

succinimide. The foregoing maleimide (0.05 g.) was dissolved in acetone (3 ml.). To the solution *N*-2-(α -thiolnapthyl)-acetamide (1.1 equivalents) in acetone (3 ml.) was added dropwise (5 min.). The reaction solution was stirred for 20 min. and concentrated to an oil. Methanol was added to the oil and the mixture was concentrated until crystallization of a white substance took place. After filtration and recrystallization from acetone-methanol, 0.08 g., m.p. 208–209° was obtained. Two recrystallizations from acetone-water gave an analytical sample, m.p. 211–212°.

Anal. Calcd. for $C_{23}H_{22}N_2O_3S$: N, 5.85; S, 6.70. Found: N, 5.83; S, 6.56.

N-2-(9-Trifluoroacetamidofluorenyl)maleamic acid. *N*-9-(2-Aminofluorenyl)trifluoroacetamide (0.2 g., 0.7 mmole) reacted with maleic anhydride (0.14 g., 1.4 mmoles) in glacial acetic acid (10 ml.) giving a quantitative yield (0.27 g.) of the maleamic acid, m.p. 223–225° dec. An analytical sample was prepared by stirring the product with boiling acetone and filtering, m.p. 225–227° dec. $\lambda_{max}^{C_2H_5OH}$: 276 m μ (log ϵ 4.14), 319 (4.22). ν_{N-H} 3310, 1550; $\nu_{C=O}$ 1710; ν_{C-F} 1175 cm.⁻¹ (broad).

Anal. Calcd. for $C_{19}H_{13}F_3N_2O_4$: C, 58.47; H, 3.36; N, 7.18. Found: C, 58.54; H, 3.63; N, 7.14.

N-2-(9-Trifluoroacetamidofluorenyl)maleimide. The above maleamic acid (7.8 g.) was cyclized in acetic anhydride (30 ml.), in the presence of fused sodium acetate (1.2 g.), giving 7.1 g. (96%) of the maleimide, m.p. 255–259°. Recrystallization from benzene gave an analytical sample, m.p. 262–263°. $\lambda_{max}^{C_2H_5OH}$ 234 m μ (shoulder), 277 (log ϵ 4.36), 306 (3.83). ν_{N-H} 3330, 1550; $\nu_{C=O}$ 1730, 1710; ν_{C-F} 1180 cm.⁻¹ (broad).

Anal. Calcd. for $C_{19}H_{11}F_3N_2O_3$: C, 61.30; H, 2.98; N, 7.53. Found: C, 61.44; H, 2.98; N, 7.78.

Attempted preparation of N-2-(9-acetamidofluorenyl)-maleimide. *N*-2-(9-Trifluoroacetamidofluorenyl)maleamic acid (4 g.) was dissolved in 1*N* sodium hydroxide (50 ml.), heated on a steam bath for 3 min., and cooled. A small amount of fluffy precipitate was removed. The alkaline solution was chilled in ice and acidified to pH 4 with hydrochloric acid. The yellow precipitate was filtered, washed once with ice water, and dried giving 3.3 g., m.p. 185–190° dec.

The latter compound (1 g.) was mixed with fused sodium acetate (0.15 g.) and acetic anhydride (6 ml.) and heated on a steam bath, with shaking, for 15 min. and cooled to room temperature. The pasty mixture was stirred in 10% sodium acetate and the excess acetic anhydride destroyed with 5% sodium carbonate. The yellow solid was filtered, washed with water, and dried, giving 0.9 g. Recrystallization from acetone-benzene-ligroin gave 0.85 g., m.p. 190–192° dec. Three recrystallizations from acetone-water gave an analytical sample, m.p. 209–211° (glassy).

Anal. Found: C, 69.19; H, 5.09; N, 8.86.

Attempted preparation of N,N'-2,9-fluorenedimaleamic acid. 2,9-Diaminofluorene⁶ (1.96 g., 0.01 mole) in warm glacial acetic acid (10 ml.) was added dropwise to a warm solution of maleic anhydride (2.94 g., 0.03 mole) in glacial acetic acid (15 ml.) over a period of 20 min. The reaction mixture was stirred at room temperature for 30 min. then heated (steam bath) for 10 min. and cooled. Water dilution of the mixture gave 3.8 g. (97.5%) of an acidic substance, m.p. ~ 212° dec.

Recrystallization from acetone-methanol gave a sample, m.p. 210–211° dec. (preheated block).

Anal. Found: C, 61.44; H, 4.91; N, 5.68.

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[CONTRIBUTION NO. 304 FROM THE JACKSON LABORATORY, ORGANIC CHEMICALS DEPARTMENT, E. I. DU PONT DE NEMOURS AND CO., INC.]

m-Dioxanes and Other Cyclic Acetals

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An extensive series of substituted *m*-dioxanes has been prepared by acetalization of 1,3-glycols. Some 1,3-dioxolanes, 1,3-oxathianes, and 1,3-dioxolanes have been synthesized for comparison. Differences in the ease of acetalization have been noted.

The study of catalytic reactions of *m*-dioxanes¹ required the preparation of a variety of *m*-dioxanes and related acetals. Although the basic synthetic method, direct acid-catalyzed reaction of 1,3-diols (or in a few cases, 1,2- or 1,4-diols) with aldehydes or ketones has long been known, it was necessary to develop refinements of this procedure to obtain satisfactory yields of certain acetals.

Some unstable aldehydes—*e.g.*, chloroacetaldehyde and malonaldehyde—are marketed as their methyl or ethyl acetals. These were conveniently converted to the *m*-dioxanes by interchange with the diol in the presence of boron trifluoride or *p*-toluenesulfonic acid. The lower alcohol was distilled during the interchange to shift the equilibrium.

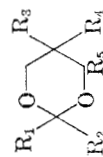
Although quantitative kinetic experiments were not performed, the qualitative effects of substituents

on the rate and equilibria were noted. The aromatic aldehydes reacted very rapidly, with simple aliphatic aldehydes next in line. Ketones seemed to react rapidly, but the equilibrium position was less favorable. With acetone, very little product was formed (infrared) until the water was removed from the distillate by drying it with calcium chloride. It was surprising to find that the cyclopentanone ketal (#11)² was hydrolyzed rapidly by distilled water, in which the dissolved carbon dioxide must function as the acid catalyst. This was not the case with the acetone (#10) and cyclohexanone (#12) ketals. These results are in line with the prediction from the I-strain principle,³ which teaches that reactions in which a ring carbon atom changes from

(2) The arabic numerals are those assigned to the acetals in the tables.

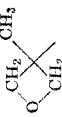

(3) H. C. Brown, R. S. Fletcher, and R. B. Johannessen, *J. Am. Chem. Soc.*, **73**, 212 (1951).

(1) C. S. Rondestvedt, Jr., and G. J. Mantell, *J. Am. Chem. Soc.*, **82**, 6419 (1960).

TABLE I. *m*-DIOXANES

| Acetal No. | R ₁ | R ₂ | R ₃ | R ₄ | R ₅ | R ₆ ^a | B.P., Mm. | n _D ²⁵ (M.P.) (Cryst. Solv. ^b) | Yield, % | Formula | Calcd., % | | Found, % | |
|-----------------|---|-----------------|---|-----------------|-----------------|-----------------------------|-------------------------------------|--|---|---|-----------|-------|----------|------|
| | | | | | | | | | | | C | H | C | H |
| 1 | H | H | CH ₃ | CH ₃ | CH ₃ | CH ₃ | 126.5/atm. | 1.4190 | 97 | C ₈ H ₁₂ O ₂ ^c | 64.58 | 10.84 | 64.5 | 10.8 |
| 2 | CH ₃ | H | H | H | H | H | 109-110/atm. | 1.4119 | 63 | C ₈ H ₁₀ O ₂ ^d | 68.4 | 11.4 | 68.6 | 11.0 |
| 3 | CH ₃ | H | CH ₃ | CH ₃ | CH ₃ | CH ₃ | 130-131/atm. | 1.4134 | 88 | C ₇ H ₁₄ O ₂ | — | — | — | — |
| 4 | (CH ₃) ₂ CH | H | CH ₃ | CH ₃ | CH ₃ | CH ₃ | 165-167/atm. | 1.4227 | 85 | C ₉ H ₁₈ O ₂ ^e | 71.0 | 11.8 | 71.1 | 11.9 |
| 5 ^f | (CH ₃) ₂ CH | H | CH ₃ | CH ₃ | CH ₃ | CH ₃ | 114-116/45 | 1.4332 | 79 | C ₁₁ H ₂₂ O ₂ | 67.57 | 9.92 | 67.6 | 10.3 |
| 6 | CH ₂ =CH | H | CH ₃ | CH ₃ | CH ₃ | CH ₃ | 83-86/70 | 1.4349 | 63 | C ₈ H ₁₄ O ₂ | 73.42 | 10.27 | 73.3 | 10.1 |
| 7 | | H | CH ₃ | CH ₃ | CH ₃ | CH ₃ | 80-81/1.5 | 1.4708 | High | C ₁₂ H ₂₀ O ₂ | 51.07 | 7.90 | 50.8 | 7.9 |
| 8 | CH ₂ CH ₂ | H | CH ₃ | CH ₃ | CH ₃ | CH ₃ | 104-105/49 | 1.4476 | 95 | C ₇ H ₁₂ ClO ₂ | 36.00 | 4.75 | 36.0 | 4.9 |
| 9 | Cl ₂ C | H | CH ₃ | CH ₃ | CH ₃ | CH ₃ | — | (129.0-129.5) (H-B) | 30 | C ₇ H ₁₁ Cl ₃ O ₂ | 66.62 | 11.19 | 66.7 | 11.3 |
| 10 | CH ₃ | CH ₃ | CH ₃ | CH ₃ | CH ₃ | CH ₃ | 144-145/atm. | 1.4178 | >73 | C ₈ H ₁₆ O ₂ | 70.55 | 10.66 | 70.6 | 10.5 |
| 11 | —(CH ₂) ₄ — | — | — | — | — | — | 103-105/36 | 1.4520 | 67 | C ₁₀ H ₁₈ O ₂ | 71.69 | 10.94 | 71.7 | 10.9 |
| 12 | —(CH ₂) ₅ — | — | — | — | — | — | 116-118/34 | 1.4610 | 87 | C ₁₃ H ₂₆ O ₂ | — | — | — | — |
| 13 | C ₆ H ₅ | H | — | — | — | — | 134-137/7 | 1.5021 ⁱ | 95 | C ₁₂ H ₁₆ O ₂ ^j | 75.69 | 8.79 | 75.7 | 8.9 |
| 14 | <i>p</i> -CH ₃ C ₆ H ₄ | H | — | — | — | — | 106/1.7 | (33) (M-W) (40.8-41.0) (M-W) | 88 | C ₁₃ H ₁₈ O ₂ | 76.88 | 9.47 | 76.9 | 9.5 |
| 15 | <i>p</i> -(CH ₂) ₂ CHC ₆ H ₄ | H | — | — | — | — | 136/4 | 1.5017 | 87 | C ₁₆ H ₂₂ O ₂ | 60.0 | 5.8 | 60.1 | 6.0 |
| 16 ^f | <i>p</i> -CF ₃ C ₆ H ₄ | H | — | — | — | — | (73) (H) | 49 | C ₁₃ H ₁₆ F ₃ O ₂ | 63.54 | 6.67 | 63.7 | 6.6 | |
| 17 | <i>p</i> -ClC ₆ H ₄ | H | — | — | — | — | 1.5050 (55.5-56.5) (H) ^k | 75 | C ₁₂ H ₁₆ ClO ₂ | 55.19 | 5.40 | 55.15 | 5.41 | |
| 18 ^m | 2,4-Cl ₂ C ₆ H ₃ | H | — | — | — | — | (57.0-57.5) | — | — | 55.19 | 5.40 | 55.00 | 5.38 | |
| 19 ^m | 3,4-Cl ₂ C ₆ H ₃ | H | — | — | — | — | (45-46) | — | — | 55.19 | 5.40 | 54.96 | 5.48 | |
| 20 ^m | 2,6-Cl ₂ C ₆ H ₃ | H | — | — | — | — | (120-121) | — | — | 70.24 | 8.16 | 70.2 | 8.0 | |
| 21 | <i>p</i> -CH ₃ OC ₆ H ₄ | H | — | — | — | — | (81.5-82.0) (H or M) | >80 | >80 | C ₁₃ H ₁₈ O ₂ | 71.45 | 9.00 | 71.4 | 9.0 |
| 22 | <i>p</i> -(CH ₂) ₂ NC ₆ H ₄ | H | — | — | — | — | (98.0-98.5) (B, D) | >75 | >75 | C ₁₄ H ₂₁ NO ₂ | 60.84 | 6.37 | 60.9 | 6.5 |
| 23 | <i>m</i> -NO ₂ C ₆ H ₄ | H | — | — | — | — | (48.0-49.0) (H, D) | 86 | 86 | C ₁₂ H ₁₆ NO ₄ | — | — | — | — |
| 24 ^o | CH ₃ | H | CH ₂ OH | CH ₃ | CH ₃ | CH ₃ | 125-135/33 | 1.4508 | 79 | C ₇ H ₁₄ O ₂ | 55.98 | 6.71 | 55.9 | 6.7 |
| 25 | CH ₃ | H | CH ₂ O Tosyl | CH ₃ | CH ₃ | CH ₃ | — | (86-87) (H-B) | 89 ^p | C ₁₄ H ₂₀ O ₅ | 55.98 | 6.71 | 56.1 | 6.7 |
| 25a | CH ₃ | H | CH ₂ O Tosyl | CH ₃ | CH ₃ | CH ₃ | — | (61-62) (H-B) | 59 | C ₁₄ H ₂₀ O ₅ | 62.76 | 9.37 | 62.9 | 9.2 |
| 26 | (CH ₂) ₂ CH | H | —CH ₂ OCH ₂ — | — | — | — | 86-89/8 | 1.4524 | 87 ^p | C ₉ H ₁₆ O ₂ | 64.48 | 9.74 | 64.6 | 9.3 |
| 27 | (CH ₂) ₂ CH | H | —OCH ₂ CH ₂ CH ₂ — | — | — | — | 112-114/26 | 1.4495 | 87 ^p | C ₁₀ H ₁₈ O ₃ | 64.48 | 9.74 | 63.8 | 10.4 |
| 27a | (CH ₂) ₂ CH | H | —OCH ₂ CH ₂ CH ₂ — | — | — | — | 138-139/25 | 1.4592 | 87 ^p | C ₁₀ H ₁₈ O ₃ | 64.48 | 9.74 | 63.8 | 10.4 |

TABLE I (Continued)

| Acetal No. | R ₁ | R ₂ | R ₃ | R ₄ ^a | B.P., Mm. | n _D ²⁵ (M.P.) (Cryst. Solv. ^b) | Yield, % | Formula | Calcd., % | | Found, % | |
|------------|--|----------------|--|-------------------------------|-------------|--|----------|---|-----------|-------|------------|-----------------------|
| | | | | | | | | | C | H | C | H |
| 28 |  | H | CH ₃ | CH ₃ | 110-112/17 | 1.4438 (42.0-42.5) (M-W) | 68 | C ₁₀ H ₁₈ O ₃ | 64.48 | 9.74 | 64.1, 64.2 | 9.8, 9.6 |
| 29 |  | H | CH ₃ | CH ₃ | 107-109/12 | 1.4558 | 82 | C ₁₀ H ₁₈ O ₂ | 64.48 | 9.74 | 64.2, 64.7 | 9.4, 9.5 |
| 30 | (CH ₃) ₂ CH | H | CH ₂ OCH ₂ CH=CH ₂ | C ₂ H ₅ | 106-108/6 | 1.4470 | 90 | C ₁₃ H ₂₄ O ₃ | 68.38 | 10.59 | 68.2, 68.2 | 10.6, 10.8 |
| 31 | CH ₂ CH ₂ CH ₂ | H | CH ₂ =CH | CH ₃ | 75-78/12 | 1.4408 | 100 | C ₁₀ H ₁₈ O ₂ | 70.54 | 10.65 | 70.6, 70.4 | 10.7, 10.9 |
| 32 | (CH ₃) ₂ CH | H | NO ₂ | CH ₃ | 142-144/18 | (56-57) (H-D) | 68 | C ₈ H ₁₆ NO ₄ ^p | 50.78 | 7.99 | 51.1, 51.1 | 8.3, 8.3 ^q |
| 32a | (CH ₃) ₂ CH | H | NO ₂ | CH ₃ | 107-137/18 | 1.4443-1.4460 | 18 | C ₈ H ₁₆ NO ₄ ^p | 50.78 | 7.99 | 51.5, 51.4 | 8.1, 8.1 ^r |
| 33 | (CH ₃) ₂ CHCH ₂ O- CH ₂ C(CH ₃) ₂ | H | CH ₃ | CH ₃ | 130-132/23 | 1.4314 | 84 | C ₁₄ H ₂₈ O ₃ | 68.81 | 11.55 | 68.9, 69.0 | 11.4, 11.4 |
| 34 | n-C ₁₁ H ₂₃ ^s | H | CH ₃ | CH ₃ | 137-143/2.2 | 1.4441 | 77 | C ₁₇ H ₃₄ O ₂ | 75.50 | 12.67 | 75.3, 75.5 | 12.8, 13.0 |
| 35 | (CH ₃) ₂ CH | H | CH ₃ | CH ₃ ^a | 98-102/26 | 1.4310 | >80 | C ₁₃ H ₂₆ O ₂ | 71.95 | 12.08 | 71.8, 72.1 | 12.1, 12.0 |
| 36 | C ₆ H ₅ | H | CH ₃ | CH ₃ ^a | 133-134/7 | 1.4995 | 90 | C ₁₈ H ₃₀ O ₂ | 76.88 | 9.47 | 76.7, 77.0 | 9.3, 9.6 |
| 37 | (CH ₃) ₂ CH | H | -CH ₂ CH=CHCH ₂ CH ₂ - | CH ₃ | 98.5-100/6 | 1.4730 | 94 | C ₁₃ H ₂₆ O ₂ | 73.42 | 10.27 | 73.46 | 10.27 |
| 38 | (CH ₃) ₂ CH | H | -CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ - | CH ₃ | 99-100.5/6 | 1.4635 | 109 | C ₁₂ H ₂₂ O ₂ | 72.68 | 11.19 | 73.4, 73.5 | 11.0, 11.0 |
| 39 | (CH ₃) ₂ CH | H | C ₆ H ₅ | C ₆ H ₅ | — | (96.5-97.5) (H) | 64 | C ₁₉ H ₃₂ O ₂ | 80.81 | 7.86 | 80.5, 80.7 | 7.9, 7.8 |

^a R₅ = H, except for Nos. 35 and 36, where R₅ = isopropyl. ^b Solvents—A = ethanol; B = benzene; C = cyclohexane; D = decolorized with Darco G-60; E = ethyl acetate; H = hexane; M = methanol; W = water. ^c M. Apel and B. Tollens, *Ann.*, 289, 44 (1896), report b.p. 126°. ^d A. Lechert, *Ann. chem.*, [6] 16, 48 (1889), reports b.p. 110-112°/768 mm. ^e R. Dworzak and T. M. Lasch, *Monatsh.*, 51, 67 (1920), report b.p. 159-161°. ^f These acetals were prepared by Harold W. Pier, to whom I am indebted. ^g % Cl—calcd., 21.54; found, 20.1, 20.0. ^h % Cl—calcd., 45.55; found, 46.8, 46.8. ⁱ n_D²⁵. ^j A. Francke and E. Gigerl, *Monatsh.*, 49, 14 (1928), report b.p. 123-124°/10 mm. m.p. 35°, 68% yield. ^k n_D²⁵. ^l % Cl—calcd., 15.64; found, 15.5, 15.8. ^m These acetals were prepared by Dr. John Harvey, to whom I am indebted. ⁿ % N—calcd., 5.96; found (Kjeldahl), 5.93; 5.97. Dumas nitrogen analyses were very erratic with this compound. ^o Trojan Powder Company, Technical Bulletin on Trimethylolthane, report b.p. 217-221°/atm. The boiling range of our product indicates it is a mixture of stereoisomers. ^p M. S. Newman, B. J. Magerlein, and W. B. Wheatley, *J. Am. Chem. Soc.*, 68, 2112 (1946), report m.p. 46°, b.p. 98-103°/0.5 mm., 73% yield. There was no mention of another stereoisomer. ^q % N—calcd., 7.40; found (Dumas), 7.2, 7.2. ^r % N—calcd., 7.40; found (Dumas), 7.2, 7.2. ^s The available dodecane was contaminated with small amounts of (apparently) higher and lower aldehydes. The acetal thus contains small amounts of homologs; to judge from the VPC analysis.

tetrahedral (the ketal) to trigonal (the cyclic ketone) are energetically more favorable with cyclopentanone derivatives than with those of cyclohexanone.

Chloral was very sluggish in its reaction with 2,2-dimethyl-1,3-propanediol, in keeping with the accepted mechanism of acetalisation.⁴ Formation of the stabilized carbonium ion intermediate from the hemiacetal will be drastically inhibited by the powerful electron withdrawal by the chlorine atoms. It was necessary to use a considerable amount of concentrated sulfuric acid to promote formation of acetal #9.

When either component of the acetal contained an additional ether oxygen, the reaction was somewhat retarded. Though only slight with an aliphatic ether (#30, 33), retardation was quite noticeable with the more basic oxygen in a tetrahydrofuran ring (#27, 29). This effect was probably also present with the two compounds containing an oxetane ring (#26, 28), but with these two a competitive reaction supervened, apparently a moderately rapid stoichiometric reaction of the acid catalyst with the oxetane ring to destroy the catalyst. A considerable quantity of polymeric ether was formed from both of these compounds.

m-Dioxanes with two different substituents at each of two positions will exist as diastereoisomeric racemates.⁵ In the present work, three acetals (#25, 27, and 32) were separated into the diastereoisomers, and one (#5) was demonstrated by vapor-phase chromatography to be a mixture of roughly equal parts of two isomers. In the other cases where stereoisomerism was possible (#24, 30, 31, 35, and 36), separation was not accomplished by distillation. From conformational analysis, one would predict that bulky groups would assume equatorial positions in the chair conformation of the *pseudo*-cyclohexane ring. It should be possible to find examples in which one isomer predominates strongly because of the greatly disparate steric requirements of the groups at C-5. That did not appear to be the case in the compounds studied in this work, for polar effects are probably responsible for the preponderance of the solid isomer of the nitro acetal #32.

EXPERIMENTAL⁶

In most cases, the diols and carbonyl compounds were high-grade commercial chemicals, and were used without purification after inspection of the infrared spectrum.

(4) E. R. Alexander, *Principles of Ionic Organic Reactions*, Wiley, New York, 1950, p. 215.

(5) Some previous stereoisomers were isolated by M. Senkus, *J. Am. Chem. Soc.*, **65**, 1656 (1943) and by authors therein cited.

(6) The author is indebted to Wallace Buskirk and James Chestnut for efficient and imaginative technical assistance. Melting points and boiling points are uncorrected. Infrared spectra were obtained with the Perkin Elmer Model 21, 221, and "Infracord" Model 137 Spectrophotometers.

Procedure for acetalization. Approximately equimolar quantities of carbonyl compound and diol were placed in a flask surmounted by a Dean-Stark moisture trap and a reflux condenser. In some cases, an excess of the cheaper component was used when it could readily be removed during workup. Hexane as an azeotropic solvent (about 100–150 ml. per mole)⁷ and 0.5 mole % of *p*-toluenesulfonic acid were added, and the mixture was refluxed, cautiously at first until any sudden exothermic reaction was spent, until the water evolution had stopped, then for an additional half hour. The cooled mixture was shaken with sodium bicarbonate solution and with water until the infrared spectrum showed no diol. Any acid present in the original aldehyde sample was removed by this procedure. After drying with potassium carbonate, the product was distilled, though in many cases the residue after removal of hexane was sufficiently pure for use. The product could sometimes be crystallized directly from the hexane solution by concentration and cooling.

The acetals prepared by this method are listed in Tables I to III without comment. Variations from this procedure are described below, using the acetal number given in the Tables. It may be noted that many of these cyclic acetals proved extraordinarily difficult to burn completely in a standard microanalytical train. Ultimately, the acetals were routinely burned at higher temperatures.⁸

Acetal #6. Acrolein reacts with alcohols to form acetals of β -alkoxypropionaldehydes. To minimize this addition to the double bond, various tricks have been proposed.⁹ In this work, the azeotroping solvent was petroleum ether (b.p. 30–60°) and only 0.003 mole % of *p*-toluenesulfonic acid was used, according to Meyers, Magerlein, and Staffen^{9a}; water evolution ceased after 7.5 hr. of reflux.

Acetal #8. Diethyl chloroacetal (Union Carbide Chemicals) was refluxed with an equimolar amount of neopentyl glycol (2,2-dimethyl-1,3-propanediol, Tennessee Eastman) under a fractionating column in the presence of 1 mole-% of *p*-toluenesulfonic acid. Ethanol was collected overhead. When most of the ethanol had been removed (about 2 hr.), benzene was added and the remaining ethanol was removed as the benzene azeotrope. The catalyst was destroyed with solid potassium carbonate and the product was distilled.


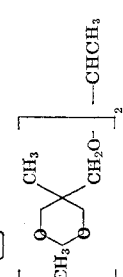
Acetal #9. Anhydrous chloral (Eastman Kodak) (0.72 mole) was refluxed with a slight excess of neopentyl glycol in hexane solution. *p*-Toluenesulfonic acid was not effective as catalyst. When 25 ml. of concd. sulfuric acid was added, the mixture darkened rapidly. The solution was refluxed gently for 1 hr. and allowed to stand overnight. The dark, crystalline mass was dissolved by warming with benzene, transferred to a separatory funnel, and 25 ml. was withdrawn from the bottom and discarded. (The mixture was so dark that no phase separation was visible.) The upper layer was shaken with 40 g. of sodium hydroxide in 600 ml. of ice water which lightened the color at once. The benzene layer was washed and dried, concentrated to 250 ml., and diluted with an equal volume of hexane. The crystalline acetal was recrystallized from 1:2 benzene-hexane. The low yield could doubtless be

(7) Occasionally benzene or toluene was used as azeotropic solvent, but hexane was preferred because most of the diols were so sparingly soluble in it that removal of excess diol was readily accomplished by water-washing the final solution. In a few cases, sulfuric, hydrochloric, or oxalic acid was used as catalyst.

(8) C. A. Rush, S. S. Cruikshank, and E. J. H. Rhodes, *Mikrochim. Acta*, No. **416**, 858 (1956).

(9) (a) R. H. Hall and E. S. Stern, *J. Chem. Soc.*, 1955, 2657; 1954, 3383. (b) J. A. Van Allan, *Org. Syntheses*, **32**, 5 (1952). (c) D. I. Weisblat, *et al.*, *J. Am. Chem. Soc.*, **75**, 5893 (1953). (d) F. J. Bellinger and T. Bewley, *Brit. Pat. 713,833*. (e) J. Habeshaw and C. J. Geach, *Brit. Pat. 715,794 and 702,206*. (f) D. G. Thomas, *U. S. Pat. 2,691,049*. (g) D. R. Meyers, B. J. Magerlein, and G. W. Staffen, *U. S. Pat. 2,678,950 and Brit. Pat. 713,088*.

TABLE II
BIS-*m*-DIOXANES

| Acetal No. | Structure ^a | B.P., Mm. | <i>n</i> _D ²⁵ (M.P., Cryst. Solv.) | Yield, % | Formula | Calcd., % | | Found, % | |
|------------|---|------------------------|--|----------|---|-----------|------|------------|-------------------|
| | | | | | | C | H | C | H |
| 41 | R-R | 125/7 | (165.5-166.5) (E) | 61 | C ₁₂ H ₂₀ O ₄ | 62.58 | 9.63 | 62.4, 62.5 | 10.0, 9.8 |
| 42 | RCH ₂ R | 152/15 | (119.5-120.5) (E-C) | 85 | C ₁₃ H ₂₄ O ₄ | 63.90 | 9.90 | 63.88 | 9.94 ^b |
| 43 | RCH ₂ CH ₂ R | — | (74-75) (E-C) | >83 | C ₁₄ H ₂₆ O ₄ | 65.1 | 10.1 | 64.8, 64.9 | 10.3, 10.3 |
| 44 | RCH ₂ CH ₂ CH ₂ R | — | (69.8-70.5) (M-W) | 76 | C ₁₅ H ₂₈ O ₄ | 66.1 | 10.2 | 66.1, 65.9 | 10.2, 10.0 |
| 45 | R  R | — | (210.5-212.0) (E) | 84 | C ₁₈ H ₂₆ O ₄ | 70.56 | 8.55 | 70.4, 70.4 | 8.5, 8.6 |
| 46 |  | 120-135/2 ^c | 1.4490 | 37 | C ₁₆ H ₃₀ O ₆ | 60.35 | 9.50 | 59.6, 60.1 | 9.3, 9.0 |
| 47 | Pentaerythritol diformal ^d | 86/0.8 | (50) | 88 | C ₇ H ₁₂ O ₄ ^e | — | — | — | — |
| 48 | Pentaerythritol diisobutyral ^d | 110/0.8 | (89-90) (B-C) | 92 | C ₁₃ H ₂₄ O ₄ ^f | — | — | — | — |
| 49 | Pentaerythritol dibenzal ^d | — | (158.5-159.0) (E) | >80 | C ₁₉ H ₃₀ O ₄ ^g | — | — | — | — |


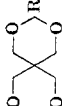
^aR=(CH₃)₂ . ^b Calcd.: O, 26.20; mol. wt., 244. Found: O, 27.2, 26.9; mol. wt. 246, 237. ^c Trojan Powder Co., Technical Bulletin on Trimethylolmethane, report b.p. 142-145°/1 mm. for trimethylolmethane sesquiacetal. ^d The *Chemical Abstracts* name of the ring system  R is 4,9-dialkyl-3,5,8,10-tetraoxaspiro[5,5]-undecane. In this paper, the acetals are named as pentaerythritol derivatives. ^e Supplied by Hercules Powder Co., used as received. ^f A. Skrabal and M. Zlateva, *Z. phys. chem.*, 119, 305 (1926), report m.p. 95°. ^g M. Apel and B. Tollens, *Ann.*, 289, 34 (1896), report m.p. 160°.

TABLE III
MISCELLANEOUS ACETALS

| Acetal No. | Acetal | B.P., Mm. | <i>n</i> _D ²⁵ (M.P., Cryst. Solv.) | Yield, % | Formula | Calcd., % | | Found, % | |
|------------|--|--------------|--|----------|--|-----------|-------|------------|-------------------------|
| | | | | | | C | H | C | H |
| 51 | 2,4,4-Trimethyl-1,3-dioxolane | 98-100/atm. | 1.3921 | 69 | C ₈ H ₁₂ O ₂ ^a | — | — | — | — |
| 52 | 2-Isopropyl-1,3-dioxepane | 163-166/atm. | 1.4312 | 58 | C ₈ H ₁₆ O ₂ | 66.62 | 11.18 | 66.4, 66.5 | 11.2, 11.2 |
| 53 | 2-Isopropyl-1,3-dioxep-5-ene | 94-99/90 | 1.4470 | 38 | C ₈ H ₁₄ O ₂ ^b | 67.57 | 9.92 | 67.8, 67.6 | 9.9, 9.9 |
| 54 | 2-Phenyl-1,3-dioxepane | 118-119/11 | 1.5210 | 38 | C ₁₁ H ₁₄ O ₂ | 74.13 | 7.92 | 74.4, 73.9 | 7.9, 7.9 |
| 55 | 2-Isopropyl-5,5-diethyl-1,3-oxathiane ^c | 127-130/18 | 1.4809 | 45 | C ₁₁ H ₂₂ OS | 65.29 | 10.96 | 64.8, 65.0 | 10.9, 11.3 ^d |
| 56 | 2-Phenyl-5,5-diethyl-1,3-oxathiane ^c | — | (52-54) (M) | 80 | C ₁₄ H ₂₀ OS | 71.13 | 8.52 | 70.9, 70.8 | 8.3, 8.5 ^e |
| 57 | 1,6-Dioxaspiro[4,4]nonane ^f | — | — | — | — | — | — | — | — |
| 58 | 2,2-Dimethoxypropane ^g | — | — | — | — | — | — | — | — |
| 59 | 4,4-Dimethyl- <i>m</i> -dioxane ^h | — | — | — | — | — | — | — | — |

^a M. G. Voronkov and E. S. Tulinova, *Zhur. Obshchei Khim.*, 24, 613 (1954) [*Chem. Abstr.*, 49, 5484a (1955)], report b.p. 100.1°/762 mm., *n*_D²⁰ 1.3938. ^b K. C. Bamcock and G. R. Lappin, *J. Org. Chem.*, 21, 1366 (1956), report b.p. 170.0-170.6°/735 mm., *n*_D²⁰ 1.4484. ^c The required 3-mercapto-2,2-diethyl-1-propanol was prepared by the method of C. S. Rondenstedt, *J. Org. Chem.*, in press. ^d % S—calcd., 15.85; found, 15.7. ^e % S—calcd., 13.57; found, 13.5, 13.4. ^f Supplied by Quaker Oats Co., used as received. ^g Supplied by Dow Chemical Co., used as received. ^h Supplied by Atlantic Refining Co., used as received.

improved by decreasing the quantity of sulfuric acid, and by moderating the temperature.

Acetal #10. The distillate, consisting of benzene, acetone, and water, did not separate into two phases. Accordingly, the mixture was refluxed into a Soxhlet extractor containing a large thimble full of calcium chloride to dehydrate the distillate. The calcium chloride was renewed as it became exhausted. The catalyst was destroyed with solid potassium carbonate before the product was fractionated.

Acetal #11. When the hexane solution was washed with bicarbonate and water, the quantity of aqueous layer was larger than the volume of water added, and "schlieren" were evident at the interface. This suggests a rapid hydrolysis of the ketal by neutral water. Although the theoretical quantity of water had been removed during the reflux period, 16% of cyclopentanone was recovered when the organic layer was distilled. Omission of the water wash should materially improve the yield.

Acetals #25 and 25a. The alcohol (acetal #24) in excess pyridine reacted somewhat exothermically with *p*-toluenesulfonyl chloride added portionwise. The mixture was stirred overnight at room temperature, diluted with benzene, filtered to remove the theoretical quantity of pyridine hydrochloride, and washed thoroughly with water to remove the excess pyridine; the benzene was removed by distillation, ultimately at 10 mm., pot temperature 140°. The residue, which crystallized slowly, amounted to 91% yield. It was crystallized from hexane containing a little benzene to yield first the high-melting acetal #25. Concentration of the mother liquors yielded the impure low-melting isomer 25a. In order to recrystallize 25a, it was necessary that the hexane-benzene solution be saturated at no higher than 35°; then very slow cooling with seeding yielded crystalline material. The two isomers are present in roughly equal amounts.

Acetal #26. Oxetane-3,3-dimethanol¹⁰ and a slight excess of isobutyraldehyde in benzene reacted rapidly in the presence of *p*-toluenesulfonic acid to liberate about 10% of the theoretical water; water evolution then stopped abruptly. Several additional portions of *p*-toluenesulfonic acid were added, with repetition of this behavior. Ultimately about 90% of the theoretical water was collected. The mixture was then processed by the general procedure. Some unchanged diol was present in the still residue. This peculiar behavior suggests that the oxetane ring is slowly cleaved by a stoichiometric reaction with *p*-toluenesulfonic acid, thus destroying the catalyst.

Acetals #27 and 27a. The acetals were prepared by the general procedure from tetrahydrofuran-2,2-dimethanol (Quaker Oats Co.) and separated readily by fractional distillation. The infrared spectrum of the lower-boiling acetal has a wealth of fine structure in the region 6.8–11.0 μ absent from that of the higher-boiling isomer. Bands at 11.4 w, 11.6 vw, 12.95 w, and 14.1 μ s in the former are much weaker in the latter, while a strong band at 12.8 μ in the latter is absent from the former. The two isomers were essentially pure by VPC.

Acetal #28. Oxalic acid at room temperature converted an equimolar mixture of 3-formyl-3-methyloxetane¹¹ and neopentyl glycol in hexane to hemiacetal (infrared). Only half of the theoretical water was obtained on prolonged refluxing. *p*-Toluenesulfonic acid promoted loss of a small additional amount of water, but it was necessary to add several small portions of sulfuric acid to force the reaction to completion. A substantial amount of viscous residue remained after distillation of the acetal, showing that acid-catalyzed polymerization of the oxetane ring had taken place to some extent.

Acetal #31. The *p*-toluenesulfonic acid was not neutralized before distillation. A substantial amount of un-

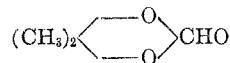
changed diol¹² was recovered, despite nearly complete removal of water. The yield of acetal was quantitative when allowance was made for unreacted diol.

Acetals #32 and 32a. Although an acetal of this structure has been reported,¹³ there was no mention of stereoisomers; the reported physical constants (m.p. 46°, b.p. 98–103°/0.5 mm.) did not agree with ours. Our liquid isomer was undoubtedly contaminated with other materials; it exhibited infrared bands at 9.69, 10.22, 12.46, and 13.0 μ s not in the solid acetal, which in turn has bands at 8.10, 11.97, and 13.6 μ , as well as much stronger absorption at 11.56 and 11.71 μ .

Acetal #33. The isobutoxypivalaldehyde was a roughly distilled pyrolyzate of acetal #4, containing about 25% of unchanged acetal. The contaminants were readily separated from acetal #33 by fractionation, and the yield figure given in the Table takes these contaminants into account.

Acetal #39. 2,2-Diphenyl-3-hydroxypropanoic acid was prepared from diphenylacetic acid by the Ivanov reaction and reduced to 2,2-diphenyl-1,3-propanediol with lithium aluminum hydride by the method of Blicke.¹⁴ The acetal prepared by the general procedure with a slight excess of isobutyraldehyde was contaminated with unchanged diol which was difficult to remove by crystallization. The crude acetal was dissolved in a minimum quantity of carbon disulfide, separated from the insoluble diol, and then recrystallized from hexane. Though the yield of crude material was high, purification was attended by considerable loss. Use of a larger excess of isobutyraldehyde would very likely have given better results.

Acetal #41. A mixture of 625 g. (6 moles) of neopentyl glycol, 625 g. (500 ml., 3.23 moles) of 30% aqueous glyoxal (Union Carbide Chemicals), 500 ml. of benzene, and 2.2 g. of *p*-toluenesulfonic acid was refluxed while removing the water. In 3.5 hr., 300 ml. was removed, and an additional 132 ml. distilled in 3 hr. more. Then 300 ml. of benzene was removed to pot temperature 127°. An infrared spectrum of the residue showed strong OH and medium carbonyl. An additional gram of *p*-toluenesulfonic acid was added and a further 56 ml. of water was collected in 2 hr. more. The OH and carbonyl absorptions were much weaker, but still present. The volatile materials were removed at 200 mm., pot temperature 100°, then 800 ml. of ethyl acetate was added to the hot residue. The mixture was chilled rapidly with stirring to yield 330 g. of diacetal, m.p. 161–163°. The analytical sample was crystallized twice more from ethyl acetate. Recrystallization and processing of the mother liquors yielded a total of 422 g. of acetal, 61% yield. The mother liquors were distilled, yielding 163 g. of pale yellow liquid, b.p. 73–108°/mm. The temperature then rose rapidly to 146°, and a second cut was obtained from 146–200°/1 mm., 150 g., containing a little of the solid acetal. The infrared spectrum of the first cut showed a weak OH, a very strong carbonyl at 5.75 μ (5.55 μ sh), but only a trace of aldehyde CH absorption at 3.7 μ . There were also strong bands at 8.2, 9.0, and 9.7 μ , and a medium band at 12.65 μ doubtless resulting from the *m*-dioxane structure. No further effort was expended on identifying this liquid fraction. It may contain some monoacetal (although the absence of the 3.7 μ



band argues against this structure), or a glycolate ester of some type may be present.

Acetal #42. The starting material was either 1,1,3,3-tetraethoxypropane (Union Carbide Chemicals) or 1-methoxy-1,3,3-triethoxypropane (Kay-Fries). Either

(12) 3,3-Dihydroxymethyl-1-butene from Celanese Corp.

(13) M. S. Newman, B. J. Magerlein, and W. B. Wheatley, *J. Am. Chem. Soc.*, **68**, 2112 (1946).

(14) F. F. Blicke and H. Raffelson, *J. Am. Chem. Soc.*, **74**, 1730 (1952). Our product melted at 105.7–106.2°, in agreement with these authors.

(10) D. B. Pattison, *J. Am. Chem. Soc.*, **79**, 3455 (1957).

(11) R. K. Miller, U. S. Pat. 2,923,645.

acetal reacted smoothly with two equivalents of neopentyl glycol in the presence of a little boron fluoride etherate. The theoretical quantity of ethanol (or methanol-ethanol mixture) was collected by slow distillation through a short column, and the residue was distilled directly in an apparatus for distilling solids.

Acetal #43. A mixture of 2,5-diethoxytetrahydrofuran (Union Carbide Chemicals), two equivalents of neopentyl glycol, and a little concentrated hydrochloric acid was warmed until homogeneous and allowed to stand overnight. The solid product was recrystallized from cyclohexane.

Acetal #44. A mixture of 1 mole of 2-ethoxy-3,4-dihydro-2-H-pyran (Union Carbide Chemicals), 2 moles of neopentyl glycol, and 5 ml. of concd. hydrochloric acid warmed spontaneously to about 60°; the clear solution rapidly became cloudy. On cooling, the product solidified. It was dissolved in about 1.2 l. of cyclohexane, 31 ml. of aqueous layer was separated, and the cyclohexane was dried with solid potassium carbonate. The solution was concentrated and crystal crops were taken.

Acetal #46. Reaction of one mole of trimethylolethane (2-hydroxymethyl-2-methyl-1,3-propanediol) (Heyden-Newport) and 1.5 moles of acetaldehyde in the presence of *p*-toluenesulfonic acid led only to the monoacetal #24. The monoacetal with *p*-toluenesulfonic acid and two additional moles of acetaldehyde liberated no more water. Finally, one-fourth mole of calcium chloride was added and the mixture allowed to stand for 3 days. Distillation then yielded the sesquiacetal which still had a weak hydroxyl absorption.

Acetals #52, 53, 54. The acid catalyst was removed before distillation, so that considerable pot residue (linear polyacetals) remained. The yields could have been improved by distillation in the presence of acid.¹⁵

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(15) K. C. Brannock and G. R. Lappin, *J. Org. Chem.*, **21**, 1366 (1956).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF LEPETIT S.P.A.]

Reactions with α -Substituted β -Propiolactones. I. 4,4-Disubstituted 2-Oxazolidinones

Research on Compounds Active on the Central Nervous System. XXIII^{1a}

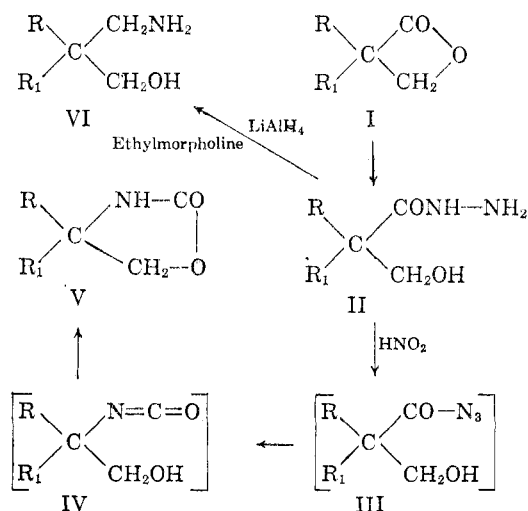
BRUNO I. R. NICOLAUS, LUIGI MARIANI, GIANGUALBERTO GALLO,^{1b} AND EMILIO TESTA

Received October 31, 1960

Several 4-mono- and 4,4-disubstituted 2-oxazolidinones have been prepared by the action of nitrous acid on the substituted β -hydroxypropionic acid hydrazides, which were obtained by the action of hydrazine on β -propiolactones. This reaction also proves the constitution of these hydrazides. The infrared spectra of the 2-oxazolidinones are discussed. The reduction of the foregoing hydrazides by lithium aluminum hydride in ethylmorpholine leads to amino alcohols under cleavage of the N—N bond. Some preliminary pharmacological results are also reported.

During our investigation on compounds active on the central nervous system we carried out a new and general synthesis of α -substituted β -propiolactones.²⁻⁴ In fact, if the easily obtained α -substituted β -aminopropionic acids are diazotized, β -propiolactones are obtained in good yield as colorless (alkyl derivatives) or greenish-yellow (aryl derivatives) fluids (only in a few cases solid compounds were obtained), having an itching action on skin and mucosae.⁵ β -Lactones easily react with hydrazine hydrate^{4,6} and substituted hydrazines, thus almost generally producing the hydrazides of α -substituted β -hydroxypropionic acids.⁷ The latter compounds, the structure of

which were previously suggested by chemical analysis (titration of the radical —CO—NH—NH₂, acetylation, etc.) and by infrared spectra (typical bands of the group —CO—NH— at 1650 cm.⁻¹),



(1) (a) Previous paper (note XXII): E. Testa, L. Fontanella, and V. Aresi, *Ann.*, in press. (b) Physical Chemical Department of Lepetit S.p.A.

(2) E. Testa, L. Fontanella, G. F. Cristiani, and F. Fava, *Ann.*, **619**, 47 (1958).

(3) E. Testa, L. Fontanella, and L. Mariani, *J. Org. Chem.*, **25**, 1812 (1960).

(4) E. Testa, L. Fontanella, G. F. Cristiani, and L. Mariani, *Ann.*, **639**, 166 (1961).

(5) A good review on β -lactones has been given by Zaugg in *Org. Reactions*, VIII, 305 (1954).

(6) B. F. Goodrich, Brit. Patent **648,886**; *Chem. Abstr.*, **45**, 8031 (1951).

(7) The research in this field is under investigation. We have seen that under special conditions the corresponding α -substituted β -hydrazinepropionic acids may be isolated.