3c:[10c] bp 96–98 °C (0.20 mm); ir (neat) 1676, 1238, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.16 (s, 18 H), 1.38 (s, $\Delta\nu_{1/2}$ = 8 Hz, 16 H), 1.85–2.25 (m, 4 H); MS *m/e* 342 (3), 148 (100).

4: bp 70–72 °C (0.1 mm); mp 48–49 °C (Et_2O) [lit.[12] bp 88–95 °C (1 mm); mp 47–49 °C]; ir ($CHCl_3$) 1255, 1245, 1145, 840 cm^{-1}, ^1H NMR ($CDCl_3$) δ 0.24 (s, 18 H), 1.16 (s, 18 H).

Preparation of 3c by Method B.[7] A THF solution of ethylmagnesium bromide was prepared from magnesium (4.86 g, 0.20 mol), ethyl bromide (25.06 g, 0.23 mol), and 125 ml of dry THF. The solution was cooled to 10–15 °C and 9.8 g (0.05 mol) of cyclododecane-1,2-dione in 30 ml of THF was added dropwise over a 30-min period. After the mixture was stirred at room temperature for 2 h, the reaction vessel was cooled in an ice bath and 21.6 g (0.20 mol) of chlorotrimethylsilane was added dropwise in approximately 30 min. After the mixture was stirred overnight at ambient temperature, pentane (500 ml) was added to the reaction solution to precipitate most of the inorganic salts. The mixture was filtered through alumina, concentrated in vacuo, and distilled to yield 5.98 g (35%) of clear colorless **3c**.

When benzil was subjected to the above conditions, a mixture of *cis*-**3a** (57%) and *trans*-**3a** (δ 0.05 ppm, 43%) was obtained in 33% yield.

Preparation of Acetylenes from Bis-Me_3Si Ethers. General Procedure A (Better of Two). Into a 65-ml round-bottom flask equipped with a magnetic stirring bar, a pressure-equalized dropping funnel, a nitrogen atmosphere, and cooled in a dry ice–acetone bath were placed the bis-Me_3Si ether (2 mmol) and 7.0 ml of dry THF. Methyllithium (4 mmol) in Et_2O was introduced dropwise to the reaction vessel over 10 min. The flask was allowed to warm slowly to room temperature then stirring was continued overnight at 30 °C. A solution of carbon disulfide (156 μl, 2.6 mmol) in 5.0 ml of THF was added at 0 °C, and the mixture was stirred at room temperature for 30 min, then at 70 °C for 30 min. The flask was cooled in an ice bath, and methyl iodide (156 μl) in THF (2 ml) was added, followed by stirring at room temperature for 30 min and then at 60 °C for 30 min. After cooling to room temperature, the mixture was diluted with 50 ml of ether. The ethereal solution was washed with water and brine, filtered through alumina, and concentrated in vacuo to yield an orange oily residue. Triethyl phosphite (2 ml) was added to the orange residue; the solution was gently refluxed under nitrogen for 3 days. The cooled reaction mixture was extracted with hexane (4 × 15 ml), and the combined organic layers were washed with water, dried, and evaporated under reduced pressure. The residue was chromatographed on silica gel (pentane elution) to yield the acetylenes, which were identical with authentic materials.

General Procedure B. To a 65-ml round-bottom flask containing pentane-washed potassium hydride (~700 mg) and dry THF (5 ml) was added a solution of bis-Me_3Si ether (2 mmol) in THF (10 ml) and this was stirred at 35 °C overnight under a nitrogen atmosphere. A solution of carbon disulfide (156 μl, 2.6 mmol) in 5 ml of THF was added to the reaction vessel, and the mixture was stirred at room temperature for 30 min, then at 70 °C for 30 min. The flask was cooled in an ice bath, and a solution of methyl iodide (156 μl) in THF (2 ml) was added, followed by stirring at room temperature for 30 min, then heating at 60 °C for 30 min. After cooling to room temperature the mixture was diluted with 50 ml of ether; then the entire solution was centrifuged. The organic solution was decanted from the residue which was subsequently washed with more ether (10 ml). The combined organic layers were treated with *tert*-butyl alcohol (5 ml) to destroy residue potassium hydride, filtered through a short column of alumina, and evaporated to leave an orange residue. After triethyl phosphite (2 ml) was added to the orange residue, the solution was gently refluxed under nitrogen for 3 days. The cooled reaction mixture was extracted with hexane (4 × 15 ml), and the combined organic layers were washed with water, dried, and evaporated. The residue was chromatographed on silica gel (pentane elution) to yield the acetylene.

Analytical Data for Acetylenes. 2a: mp 57–59 °C (lit.[14] 58–60 °C); ir ($CHCl_3$) 3070, 3050, 3000, 2210, 1600, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30–7.75 (m).

2b: bp 130–131 °C (lit.[15] 131.8 °C); ir (neat) 2970, 1460, 1380, 1340, 1280 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, J = 6.5 Hz, 6 H), 1.51 (m, 4 H), 2.12 (t, J = 5.5 Hz, 4 H).

2c:[16] ir (neat) 2220, 1099, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (m, $\Delta\nu_{1/2}$ = 10 Hz, 16 H), 2.21 (m, 4 H); ^{13}C NMR (CS_2) 111.2, 166.4, 167.3, 173.8 ppm; MS *m/e* 164 (3), 66 (100).

Acknowledgment. This work was generously supported by a grant from USPHS-NIH, 5 R01 AI 11690.

Registry No.—**1a,** 59034-61-6; **1b,** 59034-62-7; **1c,** 59034-63-8; **2a,** 501-65-5; **2b,** 1942-45-6; **2c,** 1129-90-4; **3a,** 37980-77-1; **3a** trans isomer, 26312-21-0; **3b,** 59034-64-9; **3c,** 59034-65-0; **4,** 59034-66-1; cyclododecane-1,2-dione, 3008-41-1; chlorotrimethylsilane, 75-77-4.

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New Reactions and Reagents. 5. Ketalization of 1,3-Dihydroxy-2-propanone with Alkanols. Formation of Acyclic and Cyclic Ethers Derived from Pyruvic Aldehyde[1]

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Received January 21, 1976

The transformations of 1,3-dihydroxy-2-propanone (dihydroxyacetone, DHA) and its derivatives have been of interest for over 20 years. DHA itself has been shown to undergo a variety of isomerization and dehydration reactions.[2,3] Among the more important homologues of DHA, the transformations of cortisone and related steroids containing a C-17 dihydroxypropanone moiety have been the subject of several reports. In this context it has been known for many years that the ketalization of these steroids resulted in low yields of the expected products. The generation of β-keto acetals as the by-products of these reactions was subsequently discovered in several laboratories. Their formation was eloquently postulated in terms of a Mattox rearrangement[4] involving a dehydration–ketalization sequence (Scheme I).[5–9] The rear-

Scheme I

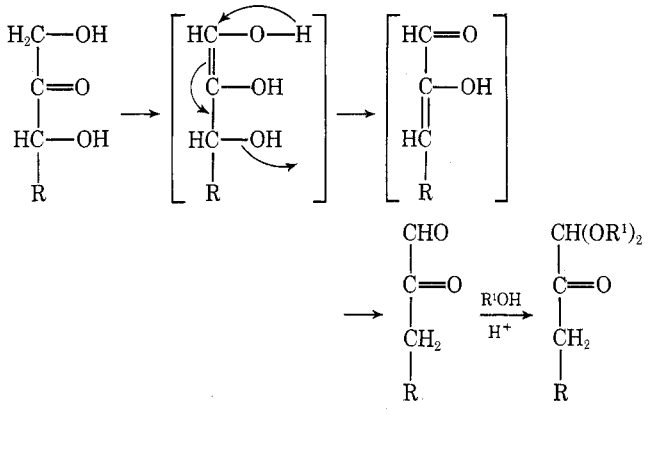


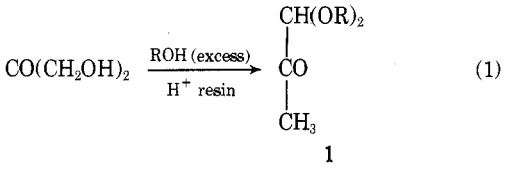
Table I. Preparation of 1,1-Dialkoxy-2-propanones (1) from DHA and Alkanols

Compd	R substituent in 1	% yield GLC	% yield Isolated	Bp, °C (mm)	NMR, δ ($CDCl_3$, Me_4Si)
1a	CH_3	96	82	82 (70)	2.2 (s, 3 H), 2.4 (s, 6 H), and 4.3 (s, 1 H)
1b	C_2H_5	99	92	82 (50)	1.23 (t, 6 H), 2.2 (s, 3 H), 3.7 (m, 4 H), and 4.53 (s, 1 H)
1c	$CH_3(CH_2)_2$	98.5	90	82 (14)	0.91 (t, 6 H), 1.57 (m, 4 H), 2.15 (s, 3 H), 3.55 (m, 4 H), and 4.5 (s, 1 H)
1d	$(CH_3)_2CH$	98	85	59 (14)	1.1 (pair of doublets, 12 H), 2.11 (s, 3 H), 3.86 (m, 2 H), and 4.55 (s, 1 H)
1e	$CH_3(CH_2)_3$	95	90	92 (29)	0.93 (m), and 1.5 (m, total 14 H), 2.15 (s, 3 H), 3.61 (m, 4 H), and 4.5 (s, 1 H)

rangement–acetalization sequence postulated in Scheme I, however, has so far not been investigated with DHA.[10] The present work reports the acid-catalyzed transformations of DHA in the presence of mono-, di-, and trihydric alkanols and the structures of the resulting ether products.

Results and Discussion

A. Reaction of DHA with Monohydric Alkanols. The protonated cation-exchange resin catalyzed reaction of DHA with monohydric alkanols resulted in the exclusive formation of the corresponding 1,1-dialkoxy-2-propanones (**1**, eq 1). GLC



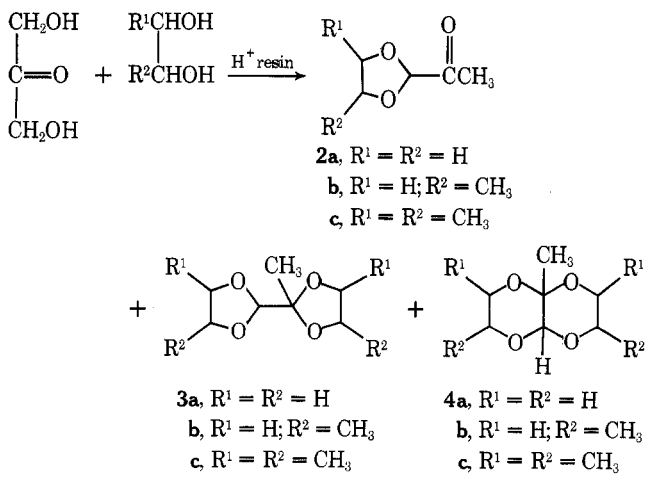
(1)

1

analysis of the reaction mixtures indicated that formation of potential by-products, such as 1,1,2,2-tetraalkoxypropanes or alkyl α,α-dialkoxypropionates, did not occur. Yields and characterization data of representative 1,1-dialkoxy-2-propanones prepared by this procedure are given in Table I.

B. Reaction of DHA with Dihydric Alkanols. The 1,2-diols offered the possibility of providing bicyclic products in addition to expected keto acetals **2**. Indeed, compounds of type **3** and **4** were also isolated from the reaction of DHA with ethylene glycol, 1,2-propanediol, and 2,3-butanediol (Scheme II). In contrast to the 1,2-diols, reaction of DHA with a 1,3-

Scheme II

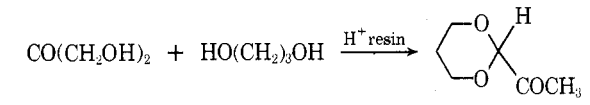


2a, $R^1 = R^2 = H$
b, $R^1 = H; R^2 = CH_3$
c, $R^1 = R^2 = CH_3$

3a, $R^1 = R^2 = H$
b, $R^1 = H; R^2 = CH_3$
c, $R^1 = R^2 = CH_3$

4a, $R^1 = R^2 = H$
b, $R^1 = H; R^2 = CH_3$
c, $R^1 = R^2 = CH_3$

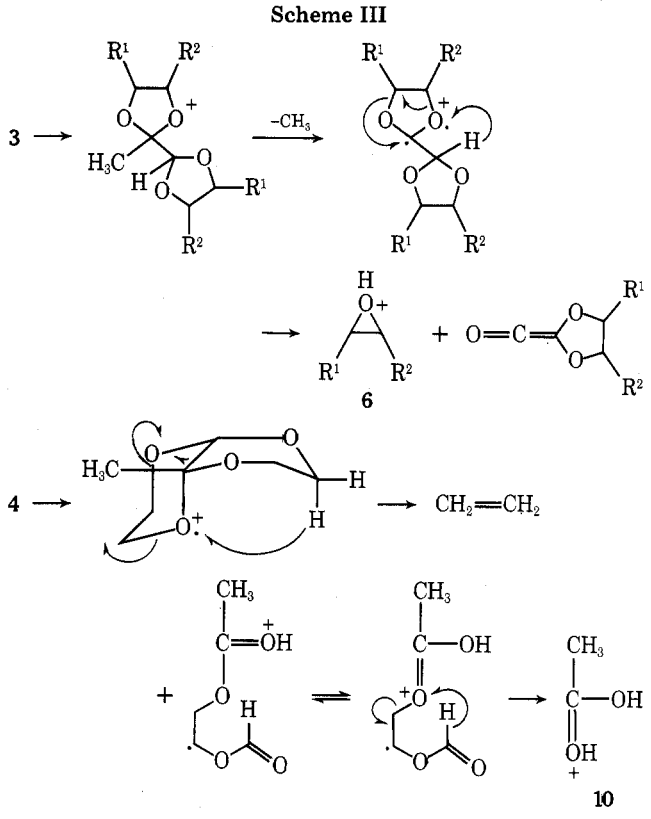
diol, for example, 1,3-propanediol, gave 2-acetyl-1,3-dioxane (**5**) exclusively. The structures of **2a–c** and **5** were established by ir, NMR, mass spectral, and C, H microanalytical data. The relative structural identity of the compounds analogous to **3**



5

and **4** has been a subject of controversy.[11] NMR and mass spectral data have been used for this purpose in recent years.[12] It was determined during the present investigation that electron-impact induced fragmentation of **3** leads characteristically to the formation of a protonated oxirane ion (**6**),[13] whereas the protonated acetic acid ion (**10**) is produced from the fragmentation of **4** (Scheme III). The principal cations

Scheme III



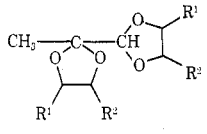
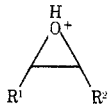
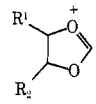
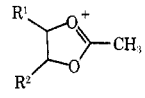
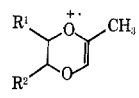
6

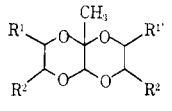
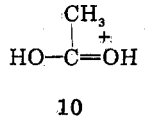
10

produced from **3** and **4** by electron impact are summarized in Table II.

The determination of the isomerism and stereochemistry of cyclic ethers **3** and **4** produced via DHA–glycol reactions offers a challenging problem. Compounds of type **3** derived from *dl*-1,2-propanediol, for example, may occur in eight possible *RS* stereomers resulting from the respective placement of methyl substituents on the two dioxolanyl moieties. Compound **3** derived from *meso*-2,3-butanediol should sim-

Table II. Principal Mass Spectral Fragments of 2-Methyl-2-(1,3-dioxolanyl)-1,3-dioxolanes (3) and 2-Methylhexahydro-*p*-dioxino[2,3-*b*]-*p*-dioxins (4)

 3	$[M]^+$	$CH_3C{\equiv}\overset{+}{O}$	 6	 7	 8	 9
a, $R_1 = R_2 = H$	160 (1)	43 (95)	45 (84)	73 (74)	87 (100)	100 (18)
b, $R_1 = H; R_2 = CH_3$	188 (0.4)	43 (82)	59 (35)	87 (27)	101 (100)	114 (18)
c, $R_1 = R_2 = CH_3$	216 (–)	43 (87)	73 (73)	101 (25)	115 (100)	128 (30)

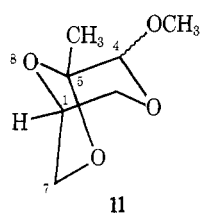
 4	$[M]^+$	$CH_3C{\equiv}\overset{+}{O}$	 10	7	8	9
a, $R_1 = R_2 = H$	160 (49)	43 (100)	61 (50)	73 (95)	87 (98)	100 (26)
b, $R_1 = H; R_2 = CH_3$	188 (40)	43 (100)	61 (68)	87 (96)	101 (98)	114 (31)
c, $R_1 = R_2 = CH_3$	216 (1.1)	43 (100)	61 (8)	101 (23)	115 (98)	128 (28)

ilarly have the possibility of providing four meso isomers.[14,15] *p*-Dioxino-*p*-dioxins 4 pose a stereochemical situation where in addition to the possibility of cis or trans ring junction,[12,16] several regiopositioned methyl substituents resulting in *RS* and meso forms are conceivable. This facet of the structural chemistry of 3 and 4 is beyond the scope of present work.

C. Reaction of DHA with Trihydric Alkanols. The acid-catalyzed reaction of DHA with glycerol resulted in the formation of a polymeric material. However, upon fortuitous addition of methanol as a solvent in this reaction, the formation of three products was detected by GLC. Component A was subsequently separated by spinning band distillation of the reaction mixture. Based on ir, NMR (60 MHz), mass

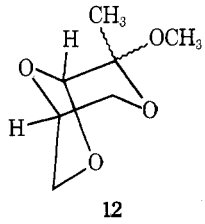
$$CO(CH_2OH)_2 + HOCH(CH_2OH)_2 + CH_3OH \xrightarrow{H^+} \underset{50\%}{\mathbf{1a}} + \underset{30\%}{A} + \underset{5\%}{B}$$

spectral, GLC (single peak, three different columns), and CH microanalytical data, three possible structures (**11, 12, 13**) were postulated for this product. The 100-MHz ^1H NMR spectrum revealed the methyl resonance as two singlets (1:1 ratio, $\Delta = 1.8$ Hz), the methoxyl protons as two singlets (1:1 ratio, $\Delta = 5$ Hz), and C-4 proton as two singlets (1:1 ratio; $\Delta = 18$ Hz). These data indicated a 1:1 mixture of C-4 axial–equatorial methoxy substituted 11 to be the most likely composition of A.[17] This fact was further supported by a ^{13}C NMR spectrum of A which showed seven pairs of peaks.



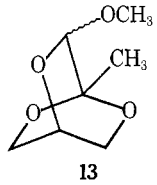
11

4-methoxy-5-methyl-3,6,8-trioxabicyclo[3.2.1]octane



12

4-methoxy-4-methyl-3,6,8-trioxabicyclo[3.2.1]octane



13

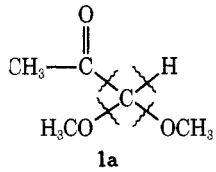
1-methyl-6-methoxy-2,5,7-trioxabicyclo[2.2.2]-octane

Product 11 was also synthesized according to eq 2.[18] The preparation of 11 containing a C-4 ethoxy or isopropoxy substituent instead of methoxy was carried out via the reaction of DHA with glycerol in the presence of corresponding alkanol.

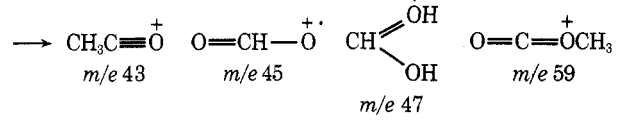
$$\mathbf{1a} + HOCH(CH_2OH)_2 \xrightarrow[\Delta]{H^+} 11 + CH_3OH \qquad (2)$$

Experimental Section[19]

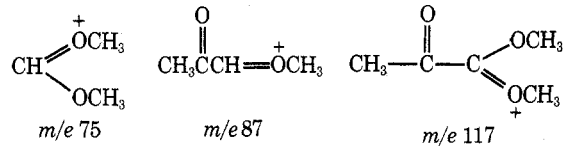
Reaction of DHA with Monohydric Alkanols (Table I). The following preparation of 1,1-dimethoxy-2-propanone (1a) is representative. A mixture of DHA[20] (90 g), methanol (270 ml), and Amberlyst-15[21] (9 g) was stirred at 100–110 °C for 4 h in a pressure vessel. After removal of catalyst by filtration, the filtrate was diluted with water and then extracted with methylene chloride. The distillation of the organic extract gave the title compound in 82% yield (GLC purity 98%). Mass spectrum (70 eV): principal cations follow.



1a



m/e 43 *m/e* 45 *m/e* 47 *m/e* 59

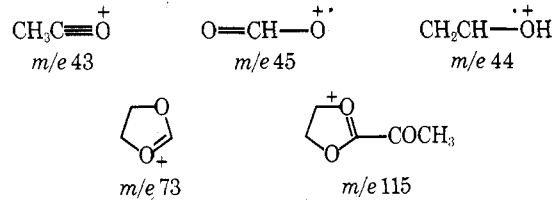


m/e 75 *m/e* 87 *m/e* 117

Reaction of DHA with Ethylene Glycol. A mixture of DHA[20] (36 g, 400 mmol), ethylene glycol (100 ml), and Amberlyst-15[22] (3.6 g) was stirred at 100–110 °C for 4 h. After cooling, the reaction mixture was diluted with water (400 ml), filtered, and extracted with methylene chloride (2 × 100 ml). GLC analysis of the extract showed the

presence of **2a**, **3a**, and **4a** in 9:69:22 ratio, respectively. After drying ($MgSO_4$) the solvent was evaporated to give 40.7 g of a clear liquid. Distillation gave 34.7 g of a product, bp 52–59 °C (1.5 mm). Fractionation on a spinning band column provided the following three compounds.

2-Acetyl-1,3-dioxolane (**2a**): yield 1 g; bp 46 °C (7 mm); n^{24}D 1.4270; ir (neat) 2900, 1730, 1355 cm^{-1}; NMR 2.20 (s, 3 H), 4.05 (s, 4 H), and 5.0 ppm (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 116 (0.8), 115 (2), 73 (100), 45 (84), 44 (57), 43 (87); principal cations follow.



m/e 43 *m/e* 45 *m/e* 44

m/e 73 *m/e* 115

Anal. Calcd for $C_5H_8O_3$: C, 51.72; H, 6.90. Found: C, 51.20; H, 6.80.

2-Methyl-2-(1,3-dioxolanyl)-1,3-dioxolane (**3a**): yield 5.2 g; bp 68–69 °C (5 mm); n^{24}D 1.4459; ir (neat) 2975, 2880, 1475, 1450, 1375, 1250, 1190, 1120, 1050, 950, 880, 810, 690 cm^{-1}; NMR 1.31 (s, 3 H), 3.73–4.13 (m, peaks at 3.96, 4.0, 4.03, 8 H), and 4.85 ppm (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 160 (1), 101 (3.5), 100 (17.5), 99 (6), 87 (100), 73 (74), 59, 58, 57, 56, 55, 43 (95).

Anal. Calcd for $C_7H_{12}O_4$: C, 52.50; H, 7.50. Found: C, 52.88; H, 7.62.

2-Methylhexahydro-*p*-dioxino[2,3-*b*]-*p*-dioxin (**4a**): yield 2.6 g; bp 74 °C (5 mm); n^{24}D 1.4611; ir (neat) 2950, 2875, 1455, 1375, 1290, 1190, 1140, 1100, 1005, 950, 930, 895, 870, 860, 790, 635 cm^{-1}; NMR 1.43 (s, 3 H), 3.41–4.26 (m, 22 peaks, 4 H), and 4.5 ppm (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 160 (49), 133 (2.4), 100 (26), 87 (98), 73 (95), 61 (50), 55 (16), 43 (100).

Anal. Calcd for $C_7H_{12}O_4$: C, 52.50; H, 7.50. Found: C, 52.17; H, 7.36.

Reaction of DHA with 1,2-Propanediol. DHA (36, g, 400 mmol) was treated with 1,2-propanediol (100 ml) in the presence of Amberlyst-15 (3.6 g) at 100–110 °C for 4 h. Usual workup gave, after distillation, 51.1 g of product, bp 59–61 °C (1.5 mm). Fractionation on a spinning band column gave a low-boiling product, presumably **2a**, a pure fraction of **3b**, and a fraction containing **3b** and isomeric **4b**. Isomeric mixture of **4b** was then separated by GLC from the latter mixture for mass spectral characterization.

2,4-Dimethyl-2-(4-methyl-1,3-dioxolanyl)-1,3-dioxolane (**3b**): yield 30.8 g; bp 69–70 °C (5 mm); n^{24}D 1.4352; ir (neat) 2975, 2925, 2875, 1450, 1375, 1250 cm^{-1}; NMR 1.2–1.43 (m, 9 H), 3.3–3.71 (m, 2 H), 3.88–4.61 (m, 4 H), 4.8, 4.81, 4.93 ppm (s, total 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 188 (0.4), 140 (80), 114 (18), 109 (87), 101 (100), 87, (27), 85 (21), 81 (22), 73 (2.5), 71 (4), 59 (35), 56, 55, 54, 53, 52, 43 (82).

Anal. Calcd for $C_9H_{16}O_4$: C, 57.50; H, 8.50. Found: C, 57.30; H, 8.61.

2,5(or 6),8(or 9)-Trimethylhexahydro-*p*-dioxino[2,3-*b*]-*p*-dioxin (**4b**): mass spectrum (70 eV) *m/e* (rel intensity) 189 (2.6), 188 (40), 115 (5), 114 (31), 101 (98), 87 (96), 73 (8), 61 (68), 59 (89), 43 (100).

Anal. Calcd for $C_9H_{16}O_4$: C, 57.50; H, 8.50. Found: C, 57.20; H, 8.62.

Reaction of DHA with *meso*-2,3-Butanediol. DHA (36 g, 400 mmol) was treated with *meso*-2,3-butanediol (100 ml) in the presence of Amberlyst-15 (3.6 g) in the usual manner. GLC examination of the reaction mixture showed three products in 10:50:40 ratio. The distillation gave 26.2 g of product, bp 50–54 °C (0.5 mm). Fractionation gave two pure and one rather contaminated fractions. The latter was believed (GLC retention time) to be 2-acetyl-4,5-dimethyl-1,3-dioxolane (**2c**), and was not characterized further.

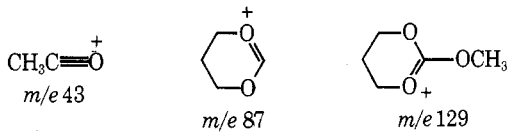
2,4,5-Trimethyl-2-(4,5-dimethyl-1,3-dioxolanyl)-1,3-dioxolane (**3c**): yield 5 g; bp 68–70 °C (4 mm); n^{24}D 1.4283; ir (neat) 3000, 2970, 2880, 1455, 1285, 1190, 1135, 1095, 1000, 950, 895, 870, 860, 790, 635 cm^{-1}; NMR 1.2–1.46 (m, 15 H), 3.51–4.0 (m, 4 H), and 4.91 ppm (m, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 143 (9.3), 129 (15), 128 (30), 115 (100), 101 (25), 99 (15), 85 (13), 73 (73), 56 (67), 55 (68), 43 (87).

Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.11; H, 9.20. Found: C, 60.77; H, 9.04.

2,5,6,8,9-Pentamethylhexahydro-*p*-dioxino-[2,3-*b*]-*p*-dioxin (**4c**): yield 2.0 g; bp 74 °C (4 mm); n^{24}D 1.4345; ir (neat) 2975, 2925, 2860, 1460, 1450, 1380, 1260, 1205, 1120, 1100, 1060 cm^{-1}; NMR 1.01–1.53 (m, 9 peaks, 15 H), 3.43–4.01 (m, 2 H), 4.05–4.65 (m, 2 H), and 4.73 ppm (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 216 (1.1), 170 (3), 143 (5), 129 (10), 128 (28), 116 (20), 115 (98), 101 (23), 99 (16), 85 (17), 73 (98), 61 (8), 56 (94), 55 (87), 43 (100).

Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.11; H, 9.20. Found: C, 61.01; H, 8.80.

Reaction of DHA with 1,3-Propanediol. A mixture of DHA (36 g), 1,3-propanediol (100 ml), and Amberlyst-15 (3.6 g) was stirred at 100–110 °C for 4 h. GLC examination revealed the formation of one product. Usual workup gave 26.1 g of a crude product which after distillation gave 18.1 g of 2-acetyl-1,3-dioxane (**5**): bp 66 °C (5 mm); n^{24}D 1.4369; ir (neat) 2941, 2857, 1739, 1429, 1282, 1242, 1149, 1111, 1042, 909, 854 cm^{-1}; NMR 1.25–1.63 (m, 2 H), 2.18 (s, 3 H), 3.6–4.38 (m, 4 H), 4.75 ppm (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 130 (0.5), 129 (4.6), 101 (11), 87 (100), 73 (21), 59 (74), 43 (84), 41 (68); principal cations follow.



m/e 43 *m/e* 87 *m/e* 129

Anal. Calcd for $C_6H_{10}O_3$: C, 55.67; H, 7.82. Found: C, 55.30; H, 7.70.

Reaction of DHA with Glycerol. A mixture of DHA (36 g, 0.4 mol), glycerol (100 ml), and Amberlyst-15 (3.6 g) was stirred at 100–110 °C for 4 h. The ir spectrum of the reaction mixture indicated the absence of any carbonyl absorptions. After the usual workup the organic extract gave no product upon distillation of solvent. This reaction was, consequently, not pursued further.

Reaction of DHA with Glycerol in the Presence of Methanol. A mixture of DHA (36 g, 0.4 mol), glycerol (36 g, 0.4 mol), methanol (100 ml), and Amberlyst-15 (3.6 g) was shaken in a Parr apparatus at 100–110 °C for 4 h. The cooled reaction mixture upon GLC examination showed the presence of 1,1-dimethoxy-2-propanone (50%), products A (30%), and B (5%). After filtration the excess solvent was distilled off and the liquid residue diluted with water (200 ml) and extracted with methylene chloride. The distillation gave 30 g of liquid product, bp 40–44 °C (0.3 mm). Fractionation on spinning band column gave 15 g of A: bp 51 °C (1.5 mm); n^{24}D 1.4450; ir (neat) 2941, 1449, 1399, 1379, 1250, 1235, 1212, 1198, 1117, 1081, 1047, 1027, 952, 909, 870 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) 1.39 and 1.41 (two s, total 3 H), 3.44 and 3.49 (two s, total 3 H), 3.7–4.06 (m, 3 H), 4.12 (s, 0.5 H), 4.18 (m, 1 H), 4.30 (s, 0.5 H), and 4.44 (br t, 1 H); ^{13}C NMR ($CDCl_3$) (14 peaks in 7 pairs, each pair is approximately of equal intensity) 104.56 and 104.02; 101.46 and 98.74; 74.47 and 73.41; 68.47 and 67.69; 66.34 and 62.75; 56.02 and 54.86; 18.79 and 17.85; mass spectrum (70 eV) *m/e* (rel intensity) 160 (0.34), 144 (3.4), 128 (18), 99 (66), 87 (3), 73 (17), 72 (5), 61 (13), 59 (13), 58 (29), 58 (38), 55 (6), 45 (5), 44 (11), 43 (100), 52 (10).

Anal. Calcd for $C_7H_{12}O_4$: C, 52.50, H, 7.5. Found: C, 52.58; H, 7.42.

Preparation of 11 from 1a and Glycerol. A mixture of **1a** (30 g), glycerol (30 g), and Amberlyst-15 (3.0 g) was stirred at 100–105 °C for 4 h. The usual workup provided 20.0 g of a liquid which was further purified by spinning band distillation to give 10.5 g of **11**. This was found identical (GLC, ir, NMR, mass spectrum) with product **11** obtained in the preceding experiment.

Reaction of DHA with Glycerol in the Presence of Ethanol. A mixture of DHA (30 g), glycerol (30 g), ethanol (90 ml), and Amberlyst-15 (3.6 g) was shaken in a Parr apparatus at 100–110 °C for 4 hr. The usual workup followed by distillation gave 19.4 g of a product, bp 85–93 °C (16 mm). Fractionation on a spinning band column gave 9.0 g of 4-ethoxy-5-methyl-3,6,8-trioxabicyclo[3.2.1]octane: bp 67 °C (4 mm); n^{20}D 1.4418; ir (neat) 2975, 2895, 1450, 1395, 1380, 1250, 1115, 1025, 960, 928, 865, 710 cm^{-1}; NMR ($CDCl_3$) 1.25 (t, 3 H, J = 7 Hz), 1.43 (s, 3 H), 3.26–4.36 (m, about 26 peaks, 7 H), and 4.48 (br d, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 149 (1.3), 145 (12), 129 (23), 115 (2), 101 (39), 100 (81), 85 (3), 73 (37), 61 (12), 58 (42), 57 (55), 43 (100).

Anal. Calcd for $C_8H_{14}O_4$: C, 55.17; H, 8.04. Found: C, 54.93; H, 8.04.

Reaction of DHA with Glycerol in the Presence of 2-Propanol. A mixture of DHA (60 g), glycerol (60 g), 2-propanol (150 ml), and Amberlyst-15 (6.0 g) was allowed to react and worked up in the above manner. After spinning band distillation, 12.1 g of 4-isopropoxy-5-methyl-3,6,8-trioxabicyclo[3.2.1]octane was obtained: bp 100–105 °C (19 mm); n^{20}D 1.4480; ir (neat) 2970, 2895, 1450, 1250, 1105, 1030, 870 cm^{-1}; NMR ($CDCl_3$) 1.2 (t, 6 H, J = 7 Hz), 1.36 (s, 3 H), and 3.26–4.56 ppm (m, 8 H); mass spectrum (70 eV) *m/e* (rel intensity) 186 (0.8), 145 (56), 129 (45), 116 (6), 100 (89), 85 (14), 86 (7), 73 (33), 61 (7), 58 (54), 57 (69), 43 (100).

Anal. Calcd for $C_9H_{16}O_4$: C, 57.42; H, 8.56. Found: C, 57.64; H, 8.34.

Acknowledgments. The author wishes to thank Dr. G. Chmurny for NMR spectral data, Messrs. T. G. Sinay, Jr., and

H. J. Slater for expert technical assistance, and Drs. R. K. Blackwood and E. B. Whipple for stimulating discussions.

Registry No.—**1a,** 6342-56-9; **1b,** 5774-26-5; **1c,** 19358-00-0; **1d,** 59044-05-2; **1e,** 19255-82-4; **2a,** 19358-03-3; **2c,** 59044-06-3; **3a,** 10374-97-7; **3b,** 38167-23-6; **3c,** 59044-07-4; **4a,** 59044-08-5; **4b,** 59043-78-6; **4c,** 59044-09-6; **5,** 59044-10-9; **11,** 59044-11-0; **14,** 59044-12-1; DHA, 96-26-4; methanol, 67-56-1; ethanol, 64-17-5; 1-propanol, 71-23-8; isopropyl alcohol, 67-63-0; 1-butanol, 71-36-3; ethylene glycol, 107-21-1; 1,2-propanediol, 57-55-6; *meso*-2,3-butanediol, 5341-95-7; 1,3-propanediol, 504-63-2; glycerol, 56-81-5; 4-ethoxy-5-methyl-3,6,8-trioxabicyclo[3.2.1]octane, 59044-13-2; 4-isopropoxy-5-methyl-3,6,8-trioxabicyclo[3.2.1]octane, 59044-14-3.

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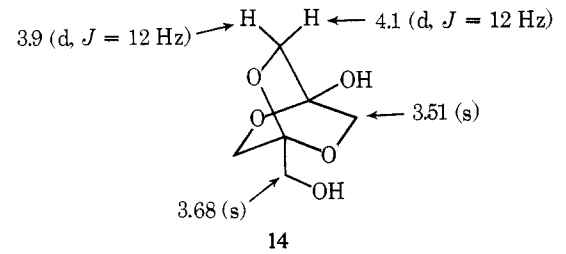
(20) Commercially available DHA (Wallerstein, Aldrich) was used in this study. DHA imparts tanning effect on skin. In addition to known monomeric and several dimeric forms,[22] we have NMR (D_2O solution) evidence for yet another possible dimer structure **14** for this compound. DHA (monomer) shows a singlet at δ 4.36 (D_2O).



14

(21) Amberlyst-15 is a sulfonated cation-exchange resin (H^+ form) marketed by Rohm and Haas, Inc. In our work we have used several brands of strongly acidic, sulfonated ion-exchange resins (H^+ form) with equally effective results.
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Novel One-Pot Synthesis of 4-Aminoquinazolines

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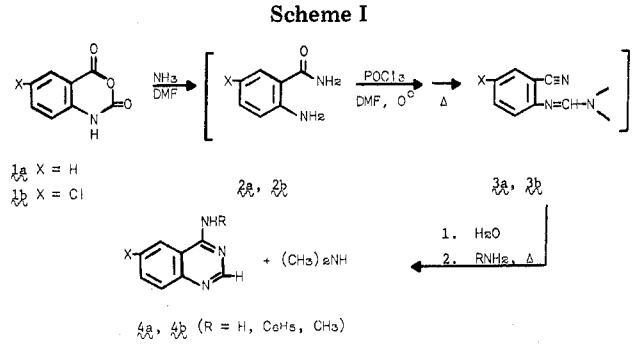
Received March 25, 1976

The biological activity of 4-aminoquinazolines has prompted development of many syntheses,[1] most of which are based on conversion of a quinazolone to a 4-chloroquinazoline that affords the desired product on treatment with an amine. However, several workers have reported syntheses based on conversion of *o*-aminonitriles or amides to amidines that cyclize to give the 4-aminoquinazoline directly.[2–5] We wish to report a general synthesis of this type (Scheme I) that can be carried out in one vessel starting with the readily available isatoic anhydrides (**1**, Scheme I). The intermediates in Scheme I need not be isolated.

Scheme I



The reaction of isatoic anhydride with ammonia has been reported to give good yields of anthranilamide only in dilute aqueous solution,[6] and 5-chloroisatoic anhydride (**1b**) gives only about 50% yields of **2b**.[7,8] We have found that treatment of **1a** or **1b** with NH_3 in DMF gives very high yields of **2a** or **2b**. Conversion of **2** to **3** is a modification of the work of Jones and Cragoe.[9] It was found that excellent yields of **3** can be obtained if the $POCl_3$ addition is carried out at 0–15 °C, followed by heating briefly at 40–60 °C. The intermediate, **3**, may be isolated, if desired, in ~80% yield, based on **1**, by dilution of the mixture with H_2O and neutralization with NaOH to cause **3** to precipitate.

In the final step a primary aliphatic or aromatic amine undergoes amidine interchange with **3** followed by cyclization and rearrangement to give the desired 4-aminoquinazoline **4** (Scheme II). Although **4** is produced by heating the final acidic DMF solution, much better yields were obtained when the mixture was made basic before heating. (See Experimental Section.)

Scheme II