REACTION OF THIOGLYCOLIC ACID AMIDE WITH ACYLACETYLENES AND METHYL PROPIOLATE

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Nucleophilic addition of thiols to substituted acetylenes occurs in a trans manner with formation of cis-isomers [1-3]. In [4-7] it was established that reactions of the thiols MeSH, BuSH, and PhSH with alkyl- and arylethynylketones in protic and aprotic solvents proceed nonstereospecifically, but gave mainly cis-adducts (70-85%). Phenylacetylene reacts with thioglycolic acid at 20°C in the presence of ascaridol also nonstereospecifically with formation of a mixture of cis- and trans-isomers of styrylthioacetic acid in a ratio of 2:1. However, this reaction gives only cis-isomers in methanol in the presence of NaOH at 50°C [8, 9].

In this work reaction of terminal and substituted α-acetylenic ketones (Ia-d) and methyl propiolate (Ie) with thioglycolic acid amide (II) was studied in MeCN without catalyst or in the presence of Et_3N and in MeOH in the presence of Et_3N.

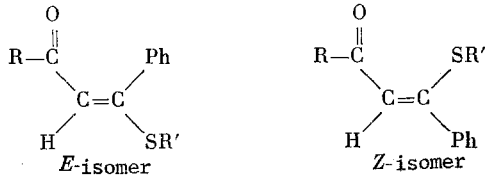
Upon reaction of benzoylacetylene (Ia) with thioglycolic acid amide (II) in equimolar ratio of the reagents in MeCN (20°C) cis-2-benzoyl-1-carbamylmethylthioethylene (IIIa) (54%) and a mixture of cis- and trans-(IIIa) were obtained in a ratio of 1:1 (20%).

$$\underset{(Ia-e)}{RCOC{\equiv}CR'} + \underset{(II)}{HSCH_2CONH_2} \rightarrow \underset{(IIIa-e)}{RCOCH{=}C(R')SCH_2CONH_2} \quad (1)$$

R = Ph, R′ = H (a); R = α-C_4H_3S, R′ = H (b); R = R′ = Ph (c); R = α-C_4H_3S, R′ = Ph (d); R = MeO, R′ = H (e).

Under the above conditions reaction of thenoylacetylene (Ib) with (II) leads to cis-1-carbamylmethylthio-2-thenoylethylene (IIIb) (26%) and a nonseparable mixture of cis- and trans- (IIIb) in a ratio of 1:1 (13%). Thus, the reaction of terminal acylacetylenes with (II) in MeCN in nonstereospecific, but selective with primary formation of cis-isomers (IIIa, b).

By reaction of (II) with 1-phenyl-2-benzoylacetylene (Ic) and 1-phenyl-2-thenoylacetylene (Id) in equimolar ratio of the reagents in MeCN, 2-benzoyl-1-carbamylmethylthio-1-phenylethylene (IIIc) and 1-carbamylmethylthio-2-thenoyl-1-phenylethylene (IIId), respectively, were obtained as a mixture of E- and Z-isomers in a 1:1 ratio.



E-isomer Z-isomer (2)

R = Ph, C_4H_3S; R′ = NH_2COCH_2.

Identification of isomers (IIIc, d) was made by comparison of chemical shifts of olefinic protons found with those calculated by [10].

Nonstereospecificity of reaction of (II) with acylacetylenes can be explained by the capacity of the C=O group to delocalize negative charge in the intermediate anion which is formed by RS-addition to the triple bond [11]. Addition of a proton to this anion is possible

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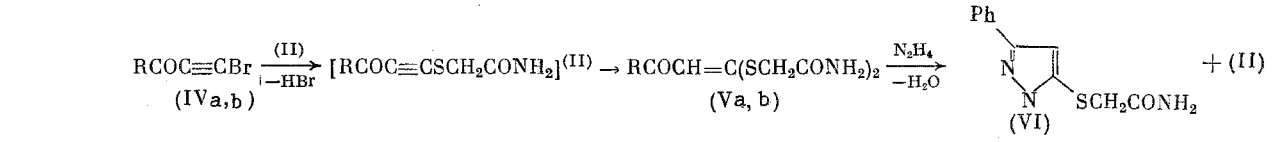
in both the cis- and trans-position. However, delocalization of negative charge in the anion is apparently not complete, in consequence of which the preference for ligand anti-substitution is maintained with primary formation of the cis-isomer [6, 7].

Reaction of (II) with methyl propiolate (Ie) in MeCN at 60°C proceeds stereospecifically with formation of trans-1-carbamyl-methylthio-2-methoxycarbonylethylene (IIIe). With addition of Et_3N and AcOH to the reaction mixture a mixture of cis- and trans-isomers was isolated in a ratio of 1:2. By reaction of 1-bromo-2-acylacetylenes (IVa, b) with (II) in MeOH in the presence of Et_3N, ketenemercaptals (Va, b) were obtained with good yield.

The mercapto group is a stronger nucleophile than the amino group [12, 13]; therefore, formation of S-mono adducts can first be expected. The reaction proceeds by direct nucleophilic Br substitution at the ethynyl C atom [14, 15] with intermediate formation of acylethynylsulfides. Nucleophilic addition of one more molecule of (II) to the latter leads to the corresponding ketenemercaptals (Va, b). Heating of ketenemercaptal (Va) with hydrazine hydrate in EtOH leads to 3-carbamylmethylthio-5-phenylpyrazole (VI)



(3)

R = Ph (a), α-C_4H_3S (b).

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument (KBr pellets) and PMR spectra on a Tesla BS-497 instrument in $CDCl_3$ relative to HMDS.

1-Benozyl-2-carbamylmethylthioethylene (IIa). To a solution of 0.65 g (5 mmoles) of (Ia) in 15 ml MeCN a solution of 0.46 g (5 mmoles) of (II) in 10 ml MeCN was added dropwise with stirring. The mixture was cooled for 3 h to 0°C. The precipitate was filtered and recrystallized from EtOH. There was obtained 0.6 g (54%) of cis-(IIIa) with m.p. of 166-168°C. Found: C 59.41; H 5.12; N 6.13; S 14.36%. $C_{11}H_{11}NO_2S$. Calculated: C 59.73; H 4.98; N 6.33; S 14.48%. IR spectrum (ν, cm^{-1}): 690 (CS), 1550 (C=C), 1640 (C=O, conj.), 1675 (C=O of amide group), 3210, 3380 (NH_2). PMR spectrum ($CDCl_3$, δ, ppm): 7.32 d (1H, COCH=, $^3J_{HH}$ = 9.7 Hz), 7.83 d (1H, SCH=), 3.50 s (2H, CH_2), 7.58-8.02 m (5H, Ph).

The solution after cis-isomer isolation was partially evaporated and cooled to 0°C. The precipitate was filtered and recrystallized from EtOH. There was obtained 0.22 g (20%) of a mixture of cis- and trans-(IIIa) (1:1) with mp 141-148°C. PMR spectrum ($CDCl_3$, δ, ppm) for trans-isomer: 7.21 d (1H, COCH=, $^3J_{HH}$ = 15 Hz), 7.85 d (1H, SCH=), 3.75 s (2H, CH_2).

1-Carbamylmethylthio-2-thenoylethylene (IIIb) was obtained analogous to (IIIa) from 0.68 g (5 mmoles) ketone (Ib) and 0.46 g (5 mmoles) amide (II). The yield of cis-isomer was 0.3 g (26%) with m.p. 200-201°C (from EtOH). Found: C 47.50; H 3.90; N 6.47; S 27.98%. $C_9H_9NO_2S_2$. Calculated: C 47.58; H 3.96; N 6.17; S 28.19%. IR spectrum (ν, cm^{-1}): 708 (CS), 1560 (C=C), 1640 (C=O, conj.), 1690 (C=O of amide group), 3200, 3390 (NH_2). PMR spectrum ($CDCl_3$, δ, ppm): 7.00 d (1H, COCH=, $^3J_{HH}$ = 10 Hz), 7.55 d (1H, SCH=), 3.50 s (2H, CH_2), 6.90-7.70 m (3H, C_4H_3S). After isolation of cis-isomer the solution was partially evaporated and cooled to 0°C. The precipitate was filtered. There was obtained 0.15 g (13%) of a mixture of cis- and trans-(IIIb) (1:1) with mp 148-156°C. PMR spectrum ($CDCl_3$, δ, ppm): for trans-isomer 7.23 d (1H, COCH=, $^3J_{HH}$ = 15 Hz), 7.61 d (1H, SCH=), 3.68 s (2H, CH_2), 6.90-7.65 m (3H, C_4H_3S).

2-Benzoyl-1-carbamylmethylthio-1-phenylethylene (IIIc) was obtained analogous to (IIIa) from 1.06 g (5 mmoles) ketone (Ic) and 0.46 g (5 mmoles) amide (II). The yield of a mixture of E- and Z-isomers (1:1) was 0.81 g (54%) with mp 144-148°C. Found: C 68.44; H 5.18; N 5.09; S 10.63%. $C_{17}H_{15}NO_2S$. Calculated: C 68.69; H 5.05; N 4.71; S 10.77%. IR spectrum (ν, cm^{-1}): 705 (CS), 1590 (C=C), 1640 (C=O, conj.), 1682 (C=O of amide group), 3200, 3380 (NH_2). PMR spectrum ($CDCl_3$, δ, ppm): 7.23 s (1H, CH=, E-isomer), 7.62 s (1H, CH=, Z-isomer), 7.52-8.10 m (10H, Ph).

1-Carbamylmethylthio-2-thenoyl-1-phenylethylene (IIId) was obtained analogous to (IIIa) from 1.06 g (5 mmoles) ketone (Id) and 0.46 g (5 mmoles) (II). The yield of E- and Z-isomer

mixture (1:1) was 0.72 g (47%) with mp 126-131°C. Found: C 59.24; H 4.13; N 4.41; S 21.40%. $C_{15}H_{13}NO_2S_2$. Calculated: C 59.41; H 4.29; N 4.62; S 21.12%. IR spectrum (ν, cm^{-1}): 700 (CS), 1590 (C=C), 1642 (C=O, conj.), 1685 (C=O of amide group), 3220, 3385 (NH_2). PMR spectrum ($CDCl_3$, δ, ppm): 7.28 s (1H, CH=, E-isomer), 7.69 s (1H, CH=, Z-isomer), 3.66 s (2H, CH_2, E-siomer), 3.55 s (2H, CH_2, Z-isomer), 7.42-8.10 (8H, Ph, C_4H_3S).

1-Carbamylmethylthio-2-methoxycarbonylethylene (IIIe). To a solution of 0.46 g (5 mmoles) of (II) in 10 ml MeCN at 60°C a solution of 0.42 g (5 mmoles) of methyl propionate (Ie) in 10 ml MeCN was slowly added and stirred for 3 h. The solvent was partially evaporated and cooled to 0°C. The precipitate was filtered and recrystallized from Me_2CO. The yield of trans-isomer with m.p. of 115-116°C was 0.75 g (85%). Found: C 41.10; H 5.32; N 8.04; S 18.54%. $C_6H_9NO_3S$. Calculated: C 41.14; H 5.14; N 8.00; S 18.29%. IR spectrum (ν, cm^{-1}): 705 (CS), 1150 (C–O), 1585 (C=C), 1650 (COOMe), 1690 (C=O of amide group), 3220, 3382 (NH_2). PMR spectrum ($CDCl_3$, δ, ppm): 5.94 d (1H, COCH=, $^3J_{HH}$ = 15.4 Hz), 7.88 d (1H, SCH=), 3.68 s (2H, CH_2), 3.82 s (3H, Me). Upon addition to 0.2 ml ET_3N and 3 ml glacial AcOH to the reaction mixture a mixture of cis- and trans-isomers (1:2) with m.p. 103-108°C (from C_6H_6) was isolated with a yield of 0.83 g (95%). PMR spectrum ($CDCl_3$, δ, ppm) for cis-isomer: 6.00 d (1H, COCH=, $^3J_{HH}$ = 9.8 Hz), 6.52 d (1H, SCH=), 3.52 s (2H, CH_2), 3.80 s (3H, Me).

1,1-Bis(carbamylmethylthio)-2-benzoylethylene (Va). To a solution of 1.04 g (5 mmoles) of 1-bromo-2-benzoylacetylene (IVa) and 0.92 g (5 mmoles) of (II) in 20 ml MeOH, 0.2 ml Et_3N was added, and the mixture was stirred for 3 h at 20°C. The solvent was partially evaporated and cooled to 0°C. The precipitate was recrystallized from Et_3N. The yield of (Va) was 0.78 g (47%), mp 184-186°C. Found: C 50.24; H 4.48; N 8.93; S 20.41%. $C_{13}H_{14}N_2O_3S_2$. Calculated: C 50.32; H 4.52; N 9.03; S 20.65%. IR spectrum (ν, cm^{-1}): 690 (CS), 1595 (C=C), 1630 (C=O, conj.), 1682 (C=O of amide group), 3210, 3380 (NH_2). PMR spectrum ($CDCl_3$, δ, ppm): 7.19 s (1H, CH=), 3.82 s, 3.91 s (4H, CH_2), 7.54 m (5H, Ph).

1,1-Bis(carbamylmethylthio)-2-thenoylethylene (Vb) was obtained analogous to (Va) from 1.07 g (5 mmoles) of 1-bromo-2-thenoylacetylene (IVb) and 0.92 g (10 mmoles) of amide (II). The yield of (Vb) was 1 g (68%), mp 202-204°C (from EtOH). Found: C 41.63; H 4.01, N 8.63; S 30.46%. $C_{11}H_{12}N_2O_3S_3$. Calculated: C 41.77; H 3.80; N 8.86; S 30.38%. IR spectrum (ν, cm^{-1}): 695 (CS), 1592 (C=C), 1630 (C=O, conj.), 1685 (C=O of amide group), 3210, 3385 (NH_2). PMR spectrum ($CDCl_3$, δ, ppm): 7.07 s (1H, CH=), 3.81 s, 3.89 s (4H, CH_2), 7.18-7.86 m (3H, C_4H_3S).

Reaction of (Va) with Hydrazine Hydrate. A mixture of 0.62 g (2 mmoles) of ketenemercaptal (Va), 6 ml of hydrazine hydrate, and 60 ml EtOH was heated until boiling and stirred for 3 h. The solvent was partially evaporated and the residue cooled to 20°C and poured into water. The precipitate was filtered and dried. There was obtained 0.26 g (55%) of 3-carbamylmethylthio-5-phenyl-pyrazole (VI) with m.p. 202-204°C (from MeCN). Found: C 56.72; H 4.81; N 18.02; S 13.69%. $C_{11}H_{11}N_3OS$. Calculated: C 56.56; H 4.72; N 18.03; S 13.73%. IR spectrum (ν, cm^{-1}): 705 (CS), 1465-1570 (C=N and C=C of pyrazole ring), 1720 (C=O), 3380, 3480 (NH_2).

CONCLUSIONS

1. Reaction of the amide of thioglycolic acid with α-acetylenic ketones and methyl propiolate gives mixtures of E- and Z-isomers of 2-acyl-1-carbamylmethylthioethylenes.

2. By the action of thioglycolic acid amide on 1-bromo-2-acylacetylenes under mild conditions the corresponding ketenemercaptals were obtained.

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OXIDATION OF 2,6-DISUBSTITUTED PHENOLS AS A ROUTE TO 3,5,3',5'-TETRASUBSTITUTED DIPHENOQUINONES AND 4,4'-DIHYDROXYDIPHENYLS

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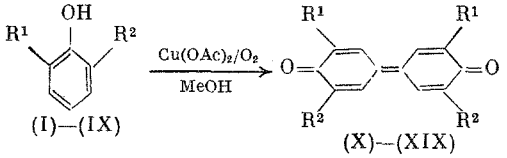
It is known [1, 2] that oxidation of 2,6-dialkylphenols (DAP) occurs smoothly forming 2,6,2',6'-tetraalkyldiphenoquinones. Nonetheless, this reaction has been used for only a limited number of materials. It was therefore of interest to broaden the scope of using oxidative dimerization for preparing diphenoquinones (DPQ) and their derivatives 4,4'-dihydroxydiphenyls which are potential antioxidants [3].

We have previously studied the oxidation of 2,6-di-tertbutylphenol (2,6-DTBP) by atmospheric oxygen [4]. In this work we have investigated 2,6-disubstituted phenols (I-IX) as substrates with catalysis by the copper acetate ammonium complex.

It should be noted that polyphenyleneoxide polymers were formed upon oxidation of 2,6-dimethyl-, 2,6-diphenyl-, and 2,6-dicyclohexylphenols. This was particularly rapid for the oxidative polycondensation of 2,6-diphenylphenol, 80% of which was converted to polymer.

As seen in Table 1, the diphenoquinone:polymer ratio resulting from phenol oxidation depended upon the degree of shielding of the hydroxyl group. The highest selectivity for the diphenoquinone was found for 2,6-DTBP, 2-tertbutyl-6-α-methylbenzyl, and 2,6-di-α-methylbenzylphenols with oxidation of 2,6-dinorbornylphenol (IX) being a little less.

The corresponding diphenoquinones X-XVIII were separated and characterized:



(I)—(IX) (X)—(XIX)

$R^1 = R^2 = Me$ (I), (X); $R^1 = Me$, $R^2 = t$-Bu (II), (XI); $R^1 = R^2 = t$-Bu (III), (XII); $R^1 = Me$, $R^2 = Ph(Me)CH$ (IV), (XIII); $R^1 = t$-Bu, $R^2 = Ph(Me)CH$ (V), (XIV); $R^1 = R^2 = Ph(Me)CH$ (VI), (XV); $R^1 = R^2 = Ph$ (VII), (XVI); $R^1 = R^2 = C_6H_{11}$ (VIII), (XVII); $R^1 = R^2 =$  (IX), (XVIII).

Conversion of the diphenoquinones to the 4,4'-dihydroxydiphenyls was carried out in conjugative reaction of the quinone with 2,6-dialkylphenol in 82-98% yield. The compounds were characterized by their IR and PMR spectra which showed characteristic differences for the quinone and phenol structures.

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