COMPETITIVE REACTIONS OF β-DICARBONYL AND β-AMINO-VINYLCARBONYL COMPOUNDS WITH ALDEHYDES IN THE SYNTHESIS OF HEXAHYDROQUINOLINES

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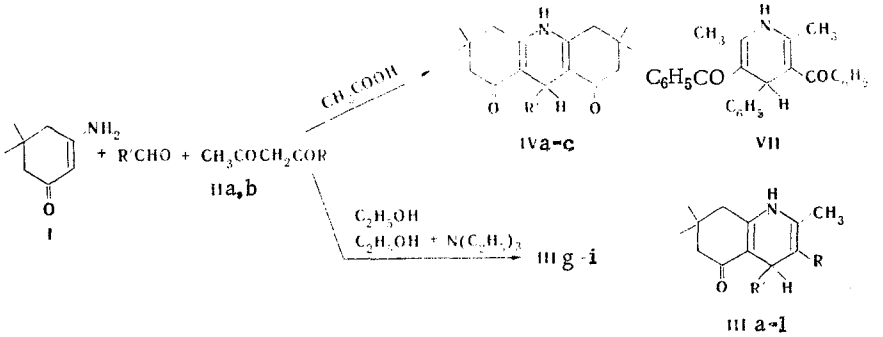
It was established that the previously found regularity in the formation of unsymmetrical 5-oxo-2,7,7-trimethyl-4-R'-3-R-1,4,5,6,7,8-hexahydroquinolines or symmetrical 3,3,6,6-tetramethyl-9-R'-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-diones from β-dicarbonyl and β-aminovinylcarbonyl compounds and an aldehyde, depending on the conditions, is also valid for acetylacetone and benzoylacetone. The competitive character of β-dicarbonyl and β-aminovinylcarbonyl compounds in the reaction was established. The order of formation of the hexahydroquinolines was determined.

It has been demonstrated [1-3] that reactions that involve the three-component condensation of a β-dicarbonyl compound (dimedone or acetoacetic ester), a β-aminovinylcarbonyl compound or a β-aminovinyl nitrile, and an aldehyde lead, depending on the medium (ethanol, ethanol with triethylamine, or acetic acid), to the formation of products with unsymmetrical structures, viz., derivatives of 5-oxo-2,7,7-trimethyl-4-R'-3-R-1,4,5,6,7,8-hexahydroquinolines (III), or products with symmetrical structures, viz., 3,3,6,6-tetramethyl-9-R'-1,2,3,-4,5,6,7,8,9,10-decahydroacridine-1,8-diones (IV).

We attempted to ascertain whether the reactions described above can be extended to other β-dicarbonyl compounds. In addition to dimedone [V, pK_a 5.2 (water) [4] and pK_a 8.37 (ethanol) [5]] and acetoacetic ester [IIc, pK_a 10.7 (water) [6] and pK_a 15.5 (ethanol) [7]], we used acetylacetone [IIa, pK_a 11.81 (ethanol) [5]] and benzoylacetone [IIb, pK_a 12.02 (ethanol) [5]]. We used β-aminocrotonic acid nitrile (VIa) and ester (VIb) and acetylacetone and benzoylacetone imines (VIc, d) as the β-aminovinylcarbonyl compounds and β-aminovinyl nitriles.

It was established that the previously found regularity is also valid for diketones IIa, b. In ethanol or ethanol containing triethylamine, it was found that dimedone imine I, the aldehyde, and acetylacetone IIa or benzoylacetone IIb form hexahydroquinoline derivatives IIIg-l contaminated by very small amounts of decahydroacridinediones IVb, c.



II a R=CH_3, b R=C_6H_5; III a R=CN, R'=H; b R=CN, R'=CH_3; c R=CN, R'=C_6H_5; d R=$COOC_2H_5$, R'=H; e R=$COOC_2H_5$, R'=CH_3; f R=$COOC_2H_5$, R'=C_6H_5; g R=$COCH_3$, R'=H; h R=$COCH_3$, R'=CH_3; i R=$COCH_3$, R'=C_6H_5; j R=COC_6H_5, R'=H; k R=COC_6H_5, R'=CH_3; l R=COC_6H_5, R'=C_6H_5; IV a R'=H, b R'=CH_3, c R'=C_6H_5

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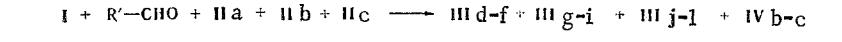
2,6-Dimethyl-4-phenyl-3,5-dibenzoyl-1,4-dihydropyridine (VII) [8], which was formed as a result of transamination, i.e., dimedone (I) + benzoylacetone (IIb) → dimedone (V) + benzoylacetone imine (VId), was detected as an impurity in the reaction of imine I, benzaldehyde, and benzoylacetone IIb in acetic acid. Imine VId undergoes cyclization with benzaldehyde to give VII.

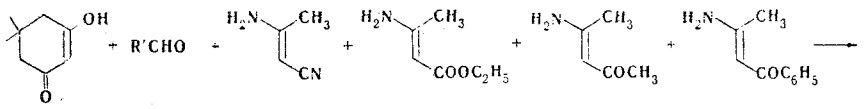
To establish the competitiveness of the β-dicarbonyl compounds we subjected a mixture of dicarbonyl compounds IIa, b and acetoacetic ester IIc (R = OC_2H_5) to reaction with imine I and an aldehyde. On the basis of the results of thin-layer chromatography (TLC) we established that quinolines IIId-i are the first products formed from acetoacetic ester IIc and acetylacetone IIa. Benzoylacetone IIb undergoes reaction after prolonged heating. This constitutes evidence that, despite its lower acidity, acetoacetic ester IIc competes successively with acetylacetone IIa and benzoylacetone IIb. The anion of acetoacetic ester IIc apparently has greater nucleophilicity in the reaction with the aldehyde. Ylidene derivatives of the β-dicarbonyl compound, to the double bond of which β-aminovinyl compounds add with subsequent cyclization to hexahydroquinolines III, are formed in all cases. When the reaction is car-



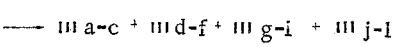
ried out in the presence of V and paraformaldehyde is used as the aldehyde, the order of formation of the quinolines is proportional to the acidities of the β-dicarbonyl compounds. Acridinedione IVa and quinoline IIIg are formed simultaneously, after which quinoline IIId is formed. Benzoylacetone IIb reacts very slowly.

However, when a mixture of dimedone V and acetoacetic ester IIc in ethanol is subjected to reaction with imine I and benzaldehyde, decahydroacridinedione IVc is formed, and only traces of hexahydroquinoline IIIf are detected. It was demonstrated that unsymmetrical three-component condensation between dimedone imine I, benzaldehyde, and dimedone V occurs in this case, since I does not form decahydroacridinedione IVc with benzaldehyde in ethanol in the absence of dimedone.

The competitiveness of β-aminovinylcarbonyl compounds was determined by a study of the reaction of dimedone V and the aldehyde with a mixture of β-aminocrotonic acid nitrile VIa, β-aminocrotonic acid ester VIb, acetylacetone imines, and benzoylacetones VIc, d. We observed the order of formation of the quinolines by means of TLC. Compounds IIIa, IIIg, and, finally, IIIh are primarily formed with paraformaldehyde. Compounds IIIb and IIIe are formed simultaneously with acetaldehyde, after which IIIh is formed. Compound IIIc is formed initially with benzaldehyde, after which IIIf and IIIi are formed; IIIl is formed only after this.



V VIa VIb VIc VId



Thus, the deciding factors in the reactivities of β-dicarbonyl compounds are their acidity and, in some cases, their nucleophilicities, i.e., their competitiveness depends on the first steps in the reaction to form the quinolines, viz., the formation of the anion and nucleophilic attack on the aldehyde carbonyl group by this anion.

The competitiveness of the aminovinylcarbonyl compounds is manifested in nucleophilic attack on the previously formed 2-ylidene-1,3-dicarbonyl compound.

Thus, by analysis of a reaction mixture that contains an aldehyde, dimedone V, and a mixture of aminovinylcarbonyl compounds we established that the most reactive (most nucleophilic) compound is β-aminocrotonic acid nitrile VIa, followed by β-aminocrotonic acid ester VIb and acetylacetone imine VIc. Benzoylacetone imine VId reacts very slowly. The activity of the β-dicarbonyl compounds in reactions with dimedone imine I and an aldehyde decreases in the order dimedone V, acetylacetone IIa and acetoacetic ester IIc, and benzoylacetone IIb.

EXPERIMENTAL

The course of the reaction was monitored by TLC on Silufol-254 plates in the following systems: chloroform–ethyl acetate (3:1) (system A) and butyl acetate–methanol–25% NH_4OH [95:5:25 (organic phase)] (system B). The substances were separated with columns filled with L 100/250 silica gel. The plates were developed in UV light. The identical character of the previously synthesized compounds was established from the absence of melting-point depressions and by chromatography.

5-Oxo-2,7,7-trimethyl-3-acetyl-1,4,5,6,7,8-hexahydroquinoline (IIIg). A mixture of 1.39 g (10 mmole) of dimedone imine I, 1 g (10 mmole) of acetylacetone IIa, and 0.3 g (10 mmole) of paraformaldehyde in 50 ml of ethanol was refluxed for 3 h, after which two-thirds of the ethanol was removed by distillation, and the concentrate was cooled and worked up to give 1.4 g (60%) of hexahydroquinoline IIIg with mp 205-207°C [3] and R_f 0.15 (system A).

5-Oxo-2,4,7,7-tetramethyl-3-acetyl-1,4,5,6,7,8-hexahydroquinoline (IIIh). A mixture of 1.39 g (10 mmole) of dimedone imine I, 1 g (10 mmole) of acetylacetone IIa, and 0.44 g (10 mmole) of acetaldehyde in 50 ml of ethanol and 0.1 ml of triethylamine was refluxed for 5 h. According to the TLC data, the reaction mixture contained only hexahydroquinoline IIIh and traces of decahydroacridinedione IVb and the starting compounds. The reaction mixture was evaporated to dryness, the residue was dissolved in 10 ml of chloroform, and the products were separated with a column filled with silica gel. Elution with chloroform yielded acetylacetone IIa, and elution with chloroform–ethyl acetate (3:1) yielded 1.2 g (48%) of hexahydroquinoline IIIh with mp 169-170°C (from aqueous ethanol). Found %: C 73.1; H 8.5; N 5.6. $C_{15}H_{21}NO_2$. Calculated %: C 72.8; H 8.6; N 5.6. The product had R_f values of 0.17 and 0.15 (systems A and B).

Reaction of Dimedone Imine I, Acetylacetone IIa, and Benzaldehyde. A) A mixture of 1.39 g (10 mmole) of I, 1 g (10 mmole) of IIa, and 1.06 g (10 mmole) of benzaldehyde in 50 ml of ethanol was refluxed for 15 h, after which it was evaporated to dryness, and the residue was dissolved in 10 ml of chloroform. The products were separated with a column filled with silica gel. Elution with chloroform gave 0.9 g (29%) of hexahydroquinoline IIIi with mp 198-200°C [3] (from aqueous ethanol) and R_f 0.23 (system A). Subsequent elution with ethyl acetate gave 0.04 g (1%) of decahydroacridinedione IVc with mp 292-294°C (dec.) [9] (from aqueous ethanol) and R_f 0.12 (systems A and B). According to the results of TLC, the reaction mixture contained, in addition to IIIi and IVc, only unchanged starting compounds.

B) The reaction proceeded similarly in ethanol with triethylamine to give hexahydroquinoline IIIi in 30% yield and decahydroacridinedione IVc in 2% yield.

C) A mixture of 1.39 g (10 mmole) of imine I, 1 g (10 mmole) of IIa, and 1.06 g (10 mmole) of benzaldehyde in 50 ml of acetic acid was refluxed for 30 min. It was established by TLC that the reaction mixture contained decahydroacridinedione IVc and the starting compounds. Removal of two-thirds of the solvent and the addition of a few drops of water yielded 1.5 g (43%) of decahydroacridine IVc.

5-Oxo-2,7,7-trimethyl-3-benzoyl-1,4,6,7,8-hexahydroquinoline (IIIj). A mixture of 1.39 g (10 mmole) of imine I, 1.62 g (10 mmole) of benzoylacetone IIb, and 0.3 g (10 mmole) of paraformaldehyde was refluxed in 50 ml of ethanol with 0.1 ml of triethylamine for 4 h, after which the mixture was evaporated to half its original volume, cooled, and worked up to give 1.8 g (66%) of hexahydroquinoline IIIj with mp 181-183°C (from ethanol) and R_f 0.27 and 0.20 (in systems A and B). Found %: C 77.3; H 7.2; N 5.0. $C_{19}H_{21}NO_2$. Calculated %: C 77.3; H 7.2; N 4.7.

5-Oxo-2,4,7,7-tetramethyl-3-benzoyl-1,4,5,6,7,8-hexahydroquinoline (IIIk). A mixture of 1.39 g (10 mmole) of dimedone imine I, 1.62 g (10 mmole) of benzoylacetone IIb, and 0.64 g (10 mmole) of acetaldehyde was refluxed in 50 ml of ethanol with 0.1 ml of triethylamine for 15 h with monitoring of the course of the reaction by TLC. The reaction mixture was evaporated to dryness, and the residue was dissolved in 10 ml of chloroform. The products were separated with a column filled with silica gel. Elution with chloroform gave benzoylacetone IIb, while elution with chloroform–ethyl acetate (3:1) gave 1.5 g (52%) of hexahydroquinoline IIIk with mp 158-160°C (from aqueous ethanol) and R_f 0.40 and 0.28 (systems A and B). Found %: C 78.0; H 7.3; N 4.6. $C_{20}H_{23}NO_2$. Calculated %: C 77.6; H 7.5; N 4.5.

Reaction of Dimedone Imine I, Benzoylacetone IIb, and Benzaldehyde. A) A mixture of 0.7 g (5 mmole) of imine I, 0.8 g (5 mmole) of benzoylacetone IIb, 0.53 g (5 mmole) of benzaldehyde, and 20 ml of ethanol was refluxed for 15 h. The reaction mixture contained

hexahydroquinoline IIIl and traces of decahydroacridinedione IVc and the starting compounds. The compounds were separated with a column filled with silica gel; elution with chloroform and ethyl acetate gave 0.53 g (29%) of IIIl with mp 207-209°C [3] (from aqueous ethanol) and R_f 0.33 (system A).

B) Hexahydroquinoline IIIl was similarly obtained in 30% yield by heating the starting compounds for 15 h in ethanol with triethylamine. According to the results of TLC, the mixture contained only the starting compounds in addition to hexahydroquinoline IIIl and traces of decahydroacridinedione IVc.

C) It was established by chromatography that when the starting compounds were refluxed for 30 min in acetic acid, the reaction mixture contained only decahydroacridinedione IVc admixed with hexahydroquinoline IIIl, dihydropyridine VII [8] (R_f 0.62 in system A), and the starting compounds. After removal of the acetic acid, the residue was dissolved in chloroform and separated with a column filled with silica gel; elution with chloroform yielded a mixture of dihydropyridine VII and hexahydroquinoline IIIl, while elution with ethyl acetate gave 0.46 g (26%) of decahydroacridinedione IVc.

Reaction of Dimedone Imine I, Acetylacetone IIa, Acetoacetic Ester IIc, Benzoylacetone IIb, and Paraformaldehyde. A mixture of 0.7 g (5 mmole) of imine I, 0.65 g (5 mmole) of acetoacetic ester IIc, 0.5 g (5 mmole) of acetylacetone IIa, 0.8 g (5 mmole) of benzoylacetone IIb, and 0.15 g (5 mmole) of paraformaldehyde was heated in 50 ml of ethanol at 70°C. The mixture was chromatographed at 2-min intervals. The following order of formation of the hexahydroquinolines was established by TLC (in the order of appearance and intensity of the spots): IIId (R_f 0.32 and 0.28 in systems A and B) and IIIg (0.17 and 0.14) appeared simultaneously after 10 min, and IIIj (R_f 0.31 and 0.25) appeared after 40 min. In addition to IIId, g, j, the reaction mixture contained only the starting compounds. After heating for 5 h, the reaction mixture was evaporated to dryness, and the residue was dissolved in 5 ml of chloroform and separated with a column filled with silica gel. Elution with chloroform gave the unchanged starting compounds, followed by 0.15 g (11%) of hexahydroquinoline IIId with mp 171-173°C [2] (from aqueous ethanol); elution with a chloroform–ethyl acetate system (3:1) gave 0.2 g (14%) of hexahydroquinoline IIIg, with mp 180-182°C (from aqueous ethanol), while elution with a chloroform–ethyl acetate system (2:1) gave 0.25 g (22%) of IIIj with mp 207-209°C [3] (from aqueous ethanol).

Reaction of Dimedone Imine I, Acetoacetic Ester IIc, Acetylacetone IIa, Benzoylacetone IIb, and Acetaldehyde. The reaction was carried out as in the preceding experiment by heating the starting compounds in ethanol at 70°C. The following order of formation of the hexahydroquinolines was established by TLC (the R_f values in systems A and B, respectively, are given): IIIe (R_f 0.45 and 0.32) and IIIh (R_f 0.17 and 0.15), followed by IIIk (R_f 0.34 and 0.25). In contrast to the preceding reaction, the formation of admixed decahydroacridinedione IVb (R_f 0.12) was observed in this case. In addition to IIIe, IIIh, IIIk, and IVb, the reaction mixture contained only the starting compounds.

Reaction of Dimedone Imine I, Acetoacetic Ester IIc, Acetylacetone IIa, Benzoylacetone IIb, and Benzaldehyde. The reaction was carried out as in the preceding experiment by refluxing the starting compounds in ethanol for 15 h. The following order of formation of the hexahydroquinolines was established by TLC: IIIf (R_f 0.39) and IIIi (R_f 0.23) and IIIl (R_f 0.33) and acridinedione IVc (R_f 0.12) (system A). In addition to these compounds, the reaction mixture contained only the starting compounds. This reaction proceeded similarly in ethanol with triethylamine. The reaction mixture, which contained IIIf, IIIi, IIIl, IVc, and the starting compounds, was evaporated to dryness, and the residue was dissolved in 10 ml of chloroform and separated with a column filled with silica gel. Elution with chloroform gave 0.6 g (17%) of hexahydroquinoline IIIf with mp 216-217°C [2] (from aqueous ethanol). Elution with ethyl acetate gave 0.05 g (1%) of decahydroacridinedione IVc (from aqueous ethanol). We were unable to separate IIIi, l.

Reaction of Dimedone Imine I, Acetoacetic Ester IIc, Dimedone V, and Benzaldehyde. A mixture of 0.7 g (5 mmole) of dimedone imine I, 0.65 g (5 mmole) of acetoacetic ester IIc, 0.7 g (5 mmole) of dimedone V, and 0.51 g (5 mmole) of benzaldehyde in 50 ml of ethanol with 0.1 ml of triethylamine was refluxed for 18 h. The reaction mixture contained decahydroacridinedione IVc and traces of hexahydroquinoline IIIf and the starting compounds. Removal of half the solvent and cooling yielded 1.5 g (86%) of decahydroacridinedione with mp 292-294°C [9] (dec., from aqueous ethanol) and R_f 0.12 (system A).

Reaction of Dimedone V, Ethyl β-Aminocrotonate VIb, Acetylacetone Imine VIc, β-Aminocrotonic Acid Nitrile VIa, and Paraformaldehyde. A mixture of 0.14 g (1 mmole) of dimedone V, 0.129 g (1 mmole) of VIb, 0.1 g (1 mmole) of imine VIc, 0.082 g (1 mmole) of nitrile VIa, and 0.03 g (1 mmole) of paraformaldehyde was heated in 20 ml of ethanol at 70°C for 1 h. The following order of formation of the hexahydroquinolines was established by TLC (the R_f values in systems A and B, respectively, are given): IIIa (R_f 0.31 and 0.25), IIIg (R_f 0.17 and 0.14), and IIId (R_f 0.32 and 0.28). In addition to the hexahydroquinolines, the reaction mixture contained the starting compounds.

Reaction of Dimedone V, Ethyl β-Aminocrotonate VIb, Acetylacetone Imine VIc, β-Aminocrotonic Acid Nitrile VIa, and Acetaldehyde. The reaction was carried out as in the preceding experiment. It was established by TLC that the hexahydroquinolines are formed in the following order: IIIb and IIIe, IIIh. In addition to these compounds, the reaction mixture contained only the starting compounds.

Reaction of Dimedone V, Ethyl β-Aminocrotonate VIb, Acetylacetone Imine VIc, Benzoylacetone Imine VId, β-Aminocrotonic Acid Nitrile VIa, and Benzaldehyde. A mixture of 1.4 g (10 mmole) of dimedone V, 0.82 g (10 mmole) of nitrile VIa, 1.29 g (10 mmole) of ester VIb, 0.99 g (10 mmole) of imine VIc, 1.61 g (10 mmole) of imine VId, and 1.05 g (10 mmole) of benzaldehyde was refluxed in 80 ml of ethanol for 15 h. The order of formation of the hexahydroquinolines was established by TLC: IIIc followed by IIIf, IIIi, and IIIl. The reaction mixture was evaporated to dryness, and the residue was dissolved in 10 ml of chloroform and separated with a column filled with silica gel. Elution with chloroform yielded the unchanged starting compounds, followed by a mixture of quinolines IIIf and IIIi, which we were unable to separate. Elution with a chloroform–ethyl acetate system (1:1) gave 0.6 g (23%) of hexahydroquinoline IIIc with mp 232-234°C [3] (from aqueous ethanol) and R_f 0.26 (system A).

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