83. **Tadashi Sasaki:** Application of Meerwein-Ponndorf Reaction to Furan and Nitrofuran Derivatives.*

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The first example of Meerwein-Ponndorf reaction in the field of furan chemistry was the preparation of furyl alcohol from furfural in the presence of aluminum ethoxide.[1] Adkins and Elofson[2] carried out this reaction by using aluminum isopropoxide and obtained yield of 75%. Recently, Baily and Lutz[3] used this reaction to prepare β-furfuryl alcohol from β-aldehyde. To obtain a pharmaceutically useful nitrofuran derivatives, made up of primary or secondary alcoholic radicals, experiments were carried out utilizing this reaction, the results of which are reported in this paper.

As previously reported by the author[4] the nitrofuran derivatives having a movable hydrogen atom in their molecules generally exhibit bactericidal actions, and furthermore, when the same molecules have an ethylenic bond which conjugates with the furan nucleus, their bactericidal activity becomes stronger. This reaction is neutral and both the ethylenic bond and the nitro radical are not affected by aluminum isopropoxide.[5]

The bacteriostatic activities of products thus obtained are given in Table I.

TABLE I.

Antibacterial Action of 5-Nitrofurylcarbinols*

	Staph. aur.			*Strept. haemol.*			*Diploc. pneum.*			*Neis. gonor.*		
Hours	24	48	72	24	48	72	24	48	72	24	48	72
Compound												
(3)	<0.5	<0.5	<0.5	<1	<1	<1	<1	<1	<1	<1	<1	<1
(5)	<0.5	<0.5	<0.5	<1	<1	<1	<1	<1	<1	<1	<1	<1
(4)	8	8	8	1	<1	<1	<1	<1	<1	<1	<1	<1
(6)	1	0.5	<0.5	1	<1	<1	1	<1	<1	1	1	<1
Furacin	16	8	8	4	4	2	8	8	4	2	2	1
Nitrofuryl alcohol acetate	0.5	<0.5	<0.5	2	1	1	2	2	1	1	1	1

	Esch. coli. com.			*Eber. typhosa*			*S. dysenteriae*		
Hours	24	48	72	24	48	72	24	48	72
(3)	<0.5	<0.5	0.5	<0.5	<0.5	0.5	<0.5	<0.5	<0.5
(5)	<0.5	<0.5	0.5	<0.5	<0.5	0.5	<0.5	<0.5	<0.5
(4)	16	16	16	4	4	2	8	4	4
(6)	1	1	1	4	2	1	2	2	1
Furancin	16	8	8	8	4	4	16	8	8
Nitrofuryl alcohol acetate	1	1	1	4	4	1	2	2	2

(Unit 10,000)

* Tests were carried out by Mr. Ohyama at the Dept. of Microbiology, Medical Faculty, University of Kyoto.

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* Paper read before the Annual Meeting of the Chemical Society of Japan, April, 1951.

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1) Meerwein, R. Schmidt: Ann., 444, 221(1925).

2) Adkins, Elofson: Quoted in "Organic Reactions," Vol II, 207(1944).

3) P. S. Baily, R. E. Lutz: J. Am. Chem. Soc., 67, 2233(1945).

4) Paper read before the Annual Meeting of the Pharmaceutical Society of Japan, 1950.

5) "Organic Reactions," II, 182.

Tokyo, for his kind supply of aluminum and isopropyl alcohol, and to Miss Iwata for her help in the elemental microanalysis.

Experimental6)

Preparation of aluminum isopropoxide—This was carried out by the method described in the Organic Reactions.7)

Furyl alcohol from furfural—Repetition of the experiment by Adkins and Elofson2) gave nearly the same yield (78%).

Nitrofuryl alcohol from nitrofurfural—a) To a solution of 14.2 g. of Al isopropoxide dissolved in 150 cc. of dry isopropyl alcohol was added 10 g. of nitrofurfural in one lot, and maintained at 80° for 0.5 hour, by which a mixture of acetone and alcohol distilled out and the solution gradually changed its color to dark brown. It took about 5~6 hours for the acetone test to become negative. The total amount of acetone distilled during this period of the reaction was about 70 cc. The same amount of isopropyl alcohol was supplied little by little to the reaction mixture during the course of the reaction. When the reaction was over, as much of the solvent as possible was removed under a slightly reduced pressure. The residual thin brown powder was hydrolyzed by 150 cc. of dil. HCl, and stirred for about 2 hrs. at around 30° to form a clear solution. This solution was then extracted with ether, the ether was washed once with the same amount of water, and dried over anhyd. Na_2SO_4. The ether was removed to give 9.2 g. of a red viscous syrup. This was further purified by distillation under a reduced pressure to give 7.8 g. of pale yellow oil, b.p$_{2.5}$ 108~113°, which turned brown upon exposure to air. Yield, 78%. The residue amounted to 1 g.

b) The same reaction was carried out without using purified Al isopropoxide. To 40 cc. of isopropyl alcohol were added 1 g. of Al, 0.5 g. of $HgCl_2$, and 0.2 cc. of CCl_4. This was warmed under reflux in a water bath for 1 day to form a clear solution. To this was added mixture of 40 cc. of alcohol and 100 cc. of benzene. After the addition of nitrofurfural, the reaction was carried out as in (a) and gave 5 g. of b.p$_3$ 115° (m.p. 32°). The residue amounted to 1.5 g., the yield being 75%.

c) When the same reaction was carried out without using either the purified alkoxide nor a mixed solvent of alcohol and benzene, the yield was reduced to 50%, with the residue of 1 g.

Furylacryl alcohol from furylacrolein—a) To a solution of 10 g. of Al isopropoxide dissolved in 100 cc. of isopropyl alcohol, 8 g. of freshly distilled furylacrolein (b.p$_{10}$ 90~102°, m.p. 51°) was added and the reaction mixture was stirred at 80° for 0.5 hour under reflux. The mixture was then allowed to distill and after 2.5 hours, the product appeared in a crystalline state. Three and a half hours after the appearance of crystals, the acetone test became negative. The amount of the distillate was approximately 80 cc. The alcohol was removed under a slightly reduced pressure, and the residual mass was hydrolyzed with 100 cc. of dil. HCl at 25°. From this ether extract was obtained 12 g. of a red oil which was purified by vacuum distillation to give 4 g. of b.p$_9$ 95~97°. The residue was 6 g. Being unstable, it easily formed dark brown polymers. Yield, 40%. *Anal.* Calcd. for $C_7H_8O_2$: C, 67.98; H, 6.45. Found: C, 68.00; H, 6.267.

b) Since furylacrolein remains partially undissolved in isopropyl alcohol, a solvent mixture of 100 cc. of alcohol and 50 cc. of benzene was used in this reaction to give 4.5 g. of oil, b.p$_{8.5}$ 94~97°. The residue was 3 g. Yield, 56%.

Nitrofurylacryl alcohol from nitrofurylacrolein—To a solution of 9 g. of alkoxide dissolved in 100 cc. of isopropyl alcohol, was added 6 g. of nitrofurylacrolein8) at 85°. The acetone test became negative after 4.5 hours. Hydrolysis was carried out as before with 100 cc. of dil. HCl, and extracted with ether to give 5 g. of a red oil which solidified to yellow crystals, m.p. 54~56°, after being kept in a desiccator. This product was further purified by vacuum distillation to give 4 g. of yellow crystals from the distillate of b.p$_1$ 125~128°. The residue amounted to 0.8 g.; yield, 66%. This product can be recrystallized from ether, is easily soluble in benzene and insoluble in water and ligroine. *Anal.* Calcd. for $C_7H_7O_4N$: N, 8.28. Found: N, 8.03.

α-Methylfurylcarbinol from acetylfuran9)—To a clear, slightly heated solution prepared from 20 g. of Al isopropoxide and 100 cc. of isopropyl alcohol was added 11 g. of acetylfuran, b.p$_{10}$ 58°, the mixture was warmed in a water bath at 90°, and kept under reflux for 1 hour. After letting the mixture distill slowly, when it changed its color from yellow to brown, the acetone test became negative after 5 hours. After distilling off the solvent, the dried brown syrup was

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6) All melting points are not corrected.

7) "Organic Reactions," II, 186.

8) m.p. 115~116°. cf. H. Saikachi, *et al.*: J. Pharm. Soc. Japan, 73, 716(1953).

9) A. Pawlinoff and G. Wagner (Ber., 17, 1968(1886)) prepared α-ethylcarbinol from furfural and $Zn(C_2H_5)_2$.

hydrolyzed at 20°. The product thus obtained, after its extraction with ether, amounted to 13 g. of a red oil which was purified by vacuum distillation to give 5 g. of a colorless, viscous, unstable oil, which darkened easily. The amount of the residue was 2 g.; yield, 44.4%. *Anal.* Calcd. for $C_6H_8O_2$: C, 64.29; H, 7.14. Found: C, 63.87; H, 7.17.

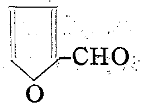
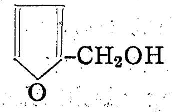
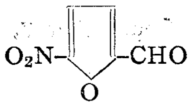
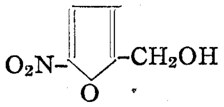
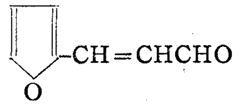
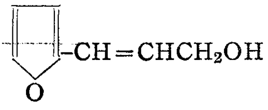
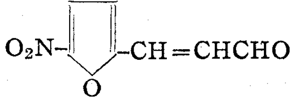
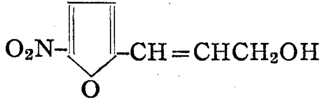
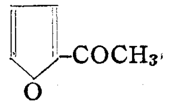
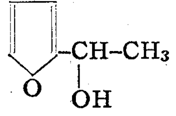
Nitro-α-methylfurylcarbinol from nitroacetylfuran—To a solution of Al isopropoxide (4 g.) in 50 cc. of alcohol was added 3 g. of nitroacetylfuran, m.p. 78°. On being heated very gently on a sand bath, the reaction mixture became black. Since nitroacetylfuran remained completely undissolved in the reaction mixture, 50 cc. of benzene was added, and this mixture was heated for more than 5 hours. The acetone test finally became negative. The amount of distillate during this period of heating was about 25 cc. The resultant brown, resinous substance was hydrolyzed by 50 cc. of dil. HCl at 20° for 3 hours, the hydrolyzed clear solution was extracted with ether, and ether was removed to give 3 g. of a red oil which solidified after standing in an ice box. This was purified by vacuum distillation to yield 1.7 g. of a light yellow viscous oil, b.p$_8$ 102∼108°. The residue amounted to 0.5 g. *Anal.* Calcd. for $C_6H_7O_4$: N, 8.92. Found: N, 9.06.

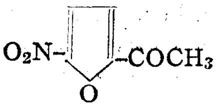
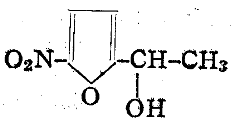
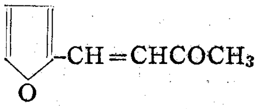
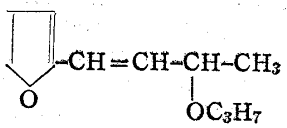
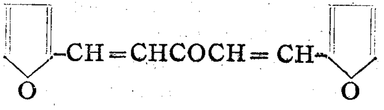
Reaction of furfurylidene-acetone—To a solution prepared from 7 g. of Al isopropoxide and 70 cc. of isopropyl alcohol was added 5 g. of freshly distilled furfurylidene-acetone, and the solution was stirred at 82° for 30 minutes, when distillation began. It took 7 hours for the acetone test to become perfectly negative. The amount of solvent distilled during this period of heating was about 50 cc. Hydrolysis was carried out under cooling with running water. The solution was extracted with ether and removal of the ether gave 5 g. of a red oil which was purified by vacuum distillation to 0.4 g. of a colorless oil. The amount of the residue was 2.5 g. As the yield of the resulting product was too small against the amount of the starting material, the same experiment was carried out by using twice the amount of materials to produce 10 g. of an oily raw material after removal of the ether. This product was purified under vacuum distillation to give 1.7 g. of oil, b.p$_{10}$ 62∼65°. The residual polymer left after distillation was 6 g. Yield, only 17%. *Anal.* Calcd. for $C_8H_{10}O_2$: C, 69.56; H, 7.25; for $C_{11}H_{16}O_2$ (if the product was isopropyl ether): C, 73.33; H, 8.88. Found: C, 73.82, 73.88; H, 7.19, 7.60.

Reaction of bisfurfurylidene-acetone—The same procedure was applied to a reaction mixture of 4.3 g. of bisfurfurylidene-acetone, 4 g. of Al isopropoxide, 40 cc. of isopropyl alcohol, and 40 cc. of benzene but the acetone test did not become negative even after a long heating. The unreacted starting material was recovered in 70∼80% yield.

The results are summarized in Table II.

TABLE II.

Exp. No.	Material	Method*	Yield	Product	Distillation residue/starting material
(1)		a	78%		3 g./10 g.
(2)		a	77%		1 g./10 g.
		b	75%		1.5 g./10 g.
		c	50%		1 g./10 g.
(3)		a	40%		6 g./ 8 g.
		b	56%		3 g./ 8 g.
(4)		a	66%		0.8 g./ 6 g.
(5)		a	44.4%		2 g./11 g.

(6)		b	56%		0.5 g./ 3 g.
(7)		a	17%		2.5 g./ 5 g. and 6 g./10 g.
(8)		a	No reaction		

* (a) refers to the use of purified isopropoxide and isopropyl alcohol as a solvent.
(b) refers to the use of purified isopropoxide and a mixed solvent.
(c) refers to not using either purified alkoxide or a mixed solvent.

Discussion

This mild and selective method of reducing carbonyl radical of furan compounds was applied successfully in terms of yields with two exceptions, (7) and (8). In the case of (7) the reduced product was dehydrolyzed during the distillation to vinylfuran which polymerized easily to a polymer of an unknown structure and the product obtained was an isopropyl ether of the reduction product, as shown by its elemental analysis. In (8) the reaction did not take place. As generally observed by other reactions, nitrofuran derivatives were more stable than furan derivatives when heated or treated chemically in the absence of alkali. These facts are substantiated by their yields and characteristics of the distillation residues. Reduction experiments (a), (b), and (c) of (2), (4) and (6) gave residuals of 1 g., 1.3 g., 1 g., 0.8 g., and 0.5 g., respectively, after distillation. These were all insoluble in ordinary solvents, such as ether, ethyl acetate, etc. In experiments (3), (5), and (7), the yields were 6 g., 3 g., 2 g., and 2.5 g. and 6 g., respectively and two experimental amounts for (3); one for (5); and two for (7). Thus it can be seen that these amounts were larger than in the former case. Their characteristics were also very different from those of the former in that they were very soluble in ether and ethyl acetate, and on account of their instability, they were thought to polymerize easily to result in larger amount of polymer during distillation.

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