to stand under nitrogen at room temperature for 10 days. The yellow solution was cooled in an ice bath, diluted with 200 ml of 95% aqueous EtOH, and treated with 8 g of $NaBH_4$ (pellets) in portions over 3 min. The mixture was stirred at 0–5° for 1 hr and then at room temperature for 8 hr. The mixture was made strongly basic with 6 *N* NaOH and extracted with CH_2Cl_2. The organic extract was washed with aqueous NaCl, dried, and concentrated to give a yellow foam. Chromatography over 15 g of activity III basic alumina gave, with benzene elution in four 30-ml fractions, a total of 0.32 g (55%) of **1** as a white solid, mp 151–152°. Recrystallization from ether gave tiny colorless crystals, mp 153–154° (lit.[9] mp 152–153°). This material was identical (infrared, tlc) with authentic **1**.[5,9,12]

N-[2-(3-Indolyl)ethyl]piperidine (7).—To a stirred ice-cold solution of 0.50 g (0.0025 mol) of **2**, 15 ml of a KH_2PO_4–$NaHPO_4$ concentrated 6.50 pH buffer solution (Radiometer, Copenhagen), 0.20 g (0.0032 mol) of $NaCNBH_3$ (Alfa Chemical Co.) in 500 ml of distilled H_2O was added dropwise over a few min 1.5 g (0.0038 mol) of a 25% aqueous solution of **3**. The solution (pH 6–7) was stirred at 0–5° for 1 hr and then allowed to stand at room temperature for 12 days. The mixture was made strongly basic with 6 *N* NaOH and extracted with CH_2Cl_2. The organic extract was washed with water, dried, and concentrated to give 0.55 g of a white crystalline mass. Chromatography over activity III basic alumina gave, with benzene elution in 12 30-ml fractions, 0.50 g (86%) of **7** as a white solid, mp 149–151°. Recrystallization from ether gave colorless prisms, mp 151–152° (lit.[9,18] mp 151–152°). This material was identical (infrared, tlc) with authentic **7**.[9,18]

Isolation of 1,2,6,7,12,12b-Hexahydroindolo[2,3-*a*]quinolizine (6) and Conversion to 4-*d*-1,2,3,4,6,7,12,12b-Octahydroindolo-[2,3-*a*]quinolizine (8).—The reaction mixture from 0.50 g of **2** and 1.2 g of a 25% aqueous solution of **3** after 4 days at 25° was cooled to 5°, made strongly basic with 6 *N* NaOH, and extracted with CH_2Cl_2. Concentration of the organic extract *in vacuo* gave **6** as an amber syrup. Tlc showed a single yellow-green spot of about the same R_f as **1** but with a distinctly different color pattern. No **1**, **2**, or **7** could be detected.

A mixture of 0.11 g of crude **6**, 0.30 g of $NaBH_4$, and 20 ml of 79% aqueous EtOH was stirred at 5° for 1 hr and then at 25° for 10 hr. Extraction with CH_2Cl_2 followed by the usual work-up and column chromatography (see entry for **1**) gave 0.027 g (24%) of pure **1**, identical (tlc, infrared, melting point) with authentic material.

A mixture of 0.125 g of crude **6**, 0.125 g of $NaBD_4$, and 20 ml of 70% aqueous EtOH was stirred at 5° for 1 hr and then at 25° for 10 hr. The usual work-up and chromatography gave 0.034 g (27%) of pure **8** (tlc; same as **1**), mp 150° dec.

Pertinent spectral data for **8** are as follows: ir ($CHCl_3$) 3460 (NH), 2930, 2850, 2800 (CH), and 2040 cm^{-1} (CD); mass spectrum (70 eV) *m/e* 227, 226, 198, 170, and 169.

12b-*d*-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine (9).—This was prepared from **10** which in turn was synthesized from **1** according to the standard method.[12,19] To a stirred solution of 0.88 g (0.0039 mol) of **1**, 0.5 ml of Et_3N, and 100 ml of dry CH_2Cl_2 at −5 to −20° was added 0.49 g (0.0045 mol) of *tert*-butyl hypochlorite in 13 ml of dry CCl_4 dropwise over 1 hr. The mixture was then stirred at 25° for 90 min, washed with water, dried, and concentrated *in vacuo* at 25° to give an amber syrup. This was dissolved in 30 ml of dry EtOH which had been saturated with HCl gas. The mixture was refluxed for 1 hr and then concentrated *in vacuo*. The residue (crude **10**) was treated with 0.60 g of $NaBD_4$ in the usual fashion. Work-up and column chromatography gave 0.25 g (29%) of pure **9** (tlc; same as **1**), mp 150–151° dec.

Pertinent spectral data for **9** are as follows: ir ($CHCl_3$) 3465 (NH), 2940, 2850, 2800, 2750, (CH), and 2000 cm^{-1} (CD); mass spectrum (70 eV) *m/e* 227, 226, 225, 198, 171, and 170.

Registry No.—**1**, 4802-79-3; **8**, 34388-08-4; **9**, 34388-09-5.

Acknowledgment.—The author is indebted to Professor Richard F. Borch (University of Minnesota) for a discussion involving the use of sodium cyanoborohydride and for kindly informing the author of related unpublished work, and to the referees for incisive comments.

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A Convenient Synthetic Approach to 3- and 4-Alkyl-2,3-dihydrofurans

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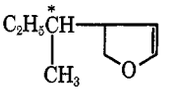
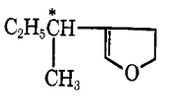
A summary survey of the possible synthetic routes leading to 2,3-dihydrofurans reported in the literature[2–7] convinced us that none could be simply applied to the preparation of optically active monoalkyl-substituted 2,3-dihydrofurans (**1a**, **2a**) containing an



1a



2a

asymmetric carbon atom directly bonded to the heterocyclic ring. Our interest in these optically active compounds and the attention received by 2,3-dihydrofurans in recent years[8–10] prompted us to develop a general procedure for the preparation of isomerically pure 2,3-dihydrofurans.

The key precursor of both series **1** and **2** is the appropriate γ-hydroxyaldehyde, readily accessible through rhodium-catalyzed hydroformylation, respectively of a 2-alkyl-allyl alcohol (Scheme I) and of a 2-alkyl-acrolein diethyl acetal[11] (followed in the second case by reduction of the free carbonyl group) (Scheme II).

The hydroformylation of allylic alcohols was long ago suggested as a promising synthetic route to γ-hydroxyaldehydes,[12] but, because of the substantial isomerization of the substrate promoted by the cobalt catalyst and simultaneous formation of several by-products,[13] no generally useful syntheses could be developed.

(1) (a) Technisch-Chemisches Laboratorium, Zürich; (b) Istituto Chimica Fisica, Pisa.

(2) (a) J. Colonge and R. Gelin, *Bull. Soc. Chim. Fr.*, 799 (1954); (b) H. Normant, *Chim. Ind. (Paris)*, **63**, 511 (1950).

(3) J. C. Anderson, D. G. Lindsay, and C. B. Reese, *Tetrahedron*, **20**, 2091 (1964).

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(8) (a) P. Scribe and J. Wiemann, *ibid.*, 2268 (1971); (b) J. P. Girault, P. Scribe, and G. Dana, *ibid.*, 2279 (1971).

(9) British Patent 849,192 (1959) and German Patent 1,064,957 (1958); *Chem. Abstr.*, **56**, 455 (1962).

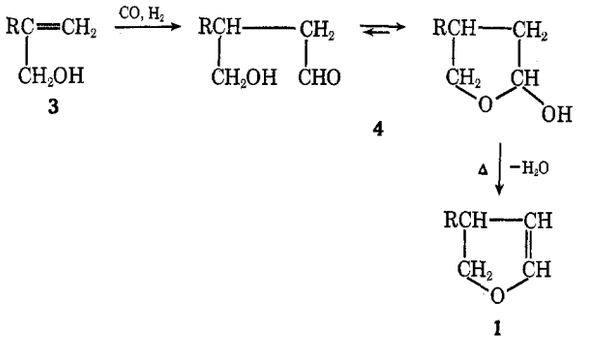
(10) M. A. Gianturco and P. Friedel, *Can. J. Chem.*, **44**, 1083 (1966).

(11) C. Botteghi and L. Lardicci, *Chim. Ind. (Milan)*, **52**, 265 (1970).

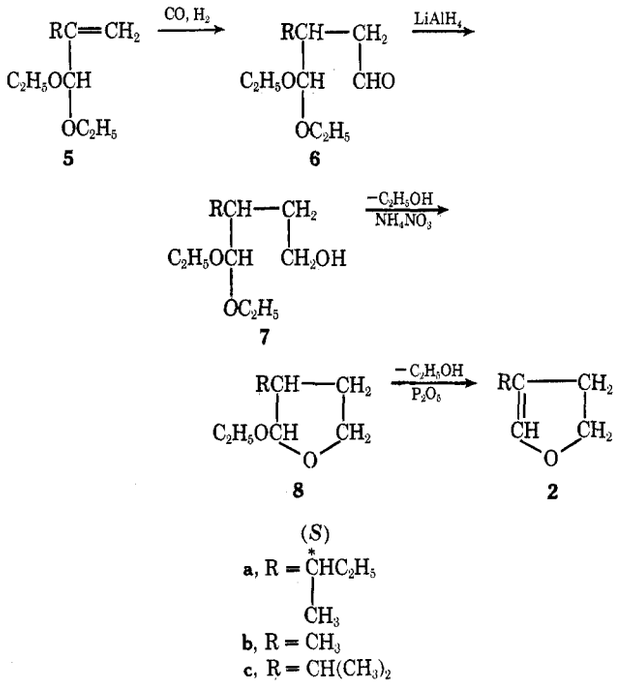
(12) P. Pino, *Gazz. Chim. Ital.*, **81**, 625 (1951).

(13) J. Falbe, "Synthesen mit Kohlenmonoxid," Springer-Verlag, West Berlin, 1967, p 46.

SCHEME I



SCHEME II



Therefore, this method has found practical use only in the case of the corresponding esters; for instance, the acetate of methallyl alcohol was used to obtain γ-acetoxy-β-methylbutyraldehyde, and hence, in two steps, 3-methyl-2,3-dihydrofuran was obtained in satisfactory yield.[6] However, using *trans*-bis(triphenylphosphine)carbonylchlororhodium(I)[14] as catalyst, we carried out the hydroformylation of **3** with exclusive formation of the desired γ-hydroxyaldehyde **4**.[15] The absence of characteristic carbonyl stretching bands in the ir spectra of **4a–c** and the absence of formyl hydrogens in their nmr spectra reveal the hemiacetalic form of the γ-hydroxyaldehydes (the hemiacetal hydrogens give their signal in the nmr spectra at δ 4.44–4.73), and rule out at the same time the formation of the possible isomers, β-hydroxyaldehydes, in the hydroformylation reaction.

Simple distillation at atmospheric pressure promotes the dehydration of **4**, and affords the 3-alkyl-2,3-dihydrofurans (**1**) exempt from isomers (the isomeric purity was established on the basis of the nmr spectra).

The cyclization of **7**, with loss of a molecule of ethanol, gave a mixture of stereoisomers **8**, the ir and nmr spectra of which showed no presence of olefinic protons.[16] The dealkoxylation of **8** was accomplished according to a known procedure,[6] upon heating in the presence of phosphoric anhydride; the resulting 4-alkyl-2,3-dihydrofurans (**2**) were isomerically pure, which was evident from their nmr spectra.

The structure of **1a–c** and **2a–c** was unequivocally confirmed by nmr analysis at 220 MHz; the spectral parameters are summarized in Table I.[17]

The nmr spectrum of **1a** shows some signals clearly split, owing to the presence of both diastereoisomers (*e.g.*, H_{2a} has a chemical shift difference of 0.01 ppm, H_{2b} 0.04 ppm, H_4 0.01 ppm). The relative peak heights of these signals give a direct measure of the diastereoisomeric composition: $(R,S)/(S,S) = 54:46$.[18]

In order to obtain an indication of the optical yield of the preparation of **1a**, a sample of this compound was dehydrogenated[10] to (+)-(*S*)-3-*sec*-butylfuran. The product obtained had $[\alpha]^{25}D$ +18.93° (*c* 8.44, mesitylene), corresponding to a minimum optical purity of 70.5%.[11]

Experimental Section

Boiling points are uncorrected. Gas chromatographic analyses were made on a Perkin-Elmer 990 gas chromatograph with FID detector using the columns specified. Infared spectra were measured on a Perkin-Elmer 221 spectrophotometer; nmr spectra at 220 MHz were obtained with a Varian spectrometer, in carbon tetrachloride solutions with tetramethylsilane as an internal standard (δ 0). Optical rotations were measured in solution in 1-dm tubes, using a Perkin-Elmer 141 polarimeter. Mass spectra were obtained with an Hitachi Perkin-Elmer RMU-6L mass spectrometer. Microanalyses were performed by the Microanalytical Laboratory, Department of Industrial and Engineering Chemistry, ETH (Zürich).

Materials.—The commercial product **3b** (Fluka A. G., Switzerland) was used without further purification. **3a** and **3c** were made according to the general procedure of Green and Hickinbottom.[19] **5a–c** were prepared from the respective α,β-unsaturated aldehydes by a known general method.[20] A common precursor of **3a**, $[\alpha]^{25}D$ +21.63° (*c* 1.655, *n*-heptane), and **5a**, $[\alpha]^{25}D$ +23.75° (*c* 2.901, *n*-heptane), was (+)-(*S*)-2-methylene-3-methylpentanal having ~95% minimum optical purity.[21]

2-Alkyl-γ-hydroxyaldehydes (4a–c).—A solution of **3** (0.4 mol) and $RhCl(CO)(PPh_3)_2$ (0.2 g) in dry benzene (80 ml) and triethyl-

(14) D. Evans, J. A. Osborn, and G. Wilkinson, *J. Chem. Soc. A*, 3133 (1968).

(15) Direct hydroformylation of allyl alcohols without appreciable isomerization was also obtained with Rh_2O_3 and tributylphosphine as catalyst: W. Rupilius, Thesis, Technische Hochschule Aachen, 1969.

(16) A gas chromatographic separation of the stereoisomers was performed and the single components were analyzed by mass spectroscopy; identical spectra for each isomer were obtained in all cases, the first significant peak corresponding to the loss of a molecule of ethanol, and the subsequent fragmentation pattern resembling that of the respective dihydrofuran **2**.

(17) Our values are in agreement with the data available in the literature: G. Dana and A. Zysman, *Bull. Soc. Chim. Fr.*, 1951 (1970), and ref 4.

(18) To determine the absolute configuration of the asymmetric carbon atom in the ring moiety of **1a**, a sample of its precursor, **4a**, was reduced with lithium aluminum hydride, and the 3-hydroxymethyl-4-methyl-1-hexanol obtained was converted into (4*S*)-3-carboxy-4-methylhexanoic acid with a known procedure: D. Pini, A. Di Corato, and L. Porri, *Chim. Ind.* (*Milan*), **53**, 505 (1971). The rotatory power of the acid obtained, $[\alpha]^{25}D$ −1.63° (*c* 0.7, carbon tetrachloride), compared with the values of the pure diastereoisomers [D. Pini, A. Di Corato, and L. Porri, *Chim. Ind.* (*Milan*), **53**, 505 (1971)] indicated the predominance of the 4*S*,3*R* isomer.

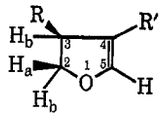
(19) M. B. Green and W. J. Hickinbottom, *J. Chem. Soc.*, 3266 (1957).

(20) J. A. van Allan, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 21.

(21) L. Lardicci, F. Navari, and R. Rossi, *Tetrahedron*, **22**, 1991 (1966).

TABLE I

NMR PARAMETERS OF 3- AND 4-ALKYL-2,3-DIHYDROFURANS



R	R′	δ_{2a}	δ_{2b}	δ_3	δ_4	δ_5	J_{2a2b}	J_{2a3}	J_{2b3}	J_{34}	J_{35}	J_{45}
H	H	4.20	4.20	2.53	4.82	6.22		8.3	10.7	2.5	2.6	2.6
t-Bu	H	4.08	4.24	2.74	4.86	6.30	−9.1	7.4	9.6	2.4	2.0	2.8
(*S*)-*s*-Bu	H	3.96,[a] 3.97[b]	4.22,[a] 4.26[b]	2.86	4.86,[a] 4.87[b]	6.30	−8.7	6.9	9.8	2.3	2.2	2.5
Me	H	3.81	4.33	3.00	4.88	6.25	−8.6	6.6	9.8	2.3	1.8	2.6
H	Me	4.24	4.24	2.47		5.94	−8.8	7.0	9.6		1.7	
H	*i*-Pr	4.32	4.32	2.53		6.03	−9.0		9.8		1.7	
H	(*S*)-*s*-Bu	4.30	4.30	2.50		6.05	−9.0		9.0		2.1	

[a] *R,S* configuration. [b] *S,S* configuration.

amine (44 ml) was shaken in a high-pressure autoclave with a 1:1 mixture of carbon monoxide and hydrogen (80 atm) at a temperature of 80°. The reaction stopped when the theoretical amount of gas was absorbed. After removal of the solvents under reduced pressure (~100 mm), fractional distillation of the crude product gave **4** in 80–90% yield. Glpc of each product, using a 16 m × 0.5 mm Carbowax 20M support coated column, showed only one peak.

4a had bp 110° (0.3 mm); mass spectrum *m/e* (rel intensity) 70 (100), 41 (68), 57 (53), 55 (42), 69 (41), 56 (37), 29 (30), 42 (16.5), 83 (14.5), 43 (14).[22]

4b had bp 66° (12 mm); mass spectrum *m/e* (rel intensity) 56 (100), 41 (72), 57 (56), 72 (20), 29 (18.5), 27 (17), 43 (16), 39 (16), 58 (15.5), 55 (15).[22]

4c had bp 63° (0.1 mm); mp 35–37°; mass spectrum *m/e* (rel intensity) 70 (100), 57 (82), 41 (51), 55 (32), 83 (23), 29 (22), 43 (19.5), 42 (19), 81 (19), 69 (18).[22]

3-Alkyl-2,3-dihydrofurans (1a–c).—Each compound **4** (5 g) was placed in a distillation apparatus and heated at atmospheric pressure with an oil bath. The temperature was raised until a slow distillation of water and dihydrofuran was noticed; 160–230° were required according to the substituent (the presence of a trace of ammonium nitrate facilitates the dehydration). Heating was maintained until completion of the reaction. The distilled organic layer was dried (K_2CO_3) and redistilled over calcium hydride to afford pure **1** (70–80% yield). Glpc of each product, using a 2 m × 2.2 mm 15% polypropylene glycol column, showed only one peak.

1a had bp 90–91° (125 mm); $n^{25}D$ 1.4407; $[\alpha]^{25}D$ +21.50° (*c* 2.228, *n*-heptane); mass spectrum *m/e* (rel intensity) 69 (100), 41 (36), 68 (17), 126 (M^+, 13.5), 39 (9.5), 29 (9), 70 (7), 27 (6), 57 (5), 55 (4).

1b had bp 68°; $n^{25}D$ 1.4161 (lit.[6] bp 69–74°; $n^{25}D$ 1.4161); mass spectrum *m/e* (rel intensity) 69 (100), 41 (67), 84 (M^+, 54), 39 (39), 27 (21), 55 (20.5), 29 (17), 53 (13), 28 (10), 83 (6.5).

1c had bp 136°; $n^{25}D$ 1.4362; mass spectrum *m/e* (rel intensity) 69 (100), 41 (37), 57 (27), 68 (21), 126 (M^+, 13.5), 39 (13), 29 (12), 43 (11), 70 (10), 27 (6).

2-Alkyl-γ-hydroxyaldehyde Diethyl Acetals (7a–c).—The hydroformylation of **5** (0.4 mol) was carried out under the same conditions used for the preparation of **4**. The crude reaction mixture containing **6**[11] was added to a suspension of lithium aluminium hydride (5.0 g) in dry ether (300 ml) and stirred overnight at room temperature. The reaction mixture was worked up by the procedure described by Hill and Schearer;[23] distillation *in vacuo* afforded **7** in 80–85% yield.

7a had bp 98–99° (0.5 mm); $n^{25}D$ 1.4386–1.4390; $[\alpha]^{25}D$ −4.81° (*c* 1.061, *n*-heptane). *Anal.* Calcd for $C_{12}H_{26}O_3$: C, 66.01; H, 12.00. Found: C, 66.22; H, 12.18.

7b had bp 112–113° (14 mm); $n^{25}D$ 1.4292. *Anal.* Calcd for $C_9H_{20}O_3$: C, 61.33; H, 11.44. Found: C, 61.64; H, 11.74.

7c had bp 80–82° (0.9 mm); $n^{25}D$ 1.4400–1.4401. *Anal.* Calcd for $C_{11}H_{24}O_3$: C, 64.66; H, 11.84. Found: C, 64.60; H, 12.00.

2-Ethoxy-3-alkyl Tetrahydrofurans (8a–c).—Each compound **7** (5 g) was placed in a distillation apparatus in the presence of a trace of ammonium nitrate and heated with an oil bath at 140–150°; slow distillation of the theoretical amount of ethanol occurred; the residue, distilled *in vacuo*, afforded **8** in 80–85% yield.

8a had bp 85–95° (14 mm); **8b** had bp 52–54° (14 mm); **8c** had bp 62–68° (14 mm).

4-Alkyl-2,3-dihydrofurans (2a–c).—Each compound **8** (5 g) was placed in a distillation apparatus in the presence of a catalytic amount of phosphorus pentoxide and heated with an oil bath at 160–180°. Ethanol and dihydrofuran distilled as soon as they were formed; complete dealkoxylation was achieved in a matter of hours. Crude **2a** and **2c** were washed with water and distilled over calcium hydride to give the pure products in 75–80% yield. A pure sample of **2b** was obtained by preparative glpc on a Perkin-Elmer F 21 gas chromatograph, using a 3 m × 8 mm column packed with 20% polypropylene glycol on Chromosorb A at 80°. Glpc of each product, using a 2 m × 2.2 mm 15% polypropylene glycol column, showed only one peak.

2a had bp 145°; $n^{20}D$ 1.4450; $[\alpha]^{25}D$ +21.18° (*c* 2.762, *n*-heptane); mass spectrum *m/e* (rel intensity) 97 (100), 41 (48), 43 (31), 126 (M^+, 22), 39 (14), 55 (13), 69 (11.5), 27 (10.5), 29 (10), 111 (6).

2b had bp 63–64°; $n^{20}D$ 1.4425; mass spectrum *m/e* (rel intensity) 84 (M^+, 100), 55 (97), 83 (48), 41 (45), 39 (44), 29 (36), 27 (31), 53 (21), 56 (19), 69 (14).

2c had bp 124°; $n^{25}D$ 1.4492; mass spectrum *m/e* (rel intensity) 41 (100), 97 (93), 43 (56), 55 (42), 112 (M^+, 38), 39 (31), 27 (30.5), 67 (29), 71 (22.5), 69 (22).

Registry No.—**1a** (*R,S*), 34314-80-2; **1a** (*S,S*), 34368-07-5; **1b**, 1708-27-6; **1c**, 34314-82-4; **2a**, 34379-54-9; **2b**, 34314-83-5; **2c**, 34314-84-6; **4a**, 34379-55-0; **4b**, 34314-85-7; **4c**, 34314-86-8; **7a**, 34314-87-9; **7b**, 34314-88-0; **7c**, 34314-89-1; **8a**, 34314-90-4; **8b**, 34314-91-5; **8c**, 34314-92-6; 2,3-dihydrofuran, 1191-99-7.

(22) The molecular ion (M^+) is not recognizable, as expected for compounds of this type, but peaks at *m/e* M + 1 (<1%) are easily identifiable.

(23) R. K. Hill and W. R. Schearer, *J. Org. Chem.*, **27**, 921 (1962).

Synthesis and Reactions of γ-Alkylthio-β-butyrolactones

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Diketene undergoes a variety of ring opening reactions to afford acetoacetate derivatives.[1] In contrast, the integrity of the β-lactone linkage may be maintained by a free-radical reaction at the olefinic linkage.

(1) D. Borrman, "Methoden der Organischen Chemie," 2nd ed, Vol. 4-II, Houben-Weyl-Müller, Ed., Georg Thieme Verlag, Stuttgart, 1968, pp 226–259.