UDC 547.725 + 615.779.932 + 541.67 + 543.422

2,4-DIMETHYL-5-NITROFURAN-3-CARBOXYLIC ACID AND ITS DERIVATIVES

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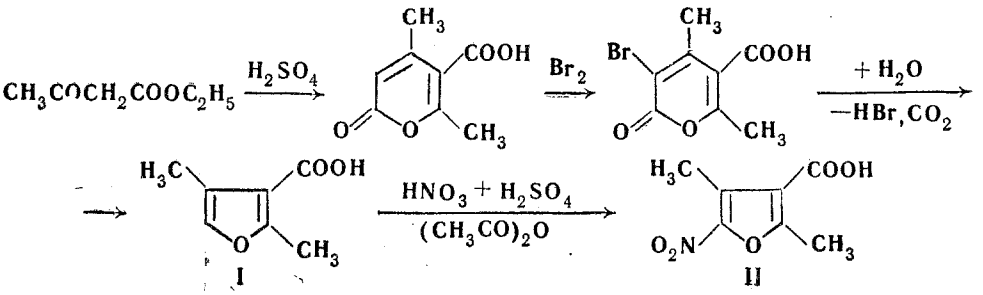
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 2, No. 6, pp. 863-867, 1966

It is found that 2,4-dimethyl-5-nitrofuran-3-carboxylic acid and its methyl ester can give comparatively stable anionic groups, which are prepared electrochemically and investigated by EPR. Their lives (80-100 sec) are 4-5 times greater than the lives of other anionic groups of the 5-nitrofuran series previously studied. Starting from 2,4-dimethyl-5-nitrofuran-3-carboxylic acid and 2,4-dimethylfuran-3-carboxylic acid, two new semisynthetic penicillins are prepared, with activities basically extending to Gram-positive microorganisms, including forms of staphylcocci resistant to benzylpenicillin. Introduction of the nitro group into the furan ring increases the stability of penicillin to acid 79-fold. Low toxicity penicillins are synthesized (LD_{50} 1000-1500 mg/kg).

At present, the rational search for new physiologically active substances, and particular for semi-synthetic penicillins, is directly bound up with a study of relationship between structure and biological activity, and of the mechanisms involved in the action of these compounds. 2,4-Dimethylfuryl-3- and 2,4-dimethyl-5-nitrofuryl-3-penicillin are potentially of interest in this connection. To a certain extent, they resemble in structure oxacillin, a new acid-stable penicillin, with an action on the penicilinase-producing nuclei of staphylococci. It was also expected that the presence of the nitrofuran group in the side chain of the penicillin molecule would give it some of the valuable properties of nitrofurans, e.g., a wide spectrum of antibacterial activity, capacity to develop resistance and enhanced acid stability. To what extent these expectations were realized will be seen below.

The acids necessary for synthesizing the penicillins, 2,4-dimethylfuran-3-carboxylic acid (I) and 2,4-dimethyl-5-nitrofuran-3-carboxylic acid (II), were prepared as follows:

Unlike furan-2-carboxylic acid, where substitution of carboxyl by nitro is observed in the course of nitration [1], acid I is nitrated without decarboxylation to give a 76% yield of II. The acid chlorides (III, IV) and methyl esters (V, VI) of acids I and II have also been made. Acid II, and its derivatives IV and VI were synthesized and their properties recorded for the first time. It is of interest to note that compounds II and VI can give comparatively stable anion groups formed by single electron reduction:



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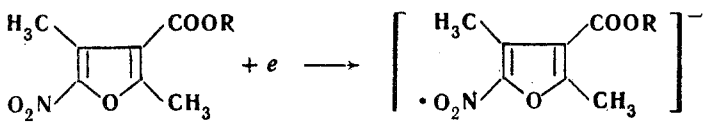
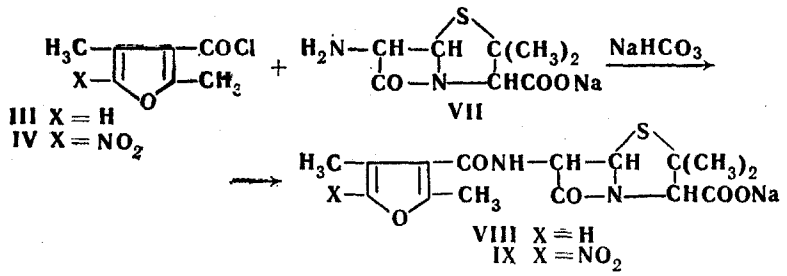


R = H, CH_3

We prepared these groups electrochemically, and studied them by EPR. Their lives (80-100 sec) are 4-5 times greater than those of other anionic groups of the 5-nitrofuran series which we previously studied [2,3].

Acylation of 6-aminopenicillanic acid (6-APA) (VII) with acid chlorides III and IV gave penicillins VIII and IX:



Using an ethereal solution of sodium butoxide in butanol these latter could be isolated as anhydrous sodium salts.

Table 1

Minimum Bacteriostatic Concentrations* (mg %) of Penicillins VII and IX, Inhibiting Growth of Penicillin-resistant Strains of Staph. a.h. for 24 hr.

Staph, a. h.	VIII	IX	Control (penicillin G)
209 P	0.012	0.026	0.017
11	0.74	6.35	16.6
14	11.50	3.07	8.3
37	2.87	6.35	66.6
38	1.49	6.35	8.3
41	1.49	6.35	16.6
50	2.87	6.35	16.6
64	5.93	3.07	111.1
66	1.49	12.70	16.6
97	1.49	6.35	33.3
117	1.49	6.35	16.6
123	5.93	12.70	16.6
163	1.49	6.35	66.6
X	11.50	12.70	16.6

*Bacteriostatic concentrations calculated on pure penicillins.

IR spectra confirmed that the penicillins synthesized contained β-lactam and thiazolidine rings (absorption in the 1770-1780 cm^{-1} region) [4, 5], the amide group (1667 cm^{-1}) [6], ionized carboxylic (1610-1620 cm^{-1}), and in the case of penicillin IX, the nitro group (1370 and 1515 cm^{-1}).

Penicillins prepared by L. V. Kruzmetra and L. N. Alekseeva were tested in vitro for antibactericidal activity in the chemotherapy division of this Institute. Basically their action is extended to Gram-positive microorganisms, though the penicillin IX also exhibits bacteriostatic activity towards Salmonella typhimurium and Proteus vulgaris at 3-5 mg % concentration.

Table 1 shows that the penicillins act on forms of Staph. a.h. resistant to benzylpenicillin, but its bacteriostatic concentration exceeds that of the semisynthetic penicillin methyl penicillin. Introduction of a nitro group at position 5 in the furan ring of the penicillin molecule did not result in significant changes in its antibacterial spectrum (as compared with penicillin VIII), but greatly increased its acid resistance (see Table 2).

The penicillins synthesized had low toxicities (LD_{50} 1000-1500 mg/kg), and were readily soluble in water.

Experimental

Nitration of 2,4-dimethylfuran-3-carboxylic acid. The 2,4-dimethylfuran-3-carboxylic acid (I) [7] used for nitration was prepared from isodehydracetic acid [8]. After purification by vacuum-sublimation (3 mm, 100° C) it had mp 123° C. The starting materials were taken in the following mole ratios [9]: acid: Ac_2O : HNO_3 : H_2SO_4 = 1:10:3:0.05.

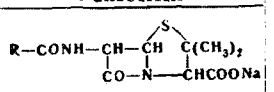
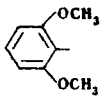
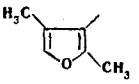
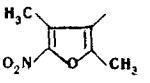
20.4 g (0.020 mole) acetic anhydride was placed in a flask fitted with a mechanical stirrer, cooled to −30° C, and 7.6 g (0.12 mole) fuming nitric acid plus a few drops of concentrated H_2SO_4 added with stirring. The temperature of the reactants was kept at about −25° C, and over 30 min a solution of 5.6 g (0.04 mole) 2,4-dimethylfuran-3-carboxylic acid in 18.6 ml AcOH added. The solution was stirred at that temperature for 1 hr, then the temperature slowly raised to +7° C, after which the transparent solution was poured into a mixture of 150 g ice and 100 ml water. The resultant pasty product was washed with water, and left under water in a refrigerator for 24 hr. The hardened mass was ground up, filtered, washed with water, and dried in a vacuum-desiccator over KOH + P_2O_5. Yield 5.64 g (76%). The nitration product was a pale-yellow powder, mp 170-176° C. Two recrystallizations from water gave 2,4-dimethyl-5-nitrofuran-3-carboxylic acid (II) as pale-yellow needles, mp 184.5-185° C. Found: C 45.69, 45.44; H 3.88, 3.56; N 7.58, 7.64%. Calculated for $C_7H_7NO_5$: C 45.41; H 3.81; N 7.57%. IR spectrum (in nujol) ν, cm^{-1}: 752 (56), 764 (76), 780 (40), 793 (50), 870 (61), 950 (65), 985 (57), 1040 (45), 1098 (66), 1145 (65), 1227 (60), 1270 (80), 1290 (82), 1350 (86), 1375 (81), 1395 (80), 1475 (80), 1515 (81), 1600 (78), 1700 (85).

The polarogram of compound II was determined. Table 3 gives the halfwave potentials ($-E_{1/2}$) and diffusion currents (i_{lim}) at the same pHs.

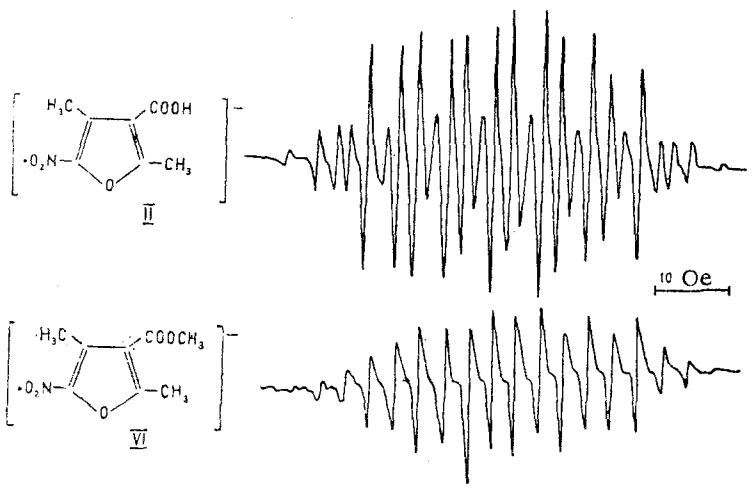
Methyl 2,4-dimethylfuran-3-carboxylate (V). This was prepared analogously to methyl furan-2-carboxylate [10], but the time for which the reactants were heated together had to be increased to 10 hr. Yield 44%. Bp 74-75° (13 mm); n_D^{20} 1.4749; d_4^{20} 1.1030. Found: MR_D 39.35. Calculated for $C_8H_{10}O_3$ with 2 F MR_D 39.32.

Table 2

Comparison of Acid Stabilities of Substituted Penicillins

Penicillin 	R	$\tau_{1/2}$ min	pH	Temperature, °C
Benzylpenicillin	$C_6H_5CH_2$	86 34	3 3	30 40
Methylpenicillin		10	3	30
2,4-Dimethylfuryl 3-penicillin		17 4	3 3	30 40
2,4-Dimethylfuryl 5-nitrofuryl 3-penicillin		316	3	40

Methyl 2,4-dimethyl-5-nitrofuran-3-carboxylate (VI). Ester V was nitrated in exactly the same way as was described for preparing acid II. 10.67 g (0.069 mole) ester V gave 12.69 g (92%) nitro compound VI, mp 37-40° C.



EPR spectra of the anionic groups of compounds II and VI.

After recrystallizing from aqueous EtOH it formed pale-yellow needles mp 43.5-44.5° C. Found: C 48.37; H 4.40; N 7.07%. Calculated for $C_8H_9NO_5$: C 48.25; H 4.55; N 7.03%.

IR spectrum (in nujol) ν, cm^{-1}: 760(52), 790(46), 815(46), 863(45), 953(42), 980(40), 1050(46), 1090(64), 1135(58), 1220(58), 1260(68), 1280(69), 1352(66), 1375(62), 1420(67), 1450(55), 1510(65), 1520(57), 1610 (52), 1735(67).

Attempts to hydrolyze ester VI with HCl or H_2SO_4 solution were unsuccessful, in both cases either the starting compound VI being recovered, or, if the solution was heated longer, VI was decomposed with evolution of nitrogen oxides.

Acid chlorides of acids I and II. 5 hr heating (55° C) of acid I with $SOCl_2$ gave its acid chloride (III), bp 54-55° (3 mm); n_D^{20} 1.5111, d_4^{20} 1.2304. Preparation of acid chloride IV requires 9 hr refluxing with 50% excess $SOCl_2$. Recrystallization of IV from petrol ether gave glistening plates mp 63° C. Found: Cl 17.10%. Calculated for $C_7H_6NO_4Cl$: Cl 17.42%.

EPR spectra of the anionic groups of compounds II and VI. The anionic groups of these compounds were prepared in the way previously described [11]. 5×10^{-3} M aqueous solutions were used, containing 20% EtOH plus subsequently added KCl to bring the concentration up to 10^{-1} M.

Table 3

Polarographic Characteristics of 2,4-Dimethyl-5-nitrofuran 3-carboxylic acid

pH	1st wave		2nd wave	
	$-E_{1/2}$, V	i_{lim}, μa	$-E_{1/2}$, V	i_{lim}, μa
3.3	0.33	1.73	1.23	0.46
7.0	0.78	0.52	1.47	1.40
10.1	0.77	0.30	1.45	1.10

The figure shows the EPR spectra of the compounds.

Table 4 gives the characteristics of the EPR spectra of the compounds.

ΔH_{NO_2} is a constant characterizing the interaction of the unpaired electron with the nitrogen of the nitro group; $\Delta H_{C^4CH_3}$ and $\Delta H_{C^2CH_3}$ characterizing interation with protons of the methyl groups at positions 2 and 4 in the furan ring. The spin density is found from the formula [12]:

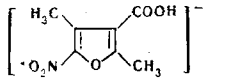
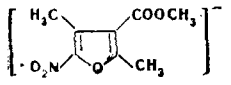
$$\rho_{C^i} = \frac{\Delta H_{C^iCH_3}}{Q}, \text{where } Q = 28 \text{ э}.$$

6-Aminopenicillanic derivatives of 2,4-dimethylfuran-3-carboxylic acid and 2,4-dimethyl-5-nitrofuran-3-carboboxylic acid.

a) 2,4-Dimethyl-5-nitrofuryl-3-penicillin. 1.93 g (0.023 mole) $NaHCO_3$, and 2.16 g (0.01 mole) 6-APA, were dissolved in 20 ml water, 14 ml acetone added, and the mixture cooled to 0° C. At that temperature a solution of 2.03 g (0.01 mole) of the acid chloride IV in 15 ml acetone was added over 30 min. Stirring was continued for a further 30 min, the solution then diluted with 100 ml ice-water, and most of the acetone vacuum-distilled off. The

Table 4

EPR Characteristics of the Anion-radicals

Free anion-radical	Splitting constants, ε			Spin density		Life, sec
	ΔH_{NO_2}	$\Delta H_{C^4CH_3}$	$\Delta H_{C^2CH_3}$	ρ_{C^4}	ρ_{C^2}	$t_{1/2}$
	13.5	6.8	4.3	0.24	0.15	100±20
	14.2	7.0	3.7	0.25	0.13	80±20

residue was extracted with ether, the extracts rejected, and the aqueous layer acidified with 5 N H_2SO_4 to pH 2.5; then the penicillin-acid was quickly extracted with ether, the extract washed with ice-water, and dried at 0–3° C over Na_2SO_4. The penicillin was precipitated by diluting the ether solution with a solution of sodium butoxide in butanol. The precipitate was filtered off, and washed with dry acetone or ether, yield 2.73 g (67.5%), pale-yellow powder, the anhydrous Na salt of penicillin IX. Its activity, as determined iodometrically, was 1158 units/mg. IR spectrum (in nujol) ν, cm^{-1}: 750 (33), 785 (38), 875 (28), 900 (26), 980 (30), 1010 (28) 1040 (32), 1100 (42), 1130 (42), 1165 (38), 1235 (46), 1260 (63), 1325 (63), 1370 (72), 1390 (65), 1410 (65), 1470 (56), 1515 (70), 1555 (55), 1610 (75), 1667 (66), 1770 (70).

b) 2,4-Dimethylfuryl-3-penicillin. Prepared similarly from the acid chloride III and 6-APA, yield 36.3%, as the anhydrous Na salt of penicillin VIII. Activity 1081 units/mg. IR spectrum (in nujol) ν, cm^{-1}: 760 (42), 785 (44), 850 (31), 900 (32), 945 (41), 1010 (36), 1045 (37), 1125 (57), 1165 (46), 1215 (51), 1285 (62), 1330 (66), 1390 (69), 1410 (72), 1470 (66), 1510 (67), 1615 (84), 1667 (79), 1775 (79).

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25 December 1965

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