[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OKLAHOMA AGRICULTURAL AND MECHANICAL COLLEGE]

The Condensation of Methylal and Other Acetals with Olefins[1]

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In the presence of boron trifluoride, anhydrous methylal adds, as methoxy and methoxymethyl groups, to all olefins tried: propylene, isobutylene, styrene, cyclohexene, α-pinene and 1,3-butadiene. Orientation corresponds to that in the analogous Prins reaction of aldehydes and olefins. Additional examples of the reaction, although they proceed less readily, are provided by ethylal and styrene and by diethyl acetal and isobutylene.

Whereas aqueous methylal serves merely as a source of formaldehyde in the Prins reaction,[2] anhydrous methylal has now been found to add to olefins in the presence of acid catalysts. The reaction parallels the addition of higher acetals to α,β-unsaturated ethers[3] and olefins.[4] It was demonstrated by Hoaglin and Hirsh that cleavage of the acetal into an alkoxyalkyl and an alkoxy fragment is involved, and that the alkoxy group becomes attached to the α-carbon atom of the unsaturated ether. Inasmuch as this olefinic carbon atom has the lower electron density of the two carbon atoms, such orientation is in accordance with that in Prins reactions of aldehydes.[5] So far as could be observed, the unsymmetrical olefins that we studied obeyed the same rule, the product resulting from Prins orientation being formed in larger yield in all cases in which proof of structure was effected.

$$RCH{=}CH_2 + CH_3OCH_2OCH_3 \longrightarrow \underset{\text{(chiefly)}}{RCH(OCH_3)CH_2CH_2OCH_3} + RCH(CH_2OCH_3)$$

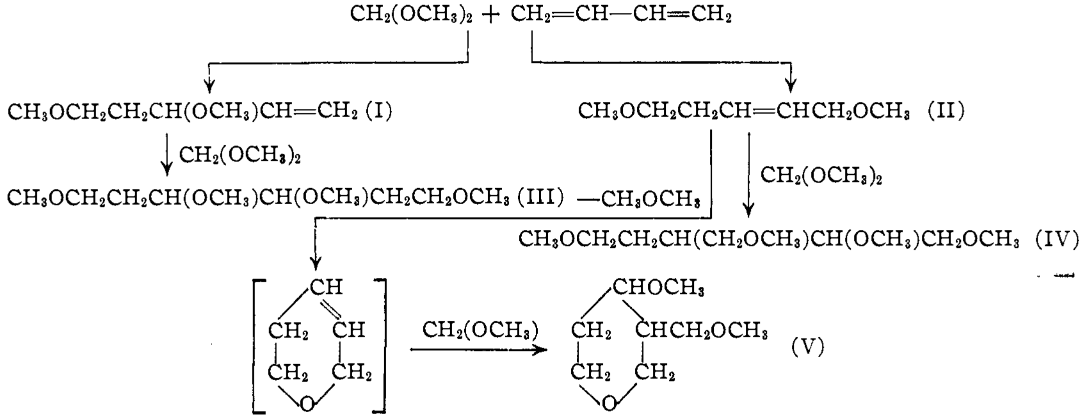
In this work the principal effort was toward establishing variability of the reagents rather than optimum conditions; hence few yields were high. Ethylene was considered unlikely to react well except at pressures above those we used, and acetylene could not be made to react. Sulfuric acid served as catalyst but was inferior to boron trifluoride; other Lewis acids were found ineffective.

Propylene with excess methylal gave two compounds. The principal one was shown to be 1,3-dimethoxybutane by the coincidence of its properties with those of a sample prepared by methylating 1,3-butanediol; the other, boiling at 116.5–118.5°, was believed to be the isomeric 1,3-dimethoxy-2-methylpropane but was never adequately purified. Of the corresponding pair of compounds derived from isobutylene, the lower-boiling one was characterized mass-spectrometrically as 1,3-dimethoxy-3-methylbutane, and the other was therefore considered to be 1,3-dimethoxy-2,2-dimethylpropane. Only one compound, concluded by analogy to be 1,3-dimethoxy-1-phenylpropane, was obtained from styrene.

The inability of Paul and Tchelitcheff to cause addition of diethyl acetal to cyclohexene is attributed partly to their use of the less active catalyst boron trifluoride etherate, and partly to the comparatively low reactivities of the olefin and the acetal. We obtained small yields of 1-methoxy-2-methoxymethylcyclohexane and its demethanolation product, 1-methoxymethylcyclohexene,[6] and evidence for the formation of 1-methoxy-2-hydroxymethylcyclohexene.

The complex reaction mixture from α-pinene, doubtless complicated by isomerization of the olefin, yielded only one pure compound. Its structure remains unproved, but analysis and inference indicate that it is 6-methoxymethylpinane.

Methylal and 1,3-butadiene gave a variety of products: 3,5-dimethoxy-1-pentene (I), by 1,2-addition; 1,5-dimethoxy-2-pentene (II), by 1,4-addition; 1,3,4,6-tetramethoxyhexane (III), by 1,2- and then 3,4-addition; and 1,2,5-trimethoxy-



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[1] From the thesis submitted by John J. Hawkins for the degree of Ph.D. at Oklahoma A. and M. College, 1952.

[2] E. Arundale and L. A. Mikeska, U. S. Patent 2,421,862, June 10, 1947.

[3] R. I. Hoaglin and D. H. Hirsh, THIS JOURNAL, **71**, 3468 (1949).

[4] R. Paul and S. Tchelitcheff, *Bull. soc. chim. France*, 125 (1951).

[5] C. C. Price, "Mechanism of Reactions at Carbon–Carbon Double Bonds," Interscience Publishers, Inc., New York, N. Y., 1946, p. 45.

[6] Compare the formation of 1-hydroxymethylcyclohexene from the olefin and formaldehyde: S. Olsen and H. Padberg, *Z. Naturforsch.*, **1**, 257, 448 (1946).

TABLE I

CONDITIONS FOR PREPARATION OF ADDUCTS FROM ACETALS AND OLEFINS

No.	Acetal,[a] ml.	Catalyst,[b] g.	Olefin	Olefin, g.	Temp.,[c] °C.	Time,[c] hr.
1	150	43	Propylene	38	25	3
2	300	16	Isobutylene	82	45	0.5
3	250	26	Styrene	130	25	1
4	300	17	Cyclohexene	87	−5	24
5	500	15	α-Pinene	120	25	2
6	700	368	1,3-Butadiene	121	0–10	2.5
7	250	26	Styrene	60	25	2
8	110	16	Isobutylene	16	45	0.5

[a] Methylal, except in Run 7 (ethylal) and Run 8 (diethyl acetal). [b] Boron trifluoride, except in Run 6 (concentrated sulfuric acid). A run like 6 using boron trifluoride gave greater yields of the dimethoxypentenes. [c] Excluding a maturation period of one or two days at about 25°.

TABLE II

ADDUCTS FROM ACETALS AND OLEFINS

Adduct	Source, run no.	Yield,[a] %	B.p.,[b] °C.	d^t_4	t	n^t_D	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Mol. wt.[c] Calcd.	Mol. wt.[c] Found	M_D Calcd.	M_D Found
1,3-Dimethoxybutane[d]	1	39	118.5–122	0.842	25	1.3905	$C_6H_{14}O_2$	61.0	60.7	11.9	11.7	118	120	33.4	33.2
1,3-Dimethoxy-3-methylbutane	2	39	140–143	.858	27	1.4049	$C_7H_{16}O_2$	63.6	63.5	12.1	11.9			37.8	37.8
1,3-Dimethoxy-2,2-dimethylpropane	2	9	149–152	.889	27	1.4134	$C_7H_{16}O_2$	63.6	63.3	12.1	12.1	132	129	37.8	37.6
1,3-Dimethoxy-1-phenylpropane[m]	3	72	151 (74 mm.)	.977	25	1.4866	$C_{11}H_{16}O_2$	73.3	73.3	8.9	9.3			52.7	53.0
1-Methoxy-2-methoxymethylcyclohexane	4	10	192.0–192.5	.928	27	1.4379	$C_9H_{18}O_2$	68.3	68.0	11.4	11.5	158	158	44.8	44.7
1-Methoxymethylcyclohexene[e]	4	10	158	.895	25	1.4526	$C_8H_{14}O$	76.2	75.8	11.1	11.3	126	126	38.1	38.1
1-Methoxy-2-hydroxymethylcyclohexene[f]	4		119–120 (40 mm.)	.986	24	1.4622	$C_8H_{14}O_2$	67.5	67.7	9.9	10.9	142	140	39.6	39.6
6-Methoxymethylpinane	5	14	139–144 (83 mm.)	.903	24	1.4660	$C_{12}H_{22}O$	79.2	79.2	12.1	12.1	182	182	54.9	54.9
3,5-Dimethoxy-1-pentene[g,h]	6	12	137	.864	30	1.4092	$C_7H_{14}O_2$	64.6	63.8	10.8	10.8	130	131	37.3	37.2
1,5-Dimethoxy-2-pentene[g,i]	6	20	163.5–164	.885	23	1.4251	$C_7H_{14}O_2$	64.6	64.0	10.8	11.4	130	131	37.3	37.2
3-Methoxy-4-methoxymethyl-tetrahydro-2H-pyran[g,j]	6	13	107 (30 mm.)	1.012	28	1.4372	$C_8H_{16}O_3$	60.0	59.7	10.0	10.3	160	156	41.9	41.6
1,2,5-Trimethoxy-3-methoxymethyl-pentane[g,k]	6	3	141.5 (40 mm.)	0.985	28	1.4288	$C_{10}H_{22}O_4$	58.3	58.0	10.7	10.5	206	204	54.9	54.2
1,3,4,6-Tetramethoxyhexane	6	2	77–80 (1 mm.)	1.047	22	1.4497	$C_{10}H_{22}O_4$	58.3	58.0	10.7	10.2			54.9	52.9
1,3-Diethoxy-1-phenylpropane	7	35	167–168 (75 mm.)	0.944	22	1.4772	$C_{13}H_{20}O_2$	75.0	74.8	9.6	9.7	208	210	61.9	62.3
2,4-Diethoxy-2-methylpentane	8	14	176	.830	25	1.4072	$C_{10}H_{22}O_2$	68.9	68.7	12.7	12.8	174	180	51.6	51.6
1,3-Diethoxy-2,2-dimethylbutane[l]	8	18	85 (45 mm.)	.851	25	1.4093	$C_{10}H_{22}O_2$	68.9	68.2	12.7	12.4	174	165	51.6	50.8

[a] Based on olefin. [b] Uncorrected; at 745 mm. unless otherwise noted. [c] By method of Hawkins and Arthur, *Anal. Chem.*, **23**, 533 (1951). [d] Physical constants of authentic 1,3-dimethoxybutane made from 1,3-butanediol: b.p. 120°, n^{22}_D 1.3916, d^{22}_4 0.844, mol. wt. 119. [e] Bromine number: calcd., 127; found, 116. [f] OH and OCH_3 tests positive. Bromine number: calcd., 112; found, 37; structure thus doubtful. Produced only in sulfuric acid-catalyzed runs. [g] O. C. Dermer and J. J. Hawkins, U. S. Patents 2,524,777 and 2,524,778, October 10, 1950. [h] Bromine number: calcd. 123, found 110; OCH_3: calcd. 47.7, found 47.2. [i] Bromine number: calcd. 123, found 110; OCH_3: calcd. 47.7, found 47.9. Literature constants[8] for this compound: b.p. 52 (10 mm.) d^{20}_4 0.8850, n^{20}_D 1.4259. [j] OCH_3: calcd. 38.7, found 38.8. [k] OCH_3: calcd. 60.3, found 58.2. [l] Literature constants for 1:1 adduct of Paul and Tchelitcheff[4]; b.p. 70–71 (20 mm.), d^{24}_4 0.841, n^{24}_D 1.4108. [m] Literature constants according to F. Straus and A. Berkow, *Ann.*, **401**, 121 (1913): b.p. 215–17° (dec.), d^{19}_4 0.983.

3-methoxymethylpentane (IV) (possibly admixed with 1,3,5-trimethoxy-2-methoxymethylpentane), by 1,4- and then 2,3-addition. Moreover, a cyclization, perhaps of II, is followed by renewed addition of methylal to yield 3-methoxy-4-methoxymethyl-tetrahydro-2H-pyran (V).[7]

Catalytic hydrogenation of I and II gave the expected dimethoxypentanes. The identity of II was established by agreement of its physical properties with those reported by Pudovik,[8] and of those of its hydrogenation product with the literature values for 1,5-dimethoxypentane.[9]

Extension of the reaction to homologs of methylal gave expected products, but the reactions proceeded less readily. Ethylal and styrene produced only 1,3-diethoxy-1-phenylpropane. From diethyl acetal and isobutylene two products were isolated, 2,4-diethoxy-2-methylpentane (VI) (characterized mass-spectrometrically) and its isomer, 1,3-diethoxy-2,2-dimethylbutane (VII).

$$CH_3CH(OC_2H_5)_2 + (CH_3)_2C{=}CH_2 \longrightarrow CH_3CH(OC_2H_5)CH_2C(OC_2H_5)(CH_3)_2 \quad (VI)$$

$$+\ CH_3CH(OC_2H_5)C(CH_3)_2CH_2OC_2H_5 \quad (VII)$$

Paul and Tchelitcheff,[4] effecting reaction between diethyl acetal and isobutylene at 90°, obtained only one 1:1 addition product, which they believed to be VI, but also isolated 2-methyl-4-ethoxy-1-pentene (VIII), derivable from VI by loss of ethanol; 2,5-diethoxy-4-methyleneheptane, from VIII by renewed addition of acetal and loss of ethanol; and *t*-butyl ethyl ether. The properties

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(7) Orientation assigned by analogy with similar derivatives of formaldehyde: O. C. Dermer, L. Kohn and W. J. Nelson, THIS JOURNAL, **73**, 5869 (1951).

(8) A. N. Pudovik, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, No. 1, 83 (1949); *C. A.*, **43**, 5737a (1949).

(9) R. Dionneau, *Ann. chim.*, [9] **3**, 259 (1915).

reported by Paul and Tchelitcheff for their 1:1 adduct agree better with those now found for VII than with those for VI. We therefore suggest that their 1:1 product was actually VII, and that VI, being less stable because its structure contains an ethoxy group on a tertiary carbon atom, in their experiments decomposed to VIII.

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Experimental

All condensations of acetals with olefins were effected in substantially the same way, the details of the several runs being summarized in Table I. A large excess of the acetal was cooled and treated with catalyst. The olefin was then added with good stirring; gaseous olefins were either liquefied and confined in a pressure bottle during reaction (Runs 2 and 8), pressed in at 30–50 lb./sq. in. in an Adams hydrogenation apparatus (Run 1, but failed for Run 2), or dispersed in the acetal at atmospheric pressure (Run 6). After reaction the mixture was poured into excess aqueous alkali. In some instances steam distillation was used at this point for preliminary purification. Heating with alkali was essential after sulfuric acid had been used as catalyst, since otherwise sulfuric ester impurities gradually decomposed during distillations. In any case the organic product was salted out with potassium carbonate, extracted with ether, dried over potassium carbonate, and fractionally distilled in a Todd column.

Hydrogenation of I with Raney nickel catalyst and hydrogen at 25–50 lb./sq. in. and room temperature gave an 89% yield of 1,3-dimethoxypentane, b.p. 140.5–141°, d^{22}_4 0.853, n^{22}_{D} 1.4025.

Anal. Calcd. for $C_7H_{16}O_2$: C, 63.6; H, 12.1; *MR*, 37.8. Found: C, 63.2; H, 12.1; *MR*, 37.2.

Hydrogenation of II in the same way produced 1,5-dimethoxypentane, b.p. 157–157.5°, d^{22}_4 0.854, n^{22}_{D} 1.4060. Literature values[9] are b.p. 159° (760 mm.), d^{15}_4 0.8616, n^{15}_{D} 1.4094.

Anal. Calcd. for $C_7H_{16}O_2$: C, 63.6; H, 12.1; *MR*, 37.8. Found: C, 63.3; H, 12.3; *MR*, 37.4.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE MEDICAL CLINIC, MASSACHUSETTS GENERAL HOSPITAL, AND THE DEPARTMENT OF BIOLOGICAL CHEMISTRY, HARVARD MEDICAL SCHOOL]

3,4-Dimethyl-D-glucosamine Hydrochloride and Derivatives[1,2]

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3,4-Dimethylglucosamine hydrochloride (2-desoxy-2-amino-3,4-dimethylglucose hydrochloride) has been prepared in crystalline form *via* two independent routes. The 3,4-dimethylglucosamine was characterized by the following N-derivatives: acetyl, carbobenzoxy and 2′-hydroxynaphthylidene.

Methylglucosamines are required as reference substances in structural studies on the numerous complex biological products which contain glucosamine. Of the three monomethyl-, the three dimethyl- and the one trimethylglucopyranosamine, only the synthesis of 3,4,6-trimethylglucosamine[3] and 3-methylglucosamine[4] have been reported. We have now prepared 3,4-dimethyl-D-glucosamine hydrochloride by two independent routes.

The first synthesis started with methyl 2-desoxy-2-(acetylamino)-α-D-glucopyranoside[5] (VII) and proceeded as shown in the accompanying diagram through VIII, XII, IX to 3,4-dimethyl-D-glucosamine hydrochloride (VI). By-products in the methylation of VIII were methyl 2-desoxy-2-(acetylamino)-3-methyl-6-trityl-α-D-glucopyranoside (XI) and a substance believed to be methyl 2-desoxy-2-(acetylamino)-4-methyl-6-trityl-α-D-glucopyranoside (I). This structure is tentatively assigned I on the basis of its high positive rotation and the fact that no shifting of the ring or migration of the trityl group has ever been observed during methylation with methyl iodide and silver oxide. We are attempting confirmation of this possibility by synthesis. The second synthesis began with X[4] and proceeded to VI by way of XI, XII and IX.

The preparation of II from IX constitutes proof that position 5 was not methylated. Barring the unlikely event of trityl migration from position 6 to 4, it is concluded that the methylglucosamine obtained is the 3,4-dimethylglucosamine. Inasmuch as the hydrochloride mutarotates from a high to a low positive value, we assume it is in the α-form.

As with glucosamine and other methylglucosamines, 3,4-dimethylglucosamine hydrochloride decomposes so extensively on heating as to make melting points worthless for identification. The N-acetyl and N-carbobenzoxy derivatives have good melting points, but their solubility properties made crystallization of small amounts of material quite difficult. On the other hand, we found that the 2-hydroxynaphthaldehyde, introduced by Jolles and Morgan[6] for the identification of glucosamine, gave an excellent, easily recrystallized derivative of 3,4-dimethylglucosamine.

Experimental

Melting points were taken on a Fisher–Johns apparatus equipped with a microscope and corresponded to "corrected melting point." Chromatograms were made with

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(1) Studies on hyaluronic acid and related substances VII. This is publication No. 131 of the Robert W. Lovett Memorial for the study of crippling disease, Harvard Medical School, Boston, Massachusetts. This work has been made possible by a grant from Eli Lilly and Company.

(2) Part of this investigation has been carried out at the Worcester Foundation for Experimental Biology, Shrewsbury, Massachsetts, aided by a grant from G. D. Searle and Company.

(3) W. O. Cutler, W. N. Haworth and S. Peat, *J. Chem. Soc.*, 1979 (1937).

(4) A. Neuberger, *ibid.*, 50 (1941).

(5) R. C. G. Moggridge and A. Neuberger, *ibid.*, 745 (1938).

(6) Z. E. Jolles and W. T. J. Morgan, *Biochem. J.*, **34**, 1183 (1940).