REACTION OF 1-MORPHOLINOCYCLODODECENE WITH ACROLEIN AND SYNTHESIS OF BICYCLO[9.3.1]PENTADECAN-15-ONE

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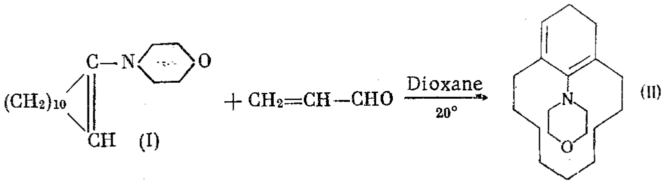
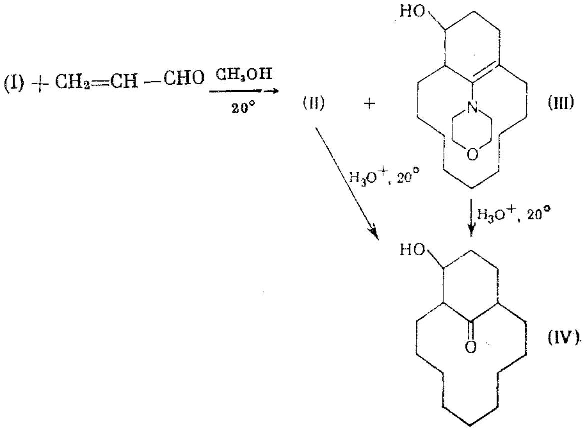
Previously it was shown [1] that 1-pyrrolidinocyclohexene reacts with acrolein in an unusual manner to give 2-N-pyrrolidinobicyclo[3.3.1]nonan-9-one. 1-Pyrrolidinocyclopentene reacts in a similar manner with acrolein. In [2] it was shown that this reaction bears a general character and is applicable to other enamines of cyclic ketones and unsaturated aldehydes. However, we obtained results different from those given in [1] when we studied the reaction of 1-morpholinocyclododecene (I) with acrolein. It was found that the reaction of (I) with acrolein in dioxane at 20°C leads in high yield to 15-morpholinobicyclo[9.3.1]-pentadeca-14,15-diene (II).



A mixture of (II) and 14-hydroxy-15-morpholinobicyclo[9.3.1]pentadec-15-ene (III) in approximately equal amounts is obtained when this reaction is run in methanol.



The mild hydrolysis of (III) with dilute HCl solution gives 14-hydroxybicyclo[9.3.1]pentadecan-15-one (IV). This same hydroxy ketone is formed from bicycle (II) by hydrolysis under similar conditions, i.e., the hydrolysis of the enamine group is accompanied by the addition of a molecule of water to the double bond in the 14 position. The treatment of bicyclic compounds (II), (III), and (IV) with 2,4-dinitrophenylhydrazine in ethanol, in the presence of H_2SO_4, leads to a common product, namely the 2,4-dinitrophenylhydrazone of hydroxy ketone (IV). The position of the hydroxy group in (IV) was proved by its oxidation with CrO_3 in AcOH to β-(2-oxocyclododecyl)propionic acid (V). Apparently, the oxidation of (IV) proceeds

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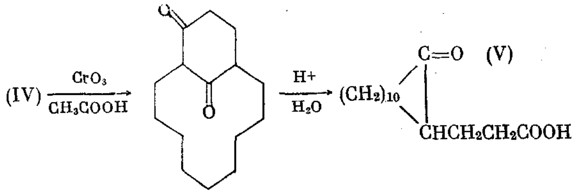
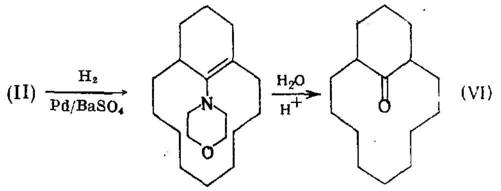
via the intermediate formation of the bicyclic β-diketone, which in acid medium is easily cleaved to acid (V), similar to the acid cleavage of bicyclo[4.3.1]decane-7,10-dione [3].



Acid (V) is identical with the acid that is obtained by the hydrolysis of the addition product of methyl acrylate to (I), and is different from (2-oxocyclododecyl)acetic acid. The latter was synthesized from (I) and bromoacetic ester, with subsequent hydrolysis of the reaction product. One mole of hydrogen is absorbed when enamine (II) is hydrogenated over $Pd/BaSO_4$, and hydrolysis of the hydrogenation product with dilute HCl solution gives bicyclo[9.3.1]pentadecan-15-one (VI) in quantitative yield. Ketone (VI) has a musk odor. When hydroxy ketone (IV) is heated with p-TsOH it easily cleaves water and gives bicyclo[9.3.1]pentadec-14-en-15-one (VII).



15-N-Morpholinobicyclo[9.3.1]pentadeca-14,15-diene (II). a) To a solution of 20 g of 1-morpholinocyclododecene in 120 ml of dioxane at 5° was gradually added 7 g of freshly distilled acrolein in 20 ml of dioxane. Then the mixture was stirred at 20°C for 3 h, the dioxane was removed under vacuum, and the residue was vacuum-distilled. We obtained 18 g (82%) of (II), bp 171-174° (1 mm), and mp 96-97° (hexane). Found: C 78.56; H 10.77; N 5.03%. $C_{19}H_{31}NO$. Calculated: C 78.89; H 10.75; N 4.85%.

b) To a solution of 20 g of 1-morpholinocyclododecene in 150 ml of methanol at 20° was gradually added 7 g of acrolein in 20 ml of methanol. A bulky white precipitate began to deposit toward the end of addition. After 3 h the precipitate was filtered and washed twice on the filter with chilled methanol. We obtained 21.2 g of product with mp 84-85°, which when recrystallized from hexane gave 8.6 g of (II), mp 96-97°, and 8.1 g of 14-hydroxy-15-morpholinobicyclo[9.3.1]pentadec-15-ene (III), mp 131-132°. Found: C 74.31; H 10.74; N 5.31%. $C_{19}H_{33}NO_2$. Calculated: C 74.25; H 10.74; N 5.56%. Infrared spectrum (ν, cm^{-1}): 1640 (C = C), 3480 (OH). From (II) and (III) by treatment with 2,4-DNPH in alcohol, in the presence of H_2SO_4, we obtained the same 2,4-dinitrophenylhydrazone of ketone (IV), mp 147-148° (AcOH). Found: C 59.89; H 7.16%. $C_{21}H_{30}N_4O_5$. Calculated: C 60.18; H 7.17%.

14-Hydroxybicyclo[9.3.1]pentadecan-15-one (IV). a) A solution of 8 g of (III) in 50 ml of $CHCl_3$ and 100 ml of 10% HCl solution was stirred at 20° for 4 h. After removal of the $CHCl_3$ and the usual workup, the product was vacuum-distilled to give 5.4 g (87%) of hydroxy ketone (IV), bp 150-151° (1 mm), and mp 123-124° (hexane). Infrared spectrum (ν, cm^{-1}): 1700 (CO), 3400-3450 (OH). Found: C 75.77; H 9.85%. $C_{15}H_{26}O_2$. Calculated: C 75.63; H 10.92%.

b) A solution of 6 g of (II) in 50 ml of $CHCl_3$ and 80 ml of 10% HCl solution was stirred at 20° for 6 h. We obtained 4.1 g (82%) of hydroxy ketone (IV), bp 150-151° (1 mm), and mp 123-124°. Infrared spectrum (ν, cm^{-1}): 1700 (CO), 3400-3450 (OH). Found: C 75.33; H 11.05%. $C_{15}H_{26}O_2$. Calculated: C 75.63; H 10.92%. Both hydroxy ketone samples when treated with 2,4-DNPH give the same 2,4-dinitrophenylhydrazone, mp 147-148° (AcOH). Found: C 60.10; H 7.02; N 13.10%. $C_{21}H_{30}N_4O_5$. Calculated: C 60.18; H 7.17; N 13.40%.

Bicyclo[9.3.1]pentadec-14-en-15-one (VII). A mixture of 3 g of hydroxy ketone (IV) and 0.1 g of p-TsOH was heated at 160° for 10 min. Then the mixture was cooled, dissolved in ether, and washed with Na_2CO_3 solution. The product was recrystallized from hexane to give 2.5 g of (VII) with mp 59-60°. Infrared spectrum (ν, cm^{-1}): 1675 (CO). Found: C 81.65; H 11.00%. $C_{15}H_{24}O$. Calculated: C 81.82; H 10.92%.

Oxidation of 14-Hydroxybicyclo[9.3.1]pentadecan-15-one. To 1 g of the hydroxy ketone in 10 ml of AcOH was added a solution of 0.6 g of CrO_3 in 5 ml of AcOH and 1 ml of water. After standing at 20° for

12 h the mixture was diluted with water and extracted with ether. After removal of the ether the solid residue was recrystallized from petroleum ether. We obtained 0.9 g of β-(2-oxocyclododecyl)propionic acid, mp 103-104°. Found: C 69.90; H 9.92%. $C_{15}H_{26}O_3$. Calculated: C 70.86; H 10.24%. The mixed melting point with an authentic sample of the acid was not depressed.

Bicyclo[9.3.1]pentadecan-15-one. A solution of 10 g of morpholinobicyclo[9.3.1]pentadeca-14, 15-diene in 60 ml of ethanol was hydrogenated over 0.1 g of $Pd/BaSO_4$ at 20° until 0.8 liter of H_2 was absorbed. The catalyst was filtered, the ethanol was distilled off, and the residue was dissolved in 80 ml of $CHCl_3$, 60 ml of 10% HCl solution was added, and the mixture was stirred at 20° for 8 h. After the usual workup and removal of the $CHCl_3$ the solid residue was recrystallized from methanol. We obtained 7 g (96%) of bicyclo[9.3.1]pentadecan-15-one, mp 71-72°. Infrared spectrum: ν_{CO} 1700 cm^{-1}. Found: C 81.10; H 11.83%. $C_{15}H_{26}O$. Calculated: C 81.08; H 11.70%.

β-(2-Oxocyclododecyl)propionic Acid. The methyl ester of β-(2-oxocyclododecyl)propionic acid was obtained as described in [4]. This ester (2 g) was hydrolyzed by refluxing with a solution of 1 g of NaOH in 20 ml of methanol for 2 h. After the usual workup we isolated 1.5 g of β-(2-ketocyclododecyl)propionate acid, mp 103-104° (hexane). Found: C 70.94; H 10.20%. $C_{15}H_{26}O_3$. Calculated: C 70.86; H 10.24%.

β-(2-Oxocyclododecyl)acetic Acid. A solution of 10 g of 1-morpholinocyclododecene and 8 g of methyl bromoacetate in 60 ml of abs. methanol was refluxed for 2 h. Then 25 ml of water was added and the stirred mixture was refluxed for 2 h. The methanol was vacuum-distilled, and the solid residue was recrystallized from hexane to give 6 g of methyl (2-oxocyclododecyl)acetate, mp 68-69°. A solution of 4 g of the ester in methanolic KOH solution (3 g KOH + 50 ml CH_3OH) was refluxed for 5 h. After the usual workup we obtained 3.5 g of (2-oxocyclododecyl)acetic acid, mp 114-115° (from hexane). Found: C 75.00; H 10.70%. $C_{14}H_{24}O_2$. Calculated: C 74.95; H 10.71%.

CONCLUSIONS

1. Depending on the solvent, the condensation of 1-morpholinocyclododecene with acrolein gives 15-morpholinobicyclo[9.3.1]pentadeca-14, 15-diene and 14-hydroxy-15-morpholinobicyclo[9.3.1]pentadec-15-ene, which on acid hydrolysis form 14-hydroxybicyclo[9.3.1]pentadecan-15-one.

2. The hydrogenation of 15-morpholinobicyclo[9.3.1]pentadeca-14, 15-diene and subsequent acid hydrolysis gave bicyclo[9.3.1]-pentadecan-15-one.

LITERATURE CITED

1. G. Stork and H. Landesman, J. Am. Chem. Soc., 78, 5129 (1956).
2. Shmushkovich, Advances in Organic Chemistry [in Russian], Vol.4, Mir (1966), p.47.
3. J. Hargreaves, P. Hickmott, and B. Hopkins, J. Chem. Soc., C, 592 (1969).
4. I. J. Borowitz, V. Bandurco, M. Heyman, and R. D. Rigby, J. Org. Chem., 38, 1234 (1973).