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SYNTHESIS OF NOVEL CONDENSED BINUCLEAR HETEROCYCLES BASED ON 1,3- AND 1,5-DICARBONYL DERIVATIVES OF 2,2-DIMETHYLTETRAHYDROPYRAN

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Treatment of 1,5- and 1,3-dicarbonyl derivatives of 2,2-dimethyltetrahydropyran with a series of binucleophiles gave condensed pyranopyrazole, pyranothiopyrimidine, pyranoisoxazole, and pyranopyridine systems.

Keywords: 5-acyl-2,2-dimethyltetrahydropyran-4-ones, 2,2-dimethyltetrahydropyran-4-one, pyrano-isoxazoles, pyranopyrimidines

A number of natural antibiotics with a broad range of activity contain the perhydropyran nucleus, e.g. streptomycin, kanamycin, and neomycin. The synthetic medicinal substances in the pyran series used in contemporary medicine are fundamentally benzopyran derivatives. The most important of these is Vitamin E, or more specifically the group of substances called tocopherols e.g. α-tocopherol, the basis of which constitutes tocol [1]. With the aim of studying the biological activity of novel pyran derivatives we have been interested in the possible synthesis of binuclear heterocycles which are condensed at the positions 3 and 4 of the pyran ring.

One possible route for preparing similar structures is the acylation of pyran-4-ones followed by cyclization with cyanoacetamide to give 3-oxopyrano[3,4-*c*]pyridine [2]. 2,2-Dimethyltetrahydropyranopyrrole [3], pyrano[3',4':5,6]pyrido[2,3-*d*]pyrimidine [4], and pyranoisoxazolidine [5] systems are known. Since the search for novel, potentially biologically active compounds is a promising goal, the object of this work was the synthesis of novel, condensed heterocycles based on 1,3- and 1,5-dicarbonyl derivatives of 2,2-dimethylpyran.

In order to prepare the β-diketones we chose the method of acylation of 2,2-dimethyltetrahydropyran-4-one enamines [**1**]. The reaction of compound **1** with morpholine gave a mixture of the isomeric enamines **2** and **3**.

It had been previously been reported [2] that the result of this reaction was just the single product **2**. Detailed analysis of the ^{1}H NMR spectra of the reaction product showed the presence of the two isomeric enamines **2** and **3**. Evidence for the presence of compound **3** came from two additional triplet signals at 2.5 and 3.80 ppm. The enamines **2** and **3** are formed in the ratio 1:1 but they could not be separated chromatographically and were used in the subsequent syntheses as the isomeric mixture.

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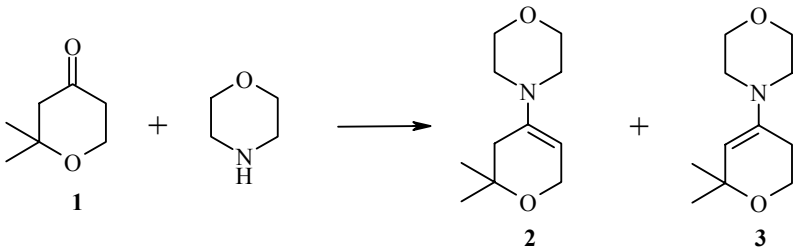
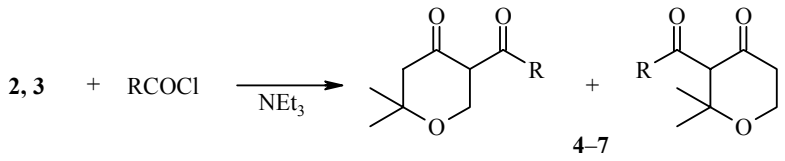


1 **2** **3**

The reaction of compounds **2** and **3** with acid chlorides under Stork conditions gave the 1,3-dicarbonyl compounds **4-7** in 33-56% yields.



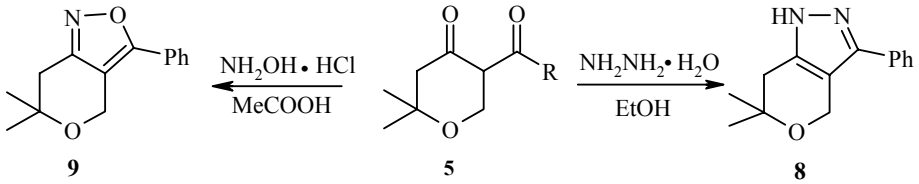
4–**7**

4 R = Me; **5** R = Ph; **6** R = 4-FC_6H_4; **7** R = 3,4-$(MeO)_2C_6H_3$

TLC and GLC data for the products **4-7** point to the presence of two compounds in each case but they were very difficult to separate using preparative GLC. The compounds have very similar retention times on the column at boiling point. We consider that, as in the case of enamines **2** and **3**, the diketones **4-7** exist as a mixture of two isomers, these also being in the ratio 1:1 according to GLC data. For this reason, a detailed interpretation of the ^{1}H NMR spectra did not prove possible (it should be noted that each of the isomeric diketones exists as a mixture of the keto and enol form). The IR spectra of the compounds **4-7** show aromatic C=C absorption bands at 1580-1630 cm^{-1} and enol form carbonyl groups at 1640-1670 and 1710-1740 cm^{-1}. Compound **4** exists almost wholly in the enol form as shown by the presence of a clearly defined C=C absorption band at 1630 cm^{-1} and OH at 3300-3500 cm^{-1} and by the absence of the characteristic absorption frequency for one of the carbonyl groups. Chromatographic mass spectroscopic analysis of compounds **5** and **6** confirms their composition: for **5** *m/z* 51, 77, 105, 147, 232 $[M]^{+\cdot}$, for **6** *m/z* 51, 75, 123, 249, 250 $[M]^{+\cdot}$.

The β-dicarbonyl compounds obtained **4-7** (as the mixture of isomers) underwent heterocyclization with such binucleophiles as hydrazine hydrate, hydroxylamine hydrochloride, and thiourea. Specific reaction conditions were chosen for each of the reactions carried out. As a result, we prepared compounds **8, 9**.

The ^{1}H NMR spectra of the compounds **8** and **9** show signals for the phenyl substituent and two methyl groups. The ^{1}H NMR spectrum of compound **8** shows two singlets for the methylene groups in the pyran ring at 2.90 and 4.90 ppm and a signal for the NH group at 7.35 ppm. In the ^{1}H NMR spectrum of compound **9** the two singlets are observed for the methylenes of the pyran ring at 2.75 and 4.90 ppm.



9 **5** **8**

The spectra of the compounds **8,9** show only one of the isomers hence it can be deduced that only the diketone with less steric hindrance takes part in the reaction.

In the reactions of the diketones **4** with all of the bis nucleophiles used, the products could not be separated.

TABLE 1. Physicochemical Parameters for Compounds **4-7**

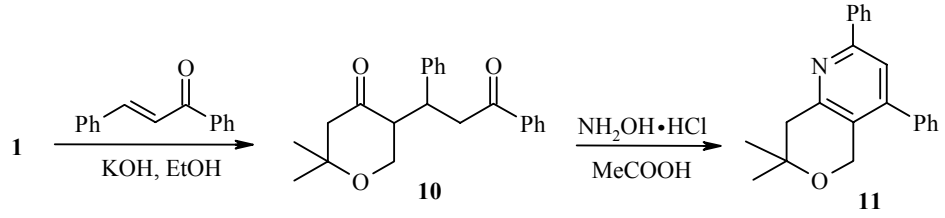
Compound	Empirical formula	Found, % / Calculated, %		bp, °C (mm Hg)	IR spectrum, ν, cm^{-1}	Yield, %
		C	H			
4	$C_9H_{14}O_3$	63.34 / 63.52	8.50 / 8.29	80-115 (11)	1720 (C=O); 1630 (C=C); 3300-3500 (OH)	37
5	$C_{14}H_{16}O_3$	72.62 / 72.39	6.70 / 6.94	138-142 (2)	1710, 1680 (C=O); 3300-3510 (OH)	56
6*	$C_{14}H_{15}FO_3$			135-142 (1.7)	1740, 1640 (C=O); 3300-3500 (OH)	39
7	$C_{16}H_{20}O_5$	65.41 / 65.74	7.00 / 6.90	175-180 (2)	1710, 1670 (C=O); 3400-3510 (OH)	32.5

* Found: F 7.35%; calculated: F 7.59%.

The reaction of the diketones **7** with hydrazine hydrate in the presence of a catalytic amount of sulfuric acid gave 3,4-dimethoxybenzoic acid.

The previously known 1,5-dicarbonyl compound **10** [6] has been prepared by the reaction of benzalacetophenone with 2,2-dimethyltetrahydropyran-4-one as a single isomer. We have found that the diketone **10** reacts with hydroxylamine hydrochloride in glacial acetic acid and cyclises to the previously unreported 7,7-dimethyl-2,4-diphenyl-5,8-dihydropyrano[4,3-*b*]pyridine **11**. The anticipated result was not obtained when carrying out the reaction in alcohol.

The ^{1}H NMR spectrum of the product **11** did not disagree with the proposed structure and the composition was shown by elemental analysis (see Experimental).



EXPERIMENTAL

Monitoring of the course of the reaction and the purity of the reaction products was carried out using TLC on Silufol UV-254 plates and by GLC on a Tsvet-152 chromatograph (0.7 m × 3 mm column, liquid phase SE30/5% on Chromaton-N-AW 0.16-0.20 mm, nitrogen carrier, temperature program 75-300° / 22°C/min). IR spectra were recorded on a Perkin-Elmer instrument using KBr. Mass spectra were obtained on an HP-5972 instrument with an electron ionization energy of 70 eV. ^{1}H NMR spectra were recorded on a Bruker A-250 (250 MHz) instrument with TMS internal standard. Melting points for the materials were determined on a Koffler block Boetius apparatus in an open capillary and are uncorrected.

2,2-Dimethyl-4-morpholinodihydropyrans (2, 3). Morpholine (15.26 g, 175.5 mmol) in benzene (10 ml) was added dropwise to a solution of 2,2-dimethyltetrahydropyran-4-one **1** (15 g, 117 mmol) in benzene (50 ml) and refluxed in a Dean–Stark apparatus until the calculated amount of water had been produced. The solvent was distilled off and the residue was distilled *in vacuo* to give a mixture of compounds **2** and **3**

(12.15 g); bp 109-112°C (4 mm Hg). Yield 52%. ^{1}H NMR spectrum, δ, ppm: **isomer 2**: 2.8 (4H, m, CH_2–N); 3.7 (4H, t, CH_2–O); 1.3 (6H, s, $2CH_3$); 2.0 (2H, s, 3-H); 4.6 (1H, t, 5-H); 4.2 (2H, m, 6-H); **isomer 3**: 2.8 (4H, m, CH_2–N); 3.7 (4H, t, CH_2–O); 1.3 (6H, s, $2CH_3$); 2.0 (2H, t, 5-H); 3.8-3.9 (2H, t, 6-H); 4.5 (1H, s, 3-H).

5-Acyl-2,2-dimethyltetrahydropyran-4-ones (5-7) (General Method). The corresponding acid chloride (54 mmol) in dry benzene (10 ml) was added dropwise with stirring to a solution of the mixture of enamines **2** and **3** (8.88 g, 45 mmol) and triethylamine (5.45 g, 54 mmol) in dry benzene (60 ml) with the reaction held at room temperature. The reaction mixture was stirred for a further 2 h, heated to reflux for 30 min, HCl (18%, 22 ml) added, and heated for a further 1 h. After cooling, the aqueous layer was separated and the benzene was washed with water to neutral reaction. The aqueous solution was basified with potassium carbonate to pH ~7 and extracted three times with benzene. The combined benzene fractions were dried over $CaCl_2$, benzene was distilled off, and the residue was distilled twice in vacuo monitoring the purity of the product by GLC analysis.

5-Acetyl-2,2-dimethyltetrahydropyran-4-one (4) was prepared similarly but after the addition of acetyl chloride the mixture was not heated but immediately hydrolyzed with HCl (18%, 22 ml) and then worked up as described above.

The physicochemical and spectrosopic properties of the compounds **4-7** are given in Table 1.

6,6-Dimethyl-3-phenyl-4,7-dihydro-(2H)-pyrano[4,3-*c*]pyrazole (8). A mixture of the diketones **5** (0.5 g, 2.1 mmol) and hydrazine hydrate (0.105 g, 2.1 mmol) in alcohol (6.2 ml) was refluxed for 4 h. The alcohol was evaporated off and the residue was recrystallized from i-PrOH to give compound **8** (300 mg) with mp 172-175°C. Yield 65.7%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.3 (6H, s, $2CH_3$); 2.9 (2H, s, 7-H); 4.9 (2H, s, 4-H); 7.3 (1H, s, NH); 7.5-7.9 (5H, m, Ph). Found, %: C 73.31; H 7.25; H 12.35. $C_{14}H_{16}N_2O$. Calculated, %: C 73.66; H 7.06; N 12.27

6,6-Dimethyl-3-phenyl-4,7-dihydro-(2H)-pyrano[4,3-*c*]isoxazole (9). A mixture of the diketones **5** (0.5 g, 2.1 mmol), hydroxylamine hydrochloride (0.21 g, 3.1 mmol), and glacial acetic acid (5 ml) was refluxed for 5 h, poured into water, and taken to neutral reaction. The obtained solution was extracted with benzene, solvent was distilled off, and the residue was recrystallized from alcohol to give compound **9** (120 mg); mp 95-97°C. Yield 26%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.4 (6H, s, $2CH_3$); 2.8 (2H, s, 7-H); 4.9 (2H, s, 4-H); 7.4-7.7 (5H, m, Ph). Found, %: C 72.95; H 6.73; N 6.23. $C_{14}H_{15}NO_2$. Calculated, %: C 73.34; H 6.59; N 6.11.

7,7-Dimethyl-2,4-diphenyl-5,8-dihydropyrano[4,3-*b*]pyridine (11). A mixture of the 1,5-diketone **10** (1 g, 3 mmol) (obtained according to [6]) and hydroxylamine hydrochloride (0.479 g, 6 mmol) in glacial acetic acid (10 ml) and alcohol (2 ml) was refluxed for 7 h. The reaction mixture was poured into water, basified to pH ~8-9, and extracted twice with benzene. The benzene was distilled off and the residue was recrystallized from *i*-PrOH. Standing the mother liquor for one week at -5°C gave compound **11** (0.38 g); mp 84-85°C. Yield 40%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.4 (6H, s, $2CH_3$); 3.0 (2H, s, 8-H); 4.7 (2H, s, 5-H); 7.2-7.9 (11H, m, Ar and Py). Found, %: C 83.90; H 6.76; N 4.21. $C_{22}H_{21}NO$. Calculated, %: C 83.78; H 6.71; N 4.44.

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