ALCOHOLS OF THE NITROFURAN SERIES

II. Reduction of α-Ethyl-β-(5-nitro-2-furyl)acrolein and 5-(5-Nitro-2-furyl)-penta-2,4-dienal with Sodium Borohydride*

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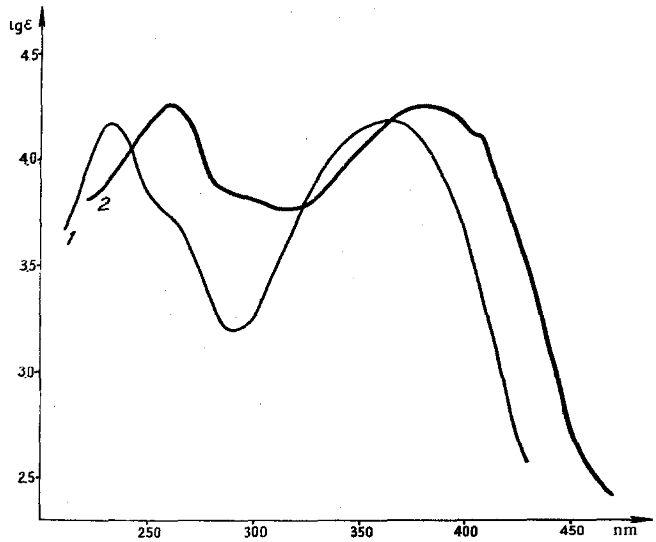
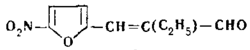
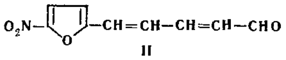
By reducing the corresponding aldehydes with sodium borohydride, α-ethyl-β-(5-nitro-2-furyl)allyl alcohol and 5-(5-nitro-2-furyl)penta-2,4-dienol have been obtained. A number of their esters have been synthesized.

Continuing work on the synthesis of alcohols of the nitrofuran series from carbonyl-containing nitrofuran derivatives [1], we have subjected α-ethyl-β-(5-nitro-2-furyl)acrolein (I) and 5-(5-nitro-2-furyl)penta-2,4-dienal (II) to reduction with sodium borohydride.



UV spectra: 1) α-ethyl-β-(5-nitro-2-furyl)allyl alcohol and 2) 5-(5-nitro-2-furyl)penta-2,4-dienol in ethanol.

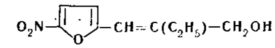

I

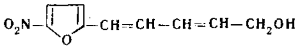

II

We performed the synthesis of I by the condensation of furfural with butyraldehyde [2] and subsequent nitration by a method somewhat modified in comparison with that developed previously in our laboratory [3]. The yield of α-ethyl-β-(5-nitro-2-furyl)acrolein diacetate was 45% as compared with the 20% achieved previously. The hydrolysis of the diacetate was carried out as usual with dilute sulfuric acid. The II was obtained by the method that we have developed previously [4].

Diethyl ether, dioxane, and tetrahydropyran were used as reaction media for the reduction of I and dioxane for II.

The reduction of the carbonyl group in aldehydes of the nitrofuran series with sodium borohydride takes place readily both at elevated and at room temperatures. The highest yields of α-ethyl-β-(5-nitro-2-furyl)allyl alcohol (III) and 5-(5-nitro-2-furyl)penta-2,4-dienol (IV) were obtained with a reduction time of 2–3 hr and a molar ratio of aldehyde to sodium borohydride of 1 : 0.5. Thus, in the case of the reduction of I with diethyl ether at room temperature and a molar ratio of I to sodium borohydride of 1 : 1, the yields of crude product as a function of the time of reaction were: after 1 hr, 78% (83% at 1 : 0.5); after 2 hr, 87% (92% at 1 : 0.5); after 3 hr, 75%; after 4 hr, 78%; and after 5 hr, 78%; at the boiling point of diethyl ether the yields were, respectively, 77, 80, 87, 68, and 76%. The reduction of I in dioxane at a molar ratio of I to sodium borohydride of 1 : 1 at room temperature gave the following average yields of III: after 1 hr, 57%; after 2 hr, 78%; after 3 hr, 57%; and after 4 hr, 59%, and the yield after 1 hr at 50° C was 86%. In tetrahydropyran, the greatest yield of III was obtained at a molar ratio of 1 : 0.5 and after 1 hr at room temperature—92%. At a ratio of 1 : 1 the yield after 1 hr was 67% and after 2 hr 68%, and the yield after 1 hr at 50° C was 73%. Compound III is readily soluble at room temperature in methanol, ethanol, diethyl ether, dimethylformamide, and acetone, and extremely sparingly soluble in water.


III


IV

Compound II was reduced only in dioxane, since it is sparingly soluble in tetrahydropyran and diethyl ether. At a molar ratio of 1 : 1 and at room temperature after 1 hr, the yield of IV was 100% while at 50° C after 1 hr it was 79% and after 2 hr 90%. Compound IV is readily soluble in acetone, methanol, and ethanol, sparingly soluble in diethyl ether and extremely sparingly soluble in water.

The selective reduction of only the carbonyl group without an attack of the multiple bonds of the furan ring and the nitro group is confirmed by the UV spectra. The spectrum of III has two characteristic maxima at 234 and 364 nm and that of IV at 261 and 381 nm (see figure).

The reaction of the alcohols III and IV with carboxylic acid chlorides gave a number of esters consisting of yellow crystalline substances (see table). Their

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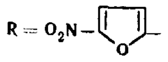
*For part I, see [1].

Esters of 5-(5-Nitro-2-furyl)penta-2, 4-dienol and of α-Ethyl-β-(5-nitro-2-furyl)allyl Alcohol



Compound	Formula	Solvent for recrystallization[a]	Mp, °C	Empirical formula	N, % found	N, % calculated
V	$R—CH=CH—CH=CH—CH_2OCO—C_6H_5$	A	91—93	$C_{16}H_{13}NO_5$	4.75	4.67
VI	$R—CH=CH—CH=CH—CH_2OCO—C_4H_2BrO^b$	B	111—113	$C_{14}H_{10}BrNO_6$	3.66	3.85
VII	$R—CH=CH—CH=CH—CH_2OCO—R$	C	151—152	$C_{14}H_{10}N_2O_8$	8.51	8.38
VIII	$R—CH=CH—CH=CH—CH_2OCO—CH=CH—R$	A : C = 1 : 1	115—117	$C_{16}H_{12}N_2O_8$	7.97	7.77
IX	$R—CH=CH—CH=CH—CH_2OCO—C_4H_3O^c$	A : C = 5 : 1	100—102	$C_{14}H_{11}NO_6$	4.87	4.84
X	$R—CH=CH—CH=CH—CH_2OCO—CH=CH—C_4H_3O^c$	D : C = 1 : 1	96—97	$C_{16}H_{13}NO_6$	4.52	4.79
XI	$R—CH=CH—CH=CH—CH_2OCO—C_5H_4N^d$	D : C = 1 : 1	115	$C_{15}H_{12}N_2O_5$	9.57	9.33
XII	$R—CH=CH—CH=CH—CH_2OCO—C_5H_4N^e$	D : C = 1 : 2	145	$C_{15}H_{12}N_2O_5$	9.21	9.33
XIII	$R—CH=C(C_2H_5)—CH_2OCO—C_6H_5$	A	76—77	$C_{16}H_{15}NO_5$	4.76	4.65
XIV	$R—CH=C(C_2H_5)—CH_2OCO—R$	A	86—87.5	$C_{14}H_{12}N_2O_8$	8.29	8.33
XV	$R—CH=C(C_2H_5)—CH_2OCO—C_4H_3O^c$	A	90—92.5	$C_{13}H_{13}NO_6$	4.80	5.02
XVI	$R—CH=C(C_2H_5)—CH_2OCO—CH=CH—R$	A : C = 2 : 1	111—113	$C_{16}H_{14}N_2O_8$	7.93	7.73
XVII	$R—CH=C(C_2H_5)—CH_2OCO—CH=CH—C_4H_3O^c$	A	96—98	$C_{16}H_{15}NO_6$	4.56	4.41
XVIII	$R—CH=C(C_2H_5)—CH_2OCO—C_5H_4N^d$	A	80.5—82.5	$C_{15}H_{14}N_2O_5$	9.34	9.26
XIX	$R—CH=C(C_2H_5)—CH_2OCO—C_5H_4N^e$	A	93—95	$C_{15}H_{14}N_2O_5$	9.36	9.26
XX	$R—CH=C(C_2H_5)—CH_2OCO—CH_2Cl$	B	48—50	$C_{11}H_{12}ClNO_5$	5.08	5.12
XXI	$R—CH=C(C_2H_5)—CH_2OCO—CH_2Br$	A	35—36	$C_{11}H_{12}BrNO_5$	4.71	4.40
XXII	$R—CH=C(C_2H_5)—CH_2OCO—CH_2I$	A	67—69	$C_{11}H_{12}INO_5$	3.59	3.83

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[a] A is ethanol; B is isopropanol; C is acetone; D is methanol. In [b] C_4H_2BrO is 5-bromo-2-furyl; [c] C_4H_3O is 2-furyl; [d] C_5H_4N is 3-pyridyl; [e] C_5H_4N is 4-pyridyl.

yields amounted to 80–100% (IX to XI, 40–60%) for the crude reaction products.

In esters of halogen-substituted acetic acids, a chlorine atom is readily replaced not only by iodine but, under suitable conditions, also by bromine. The physiological activity of the esters synthesized is being studied.

EXPERIMENTAL

α-Ethyl-β-(5-nitro-2-furyl)acrolein (I). With stirring and cooling to 0° C, 24.8 ml (0.59 mole) nitric acid (d 1.51) and sulfuric acid (d 1.84) to an amount of 5% of the weight of nitric acid were added to 980 ml of acetic anhydride. The nitrating mixture so prepared was cooled to –30° C, and over 1 hr at a temperature of from –30 to –35° C, a solution of 60 g (0.39 mole) of α-ethyl-β-(2-furyl)acrolein in 160 ml of acetic anhydride was added dropwise. The mixture was stirred for a further 1 hr at the same temperature. The contents of the flask were poured onto 3 kg of ground ice and stirred for 4 hr. The orange precipitate that dedeposited was filtered off and washed with ice water (about 1200 ml). Mp 92–94° C (from 280 ml of ethanol).

α-Ethyl-β-(5-nitro-2-furyl)allyl alcohol (III). a) A solution of 20 g (0.1 mole) of I in 400 ml of diethyl ether was added from a dropping funnel over 30 min with constant stirring to a suspension of 3.8 g (0.1 mole) of sodium borohydride (containing 88% of the pure substance) in 48 ml of diethyl ether (temperature of the reaction mixture 21–30° C), and then the mixture was heated on the water bath at the boiling point of the ether for 2 hr. For cooling, it was stirred for another 30 min. Then 47 ml of 1 N hydrochloric acid was carefully added with stirring. Stirring was continued for 30 min, the precipitate formed was filtered off, the ethereal layer was separated off, and the aqueous layer was extracted with 25 ml of ether. The combined ethereal extracts were washed with water (2 × 100 ml), dried, and the ether was distilled off (finally in the vacuum of a water pump). The residue—a red-brown viscous liquid—was placed in the refrigerator, where it changed into an orange-yellow crystalline mass. The yield of III was 17.2 g (85.1%); mp 30–32° C. The crude reduction product was dissolved in ethanol (1 g in 3 ml), activated carbon was added, and the mixture was boiled in the water bath for a few minutes. Then it was filtered, an equal volume of water was added, and it was placed in a mixture of ethanol and dry ice and stirred until a yellow crystalline precipitate appeared. This was filtered off and dried in vacuum at room temperature. Twice-recrystallized III had mp 36.5–38° C. Found, %: C 54.46; H 5.38; N 7.60. Calculated for $C_9H_{11}NO_4$, %: C 54.82; H 5.62; N 7.10.

b) To 0.96 g (0.025 mole) of sodium borohydride in 8.5 ml of dioxane was added 5 g (0.025 mole) of I (mp 72–73° C) in 25 ml of dioxane at a temperature for the reaction mixture of 19–28° C. Then the mixture was heated in the water bath at 50° C for 1 hr and was stirred for 30 min, after which 2.6 ml of 1 N hydrochloric acid was added to it. The mixture was stirred for another 30 min and then filtered. The filtrate was dried and the dioxane was distilled off in the vacuum of a water pump to give 4.1 g (81.9%) of a red-brown viscous liquid. It did not crystallize on prolonged standing in the refrigerator.

c) To 0.96 g (0.025 mole) of sodium borohydride in 9.8 ml of tetrahydropyran was added 5 g (0.025 mole) of I (mp 72–73° C) in 25 ml of tetrahydropyran over 19 min. The temperature of the reaction mixture was 19–28° C. Then it was heated in the water bath at 50° C for 1 hr. After 30 min, 3.2 ml of 1 N hydrochloric acid was added (20–28° C). It was stirred for another 30 min, filtered, and dried. The tetrahydropyran was distilled off in the vacuum of a water pump to leave 3.7 g (72.9%) of a red-brown viscous liquid which crystallized in the refrigerator after some time to form an orange-brown mass.

5-(5-Nitro-2-furyl)penta-2,4-dienol (IV). A solution of 5 g (0.025 mole) of II (mp 123–124° C) in 50 ml of dioxane was added to 0.96 g (0.025 mole) of sodium borohydride in 8.5 ml of dioxane (temperature of the reaction mixture 22–32° C). The mixture was stirred for 1 hr and then for another 30 min, after which 5.8 ml of 1 N hydrochloric acid was added. After stirring for 30 min it was filtered. The filtrate was dried and the dioxane was distilled off in the vacuum of a water pump. The residual viscous brown liquid—5.1 g (100%)—crystallized in the refrigerator to form a brown mass. On recrystallization from ethanol—water (1 : 1) with the addition of activated carbon, the IV precipitated in the form of a yellow crystalline substance, mp 69–70° C. Found, %: C 55.04; H 4.61; N 7.04. Calculated for $C_9H_9NO_4$, %: C 55.37; H 4.64; N 7.18.

1-Benzoyloxy-5-(5-nitro-2-furyl)penta-2,4-diene (V). With stirring and cooling, benzoyl chloride was added to a solution of 2 g (0.01 mole) of IV in 2 ml of absolute pyridine until the dense mass of precipitate ceased to be formed. With continued stirring and cooling, 20 ml of ice water was added. Then, the precipitate was filtered off, washed on the filter with ice water, and dried in the air. The yield of crude V was 2.8 g (92.2%).

The esters VI–XX were obtained similary. The chlorides of 5-bromo-2-furancarboxylic, 5-nitro-2-furancarboxylic, and β-(5-nitro-2-furyl)acrylic acids and the hydrochlorides of the chlorides of nicotinic and isonicotinic acids were dissolved in the minimum amount of absolute acetone and the chloride of β-(2-furyl)acrylic acid in absolute benzene.

α-Ethyl-β-(5-nitro-2-furyl)allyl bromoacetate (XXI). A solution of 0.8 g (0.008 mole) of sodium bromide in 16.4 ml of dimethylformamide was added to a solution of 2 g (0.007 mole) of **XX** in 4 ml of dimethylformamide. The mixture was left at room temperature for 24 hr, and then the precipitate of sodium chloride was filtered off. The solvent was distilled off in the vacuum of a water pump. The residual brown viscous liquid was heated with 20 ml of ice water, well stirred, and placed in the refrigerator. The brown precipitate was filtered off, washed with ice water, and dried in the air. The yield of crude **XXI** was 1.9 g (81.9%).

α-Ethyl-β-(5-nitro-2-furyl)allyl iodoacetate (XXII). A solution of 1.1 g (0.007 mole) of sodium iodide in

6.7 ml of absolute acetone was added to a solution of 2 g (0.006 mole) of **XXI** in 4 ml of absolute acetone. A copious white precipitate deposited immediately. The vessel was closed and left to stand at room temperature for 24 hr. On the following day the mixture was filtered off and the precipitate was washed with a small amount of absolute acetone. After the acetone had been distilled off, a viscous brown liquid remained which was treated with 20 ml of ice water. The dark yellow crystalline precipitate was filtered off, washed with ice water, and dried in the air. The yield of crude XXII was 2.0 g (91.2%).

Compound **XXII** was obtained from **XX** similarly.

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