[A CONTRIBUTION FROM THE CHEMISTRY DIVISION OF EATON LABORATORIES, INC.]

Hydrazinoalkanols

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A number of new hydrazinoalkanols have been prepared and characterized as their acid oxalate salts. The methods of synthesis included the condensation of hydrazine with epoxides or halohydrins, the reduction of α-hydrazino acid esters with lithium aluminum hydride and the reaction of amines with hydroxylamine-O-sulfonic acid. Several of the hydrazinoalkanols were cyanated to give the corresponding semicarbazides which were isolated as 5-nitro-2-furaldehyde derivatives.

During the continuing investigation of 5-nitro-2-furaldehyde semicarbazones,[1] it became necessary to prepare a number of hydrazinoalkanols. Two methods for preparing the latter have been previously reported. The reaction between hydrazine hydrate and alkylene epoxides has been used to prepare a variety of hydrazinoalkanols.[2,3] Secondly, the action of hydroxylamine-O-sulfonic acid on ethanolamine to give 2-hydrazinoethanol has been reported.[1]

In addition to these known procedures this paper reports two additional methods which have been used to prepare some new hydrazinoalkanols, the reduction of esters of hydrazinoacids with lithium aluminum hydride and the reaction of chlorohydrins with hydrazine hydrate.

The reaction between hydrazine hydrate and epoxides is the simplest to run since isolation of the product involves only a distillation, with no solid inorganic bi-products to interfere. With 1,2-epoxides, only 1-hydrazino-2-alkanols were isolated, as would be expected from the reaction of amines with epoxides.[3,4] Hydrazinoalkanols prepared from epoxides and hydrazine hydrate included 1-hydrazino-2-propanol, 1-hydrazino-2-butanol, 1-hydrazino-2-hexanol and 3-hydrazino-2-butanol.

The condensation of the two isomeric propylene chlorohydrins with hydrazine hydrate was also used to prepare 1-hydrazino-2-propanol. 1-Chloro-2-propanol, as expected, gave only 1-hydrazino-2-propanol. 2-Chloro-1-propanol when condensed with hydrazine hydrate in the presence of sodium hydroxide at 95–100° also gave exclusively 1-hydrazino-2-propanol. This agrees with the theory that the reaction of halohydrins under basic conditions proceeds through the epoxide.[5] However, when the reaction was run at 28°, with no sodium hydroxide present, both 2-hydrazino-1-propanol and 1-hydrazino-2-propanol were obtained. Although it is possible that at this temperature the epoxide is still formed exclusively and reacts to give the two isomers, it is more probable that some direct substitution occurs along with epoxide formation. Another example which tends to confirm this hypothesis is the reaction of 4-chloro-1-butanol with hydrazine hydrate at 95–100° in the presence of sodium hydroxide which gave tetrahydrofuran exclusively. However, when the reaction was carried out at 30° (with no caustic), the desired 4-hydrazino-1-butanol was obtained. The reaction of 3-chloro-1-propanol with hydrazine hydrate went smoothly to give 3-hydrazino-1-propanol, no attempt being made to determine whether or not trimethylene oxide was an intermediate.

The reduction of hydrazinoacid esters with lithium aluminum hydride served to provide the desired 2-hydrazino-1-alkanols. This method of synthesis parallels the work of Karrer,[6] who reduced a number of aminoacid esters to 2-amino-1-alkanols. In this fashion, 2-hydrazino-1-propanol and 2-hydrazino-1-hexanol were obtained

In the reduction of ethyl α-hydrazinopropionate, some 2-amino-1-propanol was isolated along with the desired 2-hydrazino-1-propanol. This finding has not yet been explored but may have some bearing on the observation of Hanna and Schueler,[7] who found that in the reduction of N-nitrosodiphenylamine with a large excess of lithium aluminum hydride, only diphenylamine was isolated.

The action of hydroxylamine-O-sulfonic acid on 2-amino-1-propanol was also used to prepare 2-hydrazino-1-propanol.[8]

Several of the hydrazinoalkanols were cyanated to give solutions of the corresponding 2-(hydroxyalkyl) semicarbazides which were isolated as the 5-nitro-2-furaldehyde derivatives.

Experimental[9]

Halohydrins.—1-Chloro-2-propanol was purchased from Carbide and Carbon Chemical Corporation and used without further purification. 3-Chloro-2-butanol was prepared by the method of Wilson and Lucas[10] in 31% yield. 2-Chloro-1-propanol,[11] 2-bromo-1-butanol and 2-bromo-1-hexanol were prepared by the reduction of the corresponding acid with lithium aluminum hydride. Since all three compounds were prepared by an identical procedure, only one example will be presented in detail. Table I gives the yield and physical properties of the three products.

To 350 cc. of dry ether was added 17.0 g. of lithium aluminum hydride, the mixture stirred at 30–34° for 24 hours and then cooled to 10°. A solution of 70 g. of 2-chloropropionic acid in 100 cc. of absolute ether was then slowly added over a period of one hour, keeping the internal temperature at 10–15°. After stirring at 0–10° for 90 minutes, 50 cc. of water was cautiously added, followed by 500 cc. of

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[1] G. Gever and K. Hayes, *J. Org. Chem.*, **14**, 813 (1949).

[2] E. Barnett, *Proc. Chem. Soc.*, **28**, 259 (1912); S. Gabriel, *Ber.*, **47**, 3028 (1914); A. Plisov, *Ukrainskii Khem. Zhurnal*, **3**, No. 1, Sci. pt., 125 (1928); *C. A.*, **22**, 3392 (1928).

[3] G. Benoit, *Bull. soc. chim.*, **6**, 708 (1939); 242 (1947).

[4] R. C. Elderfield, Editor, "Heterocyclic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 32.

[5] Reference 4, p. 39; H. Grimsson and L. Smith, *Acta Chem. Scand.*, **4**, 719 (1950).

[6] P. Karrer, P. Portmann and M. Suter, *Helv. Chim. Acta*, **31**, 1617 (1948).

[7] F. W. Schueler and C. Hanna, THIS JOURNAL, **73**, 4996 (1951).

[8] For the preparation of 2-hydrazinoethanol by this method see reference 1.

[9] All melting points were taken on a Fisher-Johns apparatus and are corrected.

[10] C. E. Wilson and H. J. Lucas, THIS JOURNAL, **58**, 2396 (1936).

[11] The preparation of 2-chloro-1-propanol and related compounds by this method is reported by E. Eliel and M. Hermann in a paper presented at the 122nd American Chemical Society Meeting in Atlantic City, N. J., September 14, 1952. Abstracts of papers, p. 46M. See also C. Sroog, C. Chih, F. Short and H. Woodburn, THIS JOURNAL, **71**, 1710 (1949).

TABLE I

2-HALO-1-ALKANOLS

Halohydrin	Yield, %	B.p. °C.	B.p. Mm.	3,5-Dinitrobenzoates M.p., °C.	Bromine, % Calcd.	Bromine, % Found
$CH_3CHClCH_2OH$	38	126–128[a]	740	75–76[b]	...	...
$CH_3CH_2CHBrCH_2OH$	52	79–91	32	71	23.03	22.90
$CH_3CH_2CH_2CH_2CHBrCH_2OH$	53	59–62	2	49	21.31	21.64

[a] A. Dewael, *Bull. soc. chim. Belg.*, **33**, 504 (1924), gives the boiling point as 133–134° at 761 mm. [b] C. W. Gaylor and H. M. Waddle, THIS JOURNAL, **63**, 3358 (1941), gives the melting point as 76.5°.

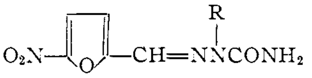
TABLE II

ACID OXALATES OF HYDRAZINOALKANOLS

Hydrazinoalkanol	Empirical formula	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1-Hydrazino-2-propanol	$C_5H_{12}N_2O_5$	127–128	33.33	33.42	6.72	6.68	15.55	15.57
2-Hydrazino-1-propanol	$C_5H_{12}N_2O_5$	115–116	33.33	33.47	6.72	6.83	15.55	15.80
3-Hydrazino-1-propanol	$C_5H_{12}N_2O_5$	126–128	33.33	33.46	6.72	6.71	15.55	15.40
3-Hydrazino-2-butanol	$C_6H_{14}N_2O_5$	149–150	37.11	37.26	7.27	7.25	14.43	14.73
1-Hydrazino-2-butanol	$C_6H_{14}N_2O_5$	114–115	37.11	36.86	7.27	6.87	14.43	14.67
4-Hydrazino-1-butanol	$C_6H_{14}N_2O_5$	109–110	37.11	36.99	7.27	7.20	14.43	14.69
1-Hydrazino-2-hexanol	$C_8H_{18}N_2O_5$	122–123	43.23	43.29	8.16	8.05	12.61	12.76
2-Hydrazino-1-hexanol	$C_8H_{18}N_2O_5$	110–112	43.23	43.36	8.16	7.98	12.61	12.78

TABLE III

5-NITRO-2-FURALDEHYDE-2-(HYDROXYALKYL) SEMICARBAZONES



R	M.p., °C.	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Soly. in water at 25°, mg./l.	H_2O max, mμ	*E*M
$-CH(CH_3)CH_2OH$	204–205	30	42.19	42.49	4.72	4.95	21.87	21.69	255	385	16,300
$-CH_2CH_2CH_2OH$	162–163	43	42.19	42.02	4.72	4.30	21.87	22.03	650	387	16,200
$-CH_2CH_2CH_2CH_2OH$	157–158	37	44.44	44.31	5.22	5.08	20.73	20.92	575	385	16,600
$-CH_2CHOH(CH_2)_3CH_3$	131–132	57	48.31	48.14	6.08	6.43	18.78	19.00	80	387	16,400

10% sulfuric acid. The ether layer was separated and the aqueous portion extracted with 150 cc. and then 100 cc. of ether. The combined ether layers were washed with a saturated sodium bicarbonate solution to remove any unreacted acid and the sodium bicarbonate washings re-extracted with 50 cc. of ether. The combined ether solutions were dried, the ether removed and the residual oil distilled.

Epoxides.—2,3-Epoxybutane was prepared by the method of Wilson and Lucas[10] in 68% yield. 2-Bromo-1-butanol was converted to 1,2-epoxybutane (87%) by the method of Levene[12] and 2-bromo-1-hexanol to 1,2-epoxyhexane (86%) by the method of Rothstein.[13]

All the hydrazinoalkanols described below were converted to oxalate salts by similar procedures. An alcoholic solution of the hydrazinoalkanol was treated with a slight excess of an alcoholic solution of oxalic acid. The solution was heated to boiling to effect solution, filtered hot and the filtrate cooled. The resulting solid was then recrystallized to analytical purity from alcohol. The physical constants of these acid oxalate salts are presented in Table II.

1-Hydrazino-2-propanol. A.—A solution of 40 g. of sodium hydroxide in 250 g. of hydrazine hydrate was heated to 95°. The external heating was eliminated and 94.5 g. of 1-chloro-2-propanol was added, dropwise with stirring, keeping the temperature at 95–100° by the rate of addition. The solution was concentrated *in vacuo*, the sodium chloride removed by filtration and the precipitate washed well with alcohol. The combined filtrates were distilled to give 65 g., 72%, of 1-hydrazino-2-propanol, b.p. 92–93° (2.0 mm.).

B.[14]—To 100 g. of hydrazine hydrate at 70° was added, slowly, under the surface of the hydrazine hydrate, 22 g. of propylene oxide. The addition was carried out at gentle reflux, the temperature of the reaction mixture dropping to 45°. After the excess hydrazine hydrate had been removed, 27 g., 78%, of 1-hydrazino-2-propanol, b.p. 100–101° (6 mm.), was obtained.

C.—Using 23.2 g. of 2-chloro-1-propanol, 62 g. of hydrazine hydrate, 62 g. of sodium hydroxide and the procedure in method A above, there was obtained 12.8 g., 59%, of 1-hydrazino-2-propanol, b.p. 86° (1.3 mm.). The identity of the product was established by the preparation of the oxalate, m.p. 127–128°, and the fact that a mixed melting point with the oxalate of the product obtained from method A (m.p. 127–128°) was not depressed. The melting point of the acid oxalate of 2-hydrazino-1-propanol (see below) was found to be 115–116°.

When the reaction was run at 28° instead of 95–100° and the sodium hydroxide was omitted, a mixture of the two isomeric hydrazinopropanols was obtained. These two products were identified by treating the mixture with diethyl carbonate, followed by condensation with 5-nitro-2-furaldehyde,[15] to give N-(5-nitro-2-furfurylidene)-3-amino-4-methyl-2-oxazolidone and N-(5-nitro-2-furfurylidene)-3-amino-5-methyl-2-oxazolidone.

3-Hydrazino-2-butanol.[16]—To a stirred solution of 155 g. of hydrazine hydrate at 60° was added, with stirring, 44.5 g. of 2,3-epoxybutane, keeping the temperature at 60–65° by the rate of addition. The solution was heated at 90–95° for one hour and then the excess hydrazine hydrate removed. The residue was distilled *in vacuo* giving 51 g., 79%, of 3-hydrazino-2-butanol, b.p. 81–85° (2.3 mm.).

1-Hydrazino-2-butanol.—Using 14 g. of 1,2-epoxybutane, 50 g. of hydrazine hydrate and the procedure used for 3-hydrazino-2-butanol, there was obtained 14.6 g., 72%, of 1-hydrazino-2-butanol, b.p. 107–110° (0.3 mm.).

1-Hydrazino-2-hexanol.—Using 29.4 g. of 1,2-epoxyhexane, 75 g. of hydrazine hydrate and the procedure used for 3-hydrazino-2-butanol, there was obtained 25.3 g., 65%, of 1-hydrazino-2-hexanol, b.p. 113° (1.2 mm.).

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(12) P. Levene and A. Walti, *J. Biol. Chem.*, **94**, 367 (1931).

(13) B. Rothstein, *Bull. soc. chim.* [5] **2**, 1936 (1935).

(14) This preparation was carried out by Mr. C. J. O'Keefe in these laboratories.

(15) The details of this and related syntheses will be published later.

(16) This synthesis was done by Dr. J. G. Michels in these laboratories.

3-Hydrazino-1-propanol.—Using 94 g. of 3-chloro-1-propanol, 250 g. of hydrazine hydrate, 40 g. of sodium hydroxide and procedure A for preparing 1-hydrazino-2-propanol, there was obtained 58.6 g., 65%, of 3-hydrazino-1-propanol, b.p. 102–104° (0.6 mm.).

4-Hydrazino-1-butanol. A.—To a solution of 7 g. of sodium hydroxide in 44 g. of hydrazine hydrate at 92° was added 18.8 g. of 4-chloro-1-butanol[17] dropwise with stirring. Shortly after the beginning of addition, the temperature of the reaction dropped to 72° and vigorous refluxing took place. The addition of the 4-chloro-1-butanol was completed in 15 minutes and the reaction mixture was refluxed for three hours, the internal temperature being 70° and that of the refluxing material 65°. Distillation of the low boiling material gave 7.0 g. of liquid, b.p. 65–66°. It was identified as tetrahydrofuran (b.p. 67°).

B.—To 23 g. of hydrazine hydrate at 25° was added 10 g. of 4-chloro-1-butanol over a period of five minutes, the temperature being kept at 27–29° by intermittent cooling. After addition was complete the reaction mixture was allowed to remain at room temperature for 20 hours. It was then diluted with 25 cc. of methanol, a solution of 2.1 g. of sodium in 30 cc. of methanol added and the precipitate of sodium chloride removed by filtration. The filtrate was stripped of methanol and excess hydrazine hydrate and the residue distilled *in vacuo* to give 5.2 g., 54%, of 4-hydrazino-1-butanol, b.p. 118° (2.0 mm.).

2-Hydrazino-1-propanol. A.—To a solution of 12 g. of potassium hydroxide in 25 cc. of water was added a solution of 37.8 g. of 2-amino-1-propanol[18] in 35 cc. of water. The solution was warmed to 95° on the steam-bath and a solution of 11.2 g. of hydroxylamine-O-sulfonic acid[1] (90% pure) in 25 cc. of water added over a period of 12 minutes. The solution was kept at 98° for 15 minutes, cooled and acidified with 50 cc. of acetic acid. The inorganic salts were removed by filtration and the filtrate warmed at 50° with 10 g. of benzaldehyde for 10 minutes. The resulting emulsion was cooled and extracted with three 50-cc. portions of ether. The ether solutions were treated with 10 g. of oxalic acid dihydrate and 50 cc. of water and the mixture steam distilled. After the benzaldehyde had been removed, the hot residue was stirred with Darco, filtered hot and the filtrate concentrated to dryness *in vacuo*. The solid residue was extracted with 50 cc. of boiling absolute alcohol which, upon cooling, gave 7.2 g., 45%, of 2-hydrazino-1-propanol oxalate, m.p. 113–114°.

B.—To a solution of 126 g. of ethyl α-hydrazinopropionate hydrochloride[19] in 700 cc. of absolute alcohol was added a solution of 17.2 g. of sodium in 400 cc. of absolute alcohol. The mixture was filtered to remove the sodium chloride and the filtrate was concentrated *in vacuo* (bath temperature did not exceed 60°) to constant weight. The residue was extracted with 250 cc. and 100 cc. of ether and the combined ether solutions dried over Drierite. The ether solution was added over a period of 90 minutes to a solution of 42 g. of lithium aluminum hydride in 500 cc. of dry ether and the mixture refluxed for 3 hours. Then, with cooling, 50 cc. of ethyl acetate was added, followed by 100 cc. of water. The mixture was filtered and the ether distilled from the filtrate, leaving a little yellow oil.

The solids from the ether extraction were extracted with three 400-cc. portions of boiling absolute alcohol and the alcoholic extracts concentrated *in vacuo*. The residue was combined with the residue from the ether solution and the combined oils distilled *in vacuo*. The distillate which came over up to 90° (2 mm.) was redistilled. Two fractions were collected, one 4.0 g., boiling at temperatures up to 70° (3 mm.) and the second 8.3 g., at 65–74° (0.5 mm.). Treatment of the first fraction with oxalic acid in absolute alcohol gave a crystalline oxalate which after three recrystallizations from alcohol melted at 125–126°. A mixed melting point with an authentic sample of 2-amino-1-propanol oxalate (prepared from 2-amino-1-propanol[18]) showed no depression.

Anal. Calcd. for $C_5H_{11}NO_5$: C, 36.36; H, 6.71; N, 8.48. Found: C, 36.75; H, 6.90; N, 8.40.

The second fraction was also converted to an oxalate which after three recrystallizations from alcohol analyzed correctly for 2-hydrazino-1-propanol oxalate (see Table II).

2-Hydrazino-1-hexanol.—A mixture of a solution of 92 g. of ethyl 2-hydrazinocaproate hydrochloride[20] in 75 cc. of water and 450 cc. of ether was cooled to 10° and 65 cc. of a 50% potassium hydroxide solution added slowly, keeping the temperature below 10°. The ether layer was separated and the aqueous portion extracted with 100 cc. of fresh ether. The combined ether solutions were dried over Drierite and added slowly to a stirred solution of 31 g. of lithium aluminum hydride in 600 cc. of dry ether. After addition had been completed, the mixture was refluxed for 90 minutes and then allowed to remain at room temperature overnight. After hydrolyzing with water, the solids were removed by filtration and washed twice with 300-cc. portions of ether. The ether was removed from the filtrate and the residual oil distilled *in vacuo*, giving 14.4 g. of 2-hydrazino-1-hexanol, b.p. 97° (1.5 mm.).

The solids from the reduction mixture were extracted with three 500-cc. portions of boiling absolute alcohol and the alcoholic extracts distilled *in vacuo* to give 10.8 g. more of 2-hydrazino-1-hexanol, b.p. 95° (1.1 mm.). The combined yield of 25.2 g. represents a yield of 44%.

5-Nitro-2-furaldehyde 2-(Hydroxyalkyl)-semicarbazones.—Several of the hydrazinoalkanols were converted to the corresponding semicarbazides which were isolated as their 5-nitro-2-furaldehyde derivatives. The procedure used was to dissolve the hydrazinoalkanol in water and add sufficient hydrochloric acid to give a neutral solution. A slight excess of potassium cyanate was then added and the solution allowed to remain overnight at room temperature. After acidification, an alcoholic solution of 5-nitro-2-furaldehyde was added, the resulting precipitate removed by filtration and then recrystallized from aqueous alcohol. The yields and physical data are given in Table III.

Acknowledgment.—I wish to express my appreciation to Mr. Joseph A. Corrado for all the analytical data.

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[17] W. Kirner and G. Richter, THIS JOURNAL, **51**, 2503 (1929).

[18] J. Attenburrow, J. Elks, B. Hems and K. Speyer, *J. Chem. Soc.*, 510 (1949).

[19] A. Darapsky, *J. prakt. Chem.*, **96**, 251 (1917).

[20] A. Darapsky, J. Termscheid, C. Kreuter, E. Englemann, W. Engels and W. Trinius, *ibid.*, **146**, 219 (1936).