SYNTHESIS OF FUNCTIONAL MALONDIALDEHYDE DERIVATIVES FROM PROPARGYL ALDEHYDE

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The chemistry of synthetic medicinal media is the broadest and most resourceful field of fine organic synthesis, in which virtually all known classes of organic compounds and types of organic reactions are used to some degree. However, with all the diversity of the used routes, several of the most important of them can be separated, based on the use of certain types of compounds having high and diverse reactivity, permitting their use as universal fragments for the construction of more complex systems. First of all, to such types can be assigned β-dicarbonyl compounds (β-ketoaldehydes, β-ketoesters, β-diketones, malonic ester derivatives, etc.), used widely for obtaining aliphatic, alicyclic, and heterocyclic structures in the chemistry of medicinal materials and in the pharmaceutical chemistry industry (for example, in the manufacture of dimecarbine, pyrazolone analgesics, aminoachrichin, sulfadimesine, tetridine, etc.). The chemistry of β-dicarbonyl compounds has been developed very well, which cannot be said about the first and simplest representative of this class of compounds, malondialdehyde $O=CHCH_2CH=O \rightleftarrows HOCH=CHCH=O$ (I), differing significantly from the other members of the series in manner of preparation, properties, and reactivity. As a result of the high activity of both aldehyde groups and the methylene chain, (I) autocondenses very easily and cannot be isolated in individual form, which greatly hinders its use as a reagent, permitting the introduction of a trimethine fragment $-CH=CH-CH=$ [or $-CH=CR-CH=$ in the case of homologs of (I)] into complex molecules. Therefore, at present to solve this frequently occurring problem the relatively difficulty accessible functional derivatives of its enolic or dialdehyde forms, such as acetals of β-ethoxyacrolein $C_2H_5OCH=CHCH(OC_2H_5)_2$ (obtained from acrolein by a series of steps [1, 2, 3]) β-alkoxyacroleins $ROCH=CHCH=O$ (formed by decomposition of β-carbalkoxyacroleins in the presence of acidic catalysts [4]), or full acetals $(RO)_2CHCH(OR)_2$ (synthesized by condensation of orthoformic ester with vinyl esters [5, 6, 7]), are used instead of (I).

We investigated certain reactions of propargyl aldehyde (II),* which could be reduced to various types of functional derivatives of (I). In contrast to the well-studied reactions of acetylene ketones with alcohols and amines [10], the behavior of propargyl aldehyde in this relation was studied little [12] before our research [11]. Both with alcohols and with amines (II) reacts more complexly than do acetylene ketones, while the complications are associated with increased reactivity of the aldehyde groups. Reaction of (II) with alcohols proceeds only in the presence of basic catalysts (preferably tertiary amines) and can lead to various types of functional derivatives of (I) (Scheme 1) as a function of conditions. (See Scheme 1 on following page.) Upon carrying out reactions in benzene under conditions of insufficient alcohol, compounds (III), from elemental analysis and molecular weight corresponding to the addition product of an alcohol molecule and two molecules of (II), are obtained as the main product. The PMR spectra of compounds (III) indicate that they have the structure of 1-alkoxy-1-(β-formylvinyloxy)-2-propyne ["adduct" (III)] [11]; its preparation can be explained by considering the ease of formation from (II) of polyacetals (IV), detected by PMR spectral data [13], which can, as do other hydroxy compounds, add to (II) at the triple bond.

* Propargyl aldehyde can be obtained by oxidation of propargyl alcohol [8], a waste product in the manufacture of polyvinylpyrrolidone [9].

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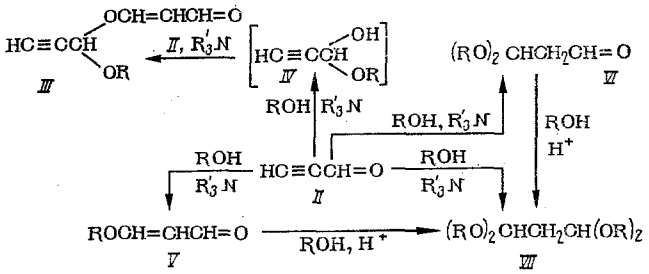
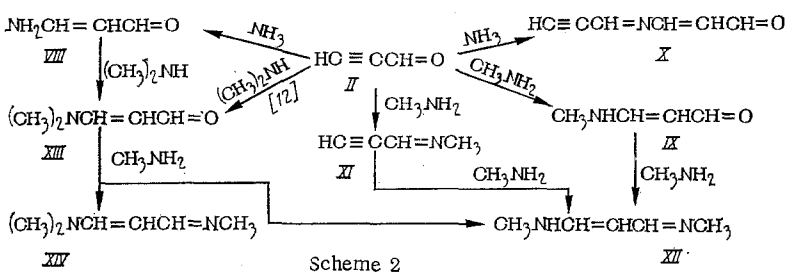


Scheme 1

Upon changing the order of component mixing and increasing their ratio to 6 : 1, the main reaction product becomes the corresponding β-alkoxyacrolein (V), which can be isolated by fractional distillation of the reaction mixture and subsequent crystallization at low temperature. A further increase in relative amount of alcohol to 50 moles per 1 mole of (II) leads to the predominate formation of β,β-dialkoxypropionic aldehydes (VI). Addition of the isolated alcohol to (II) occurs with significantly more difficulty than what is noted for primary alcohols, while tertiary butanol, in general, does not add.

In the presence of excess alcohol and traces of acid compounds (V) and (VI) are easily transformed into full acetals of malondialdehyde (VII), which can be obtained even more simply directly from (II), avoiding isolation of the intermediate compounds (V) or (VI).

Treatment of (V) with amines under mild conditions leads to formation of β-aminoacroleins [14]; unsubstituted β-aminoacrolein (VIII) and β-(methylamine)acrolein (IX) [15] were obtained for the first time in this way. Reaction between (II) and ammonia (Scheme 2) in aqueous medium leads to the formation of an unstable compound, from analytical and spectral data having the structure of β-N-(propargylidene)amino acrolein (X) [i.e., the aldehyde group of (II) participates in the reaction].



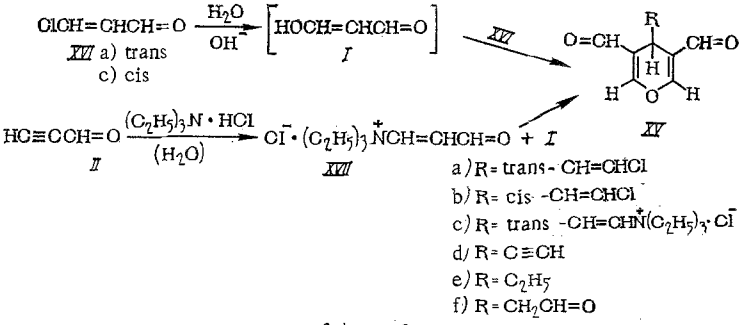
Scheme 2

Upon carrying out the process in alcoholic medium, (VIII) was obtained in high yield, probably through a stage of intermediate formation of (V). The analogous effect of methylamine on (II) in alcohol leads to formation of (IX), while in aqueous medium the azomethine derivative of propargyl aldehyde (XI) is mainly obtained, transformed upon further reaction with methylamine into the azomethine derivative of β-(methylamino)acrolein (XII). The latter was also obtained by reaction of (IX) with methylamine.

In these reactions attention is drawn by the ease of addition of amines to the carbonyl group of β-aminoacroleins. The possibility of exchange of amine residues in these compounds should also be noted. Thus, upon heating (VIII) with dimethylamine in alcohol solution β-(dimethylamino)acrolein (XIII) was obtained; upon reaction of the latter with methylamine a mixture of azomethine derivatives of β-(dimethylamino)- and β-(methylamino)acroleins (XIV and XII) [16] was obtained.

Compounds (V), (VI), and (VIII), obtained simply and in high yields by the methods presented above, are stable forms of malondialdehyde. They can successfully replace the latter in a series of reactions [17-19] and broaden significantly the possibilities of synthesis.

Certain data were also obtained during these investigations, which make it possible to hypothesize about the directions of autocondensation of malondialdehyde. It is known that free β-ketoaldehydes are trimerized rapidly into the corresponding 1,2,5-triacylbenzenes. However, autocondensation of the first representative of this homologous series, malondialdehyde, which is very rapidly transformed into a brown tar, evidently also proceeds in other directions, since 1,3,5-triformylbenzene could not be isolated from the tar. Upon studying a series of transformations (scheme 3), in which malondialdehyde is formed, we isolated stable crystalline compounds, having the structure of substituted pyrans (XV).



Scheme 3

Compounds of this type (XVa,b) are formed, for example, during hydrolysis of stereoisomeric β-chloroacroleins (XVIa,b) [20] with soda solution. We also isolated a compound having an analogous structure (XVc) during the preparation of triethyl(β-formylvinyl)ammonium chloride (XVII) by addition of triethylamine hydrochloride to (II) [in this case (I) is also partially formed]. It can be proposed that compound (XV) is obtained by crotonic condensation of (I) and the other aldehyde RCHO[(XVI) or (XVII)] present in the reaction mixture, with subsequent Michael addition of an additional molecule of (I). The preparation of (XId,e) [21] under the analogous conditions is also described in the literature. It can be proposed that the presence in the mixture of another aldehyde partially stops the process at the stage of formation of compounds (XVa-e), which do not enter into further transformations, while during autocondensation, reactive compound (XVf) is obtained, which does not interrupt the autocondensation process of (I).

EXPERIMENTAL

1-Ethoxy-1-(β-formylvinyloxy)-2-propyne ["adduct" (III), R = C_2H_5]. To a solution of 10.8 g of (II) in 120 ml of benzene was added, with stirring over 30 min and maintaining the temperature of the mixture at 25-30°, a mixture of 0.6 g of N-methylpiperidine and 28 g of absolute ethanol in 60 ml of benzene. The reaction mixture was stirred for an additional 30 min, the solvent was distilled, the residue was dissolved in 125 ml of ether and treated with carbon, the filtrate was evaporated, and the residue was distilled. We obtained 7 g (35.5%) of β-ethoxyacrolein (V, R = C_2H_5), bp 51-52.5° (5 mm), n_D^{25} 1.4710, and 8 g (51.3%) of the "adduct" (III, R = C_2H_5), bp 85-90° (2 mm), mp 55-57° (from ether). Found, %: C 62.44, 62.66; H 6.52, 6.58; mol. wt. 146.2 (cryoscopy in benzene). $C_8H_{10}O_3$. Calculated, %: C 62.32; H 6.54; mol. wt. 154.16.

β-Ethoxyacrolein (V, R = C_2H_5). To a solution of 0.3 g of N-methylpiperidine and 28 g of absolute ethanol in 30 ml of benzene was added with stirring over 1.5 h a solution of 5.4 g of (II) in 60 ml of benzene, maintaining the temperature at 25-30°. Further treatment was as in the preceding experiment. Distillation yielded a fraction boiling at 44-44.5° (2 mm). For purification it was dissolved in 5 ml of absolute ether, the mixture was frozen at −50°, and the residue was filtered and distilled after melting. We obtained 7 g (70%) of (V) (R = C_2H_5), bp 51-52° (5 mm), mp 0-2°, n_D^{20} 1.4730 [literature data [4]; bp 48-49° (2.5 mm), n_D^{20} 1.4740] and 2 g of a fraction with bp 85-90° (2 mm), mp 56-58° (from ether), which was the "adduct" (III) already described above (R = C_2H_5).

β,β-Dimethoxypropionic Aldehyde (IV, R = CH_3). To a solution of 1.2 g of N-methylpiperidine in 400 ml of methanol was added in 15 min, with good stirring and maintaining the temperature at 60°, a solution of 21.6 g of (II) in 400 ml of methanol; the mixture was stirred an additional 45 min, the methanol was distilled, the residue was dissolved in ether and treated with carbon, the ether was distilled, and the residue was distilled. We obtained 38.4 g (81%) of a fraction with bp 40-41° (7 mm), n_D^{20} 1.4098. Literature data [22]; bp 69-70° (37 mm). From PMR spectral data the material contains about 3% impurity of β-methoxyacrolein (V, R = CH_3).

1,1,3,3-Tetramethoxypropane (VII, R = CH_3). The reaction was carried out as in the preceding example; at its end the mixture was cooled, and a solution of hydrogen chloride in methanol was added to pH 4.0. The next day the mixture was neutralized by addition of sodium methoxide, the methanol was distilled, and the residue was distilled. Yield of fraction with bp 49-50.5° (5 mm) was 46.8 g (71.3%), literature data [7]: bp 66° (12 mm).

1,1,3,3-Tetraethoxypropane (VII, R = C_2H_5) was obtained analogously; treatment of compounds (V) and (VI) with alcohol in the presence of acid also leads to the formation of the corresponding tetraalkoxypropanes.

β-Aminoacrolein (VIII). 1. To a solution of 0.6 g of N-methylpiperidine in a mixture of 35 ml of absolute ethanol and 60 ml of benzene, maintaining the temperature at 25-30°, was added over an hour with stirring a solution of 10.8 g of (II) in 120 ml of benzene. The mixture was stirred an additional hour, after which excess ammonia was passed through it over 30 min; the solution was treated with carbon, and the solvent was distilled. We obtained 11.9 g (83%) of crystals, mp 99-102°, after recrystallization from a small volume of methanol mp 104-105°. Literature data [23]: mp 103-105°.

2. To a solution of 5 g of (V) (R = CH_3) in 20 ml of alcohol was gradually added 5.5 ml of concentrated aqueous ammonia solution, during which strong heat evolution of the mixture was observed. After an hour the solution was treated with carbon and evaporated in vacuum, and the residue was treated as described above. Yield 3.4 g (79%), mp 103-104°.

Azomethine Derivative (XI). To 30 ml of an aqueous solution, containing 0.1 mole of methylamine, was added, with stirring over 20 min and maintaining the temperature at 0-8°, a solution of 5.4 g of (II) in 15 ml of water. After 30 min the solution was extracted with ether (3 × 40 ml), the extract was dried with magnesium sulfate and then evaporated in vacuum, and the residue was distilled, cooling it to −5° and gradually increasing the discharging. In a receiver cooled to −60° was collected the fraction with bp 14-15° (5 mm). Yield 1.8 g (26.8%), colorless liquid, n_D^{24} 1.4640, crystallizes at −50° and polymerizes upon standing. The material is soluble in water, alcohol, ether, benzene, chloroform, and has low solubility in hexane and cyclohexane. Found, %: C 71.47, 72.09; H 7.74, 7.86; N 20.01, 20.40. C_4H_5N. Calculated, %: C 71.67; H 7.50; N 20.88.

β-N-(Propargyliden)aminoacrolein (X). The compound was obtained analogously from 134 ml of an aqueous solution containing 0.2 mole of ammonia and 10.8 g of (II). After distillation in a receiver cooled to −60° was collected 4.4 g (41%) of a colorless liquid, bp 26-28° (3 mm), mp 20-22°, n_D^{25} 1.5030. Found, %: C 67.45, 67.58; H 4.79, 4.74; N 13.75, 13.42. C_6H_5NO. Calculated, %: C 67.58; H 4.70; N 13.78. The compound is highly soluble in alcohol, ether, acetone, and benzene, and of low solubility in water and hexane; upon storing it rapidly darkens and tars.

β-(Methylamino)acrolein (IX). To a mixture of 62 ml of a 10% alcohol solution of methylamine and 65 ml of absolute alcohol was added, over 15 min at 8-10° and with strong mixing, a solution of 10.8 g of (II) in 40 ml of alcohol. After 30 min the alcohol was distilled in vacuum and the residue was distilled. We obtained 6.8 g (40%) of (IX), bp 94° (2 mm), n_D^{24} 1.5920. Literature data [23]: bp 85-87° (1.5 mm).

Azomethine Derivative of β-(Methylamino)acrolein (XII). To a solution of 0.9 g of (XI) in 7 ml of absolute alcohol was added 10 ml of an alcohol solution containing 0.013 mole of methylamine; the mixture was maintained for 1 h at 35°. The next day the solvent was distilled, and the residue was distilled in vacuum. We obtained 0.53 g (40%) of (XII), bp 43-44° (8 mm), mp 32-33°. Literature data [24]: bp 67° (13 mm).

Compound (XII) is formed in 42% yield upon reaction of (IX) with methylamine or in 56% yield upon reaction of (II) in alcohol with 2 moles of dimethylamine [in the last case 11% (IX) was isolated in addition].

Reaction of β-(Dimethylamino)acrolein (XIII) with Methylamine. To a solution of 4 g of (XIII) in 30 ml of absolute alcohol was added 25 ml of an alcohol solution containing 0.14 mole of methylamine. The next day the solvent was distilled, and the residue was distilled. We obtained 1.6 g (42%) of (XII), bp 43-44° (8 mm), mp 32-33°, and 0.6 g (13.6%) of the azomethine derivative of β-(dimethylamino)acrolein (XIV), bp 66-68° (5 mm), n_D^{25} 1.5638. Found, %: C 60.85, 60.95; H 10.32, 10.18; N 28.27, 28.37. $C_5H_{10}N_2$. Calculated, %: C 61.18; H 10.27; N 28.54.

4-(trans-β-Chlorovinyl)-3,5-diformyl-4H-pyran (XVa). To an emulsion of 0.7 g of (XVIa) [20] in 5 ml of water was gradually added an aqueous solution of 0.8 g of sodium carbonate. After stirring for 30 min the precipitated crystals were filtered, washed with water, and dried over phosphorus pentoxide. Yield 0.05 g, mp 85-86° (from dichloroethane). Found, %: C 54.44, 54.50; H 3.55, 3.65; Cl 17.83, 17.85. $C_9H_7ClO_3$, Calculated, %: C 54.42; H 3.52; Cl 17.83.

The cis isomer (XVb) was obtained analogously, mp 128.5-129.5°. Found, %: C 54.46, 54.39; H 3.56, 3.63; Cl 17.88, 18.00. $C_9H_7ClO_3$. Calculated, %: C 54.42; H 3.52; Cl 17.83.

The structure of (XVa,b) was confirmed by IR and PMR spectral data.

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