SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF DERIVATIVES OF 2-ARYL-3,4-BIS(CARBOXY)FURANS

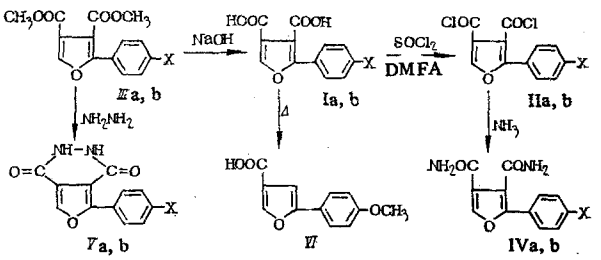
A. F. Oleinik, E. V. Adamskaya, O. V. Okinshevich, and G. N. Pershin

UDC 615. 281:547.799.2] 0.12.1

In earlier work, we have shown [1] that derivatives of 5-arylfuran-2-carboxylic acids exhibit bacteriostatic activity, and in this investigation the biological activity of the analogous 2-aryl-3,4-dicarboxylfurans has been studied.

A method has been developed for the synthesis of 2-aryl-3,4-bis(carbomethoxy)furans from 2-arylfurans by the Diels–Alder reaction [2].

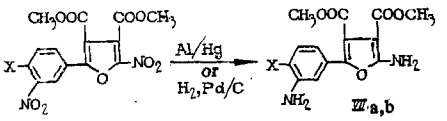
Derivatives of 2-aryl-3,4-bis(carbomethoxy)furans (IIIa and b) gave the corresponding acids Ia and b, which with thionyl chloride in the presence of a catalytic amount of DMFA were converted to the acid dichlorides (IIa and b). In the absence of DMFA, Ib formed the anhydride of 2-(p-anisyl)-3,4-bis(carboxy)furan. The diamines (IVa and b) were obtained from IIa and b. With hydrazine, IIa and b were converted into the cyclic hydrazides (Va and b).



a: X = CH_3; b: X = OCH_3.

The acid Ib readily decarboxylates on heating, the carboxyl group nearest to the aryl substituent is lost to give 2-(p-anisyl)furan-4-carboxylic acid (VI). The structure of VI was confirmed by NMR spectroscopy. In the NMR spectrum of compound VI, the proton at position 5 of the furan ring produces a signal at 8.26 ppm, split due to spin–spin coupling with the proton at position 3 with coupling constant $^4J_{H_3H_5}$ = 0.6 Hz. The signal from the proton at position 3 is superimposed on the signal from the aromatic protons at 6.96-7.72 ppm. The OCH_3 also gives rise to a signal at 3.8 ppm.

The nitro derivatives of 2-aryl-3,4-bis(carbomethoxy)furans, synthesized earlier, were reduced to the corresponding diamino derivatives (VIIa and b).



VII a: X = $NHCOCH_3$; VII b: X = OCH_3.

The antimicrobial activity was studied *in vitro* by the method of serial dilution in liquid nutrient medium [3]; 4 types of gram-positive bacteria, 5 types of gram-negative bacteria, and 5 types of pathogenic fungi were examined. All the compounds were found to be essentially inactive and did not suppress the growth of bacteria at concentrations of 250 μg/ml, or the growth of pathogenic fungi at concentrations of 500 μg/ml.

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemical Institute, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 17, No. 6, pp. 683-685, June, 1983. Original article submitted November 25, 1982.

 0091-150X/83/1706-0408$07.50

Comparison of the antimicrobial action of Ia and b with that of the 2-aryl-5-carboxyfurans [1] indicates that shifting the carboxyl substituent from the α-position to the β-position of the furan ring causes a sharp decrease in the activity of the compounds.

EXPERIMENTAL CHEMISTRY

IR spectra of the compounds in mineral oil were taken on Perkin-Elmer 457 (USA) spectrophotometer. TLC was carried out on Silufol UV-254 (ChSSR) plates; the solvent system benzene–dioxan–acetic acid (95:25:4) was used, and the spots were visualized in UV light.

2-(p-Tolyl)-3,4-bis(carboxy)furan (Ia). A solution of 4.0 g of IIIa [2] in 50 ml of 30% sodium hydroxide was refluxed for 4 h, cooled, and acidified with hydrochloric acid to pH 1. The precipitated material was filtered off, and washed with water to give 3.0 g (84%) of Ia, mp 208-210°C. Found, %: C 63.6; H 4.1. $C_{13}H_{10}O_5$. Calculated, %: 63.4; H 4.0.

2-(p-Anisyl)-3,4-bis(carboxy)furan (Ib). Using the method described above, Ib was prepared in 91% yield, mp 207-209°C. R_f 0.57. Found, %: C 59.8; H 4.1. $C_{13}H_{10}O_6$. Calculated, %: C 59.5; H 3.8.

2-(p-Tolyl)-3,4-bis(chlorocarbonyl)furan (IIa). A suspension of 0.8 g of Ia in 10 ml of dry benzene was mixed with 7 ml of thionyl chloride and 1 ml of DMFA and refluxed for 8 h. The solvent was evaporated in vacuum, a further 25 ml of benzene was added, and the solvent again evaporated in vacuum. A yield of 0.6 g (59%) of IIa was obtained with mp 68-70°C (from hexane). Found, %: C 51.1; H 2.8. $C_{13}H_8Cl_2O_3$. Calculated, %: 55.2; H 2.7.

2-(p-Anisyl)-3,4-bis(chlorocarbonyl)furan (IIb) was prepared in 55% yield by the same method. The product had mp 86-88°C (from hexane). Found, %: C 52.4; H 2.9. $C_{13}H_8Cl_2O_4$. Calculated, %: C 52.2; H. 2.7.

Anhydride of 2-(p-Anisyl)-3,4-bis(carboxy)furan (III). To a suspension of 0.5 g of Ib in 10 ml of dry benzene was added 7 ml of thionyl chloride. The reaction mixture was refluxed for 3 h, concentrated in vacuum, 25 ml of benzene added, and the mixture again concentrated in vacuum to give 0.2 g (43%) of III, mp 164-166°C (from benzene). R_f 0.92. Found, %: C 63.8; H 3.5. $C_{13}H_8O_5$. Calculated, %: C 63.9; H 3.3

Diamide of 2-(p-Tolyl)furan-3,4-dicarboxylic acid (IVa). Compound IIa (0.5 g) in 15 ml of 30% aqueous ammonia was stirred for 4 h at 20°C. The precipitate was filtered off and washed with water to give 0.4 g (93%) of IVa, mp 296-299°C (from alcohol). IR spectrum, ν, cm^{-1}: 3420, 3120 (NH_2), 1690, 1650, 1620 ($CONH_2$). Found, %: C 63.9; H 4.9; N 11.1. $C_{13}H_{12}N_2O_3$. Calculated, %: C 63.9; H 4.9; N 11.5.

Diamide of 2-(p-Anisyl)furan-3,4-dicarboxylic acid (IVb). A 75% yield of IVb with mp 261-263°C (from alcohol) was obtained by the method described above. IR spectrum, ν, cm^{-1}: 3420, 3120 (NH_2), 1700, 1660, 1620 ($CONH_2$). Found, %: C 59.9; H 4.6. $C_{13}H_{12}N_2O_4$. Calculated, %: C 60.0; H 4.6.

2-(p-Tolyl)-3,6-dioxofuro[3,4-d]pyridazine (Va). To a suspension of 0.8 g (3 mmoles) of IIIa [2] in 15 ml of methanol was added 0.4 g (9 mmoles) of hydrazine hydrate. The reaction mixture was heated for 2 h at 100°C and the precipitated material filtered off to give 0.5 g (70%) of Va, mp 310-320°C (purified by reprecipitation from 10% from aqueous ammonia). IR spectrum, ν, cm^{-1}: 1680 (CO). Found, %: C 64.1; H 4.2; N 11.6. $C_{13}H_{10}N_2O_3$. Calculated, %: C 64.5; H 4.1; N 11.6.

2-(p Tolyl)-3,6-dioxofuro[3,4-d]pyridazine (Vb). A 70% yield of Vb with mp 281-284°C was obtained by the same method as Va. IR spectrum, ν, cm^{-1}: 1680 (CO). Found, %: C 60.3; H 4.0; N 10.8. $C_{13}H_{10}H_2O_4$. Calculated %: C 60.5; H 3.9; N 10.9.

2-(p-Anisyl)furan-4-carboxylic acid (VI). Compound Ib (0.7 g) was heated at 180-200°C until no more carbon dioxide gas was evolved. A yield of 0.4 g (70%) was obtained with mp 209-210°C (from alcohol). R_f 0.80. Found, %: C 66.4; H 4.6. $C_{12}H_6O_4$. Calculated, %: C 66.1; H 4.6.

2-(3-Amino-4-acetylaminophenyl)-3,4-bis(carbomethoxy)-5-aminofuran (VIIa). A. A solution of 1.3 g (3 mmoles) of 2-(3-nitro-4-acetylaminophenyl)-3,4-bis(carbomethoxy)-5-nitrofuran [2] in 50 ml of methanol was hydrogenated in the presence of 0.5 g of 5% Pd/C at 20°C and atmospheric pressure until 420 ml (18 mmoles) of hydrogen had been absorbed. The catalyst

was filtered off and the solution concentrated to give 0.6 g (54%) of VIIa, mp 187-189°C (from alcohol). R_f 0.25. Found, %: 55.4; H 5.0; N 12.1. $C_{16}H_{17}N_3O_6$. Calculated, %. C 55.3; H 4.9; N 12.1.

B. A mixture of 1.3 g of 2-(3-nitro-4-acetylaminophenyl)-3,4-bis-(carbomethoxy)-5-nitrofuran [2] and 3 g of amalgamated aluminum in 70 ml of alcohol was refluxed for 10 h. When cool, the reaction mixture was filtered and evaporated to give 0.3 g (27%) of VIIa with mp 187-189°C. R_f 0.25. There was no depression of the melting point when mixed with material obtained in A.

2-(3-Amino-4-methoxyphenyl)-3,4-bis(carbomethoxy)-5-aminofuran (VIIb). A yield of 40% of VIIb with mp 126-128°C (from alcohol) was obtained by method B above. Found, %: C 55.9; H 5.1; N 8.6. $C_{15}H_{16}N_2O_6$. Calculated, %: C 56.2; H 5.0; N 8.7.

LITERATURE CITED

1. A. F. Oleinik, T. I. Bozyakova, K. Yu. Novitskii, et al., Khim.-farm. Zh., No. 4, 46-49 (1976).
2. A. F. Oleinik, E. V. Adamskaya, and K. Yu. Novitskii, Khim. Geterotsikl. Soedin., No. 4, 453-456 (1982).
3. Methods of Experimental Chemotherapy (G. N. Pershin, ed.), Moscow (1971).

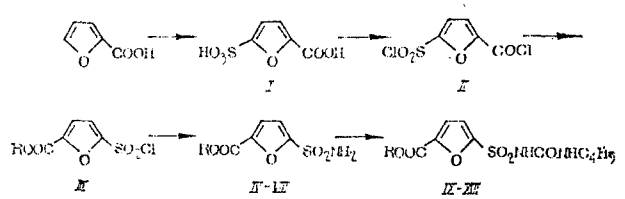
SYNTHESIS AND HYPOGLYCEMIC ACTIVITY OF N-(5-CARBOALKOXYFURAN-2-SULFONYL)-N'-BUTYL UREA

L. S. Abovyan, V. A. Shkulev, N. O. Stepanyan, A. S. Agaronyan, and O. L. Mndzhoyan

UDC 615.252.349:547.496.3'722].012.1

A large number of sulfonyl urea derivatives showing hypoglycemic activity has been synthesized in the past [1-3]. However, data on the hypoglycemic activity of derivatives of furansulfonyl urea are absent from the literature. In order to fill this need, we synthesized the N-(5-carbalkoxyfuran-2-sulfonyl)-N'-butyl ureas IX-XIII, and studied their hypoglycemic properties.

The synthesis of these compounds was accomplished according to the following scheme:



5-Sulfofuran-2-carboxylic acid (I), obtained by sulfonation of furan-2-carboxylic acid with chlorosulfonic acid, was converted to its monopotassium salt and then treated with phosphorus pentachloride to form the diacid chloride (II). From the latter was obtained the alkyl esters of 2-carboxy-furansulfonyl chloride (III) and "Diamid" (2-carboxamidofuran-5-sulfonamide, XVIII). The melting point of the Diamid prepared here (221-223°C) is different from that described in the literature [4] for Diamid (211-212°C). The starting material for the synthesis of the latter was the acid I, prepared by treatment of furan-2-carboxylic acid with oleum [4]. We established that in this case the disodium salt of I was present as a

A. L. Mndzhoyan Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSR, Erevan.

Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 17, No. 6, pp. 685-688, June, 1983. Original article submitted July 29, 1982.

0091-150X/83/1706-0410$07.50