UNUSUAL REACTION OF N,N-DIMETHYLACETAMIDE DIETHYL ACETAL WITH 2-AMINOMETHYLENE-5,5-DIMETHYLCYCLOHEXANE-1,3-DIONE. SYNTHESIS OF COUMARIN AND CARBOSTYRIL DERIVATIVES

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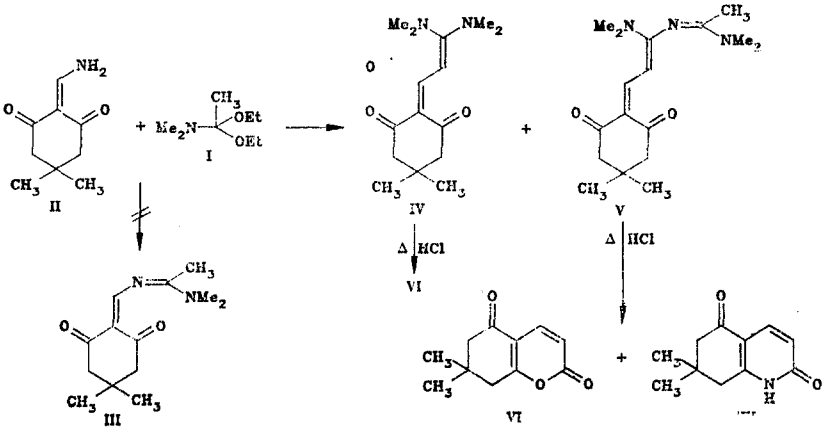
It is known that amide acetals react with primary enamines to form enamidines [1]. In contrast to this, we found that in the reaction of N,N-dimethylacetamide diethyl acetal (I) with 2-aminomethylene-5,5-dimethylcyclohexane-1,3-dione (II) [2], unexpectedly, not the enamidinodiketone II is formed, but a mixture of 1,1-bisdimethylamino-3-(2,6-dioxo-4,4-dimethyl)-cyclohexylidene-1-propene (IV) and 1-dimethylamino-1-(α-dimethylamino)ethylideneamino-3-(2,6-dioxo-4,4-dimethyl)cyclohexylidene-1-propene (V), 3:7 (PMR spectrum) is obtained in an overall yield of 90%. Compounds IV and V were separated by fractional crystallization from ethyl acetate. When the diene-diamine IV was boiled in a 10% aqueous HCl, 5-oxo-7,7-dimethyl-5,6,7,8-tetrahydrocoumarin (IV) was obtained. Under the same comditions, amidine V, or a mixture of compounds IV and V give a mixture of courmarin VI and 5-oxo-7,7-dimethyl-5,6,7,8-tetrahydrocarbostyril (VII). The following compounds were synthesized: IV {yield 38%, mp 163°C (from ethyl acetate). PMR spectrum ($CDCl_3$): 1.05 (s, 6H, 4', 4'-CH_3), 2.35 (s, 4H, 3',5'-CH_2), 3.09 (s, 12H, 1,1'-Me_2N), 6.86 (d, 1H, J = 14.7 Hz, 2CH), 7.92 ppm (d, 1H, J = 14.7 Hz, 3-CH). Mass spectrum, m/z: $M^{+\cdot}$ 264, $[M - Me_2N]^+$ 220}, V {yield 9%, mp 183°C (from ethyl acetate). PMR spectrum ($CDCl_3$): 1.03 (s, 6H, 4',4'-CH_3), 1.96 (s, 3H, α-CH_3), 2.32 (s, 4H, 3',5'-CH_2), 3.08 and 3.25 (two s, 3H, α-Me_2N in each case), 3.16 (s, 6H, 1-Me_2N), 7.46 (d, 1H, J = 14.4 Hz, 2-CH), 7.63 ppm (d, 1H, J = 14.4 Hz, 3-CH). Mass spectrum, m/z: $M^{+\cdot}$ 305, $[M - CH_3]^+$ 290; $[M - NMe_2]^+$ 261 and $[M - NMe_2 - H - CH_3]^+$ 245}, VI {yield 96; (from IV), mp 88-90°C (from heptane), according to the data in [3], mp 89-92°C}, and VII {yield 45% (from V, together with 51% of VI), mp 276°C (from ethyl acetate) according to the data in [4], mp 276°C}.



The results of the elemental analysis of compounds IV and V for C, H, and N correspond to the calculated data.

Information on the possible mechanism of this unexpected reaction and additional examples will be submitted later on.

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1-THIOCARBAMOYL-5-OXY- AND 5-THIOSEMICARBAZIDO-2-PYRAZOLINES

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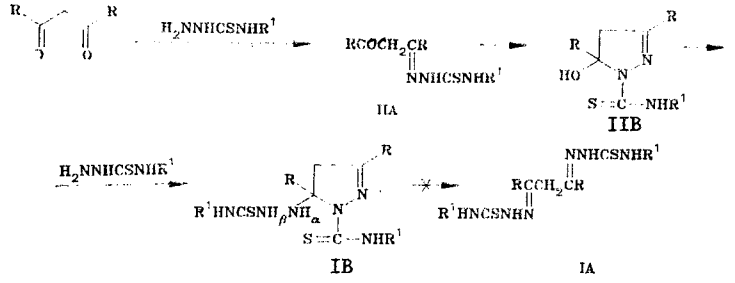
Products of the condensation of 1,3-diketones with thiosemicarbazide and its N^3-substituted homologs in a 1:2 ratio have an antitumorigenic activity. These compounds I were assumed to be bisthiosemicarbazones A [1-3], but their structure has not yet been studied.

We found that compounds I have actually a cyclic pyrazoline structure B, and not the linear structure A. We shall add that also the condensation products of these reagents in a ratio of 1:1 (II) are not monohydrazones A, as assumed in [3, 4], but the corresponding 5-hydroxypyrazolines B.



Ia-c, IIa R = CH_3, IIb R = C_6H_5; Ia, IIb R^1 = H, Ib, IIa R^1 = CH_3, Ic R^1 = C_2H_5.

Compound Ia [3]. PMR spectrum (Py-D_5): 1.58 (3H, t, J = 0.6 Hz, 3-CH_3), 1.75 (3H, s, 5-CH_3), 2.53 and 3.15 (AB system, J_{AB}^1 = 18 Hz, J^2 = 0.6 Hz, 2H, CH_2), 7.30 (1H, s, NHα), 7.96, 8.20 (2H, s, $CSNH_2$), 8.90, 9.17 (2H, s, $CSNH_2$), 9.45 ppm (1H, s, NHβ).

Derivative Ib [3]. PMR spectrum ($CDCl_3$): 1.72 (3H, s, 5-CH_3), 1.91 (3H, t, J = 0.6 Hz, 3-CH_3), 2.58 and 2.92 (AB system, J_{AB}^1 = 18 Hz, J^2 = 0.6 Hz, 2H, CH_2), 3.01 (3H, d, 5Hz, N–CH_3), 3.09 (3H, d, 5 Hz, N–CH_3), 6.65, 6.91 (2H, s, 2NH), 7.35 ppm (2H, m, 2NHCH_3).

Compound Ic [3]. PMR spectrum ($CDCl_3$): 1.15 (6H, t, J = 7 Hz, 2C_2H_5), 1.73 (3H, s, 5-CH_3), 1.93 (3H, t, J = 0.8 Hz, 3-CH_3), 2.61 and 2.91 (AB system, J_{AB}^1 = 18 Hz, J^2 = 0.8 Hz, 2H, CH_2), 3.3-3.8 (4H, m, 2C_2H_5), 6.61, 6.85 (2H, s, 2NH), 7.3 ppm (2H, m 2NHC_2H_5). ^{13}C NMR spectrum (DMSO-D_6): 14.5 and 14.6 (q, CH_3CH_2N), 15.9 (q, 3-CH_3), 23.5 (q, 5-CH_3), 37.7 (t, CH_3CH_2N), 47.1 (t, 4-C), 84.6 (s, 5-C), 154.4 (s, C=N), 174.0 and 181.8 ppm (s, 2C=S).

Derivative IIa was obtained by condensation of acetylacetone with N^3-methylthiosemicarbazide in aqueous acetic acid. Mp 95-97°C. PMR spectrum ($CDCl_3$): 1.87 (3H, s, 5-CH_3), 1.94 (3H, t, J_{H-CH} = 1 Hz, 2-CH_3), 2.79 and 3.07 (AB system, J_{AB}^1 = 18 Hz, J^2 = 1 Hz, 2H, CH_2), 3.00 (3H, d, J = 4 Hz, NCH_3), 6.30 (1H, s, OH), 7.25 (1H, m, NH). Found: C 44.7; H 7.2; N 22.3%. $C_7H_{13}N_3OS$. Calculated: C 44.9; H 7.0; N 22.4%.

Compound IIb [4]. PMR spectrum (DMSO-D_6): 4.16 and 3.84 (AB system, J = 19 Hz, 2H, CH_2), 6.80 (1H, s, OH), 7.5-8.2 (10H, m H_{arom}), 8.45, 8.65 ppm (2H, s, NH_2). ^{13}C NMR spectrum (DMSO-D_6): 51.4 (4-CH_2), 95.4 (5-C, 151.8 (C=N), 175.4 (C=S), 124.0-145.1 ppm (C_{arom}, 8 signals).

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