3-Acyl-4,6-dinitro-5-hydroxybenzofurans (VIa-c). A) A solution of 0.03 mole of nitric acid was added gradually with stirring at room temperature to a suspension of 0.01 mole of benzofuran Ia-c in 20 ml of glacial acetic acid, and the mixture was stirred for 5 h. The precipitate was removed by filtration, washed on the filter with water, and recrystallized from ethyl acetate (Table 1).

B) A cooled (to 0-5°C) nitrating mixture, prepared from 1 ml of concentrated nitric acid and 1.4 ml of concentrated sulfuric acid, was added dropwise at 10-15°C to a solution of 0.01 mole of IIa-c in 20 ml of glacial acetic acid, and the mixture was stirred at room temperature for 5 h. The resulting precipitate was removed by filtration, washed on the filter with water, dried, and recrystallized from ethyl acetate (Table 1).

No melting-point depression was observed for a mixture of samples obtained by methods A and B.

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SYNTHESIS OF NEW UNCONDENSED BIHETEROCYCLIC COMPOUNDS — 2,2-DIMETHYLTETRAHYDROPYRAN DERIVATIVES

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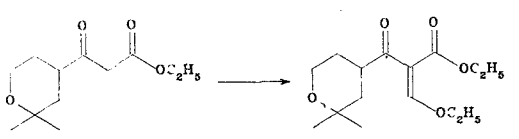
UDC 547.811+547.7.772+547.8.853+547.8.89

A method for the synthesis of α-ethoxymethylene-β-(2,2-dimethyltetrahydro-4-pyranyl)-β-oxopropionate is proposed. New uncondensed biheterocyclic compounds were obtained on the basis of the latter. A fundamental difference in the behavior of this system with 1,2-, 1,3-, and 1,4-binucleophiles is demonstrated.

The synthesis of ethoxymethylene derivatives in order to use them in heterocyclization reactions to give uncondensed biheterocycles was a continuation of research on β-keto esters of the tetrahydropyran series.

An ethoxymethylene derivative of a β-keto ester was obtained by the method in [1] on the basis of ethyl β-(2,2-dimethyltetrahydro-4-pyranyl)-β-oxopropionate [2].



I II

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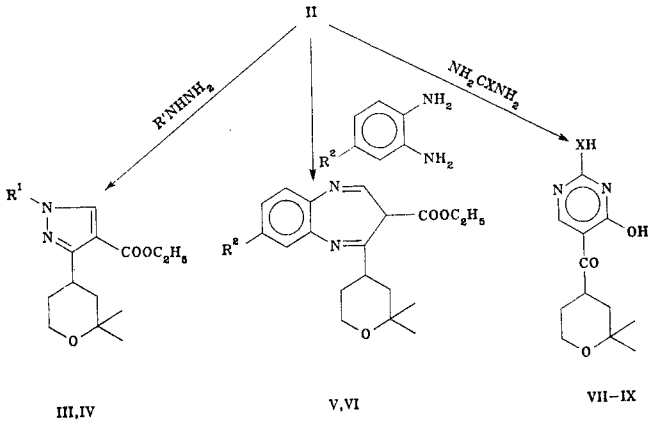
Compound II is capable of undergoing ambiguous cyclization, inasmuch as it contains three functions that compete for reaction with binucleophile. In fact, as one should have expected, cyclization products III-VI were obtained by reaction of the ethoxymethylene derivative with hydrazine, phenylhydrazine, o-phenylenediamine, and 2-amino-4-nitroaniline, as indicated in the following scheme:



III R^1=H; IV R^1=C_6H_5; V R^2=H; VI R^2=NO_2; VII X=O; VIII X=S; IX X=NH

At the same time, the products of the reaction of the ethoxymethylene derivative of the β-keto ester with urea, thiourea, and guanidine were exclusively ketones VII-IX. Numerous attempts to obtain 2-amino(mercapto, hydroxy)-4-(2,2-dimethyltetrahydro-4-pyranyl)-5-carbethoxypyrimidines were unsuccessful.

Thus the fundamental difference in the behavior of ethyl α-ethoxymethylene-β-(2,2-dimethyltetrahydro-4-pyranyl)-β-oxopropionate with 1,2-, 1,3-, and 1,4-binucleophiles is apparent. It is difficult to surmise whether the initial step is cyclization with the 1,3-binucleophile to give 5-carbethoxypyrimidines with subsequent rearrangement to 5-ketopyrimidines or whether the reaction products are formed as a result of direct cyclization at the ethoxy and carbethoxy groups as a consequence of the steric hindrance due to the heterocyclic ring. There is no doubt that the fact of the different behaviors of 1,2-, 1,3-, and 1,4-binucleophiles with ethoxymethylene derivatives of β-keto esters that contain a bulky substituent requires further study of analogous systems in heterocyclization reactions.

A study of the tranquilizing antineurotic activity of the synthesized compounds was conducted in the laboratory of convulsive states of the Institute of Fine Organic Chemistry. It was established that almost all of the synthesized compounds to some degree prevent clonic spasms and consequently have not only antispasmodic but also tranquilizing activity. The antispasmodic activity with respect to Corazole increases with the introduction of a benzodiazepine grouping into the molecule, reaching a maximum in the case of VI, which contains a nitro group in the 8 position.

EXPERIMENTAL

Thin-layer chromatography (TLC) was carried out on KSK silica gel, prepared by the method in [3], in an ether–petroleum ether system (3:1). Analysis by gas–liquid chromatography (GLC) was performed with a Khrom-4 chromatograph with packed glass columns with 5% XE-60 silicone on Chromaton N-AW, silanized with hexamethyldisilane, as the liquid phase. The IR spectra were recorded with a UR-20 spectrometer, the PMR spectra were recorded with a Varian T-60 spectrometer with tetramethylsilane as the internal standard, and the mass spectra were obtained with an MKh-1320 mass spectrometer.

Ethyl α-Ethoxymethylene-β-(2,2-dimethyltetrahydro-4-pyranyl)-β-oxopropionate (II). A mixture of 4 g (18 mmole) of I, 4 g (40 mmole) of acetic anhydride, and 3 g (20 mmole) of ethyl orthoformate was heated slowly during which the temperature of the reaction mixture rose sharply to 140°C, after which it fell to 110°C. Stirring was continued at this temperature for another 2 h, after which the unchanged substances were removed by distillation. The reaction product was distilled *in vacuo* to give 4.0 g (80%) of II with bp 180-181°C (4.5 mm), n_D^{20} 1.6890, and d_4^{20} 1.1086. IR spectrum (thin layer): 1630 (C=C), 1690 (keto C=O),

and 1710 cm^{-1} (ester C=O). PMR spectrum (in CCl_4): 7.40 (1H, s, C=CH), 4.20 (4H, q, J = 7 Hz, COO—CH_2 and =CO—CH_2), 3.60 (2H, m, 6-CH_2), 3.00 (1H, m, 4-CH), 1.50 (4H, m, 3- and 5-CH_2), 1.40 (6H, t, J = 7 Hz, COO—C—CH_3 and =COO—C—CH_3), and 1.10 ppm (6H, s, 2-CH_3). Found: C 63.5; H 8.6%; M^+ 284. $C_{15}H_{24}O_5$. Calculated: C 63.4; H 8.5%; M 284.

3-(2,2-Dimethyltetrahydro-4-pyranyl)-4-carbethoxypyrazole (III). A mixture of 0.7 g (2.5 mmole) of ester II, 0.13 g (2.5 mmole) of hydrazine hydrate, and 20 ml of ethanol was refluxed for 1 h, after which the solvent was removed by distillation, and the residue was fractionated to give 0.5 g (81%) of pyrazole III with bp 198-199°C (3.5 mm); the np^{20} and d_4^{20} values could not be determined because of the viscosity of the substance. IR spectrum (thin layer): 1620 (aromatic pyrazole ring) and 1710 cm^{-1} (ester C=O). PMR spectrum (in CCl_4): 10.00 (1H, s, NH), 7.80 (1H, s, C=CH), 4.20 (2H, q, J = 7 Hz, COO—CH_2), 3.70 (2H, m, 6-CH_2), 3.00 (1H, m, 4-CH), 1.70 (4H, m, 3- and 5-CH_2), 1.30 (3H, t, J = 7 Hz, COO—CH_3), and 1.20 ppm (6H, s, 2-CH_3). Found: C 61.7; H 8.1; N 11.2%; M^+ 252. $C_{13}H_{20}N_2O_3$. Calculated: C 61.9; H 8.0; N 11.1%; M 252.

1-Phenyl-3-(2,2-dimethyltetrahydro-4-pyranyl)-4-carbethoxypyrazole (IV). The reaction of 1.4 g (5 mmole) of ester II, 0.5 g (5 mmole) of phenylhydrazine, and 40 ml of ethanol by a method similar to that described above gave 1.3 g (80%) of phenylpyrazole IV with bp 198-199°C (2 mm) as a viscous liquid. IR spectrum (thin layer): 1600 (benzene ring), 1620 (aromatic pyrazole ring), and 1720 cm^{-1} (ester C=O). PMR spectrum (in CCl_4): 7.80 (1H, s, C=CH), 7.20 (5H, m, aromatic protons), 4.20 (2H, q, J = 7 Hz, COO—CH_2), 3.70 (2H, m, 6-CH_2), 3.00 (1H, m, 4-CH), 1.70 (4H, m, 3- and 5-CH_2), 3.70 (2H, m, 6-CH_2), 3.00 (1H, m, 4-CH), 1.70 (4H, m, 3- and 5-CH_2), 1.30 (3H, t, J = 7 Hz, COO—C—CH_3), and 1.20 ppm (6H, s, 2-CH_3). Found: C 69.4; H 7.4; N 8.4%; M^+ 328. $C_{19}H_{24}N_2O_3$. Calculated: C 69.5; H 7.4; N 8.5%; M 328.

2-(2,2-Dimethyltetrahydro-4-pyranyl)-3-carbethoxy-1,5-benzodiazepine (V). A 1.4 g (5 mmole) of II was added dropwise to 0.5 g (5.3 mmole) of o-phenylenediamine dissolved in 100 ml of refluxing toluene, and the mixture was refluxed for 1 h. The solvent was removed by distillation, and the residue, which began to crystallize, was washed with ether and dried to give 1.4 g (86%) of benzodiazepine V with mp 124-125°C and R_f 0.71. IR spectrum (mineral oil): 1600 (benzene ring), 1650 (C=N), and 1700 cm^{-1} (ester C=O). PMR spectrum (in CCl_4): 8.30 (1H, d, J = 12 Hz, N=CH), 7.00 (4H, m, aromatic protons), 4.20 (2H, q, J = 7 Hz, COO—CH_2), 3.70 (2H, m, 6-CH_3), 3.00 (1H, m, 4-CH), 1.50 (4H, m, 3- and 5-CH_2), 1.30 (3H, t, J = 7 Hz, COOC—CH_3), and 1.20 ppm (6H, s, 2-CH_3). Found: C 68.9; H 7.2; N 8.8%; M^+ 328. $C_{19}H_{24}N_2O_3$. Calculated: C 69.5; H 7.4; N 8.5%; M 328.

2-(2,2-Dimethyltetrahydro-4-pyranyl)-3-carbethoxy-8-nitro-1,5-benzodiazepine (VI). Similarly, the reaction of 1.4 g (5 mmole) of II in 100 ml of toluene and 0.8 g (5.3 mmole) of 2-amino-4-nitroaniline gave 1.6 g (87%) of nitrobenzodiazepine VI with mp 120-121°C and R_f 0.64. IR spectrum (in mineral oil): 1600 (benzene ring), 1640 (C=N), and 1700 cm^{-1} (ester C=O). PMR spectrum (in CCl_4): 8.30 (1H, d, J = 12 Hz, N=CH), 8.00 (3H, m, aromatic protons), 1.50 (4H, m, 3- and 5-CH_2), 1.30 (3H, t, J = 7 Hz, COO—C—CH_3), and 1.20 ppm (6H, s, 2-CH_3). Found: C 60.8; H 6.0; N 11.4%; M^+ 373. $C_{19}H_{23}N_3O$. Calculated: C 61.1; H 6.2; N 11.2%; M 373.

2,4-Dihydroxy-5-(2,2-dimethyltetrahydro-4-pyranoyl)pyrimidine (VII). A mixture of 1.4 g (5 mmole) of ester II, 0.3 g (5 mmole) of urea, and a solution of sodium ethoxide, prepared from 0.25 g (1 mmole) of sodium and 5 ml of ethanol, was evaporated to dryness on a water bath, and the residue was dissolved in 10 ml of water. Glacial acetic acid (1.2 ml) was added to the solution, and the mixture was stirred until its temperature reached room temperature. The precipitated crystals were removed by filtration, washed with water, and dried to give 1.0 g (80.6%) of VII with mp 185-186°C and R_f 0.36. IR spectrum (in mineral oil): 1600 (aromatic pyrimidine ring) 1665 (ring C=O), and 1680 cm^{-1} (keto C=O). PMR spectrum (in d_5-pyridine): 8.60 (1H, s, N=CH), 4.20 (1H, m, 4-CH), 3.80 (2H, m, 6-CH_2), 1.80 (4H, m, 3- and 5-CH_2), and 1.30 ppm (6H, s, 2-CH_3). Found: C 57.2; H 6.7; N 11.2%; M^+ 252. $C_{12}H_{16}N_2O_4$. Calculated: C 57.1; H 6.4; N 11.1%; M 252.

2-Mercapto-4-hydroxy-5-(2,2-dimethyltetrahydro-4-pyranoyl)pyrimidine (VIII). Similarly, the reaction of 1.4 g (5 mmole) of ester II, 0.4 g (5 mmole) of thiourea, and a solution of sodium ethoxide gave 1.2 g (91%) of VII with mp 260-261°C and R_f 0.57. IR spectrum (in mineral oil): 1600 (aromatic pyrimidine ring), 1665 (ring C=O), and 1680 cm^{-1} (keto C=O). PMR spectrum (in d_5-pyridine): 8.40 (1H, s, N=CH), 4.20 (1H, m, 4-CH), 3.80 (2H, m,

6-CH_2), 1.80 (4H, m, 3- and 5-CH_2), and 1.30 ppm (6H, s, 2-CH_3). Found: C 53.8; H 6.1; N 10.0; S 12.0%; M^+ 268. $C_{12}H_{16}N_2O_3S$. Calculated: C 53.7; H 6.0; N 10.4; S 11.9%; M 268.

2-Amino-4-hydroxy-5-(2,2-dimethyltetrahydro-4-pyranoyl)pyrimidine (IX). Similarly, the reaction of 1.4 g (5 mmole) of ester II, 0.5 g (5 mmole) of guanidine hydrochloride, and a solution of sodium ethoxide gave 1.1 g (89%) of IX with mp 256-257°C and R_f 0.44. IR spectrum (in mineral oil): 1600 (aromatic pyrimidine ring), 1665 (ring C=O), 1680 (keto C=O), and 3200-3300 cm^{-1} (NH, NH_2). PMR spectrum (in d_5-pyridine): 11.60 (2H, s, NH_2), 8.00 (1H, s, N=CH), 4.50 (1H, m, 4-CH), 3.80 (2H, m, 6-CH_2), 1.80 (4H, m, 3- and 5-CH_2), and 1.30 ppm (6H, s, 2-CH_3). Found: C 57.6; H 6.7; N 16.6%; M^+ 251. $C_{12}H_{17}N_3O_3$. Calculated: C 57.4; H 6.8; N 16.7%; M 251.

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O-ETHYLVALEROLACTONIUM TETRAFLUOROBORATE AND VALEROLACTONE DIETHYLACETAL IN THE SYNTHESIS OF CONDENSED PYRANS

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A pyrano[2,3-b]quinoline derivative was obtained by the reaction of O-ethylvalerolactonium tetrafluoroborate with ethyl anthranilate and subsequent cyclization of the intermediate imido ester. A number of derivatives of pyrano[3,2-c]pyridine and pyrano[2,3-d]pyrimidine derivatives were synthesized on the basis of valerolactone diethylacetal and α-dimethylaminomethylenevalerolactone diethylacetal.

In [1-4] we published data from a study of the properties of previously little-investigated activated lactones. These studies dealt only with butyrolactone derivatives. The aim of the present research was to investigate the properties and transformations of derivatives of a representative of a homologous series of lactones, viz., valerolactone.

Valerolactone (I) was synthesized from δ-chlorovaleric acid by the method in [5]. Activation of the lactone carbonyl group was realized by alkylation of it with triethyloxonium tetrafluoroborate to give O-ethyllactonium tetrafluoroborate (II). In [1, 2] it was shown that the complex of butyrolactone with triethyloxonium tetrafluoroborate reacts with substituted anilines to give the corresponding imido ester salts, from which one can obtain condensed three-ring compounds. Complex II also reacts smoothly with ethyl anthranilate to give an imido ester tetrafluoroborate, which is converted to the base by treatment with triethylamine. Imido ester III, without isolation in the individual state, undergoes intramolecular cyclization when it is refluxed in an alcohol solution of sodium ethoxide. The resulting sodium derivative of pyrano[2,3-b]-4-quinolone is treated with hydrochloric acid solution, and 5-oxo-2H,3,4,5,10-tetrahydropyrano[2,3-b]quinoline (IV) is isolated.

Valerolactone diethylacetal (V), which was mentioned only in [6] in connection with a study of the hydrolysis of cyclic ortho esters, was obtained by exchange decomposition of complex II with a solution of sodium ethoxide. Like butyrolactone acetal, it can react with compounds that have active methylene groups. The reactions of acetal V with cyanoacetamide and cyanoacetic ester take place by heating the reaction mixtures to 130-150°C with removal

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