.5; H, 5.6; N, 11.1%); 2-[α-*benzoylaminothiocarbonyl*-α-(p-*chlorobenzoyl*)*methylene*]-1-*methylhexahydropyrimidine* (8c), m.p. 170—171 °C (from chloroform–hexane) (Found: C, 60.3; H, 5.3; N, 10.2. $C_{21}H_{20}ClN_3O_2S$ requires C, 60.9; H, 4.9; N, 10.15%).

Oxidative Cyclization of Compounds (8).—(a) *By sulphuryl chloride*. (*i*) Oxidation of compound (8a). Compound (8a) (3.5 g) in dichloromethane (75 ml) was stirred, cooled to 5 °C, and treated with drops of sulphuryl chloride (3.5 g) for 10 min. The mixture was stirred at 30 °C for 2 h and the resultant solid was filtered off, basified with $NaHCO_3$ solution, and crystallized from acetonitrile to give 2-*benzoylimino*-3-*chloro*-4-*methyl*-4,5,6,7-*tetrahydro*-2H-*isothiazolo*-[2,3-a]*pyrimidine* (10) (0.4 g), m.p. 220—221 °C (Found: C, 54.65; H, 4.95; Cl, 12.1; N, 13.3. $C_{14}H_{14}ClN_3OS$ requires C, 54.6; H, 4.6; Cl, 11.5; N, 13.7%); *m/e* 307, 309 (M^+), 272 (M^+— Cl), 230 and 232 (M^+—Ph), and 202 and 204 (M^+— Bz); δ($CDCl_3$) 2.09 (m, CH_2), 3.26 (t, CH_2), 3.43 (s, Me), 3.71 (t, CH_2), 7.44 (m, 3 × Ar-H), and 8.3 (m, 2 × Ar-H). The dichloromethane filtrate from the above reaction was evaporated off, the residue was basified with $NaHCO_3$ solution, and then extracted with chloroform, washed (water), dried, and evaporated, to give an oil which was passed through a column of alumina in chloroform solution. Evaporation of the eluate and crystallization from ethyl acetate–hexane gave 2-*benzoylimino*-4-*methyl*-3-(p-*nitrobenzoyl*)-4,5,6,7-*tetrahydro*-2H-*isothiazolo*[2,3-a]*pyrimidine* (9a) (0.2 g) as a deep yellow solid, m.p. 265—269 °C (Found: C, 60.0; H, 4.6; N, 13.1. $C_{21}H_{18}N_4O_4S$ requires C, 59.7; H, 4.3; N, 13.3%); *m/e* 422 (M^+); δ($CDCl_3$) 2.26 (m, CH_2), 2.98 (s, Me), 3.49 (t, CH_2), 3.78 (t, CH_2), 7.2—

7.65 (5 × Ar-H), 8.09 (d, 2 × Ar-H), and 8.33 (d, 2 × Ar-H).

(*ii*) Oxidation of compound (8b). The adduct (8b) (3.8 g), on oxidation as above with sulphuryl chloride (7.1 g) in dichloromethane, gave only the chloro-compound (10) (0.25 g), m.p. and mixed m.p. 220—221 °C.

(*iii*) Oxidation of compound (8c). The adduct (8c) (1.0 g), on oxidation as above with sulphuryl chloride (0.7 g) in chloroform (30 ml), gave only the chloro-compound (10) (0.1 g), m.p. and mixed m.p. 220—221 °C.

(b) *By bromine*. Compound (8c) (4.1 g) in chloroform (50 ml) was cooled to 5 °C and a solution of bromine (1.6 g) in chloroform (15 ml) was added as drops to the stirred solution at 5—10 °C. The solvent was removed under reduced pressure and the residue was cooled, basified with 2M NaOH, and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated to give an oil which was triturated with propan-2-ol. The resultant solid was filtered off and recrystallized from ethyl acetate to give 2-*benzoylimino*-3-(p-*chlorobenzoyl*)-4-*methyl*-4,5,6,7-*tetrahydro*-2H-*isothiazolo*[2,3-a]*pyrimidine* (9c) (0.5 g), m.p. 233—236 °C (Found: C, 61.3; H, 4.8; N, 9.8. $C_{21}H_{18}ClN_3O_2S$ requires C, 61.2; H, 4.4; N, 10.2%); δ($CDCl_3$) 2.23 (m, CH_2), 2.93 (s, Me), 3.45 (t, CH_2), 3.76 (t, CH_2), and 7.26—8.0 (9 × Ar-H).

Attempted Fragmentation of the Isothiazolo[2,3-a]*pyrimidine* (9c).—(i) The isothiazolo[2,3-*a*]pyrimidine (9c) (0.4 g) was added to a solution of sodium methoxide in methanol and the mixture was refluxed for 2 h, cooled, and the solid filtered off to give unchanged (9c).

(ii) The compound (8c) (1.0 g) was dissolved in 2M NaOH (0.5 ml) and water (5 ml), stirred, and cooled to 0 °C. Aqueous hydrogen peroxide (30%; 0.5 ml) was added to the mixture which was stirred for 30 min and the solid filtered off to give unchanged (8c).

Synthesis of the Nitriles (13).—2-(α-*Benzoyl*-α-*cyanomethylene*)-1-*methylhexahydropyrimidine* (13a). A mixture of 1-methyl-2-methylthio-1,4,5,6-tetrahydropyrimidine (12) [5] (10 g) and benzoylacetonitrile (11a) [6] (10 g) in propan-2-ol (100 ml) was refluxed for 9 h, evaporated, and the residue was digested with diethyl ether. The solid was filtered off and recrystallized from propan-2-ol to give the *pyrimidine* (13a) (3 g), m.p. 142—145 °C (Found: C, 69.7; H, 6.5; N, 17.55. $C_{14}H_{15}N_3O$ requires C, 69.7; H, 6.3; N, 17.4%); δ($CDCl_3$) 1.92 (m, CH_2), 3.22 (t, 2 × CH_2), 3.27 (s, Me), 7.3—7.9 (m, 5 × Ar-H), and 11.1 (br, NH).

2-[α-*Cyano*-α-(p-*toluoyl*)*methylene*]-1-*methylhexahydropyrimidine* (13b). *p*-Toluoylacetonitrile (11b) [6] (8.0 g) and compound (12) (8.0 g), treated as above, gave the pyrimidine (13b), m.p. 189—193 °C (from propan-2-ol) (Found: C, 70.5; H, 7.0; N, 16.3. $C_{15}H_{17}N_3O$ requires C, 70.6; H, 6.7; N, 16.5%); δ($CDCl_3$) 1.95 (m, CH_2), 2.38 (s, Me), 3.25 (t, 2 × CH_2), 3.3 (s, Me), 7.2 (d, 2 × Ar-H), 7.7 (d, 2 × Ar-H), and 11.26 (br, NH).

2-[α-(*p-Chlorobenzoyl*)-α-*cyanomethylene*]-1-*methylhexahydropyrimidine* (13c). *p*-Chlorobenzoylacetonitrile (11c) [6] (2.4 g) and compound (12) (2.0 g) treated as above, gave the *pyrimidine* (13c) (0.7 g), m.p. 198—203 °C (from propan-2-ol) (Found: C, 60.8; H, 5.4; N, 15.4. $C_{14}H_{14}ClN_3O$ requires C, 61.0; H, 5.1; N, 15.2%); *m/e* 275 and 277 (M^+); δ($CDCl_3$ + CD_3SOCD_3) 2.1 (m, CH_2), 3.4 (m, 2 × CH_2), 3.39 (s, Me), 7.4 (d, 2 × Ar-H), 7.77 (d, 2 × Ar-H), and 11.12 (br, NH).

2-[α-*Cyano*-α-(2-*thenoyl*)*methylene*]-1-*methylhexahydropyrimidine* (13d). A mixture of 2-thenoylacetonitrile (11d) [7] (6.0 g) and the tetrahydropyrimidine (12) [5] (6.0 g) was refluxed in propan-2-ol (100 ml) for 9 h and the solvent was then removed under reduced pressure. The residue was passed through a column of alumina (toluene), evaporated, and crystallised, first from propan-2-ol and second from water to give the *nitrile* (13d) (1.7 g), m.p. 117—119 °C (Found: C, 58.6; H, 5.5; N, 17.3. $C_{12}H_{13}N_3OS$ requires C, 58.3; H, 5.3; N, 17.0%); δ($CDCl_3$) 2.0 (m, CH_2), 3.3 (m, 2 × CH_2), 3.33 (s, Me), 7.0—8.15 (3 × Ar-H), and 11.03 (br, NH).

2-[α-(5-*Chloro*-2-*thenoyl*)-α-*cyanomethylene*]-1-*methylhexahydropyrimidine* (13e).—5-Chloro-2-thenoylacetonitrile (11e) [7] (7.0 g) and compound (12) (6.0 g), treated as above, gave, after chromatography and recrystallization from propan-2-ol, the *pyrimidine* (13e) (2.8 g), m.p. 110—113 °C (Found: C, 50.9; H, 4.45; N, 15.3. $C_{12}H_{12}ClN_3OS$ requires C, 51.2; H, 4.3; N, 14.9%); δ($CDCl_3$) 2.05 (m, CH_2), 3.37 (m, 2 × CH_2), 3.33 (s, Me), 6.91 (d, Ar-H), 7.9 (d, Ar-H), and 10.87 (br, NH).

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