SYNTHESIS AND ANTICONVULSIVE ACTIVITY OF 2,3-DISUBSTITUTED 5,5-DIMETHYLTETRAHYDROPYRANO- AND 5,5-DIMETHYLTETRAHYDROTHIOPYRANO[3,4-b]THIOPHENES

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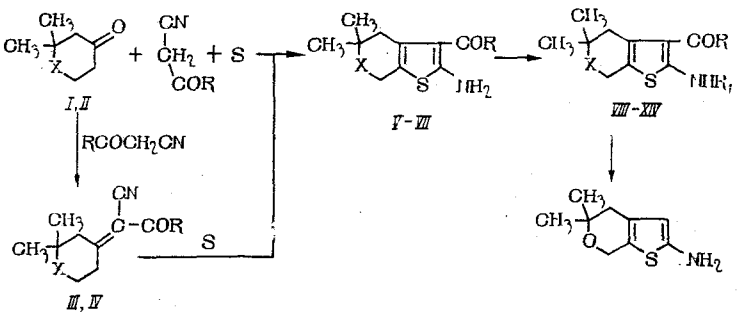
Aminoether derivatives of condensed thiophenes are of interest in possessing anticonvulsive [1] and antibacterial [2] activity. The object of this investigation was to synthesize condensed six-membered thiophenes containing sulfur and oxygen.

Condensation of 2,2-dimethyltetrahydropyran- and 2,2-dimethyltetrahydrothiopyran-4-ones (I and II) [3] with nitriles containing active methylene groups afforded the ethyl esters of 2,2-dimethyltetrahydro-4-pyranylidene- and 2,2-dimethyltetrahydro-4-thiopyranylidenecyanoacetic acids (III and IV). Reaction of these with sulfur gave 2,3-disubstituted 5,5-dimethyltetrahydropyrano[3,4-b]thiophenes (V-VII) in high yields (Table 1).



I: X = O; II: X = S;
III, V: X = O, R = OC_2H_5;
IV, VI: X = S, R = OC_2H_5;
VII: X = O, R = M = $NO_2C_6H_4$;
VIII: X = O, R = OC_2H_5, R_1 = $COCH_3$;
IX: X = S, R = OC_2H_5, R_1 = $COCH_3$;
X: X = O, R = OC_2H_5, R_1 = $COCH_2Cl$;
XI: X = O, R = OH, R_1 = H;
XII: X = S, R = OH, R_1 = H;
XIII: X = O, R = OH, R_1 = $COCH_3$;
XIV: X = S, R = OH, R_1 = $COCH_3$.

Compounds V-VII were also obtained by condensing I and II with nitriles and sulfur in a single stage, but yields were lower, and it was rather difficult to isolate the reaction products. The IR spectra of V and VI exhibit bands at 1620 (C = C), 1740 (COO), and 2240 (CN) cm^{-1}. In the 3100- to 3400-cm^{-1} region, the spectra of V and VI displayed four bands, and VII, three bands for NH_2 absorption. The broad, intense band with two maxima at 1600 and 1670 cm^{-1} and a shoulder at 1720 cm^{-1} apparently corresponds to deformational vibrations of the aromatic ring, stretching vibrations of the ethoxycarbonyl group, and deformational vibrations of the amino group of VII.

The structures of V-VII were confirmed by their PMR spectra. Thus, for V and VI, δ [5-$(CH_3)_2$ = 1.23 ppm; δ (3-OCH_2CH_3) = 1.4 ppm; δ (4-CH_2) = 2.6 ppm; δ (3-OCH_2CH_3) = 4.23 ppm; δ (7-CH_2) = 4.45 ppm; δ (NH_2) = 6.2 ppm; and for VII δ (7-CH_2) = 4.47 ppm; δ (NH_2) = 6.87 ppm; δ (C_6H_4) = 7.18 ppm].

Acylation of V and VI with acetyl chloride or chloroacetic anhydride afforded 2-acetyl (or chloroacetyl)-amino-3-ethoxycarbonyl-5,5-dimethyltetrahydropyrano (or thiopyrano) [3,4-b]thiophenes (VIII-X). The IR spectra contained bands at 1606 (NHCO), 1680 (COO), and 3280 (NH) cm^{-1} (in the spectrum of X, 3220 (NH) cm^{-1}). In the PMR spectra of VIII and IX, δ ($COCH_3$) = 2.23 ppm and δ (NH) = 12.08 ppm, and in the spectrum of X, δ (CH_2Cl) = 4.27 ppm and δ (NH) = 9.62 ppm. The chemical shifts of the remaining protons were virtually identical with those of the corresponding protons in the spectra of V-VII.

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TABLE 1. 2,3-Disubstituted 5,5-Dimethyltetrahydropyrano(or thiopyrano)[3,4-b]thiophenes

Compound	Yield, %	Melting point, deg	Found, %		Molecular formula	Calculated, %	
			N	S		N	S
V	A 77,37 B 40,0	54—5	5,53	12,62	$C_{12}H_{17}NO_3S$	5,48	12,55
VI	A 97,80 B 46,25	59—60	5,20	23,73	$C_{12}H_{17}NO_2S_2$	5,16	23,62
VII	43,80	189—191	8,76	10,00	$C_{16}H_{16}N_2O_4$	8,42	9,64
VIII	72,70	81—2	4,73	10,79	$C_{14}H_{19}NO_4S$	4,70	10,84
IX	54,31	74—5	4,55	20,68	$C_{14}H_{19}NO_3S_2$	4,47	20,44
X	68,0	110—2	3,96	9,64	$C_{14}H_{18}ClNO_4S$	4,21	9,66
XI	72,60	125—6	6,40	14,35	$C_{10}H_{13}NO_3S$	6,11	14,10
XII	68,79	94—5	5,69	26,21	$C_{10}H_{13}NO_2S_2$	5,76	26,33
XIII	75,0	165—6	5,44	12,00	$C_{12}H_{15}NO_4S$	5,20	11,90
XIV	88,24	191—2	5,00	22,59	$C_{12}H_{15}NO_3S_2$	4,73	21,69

Note. Solvents for recrystallization: V, heptane; VI, mixture of light petroleum and ether; VII and X, methanol; VIII, IX, XIII, and XIV, ethanol; XI and XII, mixture of chloroform and ether.

Alkaline hydrolysis of V, VI, VIII, and IX afforded the corresponding 2-amino(or acetylamino)-3-carboxy-5,5-dimethyltetrahydropyrano(or thiopyrano)[3,4-b]thiophenes (XI-XIV). The IR spectra of XI and XII contained NH_2 and OH absorption bands at 2320 and 3455 cm^{-1} and XIII and XIV at 3340 and 3455 cm^{-1}. Stretching vibrations of the carboxyl group attached to the aromatic heterocycle in XI-XIV were responsible for the absorption at 1645 cm^{-1}, and of the NCO group at 1670 cm^{-1}. The PMR spectra of XI and XII contained signals for the hydroxy groups at 7.6-8.4 ppm, δ (NH_2) = 5.17 ppm, and signals due to the NH group were observed for XIII and XIV at 9.35 ppm.

Reaction of XI with 85% formic acid led to the formation of 2-amino-5,5-dimethyltetrahydropyrano[3,4-b]-thiophene (XV). The IR spectrum contained three typical NH_2 absorption bands at 3200-3400 cm^{-1}. The PMR spectrum contained a sharp singlet due to the proton in the 3 position of the thiophene ring, at 5.82 ppm, and δ (NH_2) = 4.1 ppm.

The pharmacological activity of compounds V-XV was investigated using mice weighing 18-20 g, by means of methods adopted for the evaluation of substances with anticonvulsive effects, i.e., the maximum electroshock test [4], the subcutaneous corazole test [5], a test involving subcutaneous administration of arecoline, and a test involving intraperitoneal administration of nicotine. In addition, the occurrence of the "neurological deficit," which is a side effect of the drugs, was also investigated, using for this purpose the "grid-climbing" method to record orientational activity, and the "rotating-rod" method [6] to detect disturbance of motor coordination. The compounds were administered intraperitoneally as suspensions with Tween-80. The 50% effective doses (ED_{50} values) were calculated [7].

A comparative investigation of the thiophene derivatives (V-XV) showed that all the compounds displayed slight anticonvulsive activity in the maximum electroshock and nicotine and adrenaline tests. In the corazole test, however, some compounds showed marked activity which was most evident in V, VII, and VIII, and it was observed that the introduction of the m-$NO_2C_6H_4CO$ group into the 3 position weakened the anticorazole activity, whereas introduction of the acetylamino group into the 2 position increased the level of this type of activity twofold (Table 2). It is noteworthy that the compounds exhibited sedative and myorelaxant properties at lower doses than those required to suppress corazole convulsions (cf. Table 2), although VII was an exception in this respect. The latter compound was peculiar in showing virtually no myorelaxant effects at toxic dose levels. The therapeutic indices of VII, as determined by the ratio of the ED_{50} for disturbance of motor coordination to that in the anticorazole test, were higher than for the other analogs, indicating the greater selectivity of this derivative.

Thus, introduction of the m-$NO_2C_6H_4CO$ moiety into the 3 position of pyranothiophen weakened the anticorazole properties, but the therapeutic breadth of action of this compound was significantly increased.

TABLE 2. Comparative Activities of 2,3-Disubstituted 5,5-Dimethyl-4,5-dihydro-7H-pyrano- and 5,5-Dimethyl-4,5-dihydro-7H-pyrano[3,4-b]thiophenes

Compound	Antagonism to the consulsive effects of corazole	Suppression of orientational reflexes	Disturbance of motor coordination
	ED_{50}, mg/kg		
V	220 (133,3—363,0)	115 (74,1—178,2)	140 (99,2—197,4)
VII	350 (212,7—577,5)	285 (197,9—410,4)	>1000
VIII	185 (148,0—231,2)	70 (49,3—99,4)	153 (128,5—182,1)

Note. Confidence limits for P = 0.05 are given in parentheses.

EXPERIMENTAL

The IR spectra were recorded in vaseline oil on a UR-10 spectrometer with NaCl and LiCl prisms. The PMR spectra were measured on a Varian T-60 in chloroform and carbon tetrachloride, using tetramethylsilane as internal standard. Values for the signals are given in the δ scale.

Ethyl 2,2-Dimethyltetrahydro-4-pyranylidenecyanoacetate (III). A mixture of 12.8 g (0.1 mole) of I or II, 3 g (0.1 mole) of ethyl cyanoacetate, 1 ml of glacial acetic acid, and 2 ml of diethylamine was boiled in 100 ml of dry benzene for 5 h, until water had been removed completely. After cooling, the mixture was washed with water and dried over magnesium sulfate. After removal of the solvent, the product was distilled in vacuo to give 14.44 g (62.79%) of III, bp 127-129°C (1.5 mm Hg), N_D^{20} 1.4898, d_4^{20} 1.0692. Found, %: C 64.46, H 7.00, N 6.29. $C_{12}H_{17}NO_3$. Calculated, %: C 64.55, H 7.67, N 6.22.

Ethyl 2,2-Dimethyltetrahydro-4-thiopyranylidenecyanoacetate (IV). From a mixture of 14.4 g (0.1 mole) of II, 11.3 g (0.1 mole) of ethyl cyanoacetate, 1 ml of glacial acetic acid, 2 ml of diethylamine, and 100 ml of dry benzene, there was obtained as described above 18.78 g (78.59%) of IV, bp 150°C (3 mm Hg), n_D^{20} 1.5020. Found, %: N 5.88, S 13.46. $C_{12}H_{17}NO_2S$. Calculated, %: N 5.84, S 13.39.

5,5-Dimethyl-4,5-dihydro-7H-pyrano- and 5,5-Dimethyl-4,5-dihydro-7H-thiopyrano[3,4-b]-2-amino-3-ethoxycarbonyl(or m-nitrobenzoyl)thiophenes (V-VII). Method A. A mixture of 0.1 mole of III or IV, 0.1 mole of powdered sulfur, and 80 ml of 96% ethanol was heated with stirring at 50°C, and 10 ml of diethylamine was added over 30 min. The temperature was then raised to 60°C, and stirring continued until the sulfur had dissolved completely. The mixture was cooled in ice water, and poured into 200 ml of cold water followed by acidification to Congo Red with 18% hydrochloric acid. The precipitate was isolated and washed with water followed by heptane, when it crystallized completely. The crystals were filtered off, washed twice with heptane, and dried in a vacuum dessiccator. The constants are given in Table 1.

Method B. A suspension of 0.1 mole of I or II, 0.1 mole of cyanoacetic ester or ω-cyano-m-nitroacetophenone, and 0.1 mole of powdered sulfur in 120 ml of 96% ethanol was heated to 50°C, and a mixture of 5 ml of morpholine and 3 ml of diethylamine in 10 ml of ethanol was added with stirring over 30 min. The temperature rose to 60°C. The experiment was continued as described above. The constants are given in Table 1.

5,5-Dimethyl-4,5-dihydro-7H-pyrano- and 5,5-Dimethyl-4,5-dihydro-7H-thiopyrano[3,4-b]-2-acetyl-(or chloroacetyl)amino-3-ethoxycarbonylthiophenes (VIII-X). To a solution of 0.01 mole of V or VI in 30 ml of dry dioxane was added 0.01 mole of acetyl chloride or acetic anhydride during 1 h under reflux, and the mixture was then poured into cold water. The crystalline solid which separated was isolated, washed with water, and dried in a vacuum desiccator. Constants are given in Table 1.

5,5-Dimethyl-4,5-dihydro-7H-pyrano- and 5,5-Dimethyl-4,5-dihydro-7H-thiopyrano[3,4-b]-2-amino-(or acetylamino)-3-ethoxycarbonylthiophenes (XI-XIV). A mixture of 0.02 mole of V, XI, VIII, or IX and 30 ml of methanol containing 0.04 mole of sodium hydroxide was boiled for 5 h under reflux. It was then poured into 200 ml of ice water (if starting material was present, it was necessary to filter), and acidified with concentrated hydrochloric acid. The crystalline solid which separated was filtered off, washed with cold water, and dried in a vacuum desiccator. Constants given in Table 1.

5,5-Dimethyl-4,5-dihydro-7H-pyrano[3,4-b]-2-aminothiophene (XV). A mixture of 1 g (0.0054 mole) of XI and 15 ml of 85% formic acid was kept until evolution of carbon dioxide had ceased. The mixture was cooled in an ice–salt mixture, and 60% potassium hydroxide solution was added until weakly alkaline. The yellow crystalline solid which separated was filtered off, washed with water, and dried in the vacuum desiccator. Yield 0.3 g (37.5%), mp 58-60°C (from alcohol). Found, %: N 7.69, S 17.51, $C_9H_{13}NOS$. Calculated, %: N 7.63, S 17.48.

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BIOLOGICAL ACTIVITY OF TRANSFORMED STEROIDS

IX. SYNTHESIS AND BIOLOGICAL PROPERTIES OF 6α-FLUOROCYCLOHEXANO[1',2';16α,17α]PROGESTERONE

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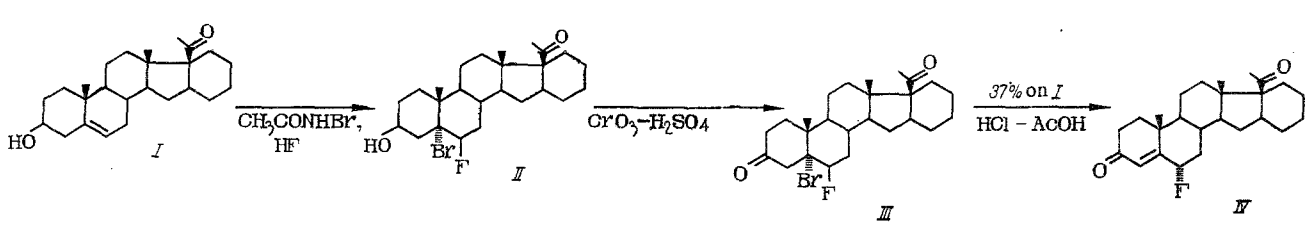
We have previously synthesized a new class of pentacyclic steroids of the pregnane series having an additional six-membered carbocycle in the 16,17 position, i.e., D_6'-pentaranes [1]. Biological tests showed these compounds to possess high gestagenic activity [2]. This communication describes the synthesis and investigation of the biological activity of a new representative of this class, 6α-fluorocyclohexano[1',2';16α,17α]pregn-4-en-3,20-dione (IV). Of the numerous methods available for introducing a fluorine atom into the steroid molecule, we chose the route involving the addition of BrF to a double bond [3]. This comprises reaction of N-bromoacetamide with the Δ^5-3-hydroxysteroid in the presence of a large excess of hydrogen fluoride at −80°C in methylene chloride, with the addition of tetrahydrofuran (in order to increase the effective concentration of fluoride ion). Treatment of cyclohexano[1',2';16α,17α]pregn-5-en-3β-ol-20-one (I) [1] with N-bromo acetamide and hydrofluoric acid in methylene chloride–tetrahydrofuran (THF) afforded the bromofluoride II. Subsequent oxidation of the 3β-hydroxy group in II with chromium trioxide and sulfuric acid in acetone gave the 3-keto derivative III. Treatment of the latter with dry hydrogen chloride in acetic acid resulted in simultaneous dehydrobromination and epimerization at C_6 to form IV.



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