

The β -diethylaminoethyl ester hydrochloride (86% yield) was recrystallized from acetone; m.p. 164–166°.

Anal. Calcd. for $C_{22}H_{28}O_2NCl$: N, 3.63; Cl, 9.19. Found: N, 3.63; Cl, 9.16.

α -Phenyl- γ -hydroxybutyric Acid and the β -Diethylaminoethyl Ester.—After the preparation of the Ivanov reagent in the described manner, the mixture was cooled to about 10°, stirred, and a chilled, ethereal solution of 44 g. (1 mole) of ethylene oxide added. Dry benzene was then added through the dropping funnel while the ether was removed by distillation. This process was continued until the temperature of the mixture reached 65°. The mixture was refluxed for 5 hours, cooled to 5°, and hydrolyzed with dilute hydrochloric acid. The organic layer was separated and extracted with 10% sodium carbonate solution. Upon acidification of the alkaline layer at 5° with dil. hydrochloric acid, an oil precipitated which solidified after it had been kept at 0° for some time; yield 11.5 g. (64%); m.p. 100–101°¹⁴ after recrystallization from isopropyl alcohol-petroleum ether.

The β -diethylaminoethyl ester hydrochloride (76% yield) was recrystallized from acetone-xylene; m.p. 94–96°.

Anal. Calcd. for $C_{16}H_{22}O_2NCl$: N, 4.44; Cl, 11.23. Found: N, 4.36; Cl, 11.29.

2,2-Diphenyl-1,3-propanediol (a) From α,α -Diphenyl- β -hydroxypropionic Acid.—The propionic acid (26.2 g.) was

(14) P. Carré and D. Libermann (*Bull. soc. chim.*, [4] **53**, 264 (1933)) found 99–100°.

placed in the thimble of a modified¹⁵ soxhlet apparatus connected to a 1-liter flask which contained 8.2 g. of lithium aluminum hydride and 600 cc. of dry ether. The mixture was refluxed until the acid had dissolved, cooled in an ice-bath, stirred and 50 cc. of water added, dropwise, followed by a mixture of 80 cc. of concd. hydrochloric acid and 100 cc. of water. The ether layer was extracted with sodium carbonate solution, dried over magnesium sulfate, and the solvent removed. The crystalline residue (23.7 g., 96%) was recrystallized from isopropyl alcohol-petroleum ether; m.p. 106–107°.¹⁶

(b) From Diethyl Diphenylmalonate.—Lithium aluminum hydride (1.7 g.) and 100 cc. of ether were placed in a flask equipped with a stirrer, dropping funnel and a reflux condenser. The mixture was stirred and 9.4 g. of the malonate in 20 cc. of ether was added slowly. The mixture was refluxed for 3 hours, and then treated in the manner described above; crude yield 6.6 g. (97%); m.p. 106–107°; mixed m.p. 106–107°.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.92; H, 7.07. Found: C, 78.78; H, 6.99.

(15) Modified in such a manner that it was not necessary for the thimble to become full before the dissolved acid could flow into the reaction flask.

(16) Dieter G. Markees and Alfred Burger (*THIS JOURNAL*, **71**, 2031 (1949)) found 102–104°.

ANN ARBOR, MICHIGAN

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[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Antispasmodics. X. 1,3-Dioxolanes and 1,3-Dioxanes

By F. F. BLICKE AND FLOYD E. ANDERSON^{1,2}

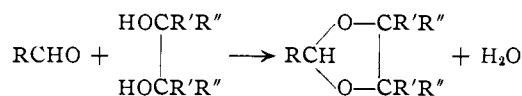
The preparation of a number of substituted 1,3-dioxolanes and 1,3-dioxanes has been described. The 1,3-dioxolanes, in which the substituents are basic-alkyl groups, exhibit antispasmodic and antihistaminic activity.

Since paraldehyde is an excellent hypnotic, it was decided to prepare a number of substances which would be analogous in their basic structure to the aldehyde, namely, 1,3-dioxolanes and 1,3-dioxanes. It had been shown by Knoefel³ that certain alkyl derivatives of these parent compounds do exhibit hypnotic activity. However, except for 4,6,6-trimethyl-1,3-dioxane which was found to be active when administered orally to rats, all of the compounds reported in Tables I and II, which were prepared and tested for hypnotic activity⁴ during this investigation, proved to be inactive or only slightly active.

Twelve basic dioxolanes (Table III) were then prepared. A typical example of this group, 2,2-diphenyl-4-dimethylaminomethyl-1,3-dioxolane, was found to be devoid of hypnotic activity but, in a detailed pharmacological study of this substance and other members of the group by Brown and Werner,⁵ it was found that some of these compounds are potent spasmolytic agents; they also exhibit antihistaminic activity.

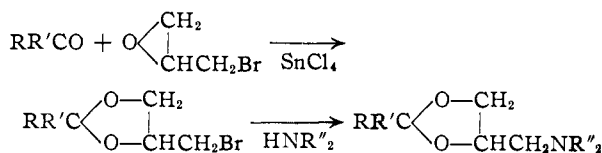
1,3-Dioxolanes were prepared from an aldehyde and a 1,2-glycol in the presence of 85% orthophos-

phoric acid. R, R' and R'' = hydrogen or alkyl,



and may be alike or different.

In order to obtain basic 1,3-dioxolanes, a ketone was allowed to react with epibromohydrin,⁶ in the presence of stannic chloride, and the bromomethyl-1,3-dioxolane obtained was then aminated



Benzophenone and epibromohydrin condensed in the presence of stannic chloride to form the crystalline 2,2-diphenyl-4-bromomethyl-1,3-dioxolane. However, when other ketones such as 2,2-di-(*p*-methoxyphenyl) ketone, di-(2-thienyl) ketone and fluorenone were substituted for benzophenone, the dioxolane could neither be obtained in crystalline form nor could it be distilled without decomposition; in these instances the crude product was aminated.

Phenyl 2-thienyl ketone reacted with epibromohydrin and stannic chloride to yield an oily dioxolane which could be distilled. When cooled, the

(6) When an attempt was made to aminate the corresponding chloromethyl compound (G. Willfang, *Ber.*, **74**, 145 (1946)) by the use of diethylamine, the chloromethyl compound was recovered unchanged.

(1) This paper represents part of a dissertation submitted by Floyd E. Anderson in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan.

(2) The Wm. S. Merrell Company Fellow.

(3) P. K. Knoefel, *J. Pharmacol. Exp. Therap.*, **50**, 88 (1934); *ibid.*, **53**, 440 (1935).

(4) Tested in the Wm. S. Merrell Company laboratories under the supervision of Dr. Harold W. Werner.

(5) Barbara B. Brown and Harold W. Werner, *J. Pharmacol. Exp. Therap.*, **97**, 157 (1949).

TABLE I

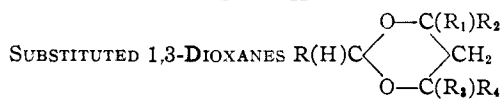


Compound 3 has a pleasant fruity odor, 4 a mild floral odor and 9 a camphor-like odor.

	R	R ₁	R ₂	R ₃	R ₄	Yield, %	°C.	B.p., Mm.
1	H	H	H	H	CH ₂ Cl	63	146-147 ^a	745
2	CH(CH ₃) ₂	H	H	H	CH ₂ Cl ^b	80	74-75	17
3	CH(CH ₃) ₂	H	H	H	CH ₂ OCH ₃ ^c	55	181-183	745
4	CH(CH ₃) ₂	H	H	H	CH ₂ OC ₆ H ₅ ^d	78	167-169	19
5	H	CH(CH ₃) ₂	CH ₃	H	CH(CH ₃) ₂ ^e	85	82	20
6	CH(CH ₃) ₂	CH(CH ₃) ₂	CH ₃	H	CH(CH ₃) ₂ ^f	91	105	23
7	H	CH ₃	CH ₃	CH ₃	CH ₃	76	124-125 ^g	745
8	CH ₃	CH ₃	CH ₃	CH ₃	CH ₃	98	133 ^h	745
9	CH(CH ₃) ₂	CH ₃	CH ₃	CH ₃	CH ₃	95	57 ⁱ	15

^a L. Henry (*Bull. soc. chim.*, [3] 13, 384 (1895)) found 150°; A. Verley (*ibid.*, [3] 21, 276 (1899)), 126° (750 mm.); German Patent 271,381 (*Chem. Zentr.*, 85, 1, 1316 (1914)), 148°. ^b *Anal.* Calcd. for C₇H₁₃O₂Cl: Cl, 21.54. Found: Cl, 21.67. ^c *Anal.* Calcd. for C₈H₁₆O₂: C, 59.97; H, 10.07. Found: C, 59.85; H, 10.20. ^d *Anal.* Calcd. for C₁₃H₁₈O₂: C, 70.24; H, 8.16. Found: C, 69.86; H, 8.04. ^e *Anal.* Calcd. for C₁₁H₂₀O₂: C, 69.72; H, 11.70. Found: C, 69.70; H, 11.77. ^f *Anal.* Calcd. for C₁₃H₂₄O₂: C, 72.85; H, 12.22. Found: C, 73.12; H, 12.18. ^g M. Delepine (*Bull. soc. chim.*, [3] 25, 581 (1901)), reported 124-125°. ^h H. S. Hill and H. Hibbert (*THIS JOURNAL*, 45, 3115 (1923)) found 133-134°. ⁱ Reference 7, b.p. 59° (13 mm.).

TABLE II

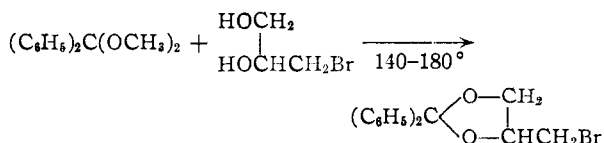


R	R ₁	R ₂	R ₃	R ₄	Yield, %	°C.	B.p., Mm.
H	H	CH ₃	CH ₃	CH ₃ ^a	71	139	743
CH(CH ₃) ₂	H	CH ₃	CH ₃	CH ₃ ^b	95	68	25
H	CH ₃	CH ₃	CH ₃	CH ₃ ^c	80	52	18
						152	733
CH ₃	CH ₃	CH ₃	CH ₃	CH ₃ ^d	83	48	14
						148	740
CH(CH ₃) ₂	CH ₃	CH ₃	CH ₃	CH ₃ ^e	80	67 ^f	17

^a *Anal.* Calcd. for C₇H₁₄O₂: C, 64.57; H, 10.84. Found: C, 64.68; H, 10.65. ^b *Anal.* Calcd. for C₁₀H₂₀O₂: C, 69.72; H, 11.70. Found: C, 69.84; H, 11.78. ^c *Anal.* Calcd. for C₈H₁₆O₂: C, 66.62; H, 11.19. Found: C, 66.51; H, 10.82. ^d *Anal.* Calcd. for C₉H₁₈O₂: C, 68.32; H, 11.46. Found: C, 68.13; H, 11.40. ^e *Anal.* Calcd. for C₁₁H₂₂O₂: C, 70.92; H, 11.90. Found: C, 70.97; H, 11.70. ^f Ref. 7, b.p. 67-73 (21 mm.).

distilled oil partially crystallized, the crystalline material may have been one of the two possible racemic compounds which could have been formed in this instance.

Another useful procedure was an acetal exchange reaction



1,3-Dioxanes were prepared by interaction of an aldehyde with a 1,3-glycol with the aid of orthophosphoric acid.

A few representative procedures are described in the Experimental Part.

Experimental Part

2-Isopropyl-4,4,5,5-tetramethyl-1,3-dioxolane.⁷—Pinacol hydrate (113 g., 0.5 mole), 108 g. (1.5 moles) of isobutyral-

(7) R. Dworzak and Theresia M. Iasch (*Monatsh.*, 51, 69 (1920)), who prepared this compound in 68% yield by the use of concd. hydrochloric acid as a condensation agent, could not obtain a halogen-free product.

dehyde and 30 cc. of 85% orthophosphoric acid were allowed to react for 12 hours at room temperature, and then warmed for 1 hour on a steam-bath. The product was extracted with ether, the extract washed well with water, dried over solid alkali and the product distilled.

4,4,5,5-Tetramethyl-1,3-dioxolane.—Pinacol hydrate (190 g., 0.84 mole), 77 g. of paraformaldehyde and 75 g. of orthophosphoric acid were heated for 12 hours on a steam-bath. The product was isolated as described above.

2,4,4,5,5-Pentamethyl-1,3-dioxolane.—A mixture of 113 g. (0.5 mole) of pinacol hydrate, 22 g. (0.5 mole) of acetaldehyde and 25 cc. of orthophosphoric acid was allowed to remain at room temperature for 3 days, and then treated in the described manner.

4,4,6-Trimethyl-1,3-dioxane.—A mixture of 50 g. (0.42 mole) of 2-methyl-2,4-pentanediol,⁸ 26 g. of paraformaldehyde and 2 cc. of orthophosphoric acid was heated on a steam-bath for 12 hours. The product was extracted with ether, the extract washed thoroughly with water, and dried over solid sodium hydroxide. The solvent was removed, and the residue fractionated.

2,4,4,6,6-Pentamethyl-1,3-dioxane.—A mixture of 100 g. (0.76 mole) of 2,4-dimethyl-2,4-pentanediol,⁹ 35 g. (0.76 mole) of acetaldehyde and 1 cc. of orthophosphoric acid was allowed to remain at room temperature for 3 days. The water which had separated corresponded to 92% of the calculated amount. The mixture was then treated in the manner described above.

2,3,5-Trimethyl-3,4-hexanediol.—To a stirred solution of methylmagnesium chloride, obtained by passing methyl chloride into a mixture of 1500 cc. of dry ether and 36.5 g. (1.50 moles) of magnesium, there was added, dropwise, 70.0 g. (0.48 mole) of isobutyroin, dissolved in 100 cc. of ether. After 12 hours at room temperature, the mixture was refluxed for 2 hours, and then treated, dropwise, with 150 cc. of a saturated ammonium chloride solution. The ether layer was separated, the solvent removed, and the residue recrystallized, with the use of Norite, from a mixture of 270 cc. of ethanol and 500 cc. of water; yield 46.8 g. (60.2%); m.p. 94-95°.

Anal. Calcd. for C₉H₂₀O₂: C, 67.45; H, 12.58. Found: C, 67.35; H, 12.58.

Epibromohydrin.—The procedure followed was that described in reference 10 except that for α,γ -dibromohydrin we substituted the easily available α,β -dibromohydrin¹¹ prepared from allyl alcohol and bromine; yield 85-90%; b.p. 134-136° (750 mm.).

Di-2-thienyl Ketone.—In a one-liter, three-necked flask fitted with a stirrer, dropping funnel and a thermometer

(8) Obtained from the Shell Chemical Company.

(9) A. Franke and M. Kohn, *Monatsh.*, 28, 1001 (1909).

(10) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 256.

(11) E. P. Kohler, *Am. Chem. J.*, 42, 375 (1909).

TABLE III
BASIC 1,3-DIOXOLANES $R(R_1)C \begin{matrix} \diagup O-CH-CH_2X \\ \diagdown O-CH_2 \end{matrix}$

R	R ₁	X	Yield, %	°C.	B.p., Mm.	Formula	Nitrogen, % Calcd.	Found
1	H	H	18	190-192	748 ^a
2	C ₆ H ₅	C ₆ H ₅	91	121-123	0.01	C ₁₈ H ₂₁ O ₂ N	4.94	4.88
3	C ₆ H ₅	C ₆ H ₅	90	129-132	.01	C ₂₀ H ₂₅ O ₂ N	4.50	4.44
4	C ₆ H ₅	C ₆ H ₅	79	172-176	.02
5	C ₆ H ₅	C ₆ H ₅	85	193-195	.01	C ₂₄ H ₃₃ O ₂ N	3.81	3.81
6	C ₆ H ₅	C ₆ H ₅	90	134-138	.01
7	C ₆ H ₅	C ₆ H ₅	94	154-156	.01	C ₂₁ H ₂₆ O ₂ N	4.33	4.10
8	C ₆ H ₅	C ₆ H ₅	84 ^e	C ₂₂ H ₂₈ O ₂ N	4.30	4.20
9	C ₆ H ₅	C ₆ H ₅ S'	76	135-139	.01	C ₁₈ H ₂₃ O ₂ NS	4.41	4.25
10	C ₆ H ₅ S	C ₆ H ₅ S	27 ^f
11	<i>p</i> -CH ₃ OC ₆ H ₄	<i>p</i> -CH ₃ OC ₆ H ₄	96	175-180	.01	C ₂₂ H ₂₉ O ₂ N	3.77	3.85
12	Biphenylene		28	163-168	.01

^a J. P. Fourneau and S. Chantalou (*Bull. soc. chim.*, [5] 12, 845 (1945)) found 106° (60 mm.). ^b Piperidino. ^c Methiodide, m.p. 157-159° after recrystallization from acetone-ether. *Anal.* Calcd. for C₂₂H₂₈O₂N: I, 27.27. Found: I, 27.49. ^d Morpholino. ^e M.p. 92-93° after recrystallization from methanol. ^f 2-Thienyl. ^g Isolated and purified as the oxalate. The yield is based on the pure oxalate which melted at 145-147° after recrystallization from butanol. *Anal.* Calcd. for C₁₈H₂₁O₂NS₂: C, 2.22; H, 2.22; N, 3.39; S, 15.51. Found: N, 3.47; S, 15.20.

TABLE III (Continued)

HYDROCHLORIDES AND HYDROBROMIDES

Compounds 2, 3, 4 and 7 were recrystallized from ethyl acetate; 6 and 8 from acetone; 10, 11 and 12 from butanol-isopropyl ether.

M.p., °C. ^a	Formulas	Analyses, %			
		Halogen		Nitrogen	
		Calcd.	Found	Calcd.	Found
2 ^b 190-191	C ₁₈ H ₂₁ O ₂ NCl	11.09	11.15
3 118-120	C ₂₀ H ₂₅ O ₂ NCl	10.19	10.28
4 146-147	C ₂₂ H ₂₈ O ₂ NCl	9.43	9.31	3.72	3.73
5 101-103	C ₂₄ H ₃₃ O ₂ NBr	17.82	17.91
6 201-203	C ₁₈ H ₂₁ O ₂ NCl	10.62	10.80	4.19	4.11
7 203-204	C ₂₁ H ₂₆ O ₂ NCl	9.85	9.77
8 192-193	C ₂₀ H ₂₅ O ₂ NCl	9.81	9.83	3.87	3.84
10 124-126	C ₁₈ H ₂₁ O ₂ NS ₂ Cl ^c	9.85	9.81	3.89	3.89
11 116-118	C ₂₂ H ₂₉ O ₂ N.C ₆ H ₅ O ₄ ^d	3.04	3.08
12 191-193	C ₂₀ H ₂₅ O ₂ NBr	20.48	20.41	3.59	3.58

^a The melting point bath was preheated to 5° below the melting point of the compound. ^b These numbers refer to like-numbered compounds in the preceding tabulation. ^c *Anal.* Calcd. for C₁₈H₂₂O₂NS₂Cl: S, 17.82. Found: S, 17.51. ^d Oxalate.

there were placed 100 g. (0.68 mole) of 2-thenoyl chloride,¹² 63 g. (0.75 mole) of thiophene and 600 cc. of dry benzene. The solution was stirred, cooled to 0°, and 160 g. (0.61 mole) of stannic chloride was added, dropwise, during a two-hour period while the temperature was maintained at 3-6°. The suspension of orange-yellow crystals was cooled and stirred for an additional two hours, and then stirred at 60° for one-half hour. A mixture of 25 cc. of concd. hydrochloric acid and 200 cc. of water was added, dropwise, the benzene layer separated, washed thoroughly with sodium hydroxide solution, and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the nearly pure ketone weighed 112.5 g. After recrystallization from ethanol, the product weighed 102 g. (77%); m.p. 87-89°.¹³

2,2-Diphenyl-4-bromomethyl-1,3-dioxolane (a).—Benzophenone (50 g., 0.27 mole), 45 g. (0.33 mole) of epibromohydrin and 250 cc. of dry carbon tetrachloride were placed in a 500-cc., three-necked flask fitted with a stirrer, dropping funnel and a thermometer. The mixture was stirred, cooled to 5° and maintained at that temperature while a solution of 10 g. (0.038 mole) of stannic chloride in 75 cc. of carbon tetrachloride was added, dropwise, during a three-hour period. To the stirred, orange-red solution there was added 16 g. of sodium hydroxide, dissolved in 40 cc. of water. After 10 minutes the organic layer was separated, dried over anhydrous sodium carbonate, the solvent removed under reduced pressure, and the residue cooled in an

ice-salt mixture. After crystallization, the product was triturated with isopropyl alcohol; yield 64.3 g. (73%); m.p. 71-73°.

Anal. Calcd. for C₁₆H₁₅O₂Br: Br, 25.04. Found: Br, 25.09.

(b).—Dimethoxydiphenylmethane^{14,15} (7.0 g., 0.031 mole) and 4.8 g. (0.031 mole) of glycerol- α -bromohydrin were placed in a small distillation flask and heated in an oil-bath at 140-180°. The methanol which distilled weighed 1.70 g.; calcd. amount 1.98 g. The residue was cooled, suspended in a very small amount of isopropyl alcohol, and filtered; yield 8.1 g. (82.7%); m.p. 71-73°.

2,2-Diphenyl-4-dimethylaminomethyl-1,3-dioxolane.—Thirty grams (0.09 mole) of 2,2-diphenyl-4-bromomethyl-1,3-dioxolane, 20 g. (0.44 mole) of anhydrous dimethylamine and 50 cc. of benzene were heated in a citrate bottle on a steam-bath for 48 hours. After the addition of concd. sodium hydroxide solution, the organic layer was separated, dried over solid sodium hydroxide, the solvent removed and the product fractionated; b.p. 121-123° (0.01 mm.); yield 24.3 g. (91.4%).

The hydrochloride was obtained when the dioxolane was treated with an ether solution of the calcd. amount of hydrogen chloride; m.p. 190-191° after recrystallization from ethyl acetate.

The methobromide was produced when 10 g. of the dioxolane, 10 g. of trimethylamine and 50 cc. of chloroform were heated in a citrate bottle on a steam-bath for 48 hours. After removal of the solvent, the residue was triturated with dry acetone, and then recrystallized from isopropyl alcohol-isopropyl ether; yield 6.5 g. (54.8%); m.p. 210-212° (dec.).¹⁶

Anal. Calcd. for C₁₉H₂₄O₂NBr: N, 3.70; Br, 21.12. Found: N, 3.72; Br, 21.24.

In order to obtain the methiodide, 4.0 g. of the dioxolane, 100 cc. of dry ether and 20 g. of methyl iodide were allowed to remain at room temperature for 23 hours. The crystalline precipitate, after recrystallization from ethanol-ether, weighed 4.2 g. (70%); m.p. 193-195°.

Anal. Calcd. for C₁₈H₂₄O₂NI: I, 29.84. Found: I, 29.55.

2-Phenyl-2-(2-thienyl)-4-bromomethyl-1,3-dioxolane.—This substance was prepared in the same manner as the corresponding 2,2-diphenyl compound. The oily product, obtained from 52.6 g. of phenyl 2-thienyl ketone,¹⁷ was distilled; b.p. 127-130° (0.01 mm.); yield 77 g. (84%).

Anal. Calcd. for C₁₄H₁₃O₂SBr: Br, 24.57. Found: Br, 24.48.

(14) J. E. MacKenzie, *J. Chem. Soc.*, 69, 987 (1896).

(15) E. Fourneau and I. Ribas Y. Marqués, *Bull. soc. chim.*, [4] 39, 699 (1926).

(16) The melting point bath was preheated to 205°.

(17) G. Stadnikoff and I. Goldfarb, *Ber.*, 61, 2341 (1928).

(12) L. W. Jones and C. D. Hurd, *THIS JOURNAL*, 43, 2444 (1921).

(13) L. Gattermann (*Ber.*, 18, 3013 (1885)) found 87-88°.

The oil, covered with dry methanol, was allowed to remain in a refrigerator for one week. The mixture of crystals and oil was filtered through a fritted-glass funnel surrounded by ice. After thorough trituration with cold methanol, the crystals melted at 49–51°.

Anal. Calcd. for $C_{14}H_{13}O_2SBr$: S, 9.86; Br, 24.57. Found: S, 9.63; Br, 24.53.

When either the oily product or the crystalline material was aminated with diethylamine, the 4-diethylaminoethyl dioxolane obtained boiled at 135–139° (0.01 mm.).

Anal. Calcd. for $C_{15}H_{23}O_2NS$: N, 4.41; S, 10.10. Found: N, 4.24; S, 10.24.

ANN ARBOR, MICHIGAN

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[CONTRIBUTION FROM THE PURDUE UNIVERSITY DEPARTMENT OF CHEMISTRY AND THE PURDUE RESEARCH FOUNDATION]

The Reducing Action of Grignard Reagents on Fluorinated Carbonyl Compounds^{1,2}

BY E. T. MCBEE, O. R. PIERCE AND J. F. HIGGINS

The reaction of Grignard reagents with trifluoroacetaldehyde, pentafluoropropionaldehyde, heptafluorobutyraldehyde, the esters of trifluoroacetic, pentafluoropropionic, and heptafluorobutyric acids, 1,1,1-trifluoroacetone, 3,3,4,4,4-pentafluoro-2-butanone and 3,3,4,4,5,5,5-heptafluoro-2-pentanone were studied in an effort to delineate the extent of the reduction observed. In all Grignard reagents containing β -hydrogens reduction was obtained, which may be attributed to the large inductive effect of the fluorinated alkyl group attached to the carbonyl grouping in these materials.

In a previous paper,³ mention was made of the reduction of pentafluoropropionaldehyde and 3,3,4,4,4-pentafluoro-2-butanone by ethyl and isopropyl Grignard reagents. In order to investigate this reaction further, the action of six Grignard reagents on both trifluoroacetaldehyde and pentafluoropropionaldehyde was compared to determine if the amount of fluorine present affects the degree of reduction and to evaluate the effect of the structure of the alkyl group of the Grignard reagent on the product obtained. In addition, the study was extended to the action of ethylmagnesium iodide on esters of trifluoroacetic, pentafluoropropionic and heptafluorobutyric acids as well as 1,1,1-trifluoroacetone, 3,3,4,4,4-pentafluoro-2-butanone, 3,3,4,4,5,5,5-heptafluoro-2-pentanone and heptafluorobutyraldehyde. The comparative amounts of addition and reduction products are summarized in Tables I and II.

Generally, reduction of carbonyl compounds by Grignard reagents has been observed in instances in which the addition reaction may be hindered sterically.⁴ Hence the reduction previously observed³ with fluorinated derivatives of propionaldehyde and 2-butanone was unexpected because of the absence of large groups and hence any significant steric factor. The results of this investigation indicate that an inductive effect, due to the close proximity of a highly electronegative fluorinated group to the carbonyl group, is affecting the course of the Grignard reaction to cause an abnormal amount of reduction. Recent work by Campbell and co-workers⁵ shows that reduction also occurs in the reaction of esters of trifluoroacetic acid with Grignard reagents.

The pronounced effect of fluorine substitution on the nature of the reaction of a Grignard reagent

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(2) Presented before the Organic Section, XIth International Congress of Pure and Applied Chemistry, New York, N. Y., September, 1951.

(3) E. T. McBee, J. F. Higgins and O. R. Pierce, in press.

(4) J. B. Conant and A. H. Blatt, *ibid.*, **51**, 1227 (1929).

(5) K. N. Campbell, J. O. Knobloch and B. K. Campbell, *ibid.*, **72**, 4380 (1950).

TABLE I

Grignard reagent	CF_3CF_2CHO		CF_3CHO	
	Redn., %	Addn., %	Redn., %	Addn., %
Methyl	0	87.0	0	67.0 ^a
Ethyl	55.5	33.6	20.0	60.0
Isopropyl	90.0	0	87.0	0
<i>t</i> -Butyl	76.2	14.3	84.0	7.0
Phenyl	0	86.0	0	88.0
Benzyl	0	83.0	0	81.0

^a This reaction was conducted by Dr. J. A. Barone.

TABLE II

Compound	REACTIONS WITH ETHYL GRIGNARD	
	Redn., %	Addn., %
$CF_3CO_2CH_3$ ^a	35.0	56.0
$C_2F_5CO_2CH_3$	66.0	29.0
$C_3F_7CO_2CH_3$ ^b	68.6	12.5
CF_3COCH_3	13.9	78.9
$C_2F_5COCH_3$	44.5	41.6
$C_3F_7COCH_3$	61.6	18.0
C_3F_7CHO	61.0	19.0

^a Campbell, ref. 5, synthesized the addition and reduction products obtained in this reaction from ethyl Grignard and ethyl trifluoroacetate and butyl trifluoroacetate, respectively.

^b Private communication.

with a carbonyl group is particularly apparent in the reaction of trifluoroacetaldehyde with isopropylmagnesium iodide. Although the principal, if not exclusive, reaction of acetaldehyde with a Grignard reagent is addition, trifluoroacetaldehyde undergoes 87% reduction to trifluoroethanol and none of the expected adduct was isolated. Since a fluorine atom is only a little larger than a hydrogen atom and hence a trifluoromethyl group is about the same size as methyl, this reducing action cannot be readily attributed to steric factors.

The experimental results indicate (Tables I and II) that as the length of the perfluorinated chain increases, the amount of reduction increases with a corresponding decrease in addition. This was found to be most significant when using ethyl Grignard reagent with trifluoroacetaldehyde and pentafluoropropionaldehyde. In the case of trifluoroacetaldehyde, the yield of reduction and addition products were 20 and 60%, respectively,