SYNTHESIS OF 3-CARBETHOXYBICYCLO[2.1.0]-2-PENTANONE

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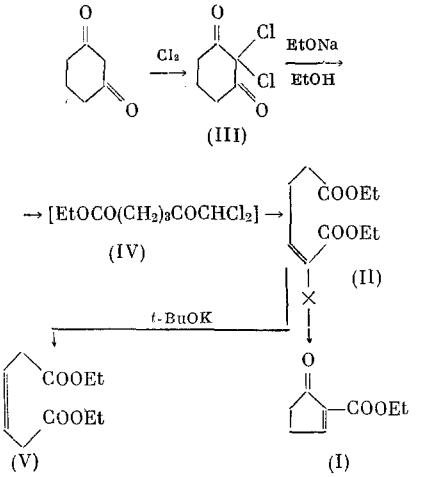
UDC 542.91:547.92

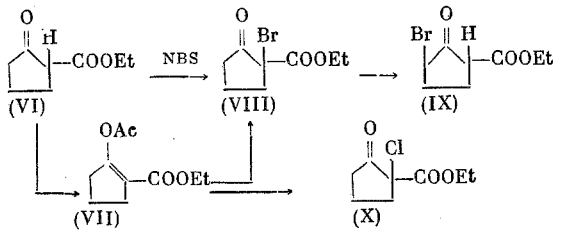
During the synthesis of steroidal compounds with a modified structure we proposed the preparation of 2-carbethoxy-2-cyclopenten-1-one (I) via the diethyl ester of dihydromuconic acid (II), which was obtained by us in an overall yield as high as 70% from dihydroresorcinol by the following scheme:



The chlorination of dihydroresorcinol in $CHCl_3$ gave the dichloro derivative (III), which under the conditions of the Favorskii rearrangement, via the aliphatic dichloroketone (IV), forms the known diester (II) [1]. The structure of (II) was confirmed by the data of the NMR spectra (the presence of signals in the vicinity of 2.49 and 3.55 ppm for the CH_2CH_2 group – the A_2B_2 portion of the A_2B_2XY system, and the signals of the two different vinyl protons of HC_2 at 5.79 and HC_3 at 5.93 ppm). Only the isomerization of diester (II) to the β,γ-unsaturated ester (V) (data of IR and mass spectra), accompanied by much tarring, occurred under the conditions of the Dieckmann condensation (comminuted sodium in ether, sodium ethylate in ethanol, or t-BuOK in toluene); the formation of cyclopentanone derivatives was not observed. Attempts to run the condensation of diester (II) under the influence of BF_3 etherate led to a complex mixture, from which we were able to isolate only the β,γ-unsaturated ester (V) by chromatographing. This isomerization was observed previously [2].

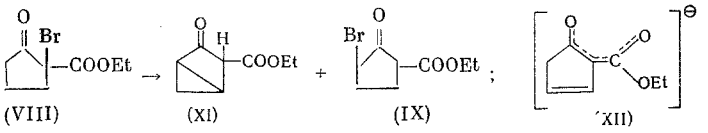
In view of this we attempted to synthesize ketoester (I) by starting with 2-carbethoxycyclopentanone (VI), into whose molecule, it would appear, the double bond could be inserted by halogenation and subsequent dehydrohalogenation. Since the conventional bromination of ketoester (VI) in glacial AcOH leads to a mixture of bromo derivatives, we studied the bromination of enol acetate (VII) in the presence of magnesium oxide. Under these conditions we were able to obtain monobromoketone (VIII) in up to 90% yield. The same monobromide is also obtained by the treatment of (VI) with N-bromosuccinimide. Since it is possible for isomerization to occur under the bromination conditions, and especially in the presence of HBr, with the formation of the more stable γ-bromides [in our case the 5-bromoketoester (IX)], it was necessary to prove the position of the Br atom.

M. M. Shemyakin Institute of the Chemistry of Natural Compounds, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 5, pp. 1086-1090, May, 1973. Original article submitted August 15, 1972.



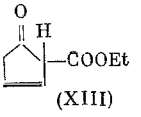
The position of the Br atom in (VIII) was confirmed by the reaction with phenol (easy cleavage of the Br atom as Br^+), which led to (VI) and bromophenols, and also by the data of the NMR spectrum, in which the signals characteristic for the CHBr and CO–CH–CO groups are absent. The chlorination of enol acetate (VII) gave chloroester (X) in quantitative yield, the structure of which was also confirmed by the NMR spectrum.

The dehydrobromination of (VIII) with alkaline reagents (NaOH or NaOEt in alcohol, Li_2CO_3 + LiCl in dimethylformamide) was accompanied by substantial tarring and led only to products of an acid character, which are apparently formed as a result of the Favorskii rearrangement. The dehydrobromination of (VIII) could be accomplished by heating with BF_3 etherate in benzene or, even better, in ether. The product $C_8H_{10}O_3$ (XI) and the stable bromide $C_8H_{11}O_3Br$ (IX) are formed here. Chloride (X) remains unchanged under analogous conditions. Based on the elemental analysis data and the mass spectrum, compound (XI) is an isomer of ketoester (I); its IR spectrum contains absorption bands that are characteristic for the acetoacetic ester system (1728 and 1760 cm^{-1}):

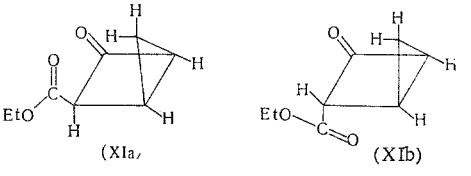


Based on the data of the UV spectrum, compound (XI) does not contain an unsaturated keto grouping. The observed absorption maximum at 249 nm, with a low intensity (ε 74), is characteristic for a carbonyl group that is conjugated with the cyclopropane ring [3]. It is known that such systems are unstable in either acid or alkaline medium and are isomerized to the corresponding olefins [4]. The formation of a product, in whose UV spectrum a substantial bathochromic shift of the absorption maximum to 286 nm (ε 14,000) was noted, was also observed when (XI) is treated with alcoholic NaOH solution. This change in the UV spectrum can be explained by the formation of anion (XII) in alkaline medium.

The signals of vinyl protons are absent in the NMR spectrum of ester (XI), which excludes either structure (I) or (XIII):



A quadruplet with a center at 3.16 ppm indicates the presence of the H atom of a β-dicarbonyl grouping in compound (XI), which is also not compatible with structure (I). In contrast, the presence of signals upfield (0.52 and 0.64 ppm) confirms the presence of a cyclopropane grouping. On this basis it is possible to assign to (XI) the structure of 3-carbethoxybicyclo[2.1.0]-2-pentanone, which, apparently, is a mixture of the exo and endo structures (XIa, b):



The structure of the formed bromide (IX) was confirmed by the data of the IR, UV and NMR spectra. Apparently (IX) is found as a mixture of the keto and enol forms. It is formed as the result of a 1, 3-rearrangement of the electrophilic Br atom at C_2 under the influence of a Lewis acid. The formation of (IX)

was also observed during the slow bromination of enol acetate (VII) in CCl_4 under conditions that excluded the removal of HBr from the reaction sphere (absence of MgO).

Only ketone (XI) was isolated when alkaline solutions, containing anion (XII), were acidified carefully.

The data obtained by us indicate that, as the result of intramolecular nucleophilic (prototropic) rearrangement, the unsaturated ketoester (I) is converted with extreme ease to the bicyclo[2.1.0]pentanone derivative, while the dehydrobromination of bromides of the (VIII) type is a convenient method for the synthesis of bicyclo[2.1.0]pentane derivatives, which are usually obtained in extremely low yields by the photolysis of compounds of the cyclohexadienone series [3].

METHOD

Enol Acetate (VII). A mixture of 30 g of 2-carbethoxy-1-cyclopentanone (VI) [5], 200 ml of Ac_2O and 100 ml was refluxed for 14 h. Vacuum-distillation gave 36 g (90%) of 2-carbethoxy-1-cyclopenten-1-ol acetate (VII) with bp 125-127° (15 mm); n_D^{20} 1.4645; d_4^{20} 1.1052; mol.wt. 198 (by mass spectrometry). Found: C 59.80; H 7.18%; MR 51.22. $C_{10}H_{14}O_4$. Calculated: C 60.39; H 7.12%; MR 49.55. Infrared spectrum (as a film): 1721 (COOEt); 1778 and 1662 cm^{-1} (vinyl acetate grouping).

Bromination of Enol Acetate (VII). To a solution of 2.0 g of enol acetate (VII) in 250 ml of CCl_4 was added 3 g of MgO, and then, with stirring, at ~20°, a solution of 0.34 ml of Br_2 in 40 ml of CCl_4 was added in 5 h; the precipitate was filtered, washed with CCl_4, and the filtrate was evaporated in vacuo. We obtained 2.31 g of the viscous bromoketoester (VIII), which decomposed easily on attempted distillation or when stored for a long time; n_D^{20} 1.4692; mol.wt. 235 (by mass spectrometry). Infrared spectrum (as a film): 1730 (COOEt), 1752 cm^{-1} (α-bromoketone). NMR spectrum (in $CDCl_3$, δ, ppm): 1.27 (quadruplet, 3H) and 4.16 (multiplet, 2H) (COOEt), 2.35 (multiplet, 2H) ($-CH_2CO-$).

Bromination of Ketoester (VI) with N-Bromosuccinimide. A mixture of 1.25 g of ketoester (VI), 1.9 g of N-bromosuccinimide and 10 ml of dry CCl_4 was refluxed for 3 h. After the usual workup we obtained 1.9 g (81%) of the pale yellow ketobromide (VIII) with n_D^{22} 1.4690.

Chlorination of Enol Acetate (VII). A solution of 10.2 g of enol acetate (VII) in 150 ml of $CHCl_3$, cooled to 0°C, was saturated with Cl_2 until a faint yellow color appeared. The reaction mixture was washed with water, dried over $MgSO_4$, and evaporated. We obtained 11.2 g (~100%) of chloroketone (X), which is unstable when distilled, with n_D^{20} 1.4548; mol.wt. 190 and 191 (by mass spectrometry). Infrared spectrum (as a film): 1736 (COOEt) and 1769 cm^{-1} (α-chloroketone). NMR spectrum (in $CDCl_3$, δ, ppm): 1.27 (quadruplet, 3H), 4.04-4.50 (multiplet, 2H), 2.40 (multiplet, 2H).

Reaction of Bromoketoester (VIII) with Phenol. A solution of 1.4 g of bromoketoester (VIII) and 0.56 g of phenol in 10 ml of absolute ether was refluxed for 15 h. After cooling, the mixture was washed with $NaHCO_3$ solution and then with water. The organic layer was dried over $MgSO_4$ and then evaporated in vacuo. The residue (oil) (based on the TLC data) was free of the starting bromoketone. The obtained oil was chromatographed on a silica gel column. The low-polar products were eluted with hexane. Elution with benzene gave 0.3 g of an oil, the IR spectrum (as a film) of which contains strong bands at 1231 and 1027 cm^{-1} (aromatic ethers), 682 and 760 cm^{-1} (C–Br bond, 1595 and 1505 cm^{-1} (aromatic ring), and 3050 cm^{-1} (C–H bond). The mass spectrum of this product contains three groups of intense peaks with m/e 199, 200, 201, 279, 280, 281, 359, 360, 361.

Reaction of Chloroketoester (X) with Sodium Ethylate. A solution of 5 g of chloroketoester (X) in 50 ml of absolute alcohol was added in drops to a solution of sodium ethylate (from 1.5 g of Na and 200 ml of absolute alcohol). The stirred mixture was refluxed for 2.5 h, and then the solvent was evaporated. Water was added to the residue and the whole was extracted with ether. The extract was dried over Na_2SO_4 and then evaporated. We obtained 0.35 g of a mixture, which contained (based on the TLC data) the starting chloroketoester (X). The aqueous alkaline layer was acidified with HCl solution and then extracted with ether. The extract was washed with water, dried over Na_2SO_4, and evaporated. We obtained 2.5 g of an oil, which was chromatographed on a silica gel column. Elution with ethyl acetate gave 2 g of a substance, which crystallized on standing. Recrystallization from alcohol gave a product with a double mp of 124-128 and 143-144°. Based on the data of the IR spectrum (in KBr) the product contains the ester grouping (1720 and 1280 cm^{-1}), and also the COOH group (1700 and a broad band at 2500-3300 cm^{-1}); mol.wt. 237 (by mass spectrometry).

The treatment of the crystalline product with a distilled ether solution of diazomethane gave a liquid ester of unestablished structure, which has the formula $C_{11}H_{19}O_4Cl$; mol.wt. 251 (by mass spectrometry). Found: C 52.09; H 7.53; Cl 13.58%. Calculated: C 52.19; H 7.57; Cl 14.01%. Infrared spectrum (as a film): 1743 cm^{-1} and a broad band in the 1200-1280 cm^{-1} region (ester groupings).

Dehydrobromination of Bromoketoester (VIII) with BF_3 Etherate. A solution of the bromoketoester (VIII) [from 1.07 g of enol acetate (VII)] and 17 ml of BF_3 etherate in 150 ml of absolute ether was refluxed for 5 h, washed with water until neutral, and the ether layer was dried over $MgSO_4$. Evaporation in vacuo gave an oil, which (based on the TLC data) is a mixture of two products. The mixture was chromatographed on a silica gel column. Elution with hexane gave 5.7 g (48%) of bromoketoester (IX) (decomposes on attempted distillation); n_D^{19} 1.5168. The IR spectrum (as a film) contains broad absorption bands in the 3320 region (OH group), 1751 (α-haloketone), 1730 ($COOC_2H_5$ group), 1669 and 1629 (enolic form of β-ketoester). Ultraviolet spectrum (alcohol): bathochromic shift, $\Delta\lambda_{max}$ = 10 nm [267 nm (ε 87) for (XII), and 257 nm (ε 11) for ketoester (VI)]; absorption bands are absent in the 230-250 nm region. The NMR spectrum (δ, ppm, in $CDCl_3$) of (XII) contains signals that are caused by the chemical shifts of the H atoms of the CHBr $-C=C$ grouping (4.9 ppm, 1H) and the CHBrCO group (4.90 ppm, 1H); two signals were also observed at 6.10 and 6.87, which are characteristic for the chemical shift of the H atom of the OH group of the enol form. Apparently, compound (XII) in $CDCl_3$ solution is found as an equilibrium mixture of three of the α-bromoketone tautomers and two of its enol forms.

On further chromatographing of the starting mixture, elution with benzene gave 5.2 g (31%) of ketoester (XI) with bp 115-117° (20 mm); n_D^{20} 1.4565; d_4^{20} 1.071; mol.wt. 154 (by mass spectrometry). Found: C 61.69; H 6.61%; MR 37.63. $C_8H_{10}O_3$. Calculated: C 62.31; H 6.54%; MR 38.14. Infrared spectrum (as a film): 1760 (CO group), 1728 cm^{-1} ($COOC_2H_5$). Ultraviolet spectrum (ethanol): λ_{max} 249 (ε 74). NMR spectrum (δ, ppm, in $CDCl_3$): 3.16 (singlet, 1H, $CO-CH-COOC_2H_5$), 1.68 (multiplet, 2H, CH_2 group); doublets at 2.36 and 2.27 (1H, HC_1), and 0.52 and 0.64 (1H, HC_4).

Preparation of Ethyl Ester of cis-Dihydromuconic Acid (II). The needed 2,2-dichloro-1,3-cyclohexanedione (III) was obtained as described in [6]. To a refluxing solution of sodium ethylate (from 20 g of Na in 600 ml of absolute alcohol) was added, with stirring, in 10 min, a solution of 80 g of dichloride (III) in 75 ml of absolute alcohol. The mixture was refluxed for 20 min and then evaporated. The residue was cooled in ice, treated with water, and carefully acidified with HCl solution. The product was extracted with ether, washed with water, then with Na_2CO_3 solution, again with water, and dried over Na_2SO_4. Evaporation of the extract, followed by vacuum-distillation, gave 32 g (67%) of the ethyl ester of cis-dihydromuconic acid with bp 130-135° (20 mm); n_D^{20} 1.4375. Infrared spectrum (as a film): 1738, 1185, and 1260 cm^{-1} ($COOC_2H_5$ group). NMR spectrum (δ, ppm, in $CDCl_3$): multiplets with centers at 1.29 and 4.16 (COOEt), 2.49-3.55 (multiplet, CH_2CH_2), 5.79 (1H, HC_2) and 5.93 (1H, HC_3).

Reaction of Diester (II) with BF_3 Etherate. A solution of 0.55 g of diester (II) in 15 ml of absolute dioxane was refluxed with 0.5 ml of BF_3 etherate for 30 h. The reaction mass was then treated with water and extracted with ether. Then the extract was dried over $MgSO_4$, evaporated in vacuo, and the residue was chromatographed on silica gel. Elution with $CHCl_3$ gave 0.4 g of an oil with n_D^{20} 1.4320; mol.wt. 200 (by mass spectrometry). The IR spectrum is devoid of bands in the 1730-1715 cm^{-1} region (α,β-unsaturated ester group) and contains an absorption band at 1747 cm^{-1}.

Attempted Cyclization of Diester (II) under the Conditions of the Dieckmann Reaction. To a stirred suspension of 0.16 g of comminuted Na in 20 ml of absolute ether was added 0.32 ml of ethyl formate, followed by the addition of 0.5 g of diester (II) at ~20°. The stirring was continued for another 3 h. The reaction mass was carefully decomposed with water and the neutral products (0.14 g) were extracted with ether. The aqueous layer was acidified with 1:1 HCl solution and also extracted with ether. The extract was washed with water until neutral and then dried over Na_2SO_4. Removal of the solvent gave 0.23 of a condensation product. Compounds of either the (I) or the (XI) type were not detected.

Analogous condensation products were also obtained when an absolute ethanol solution of ester (II) was refluxed in a N_2 atmosphere in the presence of sodium ethylate, and also when ester (II) was refluxed in toluene in the presence of t-BuOK.

CONCLUSIONS

1. In contrast to the diethyl ester of adipic acid, the diethyl ester of cis-dihydromuconic acid is not cyclized under the conditions of the Dieckmann reaction.

2. 2-Carbethoxybicyclo[2.1.0]-2-pentanone is smoothly formed by the dehydrobromination of 2-bromo-2-carbethoxy-1-cyclopentanone with BF_3 etherate.

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