SYNTHESIS OF 2-ACYLCYCLOHEXANE-1,3-DIONES THROUGH TETRAHYDROBENZISOXALONES

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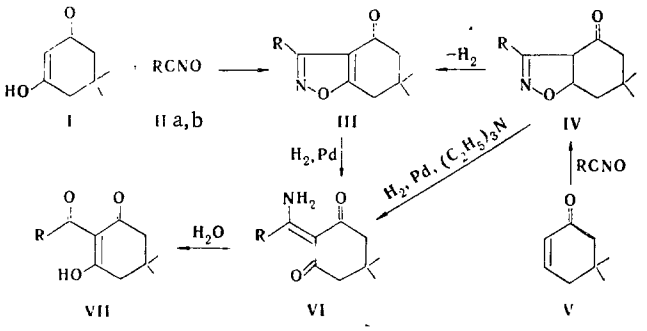
A new method was developed for the synthesis of 2-acylcyclohexane-1,3-diones from the adducts of 1,3-dipolar cycloaddition of nitrile oxides to cyclohexenones. The method is examined in the case of the preparation of 2-acetyl-, 2-enanthoyl-, and 2-benzoyldimedone.

Cyclic β-triketones or triacylmethanes have recently been playing an important role as a fundamental structural unit — synthone — in the total syntheses of a number of natural and related poly- and heterocyclic structures [1-3].

The classical method for the synthesis of cyclohexane β-triketones is C-acylation of cyclohexane-1,3-dione with acid anhydrides or chlorides. In this case, satisfactory yields of the triketones are obtained only in the case of acyl groups of the aliphatic series with a short carbon chain [$C_{(2)}$-$C_{(4)}$] or compounds with an aromatic acyl group [4-6].

In the present communication we examine a new approach to the synthesis of 2-acyl derivatives of cyclohexane-1,3-diones that is based on several transformations of the products of 1,3-dipolar cycloaddition of nitrile oxides to cyclenones.

We have previously shown [7] that the reaction of aromatic nitrile oxides, for example, benzonitrile oxide (IIb), with dimedone (I) leads to a cyclohexanoisoxazole (IIIb), which under catalytic hydrogenation conditions is converted quantitatively to an enamino diketone (VIb). The latter can be readily converted to benzoyldimedone (VIIb). However, the yield of isoxazole IIIb in this reaction was only 26%. Although the described sequence of transformation to obtain 2-acyl derivatives VII does not have preparative value (the yield of isoxazole IIIa in the reaction of I and IIa is negligible), the possibility of its realization compelled us to search for other methods for the synthesis of isoxazoles III. With this end in mind, we turned to a study of the reaction of nitrile oxides with dimethylcyclohexenone (V).



II-VII a R = CH_3; b R = C_6H_5; c R = C_6H_{13}

It is known [8, 9] that nitrile oxides react readily with the double bonds of unsaturated systems activated by conjugation with electron-acceptor groups via 1,3-dipolar cyclo-

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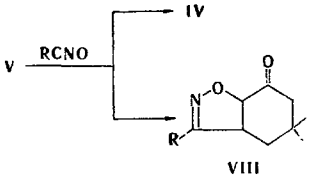
addition to give Δ^2-isoxazolines. The ease of the addition and its orientation are determined in this case by the activity of the double bond and the character of the closest substituent in the dipolarophile molecule. From general concepts [9] regarding the orientation of the addition of nitrile oxides and the character of the electron-density distribution in cyclic enone molecule V, it might have been expected that the formation of isoxazolines (IV) rather than the isomeric products of "reverse" addition (VIII) would be the chief direction of the reaction of II and V (see [10]).



VIII

a R=CH_3; b R=C_6H_5; c R=C_6H_{13}

Our data and the results of a recently published paper [11] completely confirm these concepts.

Thus isoxazoline IVa was obtained in 72% yield in the reaction of acetonitrile oxide IIa with dimethylcyclohexenone V. We did not isolate isoxazoline VIII, which is apparently formed in low yield (see [11]), and it was not used in the subsequent transformations.

The usual experimental scheme included the reaction of the nitrile oxide in situ with the enone under conditions that make it possible to reduce the dimerization process to a minimum. This was achieved by maintaining a low concentration of the reacting nitrile oxide, which was obtained by slow addition of a dilute ether solution of $(C_2H_5)_3N$ to a cooled mixture of methylhydroxamoyl chloride and a considerable excess of enone V. In addition to the described method for the preparation of acetonitrile oxide, we also used the dehydration of nitroethane by phenyl isocyanate [12, 13] or phosphorus oxychloride [13]. The indicated reagents, which are frequently used to prepare nitrile oxides from primary nitroparaffins, in our case did not offer any advantages as compared with methylhydroxamoyl chloride.

The signals in the PMR spectra of the 1-H and 6-H methylidyne protons are essential from the point of view of choosing between IVa and VIIIa for the structure of the adduct. These protons differ with respect to the character of the spin-spin coupling, regardless of the form of the isomer (a doublet from 1-H and a multiplet from 6-H) and the magnitude of the chemical shift; the latter should have a larger value for the proton attached to the carbon atom linked to the oxygen atom of the isoxazoline ring. The presence in the spectrum of a multiplet signal at weaker field (4.94 ppm) as compared with the position of the doublet (3.62 ppm) constitutes evidence in favor of structure IVa. This conclusion is unambiguously confirmed by the subsequent chemical transformations of isoxazoline IVa.

It is known [14] that Δ^2-isoxazolines can be converted to the corresponding isoxazoles by the action of N-bromosuccinimide (NBS). However, in our case the application of this method to IVa gives a complex mixture of products in which isoxazole IIIa is detected by chromatography. This result can apparently be explained by the presence of other reaction centers in the cyclohexane ring of the IVa molecule.

Isoxazole IIIa was obtained in good yield from isoxazoline IVa when chloranil was used as the dehydrating agent. The reaction product was identified by comparison with a genuine sample of IIIa. In view of the difficulties involved in the isolation of isoxazole IIIa in pure form because of the closeness of its R_f value to that of hydroquinone and the approximately identical solubilities of both products, the reaction mixture was subjected to catalytic hydrogenation. When this is done, as demonstrated in [7], isoxazole IIIa undergoes ring cleavage at the N–O bond to give enamino diketone VIa. Chromatographic separation of the mixture obtained as a result of hydrogenation gave enamino diketone VIa in 84% yield.

It is interesting to note that isoxazoline IVa under catalytic hydrogenation conditions in the presence of $(C_2H_5)_3N$ is converted in 78% yield to enamino diketone VIa, apparently through a step involving prior dehydrogenation to isoxazole IIIa. Vinylog amide VIa is quantitatively converted to 2-acetyldimedone VIIa by alkaline or acid hydrolysis.

Thus the examined sequence of reactions cyclohexenone V → isoxazoline IVa → isoxazole IIIa → enamino diketone VIa → triketone VIIa represents a new method for the synthesis of cyclic β-triketones of the cyclohexane series. Its use for the synthesis of other acyl derivatives is demonstrated by the preparation of 2-benzoyldimedone VIIb and 2-enanthoyldimedone VIIc.

Thus benzonitrile oxide reacts with dimethylcyclohexenone V to give isoxazoline IVb. This compound was dehydrogenated by means of chloranil to the known [7] isoxazole IIIb, which, without isolation in pure form, was hydrogenated on 5% $Pd/BaSO_4$. This procedure gave enamino diketone VIb, the saponification of which gave benzoyldimedone VIIb.

The use of the above-examined sequence in the case of enanthonitrile oxide without isolation in pure form of the products of the intermediate steps made it possible to obtain 2-enanthoyldimedone VIIc.

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EXPERIMENTAL

The melting points were determined with a Koffler block. The IR spectra were obtained with a UR-20 spectrometer. The PMR spectra were recorded with a JNM-PFT-100 spectrometer with tetramethylsilane as the internal standard. The mass-spectrometric data were obtained with a Varian MAT-311 spectrometer at an ionizing-electron energy of 50 eV. Thin-layer chromatography (TLC) on microplates (7.6 by 2.5 cm) with a fixed layer of Woelm silica gel and Silufol UV-254 plates in a tetrahydrofuran-hexane system (1:1) was used to monitor the course of the reactions. The chromatograms were developed in iodine vapors and in UV light. Column chromatography was performed with $H_2SiO_3 \cdot nH_2O$ (200-250 mesh).

4,4,9-Trimethyl-2-oxo-7-oxa-8-azabicyclo[4,3,0]non-8-ene (IVa). A) A solution of 2 ml of triethylamine in 150 ml of ether was added in the course of 4 h with stirring and cooling (−10°) to a mixture of 30 g of V and 1 g of methyl hydroxamoyl chloride in 20 ml of anhydrous ether, after which the mixture was allowed to stand overnight at room temperature. The precipitated $(C_2H_5)_3N \cdot HCl$ was removed by filtration, the ether was evaporated, and the excess enone was removed by vacuum distillation. The oily residue was crystallized from ether by cooling the ether solution with dry ice-acetone to give 1.4 g (72%) of IVa with mp 51-53°. IR spectrum (KBr): 1720, 2880, and 2965 cm^{-1}. PMR spectrum (CCl_4): 1.02 ppm ($4-CH_3$, s* 6H), 1.88 ppm (5-H, d, 2H, J = 10 Hz), 2.02 ppm ($9-CH_3$, s, 3H), 2.18 ppm (3-H, s, 2H), 3.62 ppm (1-H, d, J = 11 Hz), and 4.94 ppm (6-H, m). Found: C 66.5; H 8.3; N 7.7%; M (mass spectrometrically) 181. $C_{10}H_{15}NO_2$. Calculated: C 66.3; H 8.3; N 7.7%; M 181.24.

B) A few drops of triethylamine (freshly distilled over $LiAlH_4$) were added to a mixture of 1.5 g of nitroethane, 3.72 g of enone V, 6 g of phenyl isocyanate, and 50 ml of anhydrous benzene, and the mixture was stirred at room temperature for 3 days. The precipitated diphenylurea was removed by filtration, and the solvent was removed from the filtrate in vacuo. The residue was crystallized from ether by cooling the ether solution with a dry ice—acetone mixture to give 1.6 g (44%) of isoxazoline IVa, which was identical to the sample obtained in the preceding experiment.

C) A 1.7-g sample of $POCl_3$ was added dropwise with stirring in a stream of nitrogen in the course of 5 min at 0° to a solution of 1.28 g of enone V, 0.75 g of $C_2H_5NO_2$, and 4.54 g of $(C_2H_5)_3N$ in 50 ml of anhydrous $CHCl_3$, after which stirring was continued at 0° for 1 h. The mixture was then refluxed for 2 h, and the resulting solution was washed with water and Na_2CO_3 solution and dried with $MgSO_4$. The solvent was removed, and the residue was extracted with boiling hexane (five 50-ml portions). The extracts were combined and concentrated, the concentrate was cooled, and the resulting crystals were removed by filtration to give 260 mg (14%) of IVa, which was identical to the compounds described above.

Dehydrogenation of Isoxazoline IVa. A mixture of 45 mg of IVa and 70 mg of chloranil in 15 ml of tert-butyl alcohol was refluxed for 18 h. The solvent was then removed in vacuo, and the oily residue was used in the next step without additional treatment.

*Here and subsequently, s is singlet, d is doublet, and m is multiplet.

Hydrogenation of Isoxazole IIIa. The oily residue (120 mg) obtained in the preceding experiment was dissolved in 30 ml of ethanol and hydrogenated under standard conditions in the presence of 5% $Pd/BaSO_4$ (40 mg) until H_2 absorption had ceased. The catalyst was removed by filtration, and the solvent was removed by vacuum evaporation. The residue (120 mg) was chromatographed with a column filled with silicic acid (250 mesh) with gradient elution of the system with hexane–ether with increasing amounts of the latter to give 38 mg (84.5%) of enamino diketone VIa with mp 132-134°. No melting-point depression was observed for a mixture of this product with an authentic sample [15].

Saponification of Enamino Diketone VIa. A 120-mg sample of VIa was refluxed in a mixture of 20 ml of alcohol and 5 ml of 5% aqueous NaOH for 5 h. The mixture was then neutralized with dilute HCl and extracted with ether. The usual workup of the extract gave 117 mg (98%) of 2-acetyldimedone VIIa, which was identical to a genuine sample [15].

Reaction of Benzonitrile Oxide IIb with Dimethylcyclohexenone V. A solution of 1.3 g of triethylamine in 150 ml of ether was added in the course of 3 h with stirring and cooling (0°) to a mixture of 1.7 g of phenylhydroxamoyl chloride, 30 g of enone V, and 10 ml of anhydrous ether. The next day, the precipitate was separated, the ether was removed, and the excess enone was removed by vacuum distillation. The residue was crystallized from ether–hexane to give 1.8 g (68%) of 9-phenyl-2-oxo-7-oxa-4,4-dimethyl-8-azabicyclo[4,3,0]non-8-ene (IVb) with mp 123-124°. IR spectrum (KBr): 1555, 1705, 2880, and 2960 cm^{-1}. PMR spectrum ($CDCl_3$): 1.00 ppm (4-CH_3, s, 6H), 1.97 ppm (5-H, d, J = 5Hz, 2H), 2.11 (3-H, s, 2H), 4.08 ppm (1-H, d, J = 9Hz, 1H), 4.99 ppm (6-H, m, 1H), and 7.48 ppm (aromatic protons, center of a multiplet). Found: C 74.1; H 6.9; N 5.9%; M (mass spectrometrically) 243. $C_{15}H_{17}NO_2$. Calculated: C 74.0; H 7.0; N 5.8%; M 243.33.

2-Benzoyldimedone (VIIb). As described above, isoxazoline IVb (60 mg) was dehydrogenated with chloranil (70 mg), and the mixture (without isolation of isoxazole IIIb) was subjected to catalytic hydrogenation. The resulting oily product (130 mg) was chromatographed with a column as described above to give 37 mg of enamino diketone VIb with mp 273-274° ($CHCl_3$), which was identical to a genuine sample [7]. Saponification of VIb gave benzoyldimedone VIIb (in 92% yield) with mp 119-120° (mp 120° [6]). PMR spectrum (CCl_4): 1.13 ppm (5-CH_3, s, 6H), 2.29 ppm (CH_2, s, 2H), 2.53 (CH_2, s, 2H), and 7.64 ppm (C_6H_5, center of a multiplet, 5H).

2-Enanthoyl-5,5-dimethylcyclohexane-1,3-dione (VIIc). A solution of 1.1 ml of triethylamine in 150 ml of ether was added in the course of 4 h with stirring and cooling (–40°) to a mixture of 30 g of enone V, 1 g of enanthylhydroxamoyl chloride, and 20 ml of anhydrous ether, after which the mixture was allowed to stand at room temperature overnight. The resulting precipitate was removed by filtration, the ether was removed, and the excess enone was removed by vacuum distillation. The resulting oily residue was dehydrogenated with 1.6 g of chloranil by refluxing in a solution in tert-butyl alcohol for 25 h. The resulting solution was then hydrogenated under the usual conditions on 5% $Pd/BaSO_4$ until H_2 absorption had ceased. The catalyst and solvent were removed, and the residue was refluxed with 15 ml of ethanol and 20 ml of 10% aqueous KOH for 1 h. The solution was concentrated, diluted with water, acidified with HCl (1:1), and extracted with ether. The usual workup of the extract and vacuum distillation gave 0.6 g (40%) of VIIc with bp 145-146° (3 mm). IR spectrum (CCl_4): 1670, 2880, and 2970 cm^{-1}. PMR spectrum ($CDCl_3$): 0.88 ppm (CH_3, m 3H), 1.07 (CH_3, s, 6H), 1.48 (CH_2, center of a multiplet, 8H), 2.32 (CH_2, s, 2H), 2.48 (CH_2, s, 2H), 2.96 (CH_2, t, J = 8 Hz, 2H), and 17.62 ppm (OH, s, 1H). Found: C 71.5; H 9.6%; M (mass spectrometrically) 252. $C_{15}H_{24}O_3$. Calculated: C 71.4; H 9.5%; M 252.31.

Hydrogenation of Isoxazoline IVa. A solution of 90 mg of isoxazoline IVa in a mixture of 10 ml of alcohol and 2 ml of triethylamine was hydrogenated under normal conditions in the presence of 100 mg of 5% $Pd/BaSO_4$. Crystallization of the residue obtained after removal of the solvent from ether–hexane gave 70 mg (78%) of enamino diketone VIa, which was identical to a genuine sample [15].

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