TETRAHYDROFURANS

I. 2,2-DIMETHYL-4-SUBSTITUTED-4-HYDROXYMETHYLTETRAHYDROFURANS AND RELATED COMPOUNDS[1]

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ABSTRACT

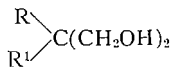
Substituted methallylmalonic esters (I) were reduced with lithium aluminum hydride to the corresponding 2-methallyl-1,3-propanediols (II). These diols II underwent cyclization on treatment with a mineral acid to the isomeric 2,2-dimethyl-4-substituted-4-hydroxymethyltetrahydrofurans (IV). II and IV were converted to the respective carbamates III and V, which exhibited pharmacological activity. The assigned structures of the cyclic compounds IV were proved by infrared analyses and the following transformations. Ring scission of 2,2-dimethyl-4-allyl-4-hydroxymethyltetrahydrofuran (IV*e*) with acetic anhydride – pyridine hydrochloride yielded 2-allyl-2-methallyl-1,3-propanediol diacetate (X*e*). Catalytic reduction of IV*e* gave 2,2-dimethyl-4-*n*-propyl-4-hydroxymethyltetrahydrofuran (IV*d*). Reductive cleavage of the tosylate VIII*b* of 2,2,4-trimethyl-4-hydroxymethyltetrahydrofuran (IV*b*) with lithium aluminum hydride yielded the known 2,2,4,4-tetramethyltetrahydrofuran (IX*b*).

While preparing 2,2-disubstituted-1,3-propanediol dicarbamates, it was noted that an intermediate, 2-allyl-2-methallyl-1,3-propanediol (II*e*), was labile to hydrochloric acid affording a compound assumed to be 2,2-dimethyl-4-allyl-4-hydroxymethyltetrahydrofuran (IV*e*). This assignment, made by analogy with a known method of preparing tetrahydrofurans (1–3), was subsequently verified. Since IV*e* possessed interesting pharmacological activity it was decided to prepare additional 2,2-dimethyl-4-substituted-4-hydroxymethyltetrahydrofurans (IV). Thus substituted methallylmalonic esters (I) were reduced to the corresponding 2-substituted-2-methallyl-1,3-propanediols (II) and subsequently cyclized by means of mineral acid. Both II and IV were converted to the corresponding carbamates III and V (Fig. 1).

Substituted methallylmalonic esters (I) were reduced by lithium aluminum hydride (4) to 2-substituted-2-methallyl-1,3-propanediols (II) (Table I). The use of sodium and

TABLE I

Substituted-1,3-propanediols



No.	R	R^1	% Yield	B.p. °C	B.p. mm
XI	H	$CH_2CH{=}CH_2$	73.5	110–112°	5
II*a*	H	$CH_2C(CH_3){=}CH_2$	74.4	75–83°	0.2–0.3
II*b*	CH_3	$CH_2C(CH_3){=}CH_2$	92.3	137–143°	27–30
II*c*	CH_2CH_3	$CH_2C(CH_3){=}CH_2$	75.0	140–147°	15–20
II*d*	$CH_2CH_2CH_3$	$CH_2C(CH_3){=}CH_2$	87.8	121–154°	15–16
II*e*	$CH_2CH{=}CH_2$	$CH_2C(CH_3){=}CH_2$	81.8	151–156°	14–15
II*f*	$CH_2C{\equiv}CH$	$CH_2C(CH_3){=}CH_2$	95.6	84–104°	0.05–0.10
II*g*	C_6H_5	$CH_2C(CH_3){=}CH_2$	61.6	128–141°	0.27–0.50

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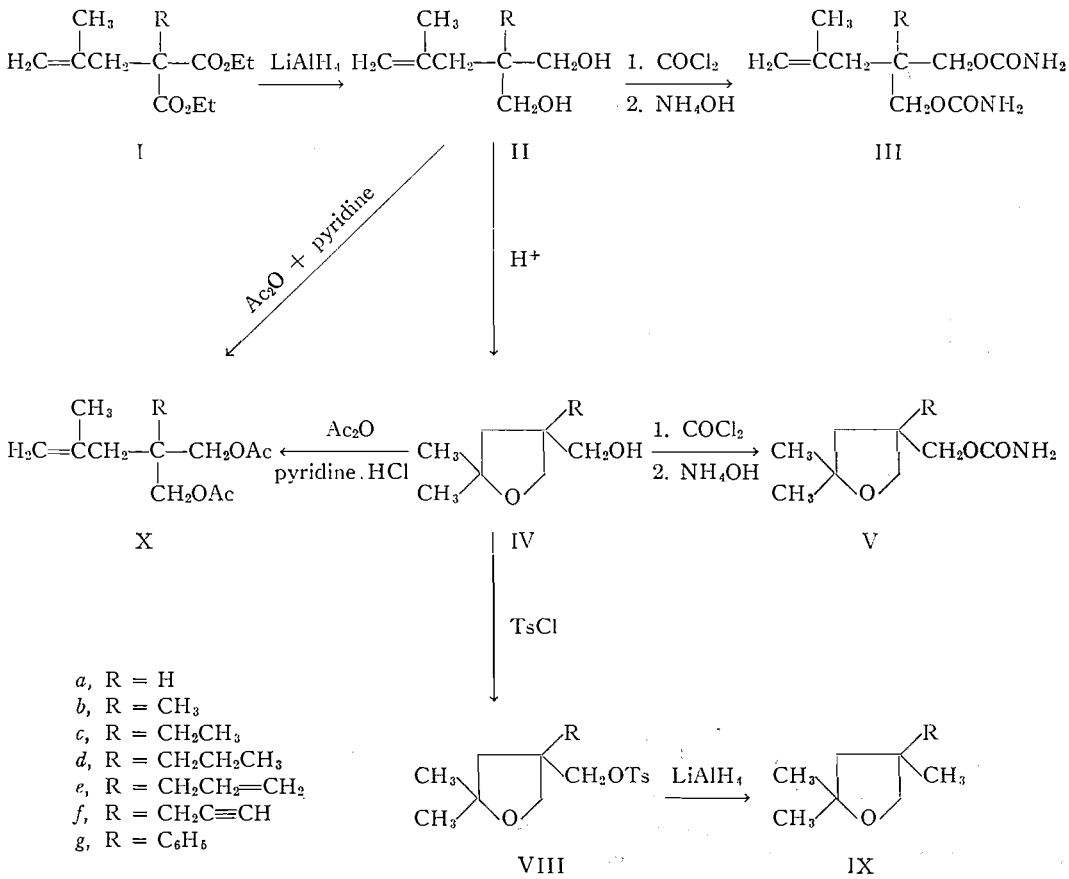


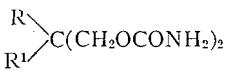
FIG. 1.

an alcohol (ethanol, 1-propanol, 1-butanol) (5) was unsatisfactory. Decomposition of the excess hydride was effected in two stages by the successive addition of methanol and water. Mineral acid was omitted in order to preclude possible ring closure between a hydroxyl and the methallyl group. The diols II were converted to the crystalline dicarbamates III (Table II).

Tetrahydrofurans have been prepared by the acid-catalyzed ring closure of γ-unsaturated monoalcohols (1–3). When 2-substituted-2-methallyl-1,3-propanediols (II) were contacted with concentrated hydrochloric or sulphuric acid, the hitherto unreported cyclic 2,2-dimethyl-4-substituted-4-hydroxymethyltetrahydrofurans (IV) were obtained. This conversion occurred most satisfactorily when the diols II were treated with 1–3 volume per cent of concentrated hydrochloric acid in the presence of a solvent. Tetrahydrofuran was particularly suitable since the cyclization was readily controlled and the reaction mixture could be used directly in the preparation of carbamates. When methanol was used as a diluent, there was no indication that it supplanted or competed with the primary alcoholic function of II because IV was the sole product. This is an interesting finding in view of the mechanism of cyclization proposed below. The use of a larger amount of acid led to a decrease in the yield of IV. For example, with 2-allyl-2-

TABLE II

Substituted 1,3-propanediol dicarbamates

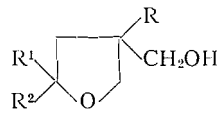


No.	R	R¹	% Yield	M.p., °C	Formula	Carbon %		Hydrogen %		Nitrogen %	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
—	H	$CH_2CH{=}CH_2$	62.8	112.5–114°	$C_8H_{14}N_2O_4$	47.52	47.39	6.98	6.71	13.86	13.80
III*a*	H	$CH_2C(CH_3){=}CH_2$	54.5	161–163°	$C_9H_{16}N_2O_4$	50.00	50.59	7.46	7.54	12.96	13.11
III*b*	CH_3	$CH_2C(CH_3){=}CH_2$	67.0	155–156°	$C_{10}H_{18}N_2O_4$	52.15	51.80	7.88	7.48	12.17	12.25
III*c*	CH_2CH_3	$CH_2C(CH_3){=}CH_2$	65.9	161–163°	$C_{11}H_{20}N_2O_4$	54.07	53.74	8.25	8.18	11.47	11.59
III*d*	$CH_2CH_2CH_3$	$CH_2C(CH_3){=}CH_2$	44.5	147–148°	$C_{12}H_{22}N_2O_4$	55.79	55.80	8.59	8.54	10.85	11.07
III*e*	$CH_2CH{=}CH_2$	$CH_2C(CH_3){=}CH_2$	43.8	130–131.5°	$C_{12}H_{20}N_2O_4$	56.22	56.29	7.87	7.80	10.93	11.00
III*f*	$CH_2C{\equiv}CH$	$CH_2C(CH_3){=}CH_2$	37.4	178–181°	$C_{12}H_{18}N_2O_4$	56.66	56.53	7.13	6.98	11.02	11.34
III*g*	C_6H_5	$CH_2C(CH_3){=}CH_2$	9.5	101.5–103°	$C_{15}H_{20}N_2O_4$	61.63	61.47	6.90	6.89	9.59	9.46

methallyl-1,3-propanediol (II*e*), not only did the expected cyclization occur, but also the allyl group and the remaining hydroxyl group tended to interact. Whereas methallyl-substituted diols underwent facile isomerization, 2-allyl-1,3-propanediol (XI) required prolonged treatment with a larger amount of acid. The cyclized products IV (Table III) were converted to the crystalline carbamates V (Table IV).

TABLE III

Substituted 4-hydroxymethyltetrahydrofurans



No.	R	R^1	R^2	% Yield	B.p. °C	B.p. mm
XII	H	CH_3	H	66.3	75–78°	5
IV*a*	H	CH_3	CH_3	65.0	—	—
IV*b*	CH_3	CH_3	CH_3	72.0	92–105°	15
IV*c*	CH_2CH_3	CH_3	CH_3	96.4	118–124°	15–20
IV*d*	$CH_2CH_2CH_3$	CH_3	CH_3	94.2	120–127°	15
IV*e*	$CH_2CH{=}CH_2$	CH_3	CH_3	91.9	122–126°	15
IV*f*	$CH_2C{\equiv}CH$	CH_3	CH_3	76.5	110–125°	8
IV*g*	C_6H_5	CH_3	CH_3	47.2	95–140°	0.1–0.2

The cyclization of 2-substituted-2-methallyl-1,3-propanediols (II) may be shown as occurring via an ionic mechanism (Fig. 2). Thus a proton adds to the olefin II to give a

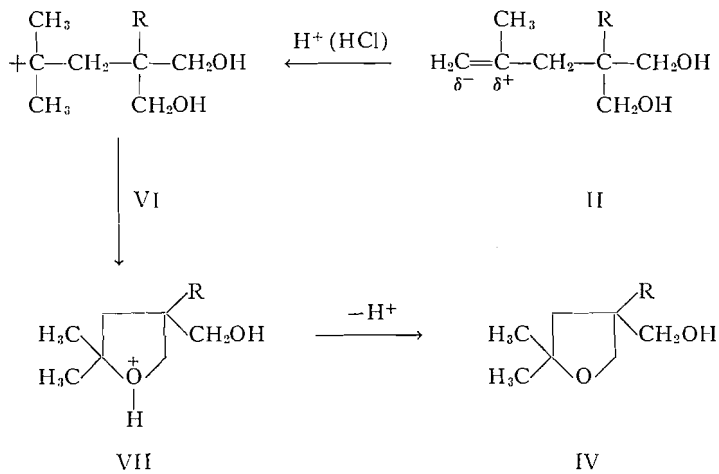
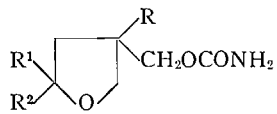


FIG. 2.

tertiary carbonium ion VI. Intramolecular reaction between the charged carbon atom of VI and one of the primary hydroxyl groups affords an oxonium ion VII from which a proton is expelled giving IV. Such a mechanism allows for the formation, via a Markownikoff addition, of a tetrahydrofuran rather than a tetrahydropyran ring and also depicts the catalytic role of hydrogen ion in promoting such a reaction.

TABLE IV

Substituted 4-carbamyloxymethyltetrahydrofurans



No.	R	R¹	R²	% Yield	M.p., °C	Formula	Carbon %		Hydrogen %		Nitrogen %	
							Calcd.	Found	Calcd.	Found	Calcd.	Found
—	H	CH_3	H	63.6	75–76.5°	$C_7H_{13}NO_3$	52.81	52.99	8.23	8.12	8.80	8.88
V*a*	H	CH_3	CH_3	41.5	99–101°	$C_8H_{15}NO_3$	55.47	55.51	8.73	8.56	8.09	8.19
V*b*	CH_3	CH_3	CH_3	83.1	46.5–47.5°	$C_9H_{17}NO_3$	57.75	57.79	9.16	9.08	7.48	7.36
V*c*	CH_2CH_3	CH_3	CH_3	74.5	53.5–54.0°	$C_{10}H_{19}NO_3$	59.66	59.63	9.51	9.50	6.96	7.17
V*d*	$CH_2CH_2CH_3$	CH_3	CH_3	57.7	59.0–59.5°	$C_{11}H_{21}NO_3$	61.36	61.28	9.83	9.44	6.51	6.56
V*e*	$CH_2CH{=}CH_2$	CH_3	CH_3	89.1	55–57°	$C_{11}H_{19}NO_3$	61.93	62.01	8.98	8.85	6.57	6.70
V*f*	$CH_2C{\equiv}CH$	CH_3	CH_3	66.2	88–92°	$C_{11}H_{17}NO_3$	62.54	62.48	8.11	7.89	6.63	7.06
V*g*	C_6H_5	CH_3	CH_3	34.9	85–86°	$C_{14}H_{19}NO_3$	67.43	67.52	7.68	7.24	5.62	5.53

Assignment of structure IV to the products of cyclization was supported by infrared absorption data. The isomerization of 2-substituted-2-methallyl-1,3-propanediols (II) to IV required an increase in the number of methyl groups from one to two, the appearance of a cyclic ether group, and the loss of the methallyl and a hydroxyl group. An inspection of the infrared spectra of II and IV showed that these changes did occur. They were exhibited by the appearance in the 7.25–7.35 μ region of a doublet (*gem*-dimethyl) in place of a single band (methyl), the loss of the 11.2 μ band (methallyl), the narrowing and shifting of the hydroxyl band from 3.0 to 2.95 μ, and finally the shifting of the 9.6–9.8 μ band (hydroxyl) to 9.5–9.6 μ (hydroxyl, cyclic ether) (6). In addition IV possessed a strong unassigned band at 12.95 μ.

Supporting evidence for the formulation of the cyclic compounds IV was obtained by cleaving the ring of IV*e*, a typical member of the group. Surprisingly, in this instance, the use of methods that have been described for the cleavage of tetrahydrofurans (7–11) led to intractable mixtures. However, the conversion was effected by applying a method used successfully in the field of sapogenin chemistry (12–14). Thus acetic anhydride – pyridine hydrochloride (12) readily converted IV*e* in excellent yield to 2-allyl-2-methallyl-1,3-propanediol diacetate (X), identical with a sample prepared by the acetylation of II*e* (Fig. 1). Hence, the methallyl and hydroxyl groups that had disappeared during the cyclization of the diol II to the isomeric IV, have reappeared upon ring opening.

Additional chemical evidence for the structures of 2,2-dimethyl-4-substituted-4-hydroxymethyltetrahydrofurans (IV) was obtained by the elimination of the hydroxyl group. Thus IV*b* was tosylated and the ester VIII*b* reduced with lithium aluminum hydride (15) to 2,2,4,4-tetramethyltetrahydrofuran (IX*b*) (Fig. 1). The infrared absorption curve and boiling point of IX*b* were the same as those previously reported (16). The 4-allyl analogue IV*e* was similarly converted to the expected 2,2,4-trimethyl-4-allyltetrahydrofuran (IX*e*) as judged by infrared analysis, where bands typical of the tosyl group appeared in the spectrum of VIII*e*, and disappeared in that of IX*e*. IV*e*, VIII*e*, and IX*e* exhibited bands denoting the presence of the allylic double bond, methyl groups, and the cyclic ether linkage.

2,2-Dimethyl-4-allyl-4-hydroxymethyltetrahydrofuran (IV*e*) was hydrogenated over platinum giving 2,2-dimethyl-4-*n*-propyl-4-hydroxymethyltetrahydrofuran (IV*d*). IV*d* was also obtained when diethyl *n*-propylmethallylmalonate (I*d*) was reduced with lithium aluminum hydride to 2-*n*-propyl-2-methallyl-1,3-propanediol (II*d*) and subsequently ring-closed with mineral acid.

The monocarbamates V were more active than the dicarbamates III upon the central nervous system of animals. The allyl derivative V*e* was particularly effective as an anticonvulsant (17). More comprehensive results of the pharmacological evaluation will be reported elsewhere.

EXPERIMENTAL

Boiling points and melting points (Fisher–Johns apparatus) are uncorrected. Infrared absorption spectra were obtained with a Beckman IR-5 spectrophotometer equipped with a sodium chloride prism. Solids were examined in potassium bromide pellets and liquids either as thin films or as solutions in carbon disulphide.

Preparation of Mono- and Di-substituted Malonates

Diethyl sodiomalonate and diethyl sodio-alkyl- (and -alkenyl-) malonates were treated

with the appropriate alkyl halide (bromide or chloride) in the customary manner giving the corresponding mono- and di-substituted malonates. These were purified by distillation *in vacuo*. The preparation of some of these malonates has been described (18). Diethyl methylmalonate (Sapon), diethyl ethylmalonate (Distillation Products Industries), diethyl *n*-propylmalonate (Sapon), and diethyl phenylmalonate (Benzol Products) were used without further purification.

Preparation of Substituted 1,3-Propanediols

The following procedure illustrates the general method used for preparing the 1,3-propanediols listed in Table I. A solution of 100 g of diethyl allylmethallylmalonate (I*e*) in 246 ml of anhydrous ethyl ether was added dropwise over a 3-hour period to a well-dispersed and vigorously stirred mixture of 22.5 g of lithium aluminum hydride in 554 ml of anhydrous ethyl ether maintained below 25° C in an atmosphere of nitrogen. The reaction mixture was stored overnight at room temperature. Excess hydride was discharged by the addition of 27.2 ml of methanol in 66 ml of ethyl ether; the resulting complexes were decomposed by the successive addition of 15.6 ml of 50% methanol and 31.2 ml of water while maintaining the temperature of the mixture below 25° C. The ethereal phase was separated and the residual solids were washed four times with ethyl ether. The combined ethereal extracts were washed with water twice, filtered, and evaporated, leaving 65.2 g (97.5%) of crude 2-allyl-2-methallyl-1,3-propanediol (II*e*). Infrared: λ_{max} 3.0 (hydroxyl), 3.25, 6.1 (unsaturation), 7.25 (methyl), 9.6–9.8 (hydroxyl), 10.9 (allyl), 11.25 (methallyl) μ. This product was distilled *in vacuo* and used directly for the preparation of either 2,2-dimethyl-4-allyl-4-hydroxymethyltetrahydrofuran (IV*e*) or 2-allyl-2-methallyl-1,3-propanediol dicarbamate (III*e*).

Cyclization of 2-Methallyl-1,3-propanediols (II)

The general procedure used for the cyclization of 2-methallyl-1,3-propanediol and 2-substituted-2-methallyl-1,3-propanediols to give the 2,2-dimethyl- and 2,2-dimethyl-4-substituted-4-hydroxymethyltetrahydrofurans, listed in Table III, is illustrated by the following example.

A solution of 65.2 g of 2-allyl-2-methallyl-1,3-propanediol (II*e*) in 40.5 ml of dry tetrahydrofuran was treated at room temperature with 1 ml of concentrated hydrochloric acid. The solution was warmed gently until, at approximately 50° C, an exothermic reaction occurred. External heating was discontinued while the temperature of the reaction mixture rose spontaneously to 94° C. The solution was then refluxed for 2 hours. The solvent was removed under reduced pressure and the residue distilled giving 59.9 g of 2,2-dimethyl-4-allyl-4-hydroxymethyltetrahydrofuran (IV*e*), b.p. 122–126° C/5 mm. The cyclization of II*e* was also effected with 0.5–1.0 volume per cent of hydrochloric acid in the absence of solvent. However, the reaction was extremely vigorous and difficult to control by external cooling. The yield of IV*e* was substantially decreased.

Cyclization of 2-Allyl-1,3-propanediol (XI)

2-Allyl-1,3-propanediol (XI) was cyclized by more drastic conditions than those described above. Thus a mixture of 11 g of XI and 1 ml of concentrated hydrochloric acid was refluxed for 17 hours. Following removal of the hydrochloric acid, distillation of the product (10.9 g) yielded 7.3 g (66.3%) of 2-methyl-4-hydroxymethyltetrahydrofuran (XII), b.p. 75–78° C/5 mm. The infrared spectrum possessed a strong band at 7.25 μ (C—CH_3) but no band indicative of a double bond.

Preparation of 2,2-Disubstituted 1,3-Propanediol Dicarbamates (III)

The procedure using tetrahydrofuran as solvent (19) was found to be superior to that wherein chloroform–toluene served as solvent and antipyrine was included as a hydrogen chloride acceptor (20). The products III (Table II) were recovered from the reaction mixtures by chilling the aqueous solutions after evaporating the organic solvent, and were recrystallized from aqueous alcohol. (Infrared: λ_{max} 2.95, 5.85, 6.2 μ (primary amide).)

Preparation of 2,2-Dimethyl-4-substituted-4-carbamyloxytetrahydrofurans (V)

The method used for preparing V (Table IV) was a modification of that applied above. The following example was typical of the procedure. A solution of 57.3 g of IV*e* in 77.6 ml of tetrahydrofuran was added dropwise during 1 hour to 55.2 g of phosgene dissolved in 63.1 ml of cold tetrahydrofuran (−8 to 4° C). The mixture was stirred for 30 minutes at this temperature and then stored overnight at room temperature. The solution was added over a 1-hour period to a stirred mixture of 276 ml of concentrated ammonium hydroxide and 3.4 g of sodium bisulphite maintained at 10–27° C (subsequent study showed that bisulphite could be omitted). After stirring for ½ hour, sufficient water was added to dissolve the solids. Distillation afforded a residue that was extracted four times with ether. The combined ethereal extracts were washed twice with 25-ml portions of water and the ether removed. The residue (72.6 g) was distilled giving 67.7 g of V*e*, b.p. 111–119° C/0.02–0.04 mm, solidifying at room temperature. The material was crystallized from ether – petroleum ether giving 64 g (89.1%) of V*e*, m.p. 55–57° C. When the distillation of crude material was omitted, V*e* was obtained in lower yield. The substance could also be crystallized from acetone – petroleum ether, aqueous methanol, or methanol – petroleum ether. Molecular weight (Rast): calc. 213; found 211, 216. Infrared: λ_{max} 3.0, 5.8, 6.2 (primary amide), 3.25, 6.1 (unsaturation), 10.95 (allyl), 7.25, 7.35 (*gem*-dimethyl), 12.95 μ.

Preparation of 2,2-Dimethyl-4-allyl-4-hydroxymethyltetrahydrofuran (IVe) from the Carbamate Ve

A mixture of 16 g of 2,2-dimethyl-4-allyl-4-carbamyloxymethyltetrahydrofuran (V*e*) (m.p. 54.0–55.5° C), 12 g of sodium hydroxide, and 250 ml of ethanol was refluxed for 8 hours. After dilution with water, the ethanol was removed by distilling *in vacuo*. The aqueous residue was cooled, saturated with sodium chloride, and extracted five times with ethyl ether. The ethereal extracts were washed with water and reduced to dryness. The resulting oily product was vacuum-distilled, yielding 8.2 g (64%) of IV*e*, b.p. 116–117° C/10–15 mm. Analysis: Calc. for $C_{10}H_{18}O_2$: C, 70.56; H, 10.66. Found: C, 70.17; H, 10.45. Main infrared absorption bands: λ_{max} 2.95, 3.25, 3.40, 3.50, 6.10, 6.90, 7.08, 7.23, 7.78, 8.24, 8.40, 8.56, 8.90, 9.4–9.75, 10.05, 10.95, 11.42, 11.60, 12.94 μ.

Preparation of 2-Allyl-2-methallyl-1,3-propanediol Diacetate (Xe)

(a) From 2-Allyl-2-methallyl-1,3-propanediol (IIe) by Acetylation

A solution of 20 g of 2-allyl-2-methallyl-1,3-propanediol (II*e*) in 110 ml of acetic anhydride and 22 ml of anhydrous pyridine was heated for 1 hour on a steam bath and then allowed to stand for 18 hours at room temperature. The solution was poured into 400 ml of cold water and the mixture stirred for 1 hour at room temperature. The mixture was extracted five times with ethyl ether and the combined ethereal extracts washed successively with water, 5% hydrochloric acid, saturated saline solution, 5% sodium bicarbonate, and finally with water. After drying over sodium sulphate, the solvent was

removed leaving 28.42 g (95%) of the crude acetate. Distillation of this product afforded 2-allyl-2-methallyl-1,3-propanediol diacetate (X*e*), b.p. 153–157° C/16 mm, λ_{max} 5.78, 8.0–8.2, 9.6–9.7 (ester), 3.25, 6.1, 10.9–11.2 (unsaturation) μ.

(b) From 2,2-Dimethyl-4-allyl-4-hydroxymethyltetrahydrofuran (IVe) by Treatment with Acetic Anhydride – Pyridine Hydrochloride

A stream of hydrogen chloride was passed into a mixture of 150 ml of acetic anhydride and 12 ml of pyridine until 5.2 g had been absorbed. After adding 22.86 g of 2,2-dimethyl-4-allyl-4-hydroxymethyltetrahydrofuran (IV*e*) the solution was refluxed for 5 hours and then stored overnight at 5° C. Excess anhydride was decomposed by adding 2000 ml of water and stirring the mixture for 1 hour. The mixture was worked up as described in procedure (*a*) to give 33.8 g (98.9%) of crude product. Several distillations of this material gave X*e*, b.p. 155–160° C/17 mm. The infrared spectrum was identical with that of the product from procedure (*a*).

Catalytic Reduction of 2,2-Dimethyl-4-allyl-4-hydroxymethyltetrahydrofuran (IVe)

A solution of 23.53 g of 2,2-dimethyl-4-allyl-4-hydroxymethyltetrahydrofuran (IV*e*) in 300 ml of ethanol was shaken with hydrogen and 0.5 g of platinum oxide under slightly positive pressure. Approximately 1 mole of hydrogen was absorbed within 30 minutes. Following removal of the catalyst, the solvent was evaporated giving 23.6 g of a yellow oil. Distillation *in vacuo* afforded 20.6 g (87.4%) of 2,2-dimethyl-4-*n*-propyl-4-hydroxymethyltetrahydrofuran (IV*d*) as a colorless oil, b.p. 50–65° C/0.06–0.07 mm. The infrared spectrum of IV*d* indicated the absence of unsaturation and was indistinguishable from that of a sample prepared from diethyl *n*-propylmethallylmalonate (I*d*) by reduction and subsequent ring closure.

Conversion of 2,2,4-Trimethyl-4-hydroxymethyltetrahydrofuran (IVb) to 2,2,4,4-Tetramethyltetrahydrofuran (IXb)

(a) 2,2,4-Trimethyl-4-tosyloxymethyltetrahydrofuran (VIIIb)

p-Toluenesulphonyl chloride (79 g) dissolved in 140 ml of redistilled pyridine was added during 1 hour to a vigorously stirred solution of 39.3 g of 2,2,4-trimethyl-4-hydroxymethyltetrahydrofuran (IV*b*) in 140 ml of redistilled pyridine, maintained at 5° C. The mixture was stirred with cooling for an additional 3 hours and left overnight at room temperature. It was poured onto crushed ice and acidified with concentrated hydrochloric acid. The mixture was extracted six times with ethyl ether, and the combined ethereal extracts washed to neutrality with water and evaporated, affording 79.5 g (97.7%) of crude tosylate VIII*b*. The substance was not purified but used directly for the following reduction. Infrared: λ_{max} 6.25, 7.3–7.4, 8.4–8.5, 10.3–10.5, 10.95, 11.3, 12.7, 14.2, 15.0 μ (aromatic, tosyl).

(b) Lithium Aluminum Hydride Reduction of 2,2,4-Trimethyl-4-tosyloxymethyltetrahydrofuran (VIIIb)

A solution of 79.5 g of tosylate VIII*b* in 400 ml of anhydrous ethyl ether was added dropwise during 1 hour at 25–30° C to 16.2 g of lithium aluminum hydride dissolved in 800 ml of anhydrous ethyl ether. The mixture was refluxed for 8 hours with vigorous stirring, cooled, and decomposed with ice and water. The solids were repeatedly extracted with ethyl ether, and the combined ethereal extracts washed with water and concentrated, yielding 27.8 g of yellow oil. Two distillations of this oil gave 12.9 g of 2,2,4,4-tetramethyltetrahydrofuran (IX*b*) boiling at 116–118° C, n_D^{20} 1.422; reported (16) boiling

point 120° C and n_D^{20} 1.4061. The infrared spectrum of IX*b* was identical with that reported (16).

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