STRUCTURES OF THE PRODUCTS OF THE REACTION OF β-AMINOVINYLCARBONYL COMPOUNDS, A β-DIKETONE, AND AN ALDEHYDE

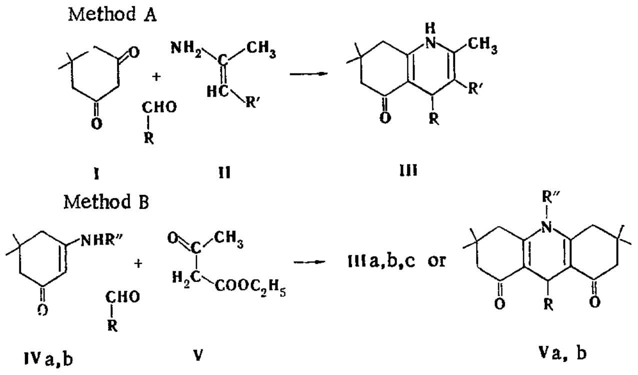
É. I. Stankevich, É. É. Grinshtein,
and G. Ya. Dubur

UDC 547.831.3'835:542.953

1,4,5,6,7,8-Hexahydroquinoline derivatives are formed in the unsymmetrical three-carbon condensation of a β-aminovinylcarbonyl compound, dimedone, and an aldehyde, regardless of the medium. Hexahydroquinolines were isolated in neutral and basic media, in the condensation of a β-aminovinylcarbonyl compound with acetoacetic ester and an aldehyde. 1,2,3,4,5,6,-7,8,9,10-Decahydroacridine-1,8-dione derivatives are formed in acidic media.

We have previously shown [1, 2] that two-ring and three-ring systems containing a 1, 4-dihydropyridine ring are readily formed in the condensation of an aldehyde, a β-dicarbonyl compound, and a β-aminovinylcarbonyl compound or bisacetonitrile. In this case, we always used cyclic derivatives as one of the last two components. Inasmuch as three different compounds enter into this reaction, this method is a variety of unsymmetrical three-carbon condensation (for example, see [3]). Only a few communications [4, 6] regarding the application of this reaction for the preparation of 3,5-unsymmetrically substituted mononuclear 1,4-dihydropyridine derivative are known. Mononuclear 1,4-dihydropyridine systems were first obtained by one of us in [7] by unsymmetrical three-carbon condensation.

In the present research we strove to ascertain some factors that promote the formation of primarily symmetrical or unsymmetrical condensation products. With this end in mind, we first varied the reaction media and then varied the combination of β-aminovinylcarbonyl and β-dicarbonyl compounds. Up until now, dimedone (I) has been used as the β-decarbonyl compound, whereas ethyl β-aminocrotonate (IIa, R' = $COOC_2H_5$), acetylacetone imine (IIb, R' = $COCH_3$), benzoylacetone imine (IIc, R' = COC_6H_5), bisacetonitrile (IId, R' = CN), and 4-aminouracil [2] (method A) have been used as the β-aminovinylcarbonyl component. In the present research we have expanded the range of application of the method by using dimedone imine (IV) and acetoacetic ester (V) (method B) as the starting reagents.



IIIa R=H, R′=$COOC_2H_5$; b R=CH_3, R′=$COOC_2H_5$; c R=C_6H_5, R′=$COOC_2H_5$;
IVa R″=H; b R″=CH_3; VIa R=C_6H_5, R″=H; b R=R″=CH_3

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 228-230, February, 1975. Original article submitted July 7, 1974.

Synthesis via methods A and B were carried out in alkaline (ethanol plus triethylamine), neutral (ethanol), and acidic (acetic acid) media, as well as in dimethyl sulfoxide (DMSO) in a few cases. In alkaline media (and probably in neutral media) the anion of the β-dicarbonyl compound, which attacks the aldehyde nucleophilically, is formed initially, according to the data in [8], this is the rate-determining step. The product of condensation of the aldehyde and the β-diketone subsequently reacts with the β-aminovinylcarbonyl compound with subsequent splitting out of water and cyclization to the hexahydroquinoline derivative. An attempt to realize unsymmetrical three-carbon condensation with acetoacetic ester in acidic media was unsuccessful. Instead of the expected hexahydroquinoline III, symmetrical reaction products – decahydroacridinediones (VI) [9] – were isolated; this is explained by the inability of acetoacetic ester under these conditions to form a reactive anion. A different reaction occurs primarily in acidic media: the β-aminovinylcarbonyl compound (IV) nucleophilically attacks the carbonyl group of the aldehyde to give a carbonium ion, which reacts with another molecule of reagent IV. The last step in the reaction is cyclization with the liberation of a molecule of ammonia.

In the condensation of dimedone with a β-aminovinylcarbonyl compound (or bisacetonitrile) and aldehydes the decisive factor is probably the high acidity of dimedone (pK_a 5.2) as compared with acetoacetic ester (pK_a 9.0), which promotes the formation of its anion even in acetic acid. In the first step in ethanol, alkaline ethanol, and acetic acid media the dimedone anion therefore nucleophilically attacks the aldehyde, after which the reaction proceeds with the formation of hexahydroquinoline III. Consequently, regardless of the medium, the combination of dimedone, a β-aminovinylcarbonyl compound, and an aldehyde makes it possible to obtain unsymmetrical condensation products. The condensation proceeds in alkaline media to give high yields of products even at room temperature. When the reaction was carried out under conditions that suppress the dissociation of dimedone (glacial acetic acid plus concentrated HCl), the hexahydroquinoline was not detected.

It follows from the experimental data that the presence of a basic agent that facilitates the formation of anion of the β-diketone promotes the formation of products of unsymmetrical three-carbon condensation fo a β-dicarbonyl compound, a β-aminovinylcarbonyl compound, and an aldehyde. The unsymmetrical three-carbon condensation proceeds in acidic media only with β-dicarbonyl compounds that are capable of dissociation to a sufficient degree under the given conditions.

EXPERIMENTAL

The electronic spectra of ethanol solutions of the compounds were recorded with a Specord UV-vis spectrophotometer. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The molecular weights were measured with an MKh-1303 mass spectrometer. The purity of the synthesized compounds was investigated by means of ascending chromatography on Filtrak FN-1 paper in 4% sodium citrate solution.

5-Oxo-2,7,7-trimethyl-4-phenyl-3-ethoxycarbonyl-1,4,5,6,7,8-hexahydroquinoline (IIIc). A mixture of 1 g (7.2 mmole) of dimedone imine (IVa), 0.94 g (7.2 mmole) of acetoacetic ester (V), and 0.76 g (7.2 mmole) of benzaldehyde was refluxed in 20 ml of ethanol for 20 h. The solvent was partially removed by distillation, several drops of water were added, and a light-yellow crystalline substance precipitated. The product was soluble in alcohol and benzene and gave a dark-yellow coloration in alcoholic alkali. The yield of product with mp 216-217° (from aqueous alcohol) and R_f 0.63 was 0.98 g (21%). No melting-point depression was observed for a mixture of this product with the substance previously synthesized in [1]. IR spectrum: 1608, 1645, 1697, 3190, and 3265 cm^{-1}. UV spectrum (in ethanol), λ_{max}, nm (ε): 241 (33,000), 275 (shoulder), and 365 (15,500).

Hexahydroquinoline IIIc was obtained in 35% yield by heating the product in the presence of triethylamine for 11 h. The yield was 62% when it was prepared at room temperature via method A (for 7 days); when it was prepared by method A by heating the reaction mixture in acetic acid for 1 h the yield was 45%, as compared with 82% in the case of heating for 8 h in DMSO containing 0.1 ml of triethylamine. A mixture of hexahydroquinoline IIIc and 2,6-dimethyl-4-phenyl-3,5-diethoxycarbonyl-1,4-dihydropyridine was obtained in the absence of triethylamine in DMSO.

5-Oxo-2,7,7-trimethyl-3-ethoxycarbonyl-1,4-5,6,7,8-hexahydroquinoline (IIIa). This compound, with mp 173-174° (from dioxane), was obtained as a light-yellow crystalline substance in 13% yield via method B. In alcoholic alkali solution it gave a dark-yellow coloration. UV spectrum (in ethanol), λ_{max} nm (ε): 240 (18,800), 260 (shoulder), and 382 (7150). Found: C 69.1; H 7.9; N 5.2%. $C_{15}H_{21}NO_3$. Calculated: C 68.4; H 8.0; N 5.3%.

5-Oxo-2,4,7,7-tetramethyl-3-ethoxycarbonyl-1,4,5,6,7,8-hexahydroquinoline (IIIb). This compound, with mp 202-204° (from aqueous ethanol), was obtained in 40% yield as a light-yellow crystalline substance by method B. It dissolved in alcoholic alkali to give a yellow solution. UV spectrum (in ethanol), λ_{max}, nm (ε): 240 (43,000), 258 (shoulder), and 363 (18,000). Found: C 69.2; H 8.6; N 5.5%. $C_{16}H_{23}NO_3$. Calculated: C 69.3; H 8.4; N 5.1%.

3,3,6,6-Tetramethyl-9-phenyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione (VIa). A mixture of 1 g (7.2 mmole) of imine IVa, 0.94 g (7.2 mmole) of ester V, and 0.76 g (7.2 mmole) of benzaldehyde was refluxed in 40 ml of acetic acid for 1 h. Two thirds of the solvent was removed by distillation, and a few drops of water were added to the residue to give a yellow crystalline substance that gave a yellow coloration with green fluorescence in sodium methoxide. The product had mp 292°. UV spectrum (in ethanol), λ_{max}, nm (ε): 250 (14,500), 375 (7350). The product had R_f 0.61 [9]. Found: C 78.8; H 7.7; N 4.0%. $C_{23}H_{27}NO_2$. Calculated: 79.1; H 7.7; N 4.0%.

3,3,6,6,9,10-Hexamethyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione (VIb). This compound was obtained by refluxing 1 g (6.5 mmole) of imine IVb, 0.85 g (6.5 mmole) of ester V, and 0.29 g (6.5 mmole) of acetaldehyde in 30 ml of acetic acid for 1 h. A crystalline yellow substance with mp 216-217° (from aqueous ethanol) precipitated after partial removal of the solvent by distillation from the yellow reaction mixture and the addition of water. The yield was 0.5 g (26%). UV spectrum (in ethanol and ethanol containing alkali), λ_{max}, nm (ε): 255 (37,000), 275 (22,000), and 375 (12,500). IR spectrum: 1545, 1620, and 1645 cm^{-1}. Found: C 75.8; H 9.0; N 4.6%. M 301 (from mass spectrum). $C_{19}H_{27}NO_2$. Calculated: C 75.7: lated: C 75.7; H 9.0; N 4.6%.

LITERATURE CITED

1. É. É. Grinshtein, É. I. Stankevich, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., 1118 (1967).
2. É. É. Grinshtein, É. I. Stankevich, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 1, 395 (1967).
3. H. Hellman and D. Dieterich, Ann., 656, 53 (1962).
4. V. Petrow, J. Chem. Soc., 884 (1946).
5. J. A. Berson and E. Brown, J. Amer. Chem. Soc., 77, 444 (1955).
6. T. Kametani, K. Ogasawara, and A. Kozuka, Yakugaku Zasshi, 86, 815 (1966); Chem. Abstr., 65, 20,092 (1966).
7. É. I. Stankevich and G. Ya. Vanag, Izv. Akad. Nauk Latv. SSR, Ser. Khim., 311 (1962).
8. M. Laloi-Diard and M. Rubinstein, Bull. Soc. Chim. France, 748 (1968).
9. É. I. Stankevich, Dissertation, Riga (1962), p. 50.