glass funnel and extracted with ten 20-ml. portions of dry ether. The ether was removed by evaporation at room temperature. Yield, 1.5 g., white crystals. Nonaqueous titration showed it to be free of the basic isomer.

Anal. Calcd. for $C_{15}H_{14}N_4$: C, 71.97; H, 5.64; N, 22.39. Found: C, 71.80; H, 5.51; N, 22.28.

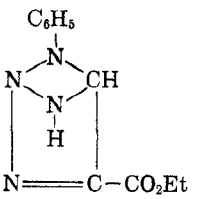
Relative rates of irreversible isomerization (I to II). *Table V.* One g. of each compound in 8 ml. of dry pyridine was refluxed 0.5 hr. on a preheated sand bath. The reaction mixture was poured into 150 ml. of ice water. The product was filtered, washed several times with water and thoroughly dried. The acidic isomer content was determined by titration in nonaqueous solvent.[7]

Equilibrium measurements in homogeneous melts, Table VI. Known quantities of I and II, respectively, were taken in sample tubes with standard inner joints which could be fitted to the two side necks of a 500 ml. 3-necked flask. A reflux condenser and a thermometer well were fitted to the central neck of the flask. Boiling *trans*-decalin gave a temperature of 184–185°. The samples were maintained at this temperature in the molten condition for a known period of time, after which they were chilled to ice temperature and then estimated for type II isomer by nonaqueous techniques.[7,25]

Acknowledgment. A grant-in-aid in support of this investigation from the Office of Naval Research is gratefully acknowledged.

(25) Dimroth, *Ann.*, **377**, 211 (1910) and Brown, Hammick, and Heritage, *J. Chem. Soc.*, 3820 (1953) used alcoholic potassium hydroxide as titrant and phenolphthalein as visible indicator. The accuracy of this work is questionable. For example, the titration of 4-phenyl-5-anilino- and 4-phenyl-5-(*m*-chlorophenyl)amino-1,2,3-triazoles, respectively, in dry ethanol as solvent, sodium methoxide in dry methanol as the titrant and phenolphthalein as visible indicator, gave consistently only 85 to 87 per cent recoveries. Furthermore, it was found necessary to standardize on the shade of the pink (or the red) of the indicator endpoint, otherwise the recovery values were found to lie anywhere between 68 to 98% recoveries (only the stronger 4-substituted-5-(substituted)amino-1,2,3-triazoles gave the higher recovery values. Details of this study are reported elsewhere.[7]

(26) Attention is directed to the polemic between Dutt [*J. Chem. Soc.*, 265 (1923); 2476 (1924)] and Dimroth[5] regarding the structure of II (R_1 = C_6H_5; R_2 = CO_2Et). Dutt considered the structure to be as indicated at end of this footnote. Attempts to answer this on chemical grounds were made by Dimroth and Michaelis.[9] However, it can be stated that the arguments on either side were not entirely convincing. Dutt's hypothesis of a bicyclic intermediate does not definitely account for the influence of R_1 in I and II on either the position of equilibrium or the relative rate of isomerization.[8] The high degree of ring strain required by this type of intermediate would make its formation very unlikely. W. L. Garbrecht, and R. M., Herbst, *J. Org. Chem.*, **18**, 1269 (1953) have suggested a similar bicyclic intermediate to account for the isomerization of substituted 5-aminotetrazoles[6,16] which is open to the same objections.



CHICAGO 14, ILL.

[CONTRIBUTION FROM ORGANIC CHEMICALS DEPARTMENT RESEARCH DIVISION, JACKSON LABORATORY, E. I. DU PONT DE NEMOURS & CO., INC.]

Seven-Membered Cyclic Acetals

DEXTER B. PATTISON

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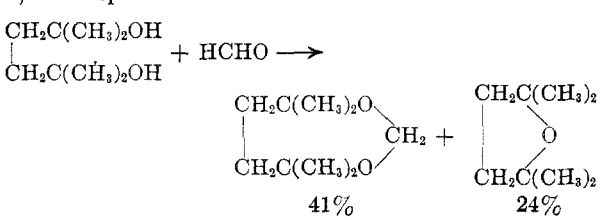
The general method for the synthesis of 1,3-dioxepane has been extended to eight novel seven-membered cyclic acetals, including 1,3-dioxep-5-ene. The method has been improved.

This paper describes the preparation and properties of various seven-membered cyclic acetals derived from aldehydes and dihydric alcohols containing four carbon atoms between hydroxyl groups. There are two competing reactions which can occur, either ring closure to the desired seven-membered acetal or dehydration of the glycol to a tetrahydrofuran derivative. This is illustrated below in the equation for the synthesis of 4,4,7,7-tetramethyl-1,3-dioxepane.



Substituents on the alpha carbon atoms and to a much lesser extent on the beta position of the diol favor the formation of the tetrahydrofuran derivative and lower the yield of the 1,3-dioxepane. On the other hand, with a double bond beta to the hydroxyl groups of the diol only a trace of dihydrofuran could be isolated.

The reaction of *cis*-2-butenediol-1,4 with formaldehyde to give 1,3-dioxep-5-ene[1] and the reaction of *cis*-2-butenediol-1,4 with various aldehydes to give substituted 1,3-dioxep-5-enes[2] has been described in recent papers. The double bond in 1,3-dioxep-5-ene appears to have normal double bond activity. 1,3-Dioxep-5-ene adds bro-

(1) W. Reppe, *et al.*, *Ann.*, **596**, 1 (1956).

(2) W. Brannock and G. Lappin, *J. Org. Chem.*, **21**, 1366 (1956).

mine readily in almost quantitative yield to give 5,6-dibromo-1,3-dioxepane, and addition of chlorine gives 5,6-dichloro-1,3-dioxepane.

In the literature only 1,3-dioxepane[3] and derivatives with a methyl[4,5] or furyl[6] substituent in the 2-position have been described, and yields have been mediocre. The synthesis of 4,4′,7,7′-tetramethyl-bis(1,3-dioxepane) from glyoxal and 2,5-hexanediol[7] has been described. The present work has shown that 1,3-dioxepane can be made easily in 90% yield and substituted derivatives can also be made in high yield as shown in Table I.

TABLE I

ACETALS FROM DIOLS AND ALDEHYDES

Diol	Aldehyde	% Yield of Cyclic acetal	% Yield of Furan derivative	Properties of the Cyclic Acetals: B.p., °C.	Pressure mm.	n_D^{25}	Found % C	Found % H	Calcd. % C	Calcd. % H
1,4-Butanediol	Formaldehyde	90	3	119	760	1.4275	58.5	10.1	58.8	9.8
2-Methyl-1,4-butanediol	Formaldehyde	78	2	72	93	1.4269	62.0	10.4	62.1	10.4
2,5-Hexanediol	Formaldehyde	82	4	80	80	1.4230	63.4	10.7	64.6	10.8
2,5-Dimethyl-2,5-hexanediol	Formaldehyde	41	24	112	115	1.4365	68.5	11.5	68.4	11.4
2,2,3,3-Tetrafluoro-1,4-butanediol	Formaldehyde	84	1	132	760	1.3620	34.7	3.5	34.5	3.5
2-Butenediol-1,4	Formaldehyde	69	0.5	127	760	1.4540	60.0	8.3	60.0	8.0
2-Butenediol-1,4	*n*-Heptaldehyde	53	...	93	2	1.4527	71.7	11.1	71.7	10.9
2-Butenediol-1,4	Benzaldehyde	30	...	114	3.5	1.5387	74.2	6.9	75.0	6.8

All of these compounds appeared to be homogeneous and had definite boiling points except in one case. 4,7-Dimethyl-1,3-dioxepane apparently was a mixture of two isomers, which had different refractive indices and about 6–8° difference in boiling point. They are believed to be *cis* and *trans* isomers.

EXPERIMENTAL

Most of the diols used in this work are commercially available. In two cases studied purification of the diol did not improve the yield of the resultant cyclic acetal. 2-Methyl-1,4-butanediol was made by Dr. J. Burt of this laboratory by the reduction of dimethyl 2-methylsuccinate under 4500 p.s.i. hydrogen pressure using Harshaw 1402P copper chromite catalyst at 250° for 5 hr. Preparation of 2,2,3,3-tetrafluoro-1,4-butanediol[8] and 5,5,6,6-tetrafluoro-1,3-dioxepane was done by Dr. S. Dixon of this laboratory.

1,3-Dioxepane. The writer placed 3013 g. of commercial 1,4-butanediol (33.5 moles), 1100 g. paraformaldehyde (34.8 moles, assuming 95% purity), 2 g. *N*-phenyl-2-naphthylamine, 5 g. *p*-toluenesulfonic acid, and some boiling chips in a 5-liter flask fitted with a thermometer with the bulb near the bottom of the flask, a dropping funnel, and a condenser arranged for downward distillation. The mixture was heated rapidly. The distillate initially contained two layers which were separated. The upper layer was mostly 1,3-dioxepane, and the lower layer contained mostly water together with 11–13% formaldehyde and some 1,3-dioxepane. As the distillation proceeded, the amount of aqueous layer decreased and eventually 1,3-dioxepane came over with no aqueous layer.

When the volume in the distillation pot was 500–1000 ml., part of the aqueous distillate was returned dropwise to the pot so that the pot temperature was maintained at 180–200°. Distillation was continued until almost no material remained in the flask. The last 200–500 ml. of the distillate was light brown and the rest was colorless.

To the combined water fractions, cooled below 20°, 200 g. of potassium carbonate was added, and the upper layer combined with the rest of the 1,3-dioxepane. The 1,3-dioxepane, cooled below 20°, was washed with 300 g., then 200 g. of cold 40% sodium hydroxide solution (more water may be added if needed to dissolve insolubles), and dried with 20 g. sodium hydroxide pellets and 100 g. anhydrous sodium sulfate.

The 1,3-dioxepane was put in a still pot, 20–30 g. of sodium was added, and the mixture was distilled at atmospheric pressure. If alkali is not present, reduced pressure (<150 mm.) is required for this distillation. The products were 80 g. (3%) of tetrahydrofuran and 3090 g. (90%) of 1,3-dioxepane, b.p. 119° at atmospheric pressure or 70° at 150 mm.

1,3-Dioxep-5-ene was made by the same general method as 1,3-dioxepane except that near the end of the initial distillation, during water addition, the pot temperature rose rapidly to about 350° leaving a large tarry residue in the flask. This reaction should be carried out in a hood behind a safety shield.

5,6-Dibromo-1,3-dioxepane. To a solution of 100 g. 1,3-dioxep-5-ene (1.0 mole) in 700 ml. chloroform cooled to −55°, there was added dropwise with rapid stirring a solution of 140 g. bromine (0.875 mole) in 700 ml. chloroform during 3 hr., during which time the yellow color completely disappeared. At 0°, the colorless solution was washed with 300 ml. of 10% sodium sulfite, and then washed twice with 200 ml. water. Chloroform was removed by evaporation under reduced pressure below 50°. The residue, 5,6-dibromo-1,3-dioxepane, weighed 231 g. (101%) and on standing became a mass of white crystals with a trace of oil. Recrystallization from petroleum ether gave fine white needles, m.p. 39–40°.

Anal. Calcd. for $C_5H_8Br_2O_2$: C, 23.05; H, 3.08; Br, 61.58. Found: C, 22.85; H, 3.25; Br, 61.50.

5,6-Dichloro-1,3-dioxepane. To a solution of 117 g. 1,3-dioxep-5-ene (1.17 moles) in 700 ml. chloroform cooled to −55, there was added dropwise a solution of 82 g. chlorine

(3) J. W. Hill and W. H. Carothers, *J. Am. Chem. Soc.*, **57**, 926 (1935).

(4) H. S. Hill and H. Hibbert, *J. Am. Chem. Soc.*, **45**, 3115 and 3130 (1923).

(5) German Patent 805,520, to Badische Aniline and Soda Fabrik, May 21, 1951.

(6) A. Hinz, G. Meyer, and G. Schücking, *Ber.*, **76B**, 687 (1943).

(7) M. M. Sprung and F. O. Guenther, *J. Am. Chem. Soc.*, **73**, 1884 (1951).

(8) E. T. McBee, W. F. Marzluff, and O. R. Pierce, *J. Am. Chem. Soc.*, **74**, 444–6 (1952).

(1.17 moles) dissolved in 700 ml. chloroform during 1 hr. at −50°. The solution was kept 1 hr. at −50° and warmed gradually over 2 hr. to −10°C. The liquid was washed with 300 ml. of 10% sodium sulfite, twice with water, and dried over anhydrous sodium sulfate. After evaporating chloroform, 151 g. (75%) of colorless 5,6-dichloro-1,3-dioxepane boiling at 56° at 1 mm. was obtained.

Anal. Calcd. for $C_5H_8Cl_2O_2$: C, 35.12; H, 4.68; Cl, 41.50. Found: C, 40.75; H, 5.00; Cl, 40.75.

2-Hexyl-1,3-dioxep-5-ene. A mixture of 114 g. *n*-heptaldehyde (1.0 mole), 88 g. 2-butenediol-1,4 (1.0 mole), and 0.2 g. *p*-toluenesulfonic acid was heated gradually to 150°. The distillate had two layers. The lower aqueous fraction was discarded, and the upper *n*-heptaldehyde fraction was returned to the still pot. After water evolution became slow the pressure was lowered gradually to 2 mm., keeping the oil bath temperature 150°, and the distillate was dried over sodium sulfate. Redistillation gave some low-boiling fractions and 98 g. (53%) of 2-hexyl-1,3-dioxep-5-ene, boiling at 93° at 2 mm.

WILMINGTON 98, DEL.

[COMMUNICATION NO. 1873 FROM THE KODAK RESEARCH LABORATORIES]

By-products of the Willgerodt Reaction Applied to α- and γ- Picoline

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An additional by-product of the Willgerodt reaction of aniline, γ-picoline, and sulfur has been identified as *N,N'*-diphenylisonicotinamidine and its structure confirmed by independent synthesis. The structure of 2-(4-pyridyl)benzothiazole also obtained in this reaction has been confirmed by an independent synthesis. The Willgerodt reaction of aniline, α-picoline, and sulfur produced 2-(2-pyridyl)benzothiazole, *N,N'*-diphenylpicolinamidine and the expected thiopicolinanilide.

In order to obtain 2-(4-pyridyl)benzothiazole (I) from readily available materials, the reaction of γ-picoline, aniline, and sulfur at elevated temperatures, as reported by Porter,[1] was carried out by a similar procedure but at 180–220°. The reaction product after distillation melted at 120–160° instead of 126–130° and, after recrystallization from alcohol, still melted in this same range. It was found that a separation into two materials, one melting at 133–135° (I) and the other melting at 194–196° (II) could be accomplished by extracting with ligroin, in which the low melting material was soluble.

The lower melting product was the desired 2-(4-pyridyl)benzothiazole, as reported and as synthesized by an independent method. Following the method as described in the literature[2] for the reaction of *o*-aminobenzenethiol with aldehydes and ketones, 2-(4-pyridyl)benzothiazoline (V) was prepared by the reaction of *o*-aminobenzenethiol (III) and 4-pyridinecarboxaldehyde (IV). Subsequent oxidation of (V) by ferric chloride produced the desired benzothiazole (I). The higher melting material (II) contained only carbon, nitrogen, and hydrogen; its molecular weight was found to be 281.

At the time of this investigation, we were unaware of the publication of Emmert and Holz[3] reporting the isolation of *N,N'*-diphenylisonicotinamidine from the reaction of γ-picoline, sulfur and either nitrobenzene or aniline under vigorous reflux. This reference was pointed out to us by H. D. Porter. The high melting material (II) was found to be the amidine derivative; its structure was confirmed by an independent synthesis following the procedure of Gerhardt,[4] for the preparation of *N,N'*-diphenylbenzamidine as outlined in Chart I.

When α-picoline, aniline, and sulfur were heated at 180–220° for 12 hr. instead of at 160° as reported,[1] the thiopicolinanilide (VIII) was obtained, but 2-(2-pyridyl)benzothiazole (X)[5] and *N,N'*-diphenylpicolinamidine (IX) were also isolated among the products of the reaction. The structures of these products were confirmed as outlined in Chart II.

EXPERIMENTAL

2-(4-Pyridyl)benzothiazole (I) *and N,N'-diphenylisonicotinamidine* (II). A suspension of 96.2 g. (3.0 g. atom) of sulfur, 93.1 g. (1.0 mole) of γ-picoline and 139.7 g. (1.5 moles) of aniline was heated under reflux for 24 hr., the inner temperature rising from 180 to 220°. The unreacted aniline and γ-picoline were removed by distillation under a vacuum at 7 mm. and, on continuing the distillation, the material boiling at 198–220° (7 mm.) was collected. On recrystallization from absolute alcohol, the distillate consisted of a yellow, crystalline material, m.p. 120–160°. An alternate method consisted in removing the unreacted aniline and γ-picoline by distillation under a vacuum and crystallizing the tarry residue out of absolute alcohol; the yellow crystalline material again melted at 120–160°; and distillation, b.p. 200–210° at 2 mm., as well as subsequent recrystallization from absolute alcohol, did not alter the melting point range. Extraction of this material for 16 hr. in a Soxhlet extractor with ligroin (b.p. 65–75°) produced a soluble frac-

(1) H. D. Porter, *J. Am. Chem. Soc.*, **76**, 127 (1954).

(2) A. W. Hofmann, *Ber.*, **13**, 1236 (1880); M. Claasz, *Ber.*, **45**, 1031 (1912); M. T. Bogert and A. Stull, *J. Am. Chem. Soc.*, **47**, 3078 (1925); H. P. Lankelma and P. X. Sharnoff, *J. Am. Chem. Soc.*, **53**, 2654 (1931).

(3) B. Emmert and A. Holz, *Chem. Ber.*, **87**, 676 (1954).

(4) C. Gerhardt, *Ann.*, **108**, 219 (1858).

(5) B. Emmert and M. Groll, *Chem. Ber.*, **86**, 208 (1953).