

CHEMISTRY OF FURANIDINE SERIES KETONES

IV. Expansion of Oxacyclic Ketones and α -Diketones Diazoacetic Ester*

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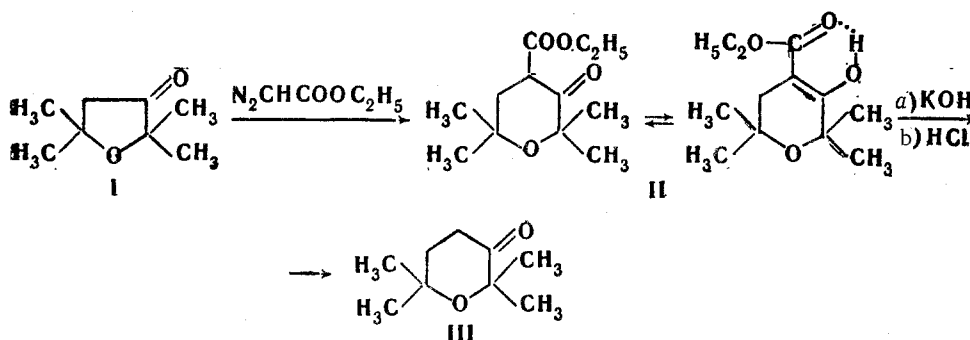
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For the first time, oxacyclic ketones and α -diketones are reacted with diazoacetic ester in the presence of a Lewis acid. It is found that 2,2,5,5-tetramethylfuranid-3-one (I) and 2,2,5,5-tetramethylfuranidine-3,4-dione (IV) undergo ring enlargement between the third and fourth carbon atoms in the ring, to give, respectively, 4-ethoxycarbonyl-2,2,6,6-tetramethyltetrahydropyrone-3 (II) and 4-ethoxycarbonyl-2,2,6,6-tetramethyltetrahydropyran-3,5-dione (V), with the characteristic properties of β -ketoesters.

In 1959, Yu. K. Yur'ev, I. K. Korobitsyna, and K. K. Pivnitskii showed that diazomethane could be successfully used to effect ring enlargement of tetrahydrofuran ketones and α -diketones [1]. It was shown that reaction of 2,2,5,5-tetraalkylfuranid-3-ones with diazomethane (in methanol) gives 2,2,6,6-tetraalkyltetrahydropyrones-3, along with an insignificant amount of 2,2,6,6-tetraalkyltetrahydropyrones-4. The yield is 40-50%, depending on the kind of substituents in the starting ketone, and how the diazomethane is introduced [2, 3]. In a similar way 2,2,5,5-tetraalkylfuranidine-3,4-diones give 2,2,6,6-tetraalkyltetrahydropyran-3,5-diones, which were isolated from the reaction products as methyl ethers of the enol forms (40-50%) [2, 4].

Diazoacetic ester is less nucleophilic than diazomethane and its homologs, and hence less reactive towards carbonyl compounds, so that it is less suitable for ring expansion. It is only in recent years that some papers have described use of diazoacetic ester for synthesis of corresponding homoketones from alicyclic monoketones [5, 6, 7] and α -diketones [8, 9]. A large excess of ester and catalysts as energetic as Lewis acids were always used. Use of diazoacetic ester for expanding heterocyclic ketones and α -diketones has never been investigated.

We have now shown that reaction of 2,2,5,5-tetramethylfuranid-3-one (I) with diazoacetic ester in the presence of boron trifluoride etherate in ether solution, leads to ring enlargement and formation of 4-ethoxy-carbonyl-2,2,6,6-tetramethyltetrahydropyrone-3 (II) (yield 15-16% based on the reacted furanidone I); the isomeric 3-ethoxycarbonyl-2,2,6,6-tetramethyltetrahydropyrone-4 was not found among the products.



The ethoxycarbonyltetrahydropyrone II, like other β -ketoesters, is in equilibrium with its enol form, as is indicated by the violet color given with aqueous methanolic ferric chloride solution, ready solubility in alkali and bromine water being decolorized. A cis-enol structure for compound II is also confirmed by formation of a copper chelate (on adding a saturated solution of copper acetate); after treating the latter with dilute sulfuric acid, the β -ketoester can be isolated chromatographically pure.

The IR spectrum of compound II, with intense absorption bands at 1630 and 1662 cm^{-1} , and low-intensity diffuse absorption in the 2600-2900 cm^{-1} region for the enol, plus a weak keto-form absorption at 1720 and 1750 cm^{-1} , indicates considerable enolization, and stable intramolecular hydrogen bonding [10]. The UV spectrum of compound II shows intense absorption with λ_{max} 255 $\text{m}\mu$ (heptane) and 254 $\text{m}\mu$ (ethanol); the unchanging positions of the absorption bands with change in solvent polarity also indicates involvement of the β -dicarbonyl group in stable chelate-type

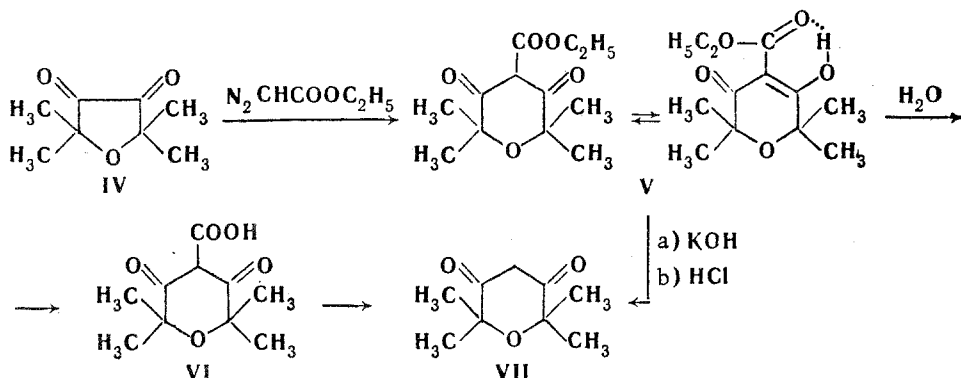
* For Part III see [17].

hydrogen bonding [11].

Molecular refraction results indicate that compound II contains 60–65% enol.

Hydrolysis and decarboxylation of ethoxycarbonyltetrahydropyranone II gives 2,2,6,6-tetramethylhydropyran-3 (III). The identity of this latter compound with authentic 2,2,6,6-tetramethyltetrahydropyran-3 is shown by the complete agreement between physical properties, by thin-layer and gas chromatography, and by the identical properties of the benzylidene derivatives and semicarbazones. The latter compounds, after a single recrystallization, have the properties given in the literature.

Enlargement of the ring of 2,2,5,5-tetramethylfuranidien-3,4-dione (IV) by diazoacetic ester also proceeds with insertion of the diazoacetic ester moiety between the third and fourth carbon atoms in the furanidine ring. With boron trifluoride etherate as the catalyst, the yield of 4-ethoxycarbonyl-2,2,6,6-tetramethyltetrahydropyran-3,5-dione (V) is 34% (calculated on the reacted α -diketone IV).



However, the liquid diketoester V contains a considerable amount of solid 2,2,6,6-tetramethylhydropyran-3,5-dione 4-carboxylic acid (VI) as impurity. It is considered that diketoester V is the primary reaction product. However, when the reaction products are decomposed with water, the mixture becomes strongly acid, and under those conditions ester V is hydrolyzed to acid VI.

Use of a different catalyst, zinc chloride, for the reaction between diketone IV and diazoacetic ester gave better results, pure diketoester V being obtained in 60% yield (calculated on the reacted ketone IV), without any acid VI as impurity.

Being soluble in dilute alkalis, the diketoester V also exists as an equilibrium mixture of keto and enol forms, decolorizing bromine water, and giving an intense violet color with an aqueous methanolic solution of ferric chloride. With a copper acetate solution it readily gives the copper chelate.

In the IR spectrum of diketoester V, weak absorption at 1730 and 1768 cm^{-1} corresponds to the keto form, and intense absorption at 1590, 1645, and 1692 cm^{-1} , and a diffuse band at 2500–2800 cm^{-1} [10] correspond to the enol form. The UV spectrum of the diketoester V exhibits intense absorption with λ_{max} 252 $\text{m}\mu$ (cyclohexane) and 254 $\text{m}\mu$ (ethanol). Molecular refraction data show that it contains 62–67% enol.

Diketoester V is readily hydrolyzed and decarboxylated by treating it with dilute potassium hydroxide solution, and then acidifying, giving 2,2,6,6-tetramethyltetrahydropyran-3,5-dione (VII) (84% yield), whose identity with authentic 2,2,6,6-tetramethyltetrahydropyran-3,5-dione was shown by the agreement between physical properties, by thin-layer chromatography, and by the identity of their oximes.

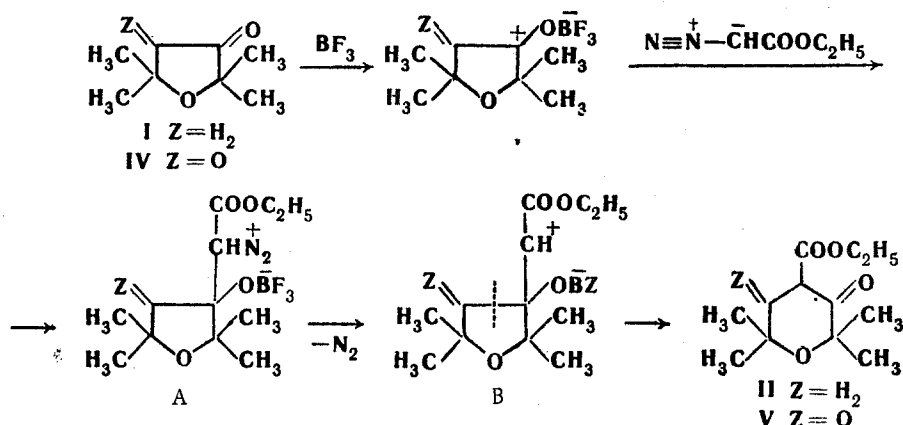
Acid VI is readily decarboxylated by heating at 130° C, or by heating at 80° C in 2 N hydrochloric acid, to give the tetrahydropyran-3,5-dione VII. It undergoes partial decarboxylation even on standing at room temperature.

The IR spectrum of acid VI exhibits marked displacement of the carbonyl absorption band, connected with enolization of VI and formation of various kinds of hydrogen bonds. Only a very intense band at 1597 cm^{-1} can be ascribed to a carbon-carbon double bond of the enol form. A distinct hydroxyl absorption band is lacking; there is only a very diffuse low-intensity absorption band at 2520–2870 cm^{-1} . The UV spectrum of acid VI has an absorption maximum at λ_{max} 256 $\text{m}\mu$ (ethanol, cyclohexane).

The ketoester II, diketoester V, and acid VI which we have prepared have the characteristic properties of β -dicarbonyl compounds: they are in equilibrium with their cis-enol form, which readily undergoes stable chelate-type intramolecular hydrogen bonding, and they readily undergo hydrolysis and decarboxylation.

In agreement with the view expressed in the literature [7,12], we consider that in the reaction which we have

investigated, the reactants initially react to form a coordinate link between the carbonyl group of ketone I or diketone IV and the Lewis acid. The diazoacetic ester then reacts with the carbonyl component thus activated, to give a diazonium-betaine structure A.



By nucleophilic expulsion of nitrogen, the latter is converted to the carbonium ion B which undergoes stabilization by migration of groups. With the furanidone I the methylene group migrates, giving compound II, while with diketone IV the carbonyl group migrates, to give compound V. As the migration is anioniotropic, the group which will migrate preferentially is the one with the greatest electron affinity. Here methylene and carbonyl groups migrate rather than an isopropyl one. Steric factors also favor such a reaction course.

The high yield of diketoester V as compared with ketoester II is apparently due to the high reactivity of diketone IV (in comparison with monoketone I), where the carbonyl carbon atom's nucleophilicity is increased through interaction of adjacent carbonyl groups. These results are in agreement with analogies in the literature [2-4].

It should be mentioned that in every case (where the reaction mixture contained diazoacetic ester, Lewis acid, and diethyl ether) ethoxyethyl acetate was observed to be formed in considerable quantity (20-30%), as was proved by gas-liquid chromatography, authentic ethoxyethyl acetate being used as a marker.

Experimental

Boron trifluoride etherate was prepared in the usual way [13], diazoacetic ester was synthesized from ethyl glycolate [14], and the furanidinedione IV was prepared by oxidation of furandione I [15].

4-Ethoxycarbonyl-2,2,6,6-tetramethyltetrahydropyrone-3 (II). 8.5 g (0.078 mole) diazoacetic ester in 20 ml dry ether was dropped into a stirred solution of 7 g (0.05 mole) boron trifluoride etherate and 7 g (0.05 mole) 2,2,5,5-tetramethylfuranid 3 one (I) in 15 ml dry ether, the system being protected from access of moisture in the air. The reaction mixture was stirred and gently heated for 1.5-2 hr, cooled, diluted with ether, and then repeatedly washed with water, till the washings were neutral. The ether solution was dried and vacuum-distilled, to give 1) 5.5 g of a mixture of ethoxyethyl acetate and unchanged furanidone I, bp 36-42° (8 mm), n_D^{20} 1.4130. The literature [16] gives for ethoxyethyl acetate bp 158° (760 mm), n_D^{20} 1.4029, and for the furanidone I [15] bp 149° (760 mm), n_D^{20} 1.4202. Gas-liquid chromatogram with a UKh-1 instrument: stationary phase 10% polyethylenglycol adipate on INZ-300 brick, T 144° C, column l = 2.5 m, gas v = 28 ml/min, paper v 240 mm/hr, t_R ethoxyethyl acetate 7.82 min, t_R furanidone I 6 min. Under the same conditions, the exit times for pure authentic specimens of these compounds were identical with the above.

Fraction 2): 2.3 g crude ketoester II, bp 98-101° (6 mm), n_D^{20} 1.4580. Found: C 62.78, 62.76; H 8.79; 8.78%. Calculated for $\text{C}_{12}\text{H}_{20}\text{O}_4$: C 63.14; H 8.78%.

In the flask there remained about 3 g of resin which did not distil.

Purification of ethoxycarbonyltetrahydropyrone II through its copper chelate. 2.3 g crude ketoester II in 7 ml EtOH was added to 30 ml of a saturated solution of copper acetate, the mixture left in a refrigerator for some days, the precipitate filtered off, and washed with water. Yield of Cu chelate compound II, 1.3 g (50%), mp 145.5-146.5° C (ex aqueous EtOH), minute dark-green crystals. Found: C 56.18, 56.28; H 7.52, 7.68%. Calculated for $\text{C}_{24}\text{H}_{38}\text{CuO}_8$: C 55.72; H 7.34%. UV spectrum: λ_{max} (EtOH) 268 mμ; ε 12340. IR spectrum: (cm^{-1}): 2912 strong, 2876 strong, 1608 medium, 1466 very strong, 1380 strong, 1332 medium, 1290 medium,

1270 medium, 1245 medium, 1235 medium, 1208 medium, 1160 medium, 1130 medium, 1040 medium, 1025 medium, 996 weak, 965 weak, 852 weak.

In a long separating funnel, a solution of 3.2 g (0.0064 mole) β -ketoester (II) Cu chelate in 30 ml ether was shaken with 3.4 ml 20% H_2SO_4 , the ether layer separated off, and dried over $MgSO_4$. The residue left after distilling off the ether was vacuum-distilled to give 2.48 g (87%) 4-ethoxycarbonyl-2,2,6,6-tetramethyltetrahydropyran-3 as a colorless oily liquid, 76-77° (15 mm), d_4^{20} 1.0370, n_D^{20} 1.4683, MR_D 61.22. Calculated for $C_{12}H_{20}O_4$: MR_D 59.18 (ketone), MR_D 62.2 (enol).

Chromatogram with a Tsvet-I instrument: stationary phase 10% cyanoethylated mannitol on Cellite-545; column 1 1.2 m; T 140° C; gas v 37 ml/min; paper v 360 mm/hr; t_R 2.1 min. Found: C 63.14, 63.13; H 8.92, 8.73%. Calculated for $C_{12}H_{20}O_4$: C 63.14; H 8.78%. IR spectrum (cm^{-1}): 2982 strong, 2950 medium, 2912 weak, 2600-2900 weak, 1750 weak, 1720 weak, 1662 very strong, 1630 strong, 1485 medium, 1450 medium, 1408 medium, 1382 medium, 1370 medium, 1320 strong, 1280 very strong, 1260 very strong, 1230 strong, 1214 strong, 1168 medium, 1140 strong, 1040 strong, 1025 strong, 1010 medium, 830 medium.

2,2,6,6-Tetramethyltetrahydropyran-3 (III). 1.5 g (0.0066 mole) β -ketoester II and 1.5 g KOH in 21 ml water were heated and stirred together for 10 min on a water-bath, cooled, and with stirring 4 N HCl added to bring the pH to 1-2. Then the mixture was heated on the water-bath for 2 min, cooled rapidly, and the tetrahydropyran III salted out with $MgSO_4$. The ether extracts were dried over $MgSO_4$, the ether distilled off, and the residue vacuum-distilled to give 0.56 g (55%) colorless liquid with a camphoraceous odor, bp 58-60° (85 mm), n_D^{20} 1.4413. The literature [2,3] gives 62-63° (9 mm); n_D^{20} 1.4413; semicarbazone mp 197-198° C; benzylidene derivative mp 79-80°.

That the compound III obtained was identical with authentic 2,2,6,6-tetramethyltetrahydropyran-3 was shown by thin-layer chromatography, using neutral alumina, grade 2 activity, with benzene as the eluant, R_f 0.71, and by gas-liquid chromatography with an UKh-1 instrument: stationary phase 10% tricyanoethoxypropane on INZ-600 brick, T 146°; column 1 2.5 m; gas v 21 ml/min; paper v 240 mm/hr; t_R 6.75 min. The exit time for the pure authentic compound was the same.

Semicarbazone: of compound III, mp 193-197° C (ex very dilute EtOH); mixed mp with authentic semicarbazone undepressed, at 196° C.

Benzylidene derivative of compound III mp 78-79° C (ex water), mixed mp with authentic benzylidene compound mp 80° C, undepressed.

4-Ethoxycarbonyl-2,2,6,6-tetramethyltetrahydropyran-3,5-dione (V). a) A solution of 8.5 g (0.078 mole) diazoacetic ester in 20 ml dry ether was added slowly with stirring, over a period of 2 hr, to a solution of 6.5 g (0.045 mole) boron trifluoride etherate and 7 g (0.045 mole) 2,2,5,5-tetramethylfuranidine-3,4-dione (IV) in 20 ml dry ether. Then stirring was continued, with gentle heating, for 40 min. After cooling the products were washed with water until the wash water was neutral, the ether extracts dried over $MgSO_4$, the ether distilled off and the residue vacuum-distilled, to give 1) 5 g of a mixture of ethoxyethylacetate and diketone IV, bp 36-53° C (9 mm); the literature [15] gives for the diketone IV bp 55° C (10 mm).

Gas-liquid chromatography with a UKh-1 instrument; stationary phase polyethyleneglycol adipate on INZ-600 brick, T 144° C, column length 2 m, gas v 28 ml/min; paper v 240 mm/hr; t_R diketone IV 10.5 min; t_R ethoxyethyl acetate 7.82 min. The exit times for pure authentic compounds were the same; 2) 1.6 g 2,2,6,6-tetramethyltetrahydropyran-3,5-dione-4-carboxylic acid (VI), bp 90-94° C (2.5 mm), quickly crystallizes, mp 72-74° C (ex petrol ether at -30° C). Readily soluble in alkalis and non-polar organic solvents, slightly soluble in water. Found: C 55.73, 55.78; H 6.67, 6.78%. Calculated for $C_{10}H_{14}O_5$: C 56.08; H 6.54%. IR spectrum (cm^{-1}): 3630 very weak, 3575 very weak, 2912 very strong, 2876 very strong, 2520-2870 weak, 1690 medium, 1662 medium, 1615 medium, 1597 medium, 1468 very strong, 1456 very strong, 1410 medium, 1380 medium, 1350 medium, 1265 medium, 1195 medium, 1170 medium, 1160 medium, 1034 weak, 990 weak, 965 weak, 920 weak, 900 weak; 3) 2.2 g liquid bp 95-99° C (2.5 mm) from which crystals separated on standing, these being a mixture of diketoester V and acid VI.

b) A solution of 8.5 g (0.078 mole) diazoacetic ester in 20 ml dry ether was added slowly, with stirring, to a solution of 7 g (0.045 mole) diketone IV and 6 g (0.045 mole) $ZnCl_2$ in 20 ml dry ether, after which the mixture was gently heated and stirred for 40-50 min. The products were cooled, and 150 ml ether with a little water added. The white flocculent precipitate formed was decomposed with 0.4 N HCl, pH 4-5. The ether layer was washed with water, dried over $MgSO_4$, the ether distilled off, and the residue vacuum-distilled, to give: 1) 4.9 g of a mixture of ethoxyethyl acetate and α -diketone IV, bp 36-53° C (9 mm). The gas-liquid chromatogram resembled that in experiment a). 2) 5.6 g diketoester V (60% on the reacted diketone IV); bp 94.5-96° C

(2 mm), d_4^{20} 1.13402; n_D^{20} 1.4825. Found: C 59.52, 59.36; H 7.65, 7.52%; MR_D 61.02. Calculated for $C_{12}H_{18}O_5$: C 59.51; H 7.44%; MR_D 59.12 (ketone); MR_D 62.1 (enol). IR spectrum (cm^{-1}): 2985 very strong, 2940 medium, 2500–2800 weak, 1768 weak, 1732 weak, 1692 very strong, 1643 strong, 1590 very strong, 1530 weak, 1480 medium, 1450 weak, 1415 strong, 1380 strong, 1350 medium, 1300 strong, 1272 strong, 1225 strong, 1195 strong, 1175 strong, 1100 weak, 1030 strong, 925 weak, 915 weak.

Copper chelate of diketoester V. Addition of 10 ml saturated Cu acetate solution to 0.7 g (0.0029 mole) compound V in 3 ml EtOH gave 0.75 g (95%) of the Cu chelate of diketoester V, bluish-green crystals mp 122.5–123.2° C (ex EtOH). Found: C 59.26, 52.83; H 6.70, 6.49%. Calculated for $C_{24}H_{34}CuO_{10}$: C 52.76; H 6.24%.

2, 2, 6, 6-Tetramethyltetrahydropyran-3, 5-dione (VII).

a) 0.6 g (0.0025 mole) diketoester V and 15 ml 10% KOH were heated together on a boiling water-bath for 5 min, the products cooled, brought to pH 1 with 4 N HCl, and heated for a further 10 min. Yield of 2, 2, 6, 6-tetramethyltetrahydropyran-3, 5-dione (VII) 0.35 g (84%), mp 156–158° C. The literature [4] gives mp 159–159.5° C, dioxime mp 160–161° C.

b) 0.5 g (0.0023 mole) acid VI and 30 ml 2 N HCl were stirred together and heated on a boiling water-bath for 15 min, to give 0.32 g (92%) β -diketone VII, mp 159–159.5° C.

c) 0.15 g (0.0007 mole) acid VI was heated in a tube sealed at one end, the temperature being slowly raised to 130° C; CO_2 was found to be evolved, and at 130–140° C the mass solidified and melted at 158° C. Yield of β -diketone VII 0.096 g (92%). Undepressed mixed mp of 158–159° C with authentic 2, 2, 6, 6-tetramethyltetrahydropyran, 3, 5-dione. Thin-layer chromatography on alumina (grade II activity), R_f 0.078 (eluant EtOH), also proved the identity of the compound with authentic compound.

Dioxime, mp 160–161° C (ex aqueous EtOH), mixed mp with an authentic specimen undepressed.

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