at room temperature to 40 lb./sq. in. of hydrogen pressure in the presence of 0.1 g. of platinum oxide. After being shaken for 18 hours, the reaction mixture was filtered, diluted with water and extracted with ether. The ether extract was washed with sodium carbonate solution, dried and evapoated to give an oil which deposited crystals after standing in an ice-box. Recrystallization from methanol yielded 0.06 g. of white crystals, m.p. 44–44.5°. *Anal.* Calcd. for $C_{19}H_{32}O$: C, 82.54; H, 11.66. Found: C, 82.22, 82.19; H, 11.69, 11.69. An infrared spectrum showed the presence of carbonyl and unsaturation bands at 5.95–6.0 and the absence of hydroxyl. Ultraviolet absorption maxima were found at 234 mμ (ε 8000) and 343 mμ (ε 410).

WILMINGTON 98, DEL.

[CONTRIBUTION FROM THE PHARMACEUTICAL INSTITUTE OF THE MEDICAL SCHOOL, UNIVERSITY OF KYUSHU, JAPAN]

Synthesis of Furan Derivatives. XV. 5-Nitrofuryl Polyene Aldehydes

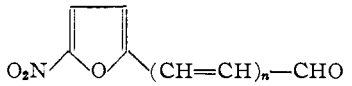
BY HARUO SAIKACHI AND HARU OGAWA

RECEIVED OCTOBER 14, 1957

Four 5-nitrofuryl polyene aldehydes (I, n = 1 to 4) were prepared stepwise from 5-nitrofurfural by repeated condensation with methyl vinyl ether in the presence of boron trifluoride etherate. This method gives considerably better yields than aldol condensation with acetaldehyde. Evidence is presented that the intermediates in this reaction are 1,3-dioxanes (II). The absorption maxima of the polyene aldehydes agree well with the Lewis and Calvin equation. Oximes, semicarbazones, thiosemicarbazones and aminoguanidine derivatives of the aldehydes were prepared, and some were tested for bacteriostatic activity. The oxime of the n = 2 aldehyde is highly active *in vitro* against *M. tuberculosis*, and is of low toxicity in the mouse.

Several years ago it was discovered by American researchers that 5-nitrofurfural semicarbazone and some related compounds possessed notable bacteriostatic and bactericidal activity.[1] The nitro group is essential: in its absence there is little or no activity. Although the exact mechanism of action is not known, it is thought that the compounds inhibit some enzyme system involved in the carbohydrate metabolism of the microörganisms.[2]

We have been investigating this class of compounds for several years.[3] From consideration of reported activities, it appeared to us that the interpolation of a chain of conjugated double bonds between the nitrofuran ring and the aldehyde group might be expected to enhance the antibacterial activity, and this prediction appeared to be borne out by results with three derivatives of 5-nitrofurylacrolein (I, n = 1) previously reported.[3] We have therefore tried the effect of further extension of the polyene chain.



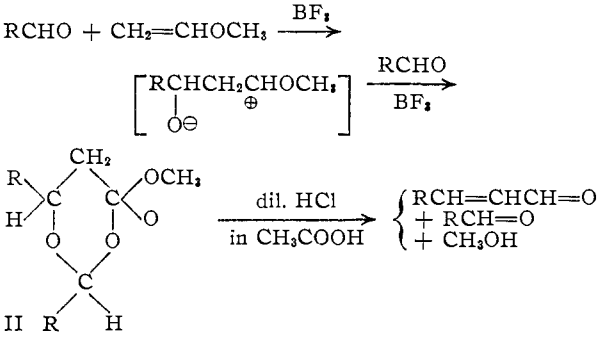
I

Our first approach to the synthesis of I (n = 2 and 3) was by the aldol condensation of 5-nitrofurylacrolein with acetaldehyde in the presence of piperidinium acetate, in the same way that we had previously prepared 5-nitrofurylacrolein itself. It was necessary to chromatograph the dark, resinous reaction product on alumina. The desired aldehydes were indeed obtained in this way, but in very poor yields.

In the meantime we had found that the condensation of 5-nitrofurfural with methyl vinyl ether in the presence of boron trifluoride etherate[4] is preferable to the aldol condensation for the preparation of 5-nitrofurylacrolein. In this reaction, unlike the aldol condensation, hardly any resinous by-product is formed, and the one-molar excess of 5-nitrofurfural which must be used is easily recoverable from the reaction mixture.

We therefore applied this same procedure successively to 5-nitrofurylacrolein and to its higher vinylogs. In this way we succeeded in building up stepwise, in good yields, not only the n = 1 but also the n = 2, 3 and 4 members of the series. The diene and triene members were shown by mixed melting point to be identical with the specimens previously obtained by aldol condensation. The properties of these aldehydes are given in Table I.

The intermediate product in this reaction is presumed to be a *m*-dioxane (II).



II

Since the intermediate in the conversion of 5-nitrofurfural to 5-nitrofurylacrolein could not be isolated in a pure state from the brown, viscous reaction mixture, we examined instead the analogous condensation of *p*-nitrobenzaldehyde with methyl vinyl ether. From this reaction mixture, colorless needles melting at 209–211° were obtained readily. The analysis and molecular weight of this compound were in good agreement with the expected

(1) M. C. Dodd and W. B. Stillman, *J. Pharm. Exp. Ther.*, **82**, 11 (1944).

(2) R. E. Asnis and J. S. Gots, *Arch. Biochem.*, **30**, 25 (1951); M. F. Paul, *et al.*, *J. Biol. Chem.*, **206**, 491 (1954).

(3) T. Takahashi, H. Saikachi, S. Yoshina and C. Mizuno, *J. Pharm. Soc. Japan*, **69**, 284 (1949); *C. A.*, **44**, 5372 (1950); H. Saikachi, Z. Aramaki and T. Aoki, *Pharm. Bull. Japan*, **3**, 194 (1955); *C. A.*, **50**, 9371 (1956); H. Saikachi, H. Ogawa, I. Furukawa and H. Hoshida, *Pharm. Bull. Japan*, **3**, 407 (1955); *C. A.*, **50**, 13861 (1956).

(4) J. W. Copenhaver, U. S. Patent 2,543,312 (1951); R. I. Hoaglin, *et al.*, U. S. Patent 2,628,257 (1953); O. Isler, *et al.*, *Helv. Chim. Acta*, **39**, 249 (1956).

TABLE I

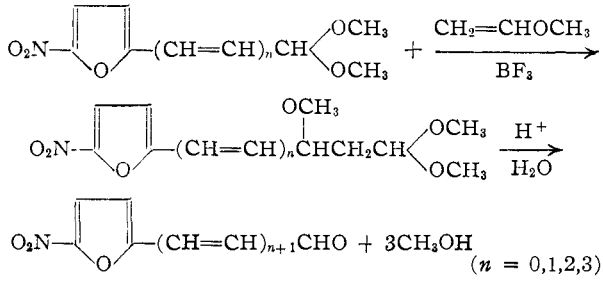
2-(5-NITROFURYL) POLYENE ALDEHYDES O_2N-(furan)-$(CH{=}CH)_nCHO$

n	Yield,[a] %	M.p., °C.	Appearance	λmax, mμ	ε (× 10^{-3})	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
0[b]		35–36	Colorless ndls.	.....	.....						
1[c]	Very poor[d] 95[d]	119	Pale yell. ndls.	238, 347	14.8, 23.2						
2	89[d] 93[e]	125	Bright yell. ndls.	272, 375	20.4, 24.0	55.96	56.16	3.65	3.63	7.12	7.25
3	87[d] 80[e]	152	Reddish-yell.	301, 401	24.5, 45.2	60.26	59.35	4.14	3.96	6.39	6.68
4	75[d]	164	Red ndls.	328, 425	28.5, 59.0	63.67	63.49	4.52	4.75	5.71	5.45

[a] Calculated on the basis of the recrystallized products. [b] H. Gilman, *et al.*, THIS JOURNAL, **52**, 2550 (1930); **53**, 1923 (1931). [c] H. Saikachi, *et al.*, *J. Pharm. Soc. Japan*, **69**, 284 (1949). [d] From dimethyl acetal. [e] From aldehyde.

formula $C_{17}H_{16}O_7N_2$, and its infrared spectrum showed a doublet at 9.26 and 9.35 μ, characteristic of *m*-dioxanes.[5] Hydrolysis with dilute HCl in acetic acid gave equimolar quantities of *p*-nitrocinnamaldehyde, *p*-nitrobenzaldehyde and methanol. On the basis of this evidence it may be concluded that the 209–211° compound is 2,4-di-(*p*-nitrophenyl)-6-methoxy-1,3-dioxane (II, R = *p*-nitrophenyl), and that II (R = 5-nitrofuryl) is unquestionably formed in the analogous condensation with 5-nitrofurfural.

Since acetals as well as free aldehydes can be employed in this condensation,[6] we prepared dimethyl and diethyl acetals of I (n = 0–3) by the orthoformate method. By condensation with methyl vinyl ether in chloroform, these acetals (Table II) could be converted to the vinylogous aldehydes



The yields in this version of the reaction were generally not so good as from the free aldehydes, but the advantage of using the acetal reaction (method C) is that excess acetal is not used as opposed to the aldehyde reaction (method B) and hence does not have to be recovered.

The ultraviolet absorption spectra of the four 5-nitrofuryl polyene aldehydes in ethanol are shown in Fig. 1 and in Table I. The shift of the absorption maximum to longer wave lengths with increasing conjugation parallels that of the unsubstituted furyl polyene aldehydes.[7] The absorption bands are broad and devoid of discernible fine structure; although precise location of the maxima is difficult, it is clear from Fig. 2 that this spectral series agrees very well with the Lewis and Calvin[8] relationship, $\lambda^2 = kn$.

The three aldehydes with n = 2, 3 and 4 were condensed with semicarbazide, thiosemicarbazide, hydroxylamine and aminoguanidine. Of the re-

(5) Tschamler and Leutner, *Monatsh.*, **83**, 1502 (1952).
(6) R. I. Hoaglin and D. H. Hirsh, THIS JOURNAL, **71**, 3468 (1949).
(7) E. R. Blout and M. Fields, *ibid.*, **70**, 189 (1948).
(8) G. N. Lewis and M. Calvin, *Chem. Revs.*, **25**, 273 (1939).

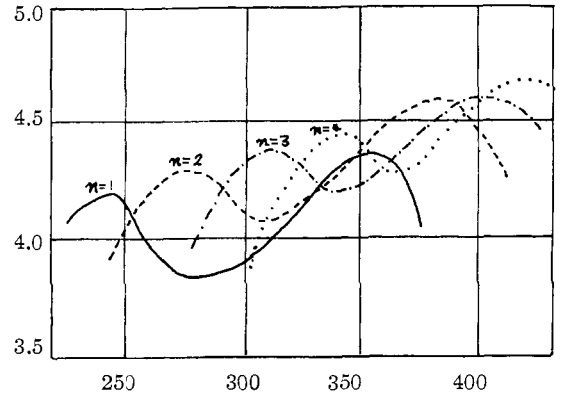


Fig. 1.—Ultraviolet absorption spectra of 5-nitrofuryl polyene aldehydes (I, n = 1 to 4) in ethanol.

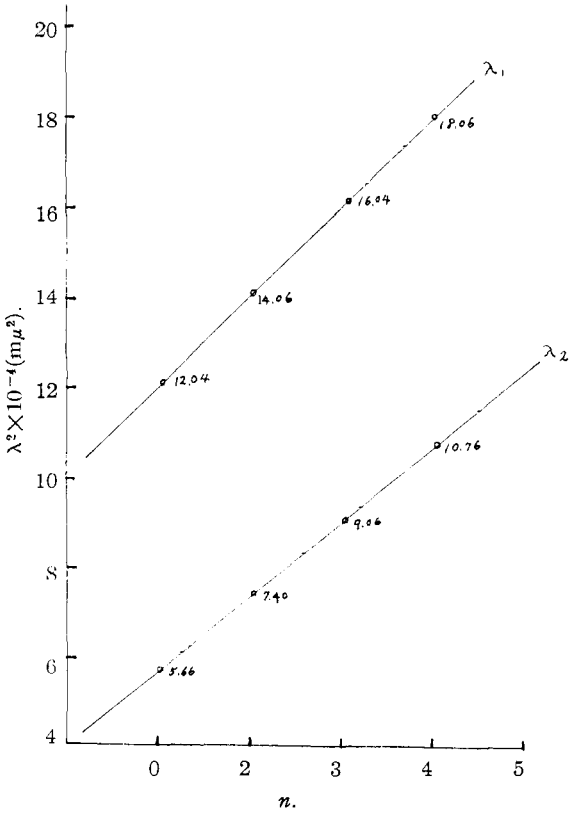
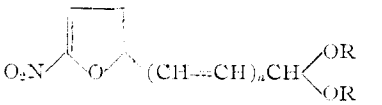


Fig. 2.—Absorption maxima of 5-nitrofuryl polyene aldehydes plotted according to Lewis and Calvin, showing fit within experimental error.

TABLE II

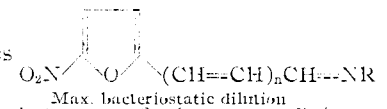
ACETALS OF 2-(5-NITROFURYL) POLYENE ALDEHYDES



n	R	Yield, %	M.p. or b.p. °C. (mm.)	Appearance	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
0	CH_3	82	113–115 (2)	$n^{20}D$ 1.5188	44.92	45.12	4.85	4.97	7.48	7.70
0	C_2H_5	84	12–122 (3)	$n^{20}D$ 1.4994	50.23	50.34	6.09	6.18	6.51	6.80
1	CH_3	95	58–59.5	Pale yell. ndls.	50.70	50.88	5.20	5.47	6.57	6.47
1	C_2H_5	90	56–56.8	Pale yell. ndls.	54.76	54.98	6.27	6.03	5.81	5.71
2	CH_3	93.2	72–74	Yell. prisms	55.23	55.49	5.47	5.33	5.86	5.75
3	CH_3	90	77–78	Orange-yell. prisms	58.86	58.92	5.70	5.82	5.28	5.41

TABLE III

NITROGENOUS DERIVATIVES OF 5-NITROFURYL POLYENE ALDEHYDES



Number	n	R	M.p., °C.	Nitrogen % Calcd.	Nitrogen % Found	Max. bacteriostatic dilution *Mycobact. tuberculosis*[a]	*Staph. aureus*[b]	*Esch. coli*[b]	LD_{50},[d] mg./kg.
III	2	=NOH	192	13.46	13.31	$1:256 \times 10^4$	$1:32 \times 10^4$	$1:64 \times 10^4$	>800
IV	3	=NOH	194	11.96	11.83	$1:128 \times 10^4$	$1:32 \times 10^4$	$1:64 \times 10^4$	>800
V	4	=NOH	204	10.77	10.60	...	...	...	...
VI	2	=NHCONH$_2$	240d.	22.39	32.18	...	...	...	...
VII	3	=NHCONH$_2$	242d.	20.28	20.10	...	...	...	...
VIII	4	=NHCONH$_2$	245d.	18.54	18.40	...	...	...	...
IX	2	=NHCSNH$_2$	198d.	21.05	20.88	...	...	...	...
X	3	=NHCSNH$_2$	216d.	19.17	18.85	...	$1:10^3$	$1:10^4$	...
XI	4	=NHCSNH$_2$	230d.	17.60	17.51	...	...	...	...
XII	2	=NHC(=NH)NH$_2$·HCl	235–236d.	24.49	24.34	...	$1:16 \times 10^4$	$1:8 \times 10^4$	300
XIII	3	=NHC(=NH)NH$_2$·HCl	237–238d.	22.46	22.21	...	$1:32 \times 10^4$	$1:16 \times 10^4$	200
XIV	4	=NHC(=NH)NH$_2$·HCl	252–255d.	20.79	20.72	...	...	...	...
Streptomycin			...	...	...	$1:128 \times 10^4$	...	...	...
Isonicotinic acid hydrazide			...	...	...	...	...	...	300

[a] Strain $H_{37}RV$, incubated 4 weeks in Kirchner culture medium. [b] Strain 209p, incubated 98 hours. [c] Incubated 98 hours. [d] Intraperitoneal injection in ddN strain mice.

sulting twelve derivatives (Table III), five were screened for bacteriological activity and acute toxicity; of these, 5-[2-(5-nitrofuryl)]-2,4-pentadienal oxime (III) proved to be outstandingly active and non-toxic. As Table III shows, the activity of III against *M. tuberculosis* under these conditions is twice that of streptomycin.

Acknowledgment.—We wish to express our appreciation to Mitsubishi Chemical Co. Ltd. and Ueno Pharmaceutical Co. Ltd., of Japan, for contributing many important intermediates for this work. For the microbiological screening we are indebted to Professor Dr. T. Toda and Dr. T. Tokunaga of the Department of Bacteriology, Medical Faculty, University of Kyushu.

Experimental

Preparation of 5-(5-Nitrofuryl)-2,4-pentadienal and 7-(5-Nitrofuryl)-2,4,6-heptatrienal (Method A).—To a solution of 20 g. (0.123 mole) of 5-nitrofurylacrolein (m.p. 119°) and 10.6 g. (0.24 mole) of freshly distilled acetaldehyde in 250 cc. of dry chloroform was added carefully with stirring at −5° during two hours, 3.0 g. of piperidinium acetate. The reaction temperature was raised gradually to 45–50° within five hours and then allowed to stand overnight at room temperature.

The resulting deep brownish-yellow reaction mixture was treated with 3 cc. of ethanol saturated with hydrogen chloride in an ice-box for ten minutes. The mixture was then washed twice with 150 cc. of water, the brownish chloroform layer was separated, dried over anhydrous sodium sulfate and filtered. The solvent was removed under reduced pressure, leaving a dark oily residue. After standing at room temperature, reddish-orange crystals gradually deposited. The crystalline mass was filtered off and recrystallized from benzene three times to yield 6.0 g. of yellowish-orange prisms melting at 80–104°. A benzene solution of 1.5 g. of this product was chromatographed on a column of 70 g. of alumina in the absence of light. Elution with a mixture of benzene and ethyl acetate (29:1) resulted in the following three fractions: the first fraction readily gave yellow needles melting at 114–120°; the second, orange leaves melting at 145–149°; the last resinous matter. Two recrystallizations of the above two crystalline products from ethyl acetate gave 0.22 g. of yellow needles melting at 124–125° and 0.1 g. of orange prisms melting at 150–152°, respectively. The mixed melting points of these compounds with authentic specimens of 5-(5-nitrofuryl)-2,4-pentadienal and 7-(5-nitrofuryl)-2,4,6-heptatrienal, respectively (see below), showed no depression.

Preparation of 5-Nitrofuryl Polyene Aldehydes with Methyl Vinyl Ether (Method B).—The following general procedure was first used for preparation of the three polyene aldehydes listed in Table I. Into a stirred solution of the nitrofuryl aldehyde (0.279 mole) in 50 cc. of dry benzene, containing a small amount of $BF_3 \cdot O(C_2H_5)_2$ as catalyst, 0.1 mole of methyl vinyl ether was gradually bubbled at 15°. The color of the reaction mixture first became pale green and then gradually changed to dark brown. The reaction mixture was then heated on a water-bath at 35° for one hour, cooled to room temperature, and washed consecutively with 5% sodium acetate, and with water.

The benzene layer was dried over anhydrous sodium sulfate, and filtered. Removal of the solvent gave a viscous reddish-orange residue. Unfortunately, various attempts to crystallize the each crude residue were unsuccessful. Consequently, the resinous residue was hydrolyzed by heating on a water-bath at 70–80° for three hours with a mixture of 3 cc. of concentrated hydrochloric acid, 17 cc. of water and 20 cc. of acetic acid. The reaction mixture was concentrated under diminished pressure until reddish-brown prisms deposited; then the mixture cooled in an ice-box.

The crystalline material was filtered off, washed well with water and then with methanol or ethyl acetate. Recrystallization of the crude product from ethyl acetate gave reddish needles melting at the temperatures summarized in Table I. In order to recover one mole of the unchanged aldehydes, the following procedure was employed. After evaporating the combined mother liquors and removing the solvent, the residue was carefully extracted many times with warm benzene and the combined extracts dried over anhydrous sodium sulfate and filtered. Removal of the benzene left a dark brown oily residue, which crystallized on standing in the ice-box. The crude unchanged aldehydes, except for 5-nitrofurfural, were recrystallized from ethyl acetate. The 5-nitrofurfural was recovered in 86% yield by vacuum distillation.

Preparation of 5-Nitrofuryl Polyene Aldehydes from Dialkyl Acetals (Method C).—Into a stirred solution of 0.1 mole of the nitrofuryl aldehyde dimethyl or diethyl acetal in 60 cc. of dry chloroform containing a catalytic quantity of $BF_3{\cdot}O(C_2H_5)_2$ was bubbled 0.1 mole of methyl vinyl ether at 35°. The temperature was controlled by the rate of addition of methyl vinyl ether. As the temperature rose to 45° the reaction mixture turned brownish-black. The mixture was then shaken with 5% sodium acetate and washed well with cold water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to a viscous oily residue. This was hydrolyzed with a mixture of 125 cc. of acetic acid, 5 cc. of 3% hydrochloric acid and 60 cc. of water on a water-bath at 90–95° for four hours. On cooling, crude crystals deposited which were filtered off and washed with a small amount of cold methanol. In order to remove adhering resinous matter, the crude crystals were dissolved in hot benzene, filtered, and the solvent removed by distillation. Recrystallization of the crude crystals from ethyl acetate gave a pure product, except for 5-nitrofurfural dimethyl and diethyl acetal, in about 75–87% yield. The products obtained by this method were identical with these obtained by method B.

Condensation of *p*-Nitrobenzaldehyde with Methyl Vinyl Ether in the Presence of BF_3.—Into a stirred solution of 10 g. (0.066 mole) of *p*-nitrobenzaldehyde in 70 cc. of dry benzene containing a catalytic quantity of $BF_3{\cdot}O(C_2H_5)_2$ was gradually bubbled 2.0 g. (0.035 mole) of methyl vinyl ether at 25°. After addition of the vinyl ether, stirring was continued for an additional hour, when colorless needles gradually deposited from the reaction mixture. These were filtered off and washed with a small amount of warm ethyl acetate to remove unchanged *p*-nitrobenzaldehyde. Recrystallization of the crude product from benzene gave 8.5 g. of colorless needles melting at 209–211°.

Anal. Calcd. for $C_{17}H_{16}O_7N_2$: C, 56.66; H, 4.44; N, 7.78; mol. wt., 360.3. Found: C, 56.64; H, 4.35; N, 7.83; mol. wt. (Rast's method), 355.2.

An analogous crystalline intermediate was not obtained in the case of 5-nitrofurfural using the same procedure. A mixture of 5.0 g. of the crystalline intermediate (presumed to be the *m*-dioxane type), 2.5 cc. of concentrated hydrochloric acid, 30 cc. of acetic acid (or 20 cc. of dioxane) and 2.5 cc. of water was heated on a water-bath for three hours. Concentrating the reaction mixture under reduced pressure and cooling to room temperature gave a pale yellow crystalline mass. This was filtered off, and two crystallizations from absolute ethanol gave 1.8 g. of colorless needles, melting at 140–142°. The mixed melting point with authentic *p*-nitrocinnamic aldehyde[9] was 140–142°. Additionally, concentrating the filtrate from the earlier reaction mixture under reduced pressure and cooling in an ice–salt-bath gave a darkish orange crystalline mass. This was filtered off, and two recrystallizations from water gave 3.6 g. of colorless needles, melting at 106°. This mixed melting point with authentic *p*-nitrobenzaldehyde was 105–106°.

Preparation of Acetals.—The following procedure was used in all cases: A solution of 0.1 mole of the aldehyde in 0.1 mole of methyl orthoformate (or ethyl orthoformate) was heated on a water-bath for one hour in the presence of *p*-toluenesulfonic acid as catalyst. On cooling, the reaction mixture was diluted with 200 cc. of ether, washed well with 5% sodium acetate, dried over anhydrous sodium sulfate and filtered. After removal of the solvent, the residue solidified on cooling. Recrystallization from methanol (or ethanol) gave pale yellow prisms in good yield. The properties of six dialkyl acetals prepared by the above procedure are recorded in Table II.

Condensation of 5-Nitrofuryl Polyene Aldehydes with Hydroxylamine, Semicarbazide, Thiosemicarbazide and Aminoguanidine.—These condensation products and their antibacterial properties are listed in Table III. One-tenth mole of aldehydes was dissolved in about one liter of warm ethanol. To each was added with stirring a small excess of semicarbazide hydrochloride, thiosemicarbazide or hydroxylamine and an additional quantity of 0.2 mole of sodium acetate. Each solution was heated on a water-bath at 50° for about one hour. The reaction mixture was then cooled to +5° and the crystalline mass which formed was filtered off. Recrystallization of the crude products from a large amount of ethanol gave the compounds presented in Table III. One-tenth mole of aminoguanidine carbonate was condensed, respectively, with an equivalent amount of three polyene aldehydes (n = 2, 3 and 4) under the experimental conditions described above.

The yellowish reaction mixture in each case was made acid to congo red with concentrated hydrochloric acid (or ethanol saturated with hydrogen chloride) and the solution then cooled in an ice-box. Reddish-yellow crystals of the hydrochloride gradually deposited. After standing at room temperature for six hours, the product was filtered off and purified by three recrystallizations from ethanol to give the three polyene aldehyde aminoguanidine hydrochlorides (n = 2, 3 and 4) summarized in Table III.

(9) G. Garrara, *et al.*, THIS JOURNAL, **76**, 4391 (1954).

CITY OF FUKUOKA, JAPAN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MISSOURI]

Substituted Styrenes. III. The Syntheses and Some Chemical Properties of the Vinylphenols[1,2]

BY WESLEY J. DALE AND HENRY E. HENNIS

RECEIVED MARCH 10, 1958

The syntheses and some reactions of *o*-, *m*- and *p*-vinylphenol are described and discussed.

The effect that a strong electronegative nuclear substituent exerts on the double bond of a substituted styrene was clearly demonstrated when it was shown that enolates[3] and amines,[4] typical nucleophilic reagents, add readily to the vinyl group of *o*- and *p*-nitrostyrene.

As one phase of a series of studies in this Laboratory concerning the chemistry of a large variety of

(1) Abstracted from a portion of a thesis submitted by H. E. H. to the Graduate School of the University of Missouri in partial fulfillment of the requirements for the Ph.D. degree.

(2) Presented in part at the 130th Meeting of The American Chemical Society, Atlantic City, N. J., September 17, 1956.

(3) W. J. Dale and C. W. Strobel, THIS JOURNAL, **76**, 6172 (1954).

(4) W. J. Dale and G. Buell, *J. Org. Chem.*, **21**, 45 (1956).