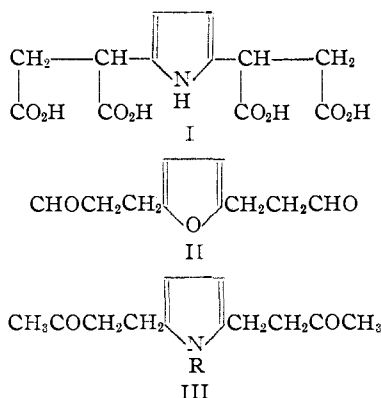


[CONTRIBUTION FROM THE POLYCHEMICALS DEPARTMENT, E. I. DU PONT DE NEMOURS & COMPANY]

Addition of Heterocycles to Conjugate Unsaturated Carbonyl Compounds: Difunctional Derivatives

BY I. D. WEBB AND G. T. BORCHERDT

Certain types of conjugated dienes, which do not readily undergo the Diels-Alder reaction, have previously been shown to add beta to very active conjugated systems in the presence of acid catalysts.¹ Thus pyrrole adds to maleic acid to form 2,5-pyrroledisuccinic acid (I),² and furan adds to acrolein to form 2-furanpropionaldehyde and 2,5-furandipropionaldehyde (II).³



While extending the applicability of this addition reaction for the preparation of certain difunctional heterocyclic compounds, we have investigated reaction conditions, and have uncovered means of obtaining improved yields of the adducts 2,5-furandipropionaldehyde and 2,5-bis-(3-oxobutyl)-furan.^{1a} We have also succeeded in adding pyrrole and N-methylpyrrole to methyl vinyl ketone to give high yields of the corresponding crystalline bis-adducts, 2,5-bis-(3-oxobutyl)-pyrrole (III, R = H) and N-methyl-2,5-bis-(3-oxobutyl)-pyrrole (III, R = methyl). Thiophene is so much less reactive than pyrrole and furan that polymerization of the unsaturated carbonyl compound predominates under the severe reaction conditions; nevertheless, 2-(3-oxobutyl)-thiophene was characterized as a product of the reaction of thiophene and methyl vinyl ketone.

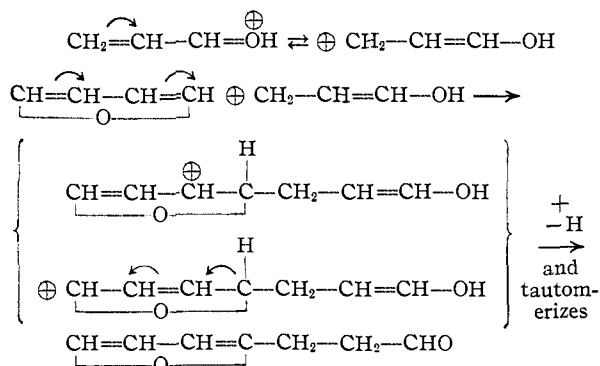
The generality of acid catalysts has been previously demonstrated.^{1a} The present investigation has demonstrated generally the beneficial effect and specifically the necessity of water as a reaction medium (or adjuvant) and the importance of acid concentration, *i.e.*, pH, upon the yields of adducts. Contrary to Scherlin, *et al.*, only polymers of furan and acrolein were obtained in the absence of water; however, when furan and acrolein were heated in the presence of an aqueous acetic acid solution of about pH 3, furanpropionaldehyde and furandipropionaldehyde could be isolated in combined yields approaching 70% with little polymer formation.

(1) (a) Alder and Schmidt, *Ber.*, **76**, 183 (1943); (b) Nazarov and Nagebina, *Chem. Abstr.*, **42**, 7736 (1948).

(2) Diels and Alder, *Ann.*, **486**, 211 (1931).

(3) Scherlin, *et al.*, *Chem. Zentr.*, **110**, I, 1969 (1939); Norton, *Chem. Revs.*, **31**, 472 (1942).

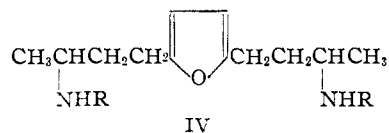
This general acid catalysis suggests that the mechanism of this type of addition reaction may involve the attack of a weak electrophilic aldehyde or ketone oxonium ion upon the carbon atom of highest electron density in the diene heterocycle. Thus furan could donate a pair of electrons to acrolein oxonium ion; when the intermediate resonating carbonium ion loses a proton and tautomerizes, furanpropionaldehyde results.



This mechanism conforms to the apparent degree of aromatic character in the heterocyclic addend; that is, ease of reaction decreases in the order pyrrole > furan > thiophene. The strongly aromatic pyridine does not react.

2,5-Furandipropionaldehyde and 2,5-bis-(3-oxobutyl)-furan were reduced and reductively aminated in moderate to excellent yields by conventional methods to the corresponding furan derivative, 2,5-furandipropylamine, 2,5-bis-(3-aminobutyl)-furan (IV, R = H) and 2,5-bis-(3-methylaminobutyl)-furan (IV, R = methyl).

The corresponding tetrahydrofuran derivatives, presented in Table I, were prepared by catalytic reduction over ruthenium catalyst in 80-87% yields. Ruthenium in general gave better yields



of tetrahydrofuran compounds than Raney nickel; ruthenium apparently does not catalyze furan hydrogenolysis as readily as nickel. With either catalyst, ammonia prevented reduction of the furan ring so that ring hydrogenation and reductive amination of the carbonyl groups could not be carried out simultaneously.

Experimental

2-Furanpropionaldehyde and 2,5-Furandipropionaldehyde (II).—A mixture of 68 g. of furan (1 mole), 28 g. of acrolein (0.5 mole), 1 g. of hydroquinone, 50 ml. of water and 5 ml. of glacial acetic acid was heated with agitation under autogenous pressure at 130° for 2 hours. The reaction mixture was cooled, diluted with 100 ml. ether and the aqueous layer

TABLE I

COMPOUNDS PREPARED BY REDUCING CORRESPONDING FURAN WITH A 10% RUTHENIUM ON CHARCOAL CATALYST IN DIOXANE SOLUTION^d

Product, tetrahydrofuran-	°C.	B. p. Mm.	<i>n</i> _D ²⁰	Yield, %	Carbon, %		Hydrogen, %		Nitrogen, %		Neut. equiv.	
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
2,5-Dipropanol ^a	135-136	1	1.4753-7	85	63.8	63.2	10.7	10.7			OH, 595	OH, 565
2,5-Bis-(3-hydroxybutyl)- ^b	141-143	1	1.4703	85	66.5	66.6	11.2	11.2			OH, 520	OH, 512
2,5-Dipropylamine ^c	102-109	2	1.4827	80							93	96.2
2,5-Bis-(3-aminobutyl)- ^c	112-117	0.75-1.0	1.4700	85	67.2	64.0	12.2	11.8	13.1	12.0	107	109
2,5-Bis-(3-methylaminobutyl)- ^c	107-109	0.4	1.4655	85	69.3	68.1	12.5	12.6	11.6	10.8	121	123

^a Hydrogenation of furandipropionaldehyde or furandipropanol at 100°. ^b Hydrogenation of 2,5-bis-(3-oxobutyl)-furan at 100°. ^c 120-160° for reduction. ^d Ruthenium catalyst from Baker and Co., Newark, N. J. About 25-30% solution of compound in dioxane containing 10 wt. % catalyst based upon compound. Pressures H₂ 2-400 atm.

separated. The organic layer was washed with water, and ether and unreacted furan evaporated gently on a steam-bath. The residual oil was distilled at a moderate rate through a short modified Vigreux column. After furandipropionaldehyde was obtained at 40-45° (2 mm.), *n*_D²⁰ 1.4919, decomposition appeared to set in and the pressure rose to 10-15 mm. As decomposition gradually subsided, the pressure fell and furandipropionaldehyde distilled at 125-140° (2-4 mm.). Distillation was stopped before the non-distillable residue foamed up into the column. In the best run, the yields of monoaldehyde, dialdehyde and resin were 8.7 g. (14%), 23.2 g. (51%) and 7.5 g., respectively. On redistillation furandipropionaldehyde boiled at 111° (1.5 mm.) as a pale yellow liquid of *n*_D²⁰ 1.4929 which slowly set to a low-melting solid.³

2,5-Bis-(3-oxobutyl)-furan.^{1a}—In a shaking-type autoclave, 100 g. of furan (1.5 moles), 52 g. of methyl vinyl ketone (stabilized, 15% water) (0.65 mole contained), 1 g. of hydroquinone, 1 g. of sulfur dioxide and 3 ml. of water were heated 2 hours at 90° under autogenous pressure. Ether was added to the reaction mixture and the solution washed with water. Volatile material was stripped off and the products vacuum distilled. Twenty-seven grams of 2-(3-oxobutyl)-furan, b.p. 55° (1.5 mm.), *n*_D²⁰ 1.4729 (carbonyl no., calcd. 407 mg. KOH per g., found 426), and 35 g. of 2,5-bis-(3-oxobutyl)-furan, b.p. 130-135° (1.5 mm.), *n*_D²⁰ 1.4849 (carbonyl no., calcd. 540, found 548) were obtained. There remained 5 g. of resinous distillation residue.

2-(3-Oxobutyl)-thiophene.—Thiophene, 84 g. (1 mole), 50 g. of 85% aq. methyl vinyl ketone, 0.5 g. of hydroquinone, 20 g. of water and 1 g. of sulfur dioxide were heated with agitation two hours at 130° under autogenous pressure. The product was washed with water and distilled. Material boiling over a range (12.5 g.) was obtained, which upon careful rectification gave a portion b.p. 89-92° (15 mm.), 5 ml., as a pale yellow liquid with *n*_D²⁰ 1.5092, turning brown on standing. *Anal.* Calcd. for C₈H₁₀OS: C, 62.3; H, 6.55; S, 20.8; carbonyl no., 364 mg. KOH per gram of C₈H₁₀OS. Found: C, 63.1, 62.8; H, 6.83, 6.82; S, 16.0, 16.1; carbonyl no., 408. Low sulfur indicates that the product is contaminated with methyl vinyl ketone dimer.

Except in special cases, thiophene fails to undergo the Diels-Alder reaction; as a check against the possibility that the reaction product is the normal Diels-Alder adduct, thiophene and methyl vinyl ketone were heated together at 250° for 1 hr. The high boiling product contained no sulfur and thus was polymeric methyl vinyl ketone.

2,5-Bis-(3-oxobutyl)-pyrrole (III, R = H).—To a stirred mixture of 50 ml. of water containing 1 g. of sulfur dioxide, 35 g. of pyrrole (0.5 mole) and 0.5 g. of hydroquinone, heated to 60°, was added 80 g. of 85% aq. methyl vinyl ketone (1 mole contained) at such a rate that the temperature remained at 60°. This required about one hour. After an additional half-hour at 60°, with stirring, the mixture was chilled, and the pale yellow crystals were filtered and dried. The yield was 86 g. (80%). Crystallization from methanol gave white plates melting at 75-77°. *Anal.* Calcd. for C₁₂H₁₇O₂N: C, 69.5; H, 8.3; N, 6.77. Found: C, 68.7; H, 8.2; N, 6.68.

N-Methyl-2,5-bis-(3-oxobutyl)-pyrrole (III, R = methyl).—This compound was prepared from 21 g. of N-

methylpyrrole by the procedure used for pyrrole. After one crystallization from isobutyl alcohol the yield was 27 g. Recrystallization from methanol gave clusters of small white prisms of m.p. (bar) 99°. *Anal.* Calcd. for C₁₃H₁₉O₂N: C, 70.5; H, 8.7; N, 6.34. Found: C, 70.3; H, 8.7; N, 6.14.

N-Methyl-2,5-bis-(3-hydroxybutyl)-pyrrolidine.—This compound was prepared in nearly quantitative yield by reducing III (R = methyl) in methanol over Raney nickel catalyst; b.p. 128° (2 mm.) as a colorless, viscous oil of *n*_D²⁰ 1.4823. *Anal.* Calcd. for C₁₃H₂₇O₂N: C, 68.1; H, 11.9; N, 6.1; neut. equiv., 229. Found: C, 67.4, 67.9; H, 11.9, 11.8; N, 6.0; neut. equiv., 228, 231.

Picrate, recrystallized from methanol-chloroform-ether as clusters of fine yellow needles, m.p. (bar) 129.5°. *Anal.* Calcd. for C₁₉H₃₀O₉N₄: N, 12.0. Found: N, 12.3, 12.2.

2,5-Furandipropanol.—The dialdehyde (II) was reduced with lithium aluminum hydride or hydrogenated in ether solution over copper chromium oxide at 145-175° and 200 atm. (80% yield); b.p. 145° (2 mm.) as a light yellow oil *n*_D²⁰ 1.4993. *Anal.* Calcd. for C₁₀H₁₆O₃: C, 65.2; H, 8.8; OH no., 610. Found: C, 64.4; H, 8.7; OH no., 584.

2,5-Furandipropylamine.—The dialdehyde (II) (18 g.) was reductively aminated over 10 g. of Raney nickel in 1 hr. at 300 atm. and 75-90° in 100 ml. of methanol and 25 g. of ammonia. The diamine b.p. 98-112° (1-2 mm.), *n*_D²⁰ 1.5003, 10 g. (55%). *Anal.* Calcd. for C₁₀H₁₈ON₂: neut. equiv., 91 g. Found: neut. equiv., 99.5 g.

2,5-Bis-(3-aminobutyl)-furan (IV, R = H) and 2,5-bis-(3-methylaminobutyl)-furan (IV, R = methyl) were obtained in yields of 87 and 85%, respectively, by reductive amination and reductive methylation of 2,5-bis-(3-oxobutyl)-furan, as described in the previous paragraph. IV (R = H), b.p. 100° (0.5 mm.), *n*_D²⁰ 1.4900. *Anal.* Calcd. for C₁₂H₂₂ON₂: C, 68.5; H, 10.6; N, 13.3; neut. equiv., 104.1. Found: C, 67.0; H, 10.4; N, 13.1; neut. equiv., 106.4. IV (R = methyl), b.p. 113.8° (0.9 mm.), *n*_D²⁰ 1.4816. *Anal.* Calcd. for C₁₄H₂₆ON₂: C, 70.5; H, 11.0; N, 11.8; neut. equiv., 119.1. Found: C, 69.0; H, 10.8; N, 10.9; neut. equiv., 134.4.

Acknowledgment.—The authors are indebted to L. S. Malzer for technical assistance.

Summary

1. Procedures for the preparation 2,5-difunctionally substituted furans and pyrroles are described: 2,5-furandipropionaldehyde from furan and acrolein, 2,5-bis-(3-oxobutyl)-pyrrole (and N-methylpyrrole) from pyrrole (and from N-methylpyrrole) and methyl vinyl ketone, and 2,5-bis-(3-oxobutyl)-furan from furan and methyl vinyl ketone. Glycols and diamines prepared from these adducts are described.

2. Catalytic reduction of these derivatives with ruthenium catalyst gave the corresponding tetrahydrofuran compounds in excellent yields.