73–74° was 70–71°. Addition of more pentane to the filtrate from these crystals yielded 0.98 g. of compound VI, m.p. 70–71°, which separated from solution in the form of hexagonal platelets. The melting point of a mixture of this material with an authentic sample of compound VI was not depressed. The total yield of compound VI was 50%.

The oils obtained could not be crystallized from methylene chloride and pentane, nor from aqueous ethanol. Seeding with crystals of pure compound VI did not induce crystallization.

(*b*) *In water.* In 20 ml. of water was suspended 2.16 g. (0.01 mole) of ester V and 1.51 g. (0.01 mole) of compound I was added. The suspension was stirred at 25° for 0.5 hr., after which time a change in crystalline form occurred, and short needles appeared. The solid was filtered and weighed 2.15 g. It was extracted twice with 20 ml. of boiling petroleum ether (b.p. 50–60°), and the supernatent liquid was carefully decanted from the oil which formed. From these extracts 1.01 g. (83%) of benzoic acid, m.p. 119–120° was isolated. A mixed melting point of this solid with an authentic sample of benzoic acid was 121–122°.

The oil which was insoluble in petroleum ether was dissolved in methylene chloride and the solution was filtered. To the filtrate pentane was added to the point of turbidity, and an oil separated from solution. The supernatant liquid was carefully decanted, and this procedure was repeated twice yielding progressively lighter-colored oils. When this operation was carried out for the third time 0.52 g. of colorless hexagonal platelets of compound VI slowly crystallized from solution, m.p. 69–70°. A mixed melting point with an authentic sample of this compound was 71–72°.

From the original aqueous filtrate of the reaction mixture, 1.06 g. of pure compound VI, m.p. 73–74°, crystallized upon standing for 24 hr.

The total yield of compound VI was 1.58 g. (64%).

Reaction of ester V *with two equivalents of compound* I. Ester V (2.16 g., 0.01 mole) and compound I (3.02 g., 0.01 mole) were added to 15 ml. of dry ethylene chloride and the solution was allowed to stand for 3 hr. at 25°.

The solvent was removed *in vacuo,* and the light yellow solid residue was extracted twice with 20-ml. portions of petroleum ether (b.p. 50–60°). The solid obtained upon evaporation of the petroleum ether weighed 1.55 g. and was a mixture. Separation was achieved by dissolution in absolute ethanol and addition of water to the point of turbidity. The first crop of crystals which precipitated was unreacted ester V, m.p. 87–88°, and weighed 0.35 g. (16%). Partial evaporation of the filtrate *in vacuo* yielded 0.70 g. (57%) of benzoic acid, m.p. 121–122°.

The residue which was insoluble in petroleum ether was fractionated from methylene chloride and pentane by the procedure given above. Again the first three fractions were oils, weighing 0.22 g., 0.10 g., and 0.11 g., respectively. The fourth fraction was slightly impure compound VI, m.p. 67–68°, and weighed 0.37 g. The fifth fraction separated as colorless crystals, m.p. 72–73°, which weighed 1.24 g. The total yield of compound VI was 1.61 g. (65%).

Reaction of N-benzoxymethylacrylamide (VII) *with compound* I. Ester VII (2.02 g., 0.01 mole) was heated under reflux in 15 ml. of dry ethylene chloride with 1.51 g. (0.01 mole) of compound I. After 30 min., heating was discontinued because the evolution of oxides of nitrogen was observed. The reaction mixture was allowed to cool and the solvent was removed *in vacuo.* The residue was extracted several times with petroleum ether (b.p. 50–60°) from which 0.56 g. (46%) of benzoic acid was isolated upon evaporation almost to dryness.

The residue which was insoluble in petroleum ether was extracted with hot chloroform. The part of the solid which was insoluble in chloroform melted at 146–147°, and was identified as *N*-trinitroethyl-4,4,4-trinitrobutanamide[4] (IX) by a mixed melting point determination with an authentic sample which gave no depression. It weighed 0.15 g. (4% yield). From the chloroform extract an oil separated on cooling which slowly crystallized, yielding 1.14 g. of solid, m.p. 85–90°. After three recrystallizations from absolute ethanol, *N*-benzoxymethyl-4,4,4-trinitrobutanamide (VIII), m.p. 132–133°, was obtained. A mixed melting point determination with an authentic sample of this compound was not depressed. Evaporation of the chloroform filtrate yielded a sticky, orange product from which more compound VIII was obtained after several crystallizations from absolute ethanol. The total yield of compound VIII was 0.68 g. (22%).

Preparation of N-benzoxymethyl-4,4,4-trinitrobutanamide (VIII). Ester VII (0.20 g., 1.0 mmole) and 0.15 g. (1.0 mmole) compound I were fused by gentle heating on a steam cone to a yellow liquid. It solidified on cooling, and after recrystallization from benzene, 0.29 g. (83% yield) of *N-benzoxymethyl-4,4,4-trinitrobutanamide* (VIII), m.p. 126–127° was obtained. Two additional recrystallizations from aqueous ethanol raised the m.p. to 133–133.5°.

Anal. Calcd. for $C_{12}H_{12}O_9N_4$: C, 40.45; H, 3.40; N, 15.73. Found: C, 40.58; H, 3.36; N, 15.76.

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1,1-Bis(2-hydroxyethyl)hydrazones

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Although 1,1-bis(2-hydroxyethyl)hydrazine (I) has been reported[1] as an unisolated product from the reaction of ethylene oxide and hydrazine hydrate, neither it nor any of its derivatives have been isolated and identified as pure chemical individuals. The reaction of diethanolamine with chloroamine, using the techniques previously described[2,3] for other secondary amines, offers an unexplored synthetic route to this hydrazine and its derivatives.

Our study of this reaction has shown that the hydrazine (I) is formed from chloroamine and diethanolamine and can be isolated in the form of certain hydrazone derivatives. Other hydrazone derivatives are thermally unstable, as is also the hydrazine (I) itself, and cannot be isolated. The yields, 9–94%, and characteristics of twelve such hydrazones are given in Table I. Higher alkyl derivatives, such as that from undecanal, undergo decomposition at temperatures required for distillation. The phenyl and pyridyl derivatives must be carefully fractionated to avoid decomposition. 2-Ethoxypropanal, methacrylaldehyde, tiglaldehyde, alkoxybenzaldehydes, and naphthaldehyde gave

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products which decomposed on attempted fractionation. The acetophenone derivative formed as a crystalline solid which was highly unstable. Nitrogen analyses varied from +2.8% to −0.9% from theoretical on successive analyses. The product from 4-acetaminobenzaldehyde was a solid, m.p. 325°, which corresponds in composition to its 4-aminomorpholine derivatives,[3] m.p. 206°, but is clearly different therefrom and is presumably a polymeric dehydration product. Reaction of either benzaldehyde or 2-ethylhexanal 1,1,-bis(2-hydroxyethyl)-hydrazone with thionyl chloride failed to give the dichloroethyl derivative. The benzaldehyde derivative was converted to its 1,1-bis(2-chloroethyl)-hydrazone in 43.5% yield with phosphorus oxychloride.

The spectroscopic properties of the bis(2-hydroxyethyl)hydrazones show some differences on comparison with those of the dimethylhydrazones.[3,4] The absorption maxima in the ultraviolet occur at 241.3–246.6 mμ for a series of aliphatic types (Table I). This represents a shift of about 5 mμ to longer wave lengths from the position of the maxima for the dimethylhydrazones and is accompanied by a slight decrease in extinction coefficient; *i.e.*, 3.18–3.52 and 3.7–4.0 for log ε. This is attributable to a bathochromic effect produced by the hydroxyl groups. Maxima in the infrared at 1614–1650 cm.$^{-1}$ for the aliphatic types is attributable to the C–N double bond stretching vibration. The characteristic strong bands at 1070–1080 and 1470 cm.$^{-1}$ are uniformly present in the aliphatic types. Variations from these locations are noted in the aromatic types. Data for the individual compounds are given in the Table.

Preliminary screening data have shown that benzaldehyde 1,1-bis(2-hydroxyethyl)hydrazone has a ±, − rating at a dose level of 30 mg./kg. and is toxic at a dose level of 125 mg./kg. in Sarcoma 180 tumor retardation studies.[5] These results do not establish either strong or consistent activity.

Nomenclature. Although it is convenient for us to name these compounds as hydrazones, alternative names as derivatives of iminodiethanol, a systematic name for diethanolamine, may be preferred for indexing purposes. Benzaldehyde 1,1-bis(2-hydroxyethyl)hydrazone becomes *N*-benzalamino-2,-2′-iminodiethanol on this basis.

EXPERIMENTAL[6]

Details of typical preparations are given. Data for other compounds are given in Table I. The aldehydes and di-

TABLE I

1,1-BIS(2-HYDROXYETHYL)HYDRAZONES

Carbonyl Compound	Yield, %	B.P. or M.P.[a]	Physical Data[b]	Nitrogen, % Calcd.	Nitrogen, % Found	Absorption Maxima Ultraviolet[e]	Infrared[f]				
2-Ethylbutanal	51	b. 94/0.5	1.4740/25	13.85	14.01	246.6/3.52	C3330s	2890s	1614m	1471s	1071S
3-Methylbutanal	40	b. 82/0.9	1.4721/23	14.88	15.07	246.0/3.76	C3390m	2890s	1612w	1471s	1079S
1-Hexanal	46	b. 89/0.9	1.4710/27	13.85	13.97	245.8/3.47	C3400s	2934S	1650w	1471S	1078S
1-Heptanal	48	b. 104/1	1.4699/26	12.95	12.85	244.7/3.41	C3376m	2932S	1643s	1471s	1077S
1-Nonal	25	b. 109/0.5	1.4709/23	11.46	11.24	241.3/3.18	C3322m	2880S	—	1470s	1081S
Cyclopentanone	22	b. 74/0.5	1.5023/24	15.04	14.97	250.4/3.38	C3377m	2899s	1637s	1437s	1072S
Benzaldehyde	56	b. 161/0.1	1.6083/27	13.46	13.16	—	T3342m	2864s	1640s	1455s	1054S
m-Nitrobenzaldehyde[c]	40	m. 95–6C	—	16.59	16.39	—	—	—	—	—	—
p-Nitrobenzaldehyde[c]	50	m. 84.5–5EW,C	—	16.59	16.36	—	—	—	—	—	—
9-Anthraldehyde	94	m. 80–1EW	—	9.08	9.32	—	C3459s	2942m	1626m	1448m	1063S
Pyridine-2-carboxaldehyde	27	m. 53–60; b. 188/0.5	—	20.8	19.89[d]	—	K —	—	—	1428S	1038S
6-Methylpyridine-2-carboxaldehyde	9	m. 93–5B	—	18.82	18.79	—	K —	—	1595m	1441S	1050S

[a] b., boiling point in °C./mm.; m., melting point. Solids recrystallized from C, chloroform; E, ethanol; W, water; B, benzene; P, petroleum ether (b.p. 66–75°); two letters indicate the use of mixed solvents. [b] $n_D{}^{t°}$. [c] The authors are indebted to Dr. H. Keith White for preparation of these compounds. [d] Dipicrate, from boiling ethanol, m.p. 131–133°; Calcd. for $C_{22}H_{21}N_9O_{16}$; N, 18.89. Found: N, 18.94. [e] λ_{max}/log ε. [f] Wave members cm.$^{-1}$ Solvent C, chloroform; T, carbon tetrachloride; K, potassium bromide; s, strong, S very strong; m, medium, w, weak.

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(4) Richard H. Wiley and Gether Irick, *J. Org. Chem.*, 24, 1925 (1959).

(5) The authors are indebted to Drs. C. C, Stock, D. A. Clarke, and R. K. Barclay, Sloan-Kettering Institute, for conducting these tests. The procedure and rating scales are given in *Cancer Research, Suppl. No 1*, p. 91 (1953) and *Suppl. No. 2*, p. 179 (1955).

(6) Analyses by Micro Tech Laboratories.

ethanolamine were commercial materials. The aliphatic aldehydes were redistilled before use.

1,1-Bis(2-hydroxyethyl)hydrazine solution. Concentrated ammonium hydroxide (13.4 ml.) was added slowly to 161 g. (0.113 mole) of cold (0°), 5.25% commercial sodium hypochlorite solution. The temperature was held below 5° during the addition. To this cold solution was added 12.5 g. (0.113 mole) of diethanolamine. The solution was warmed to room temperature slowly (6 hr.) and used in the following preparations in which it is designated as hydrazine solution (A).

9-Anthraldehyde 1,1-bis(2-hydroxyethyl)hydrazone. The hydrazine solution (A) prepared as described above was concentrated to a volume of 50 ml. by heating on a steam bath under vacuum. Seventy-five milliliters of methanol were added and the solution filtered to remove the precipitated sodium chloride. Two grams of 9-anthraldehyde were added to 21.5 ml. of this solution and the mixture heated to reflux for 18 hr. The orange crystals which separated upon cooling to room temperature were collected, dried, and taken up in 100 ml. of ether. The ether solution was washed with a dilute sodium bisulfite solution twice, then once with water, and evaporated to dryness. Recrystallization of the orange crystalline residue from ethanol-water gave 2.8 g., 93.6%, of the orange crystals, m.p. 80–81°. A second recrystallization from ethanol-water produced no change in the melting point.

1-Hexanal 1,1-bis(2-hydroxyethyl)hydrazone. To the 1,1-bis(2-hydroxyethyl)hydrazine solution (A) prepared as described above were added 100 ml. of methanol and 7.5 g. (0.075 mole) of 1-hexanal. The mixture was warmed to 50–60° for 0.5 hr. and then allowed to stand at room temperature overnight. After concentration to 100 ml. on a steam bath under vacuum, the solution was saturated with sodium chloride and extracted twice with 125 ml. portions of ether. Removal of solvent and distillation of the residue gave 6.9 g., 45.5%, of the colorless product, b.p. 89–90° at 0.9 mm.

Benzaldehyde 1,1-bis(2-hydroxyethyl)hydrazone. Twice the quantity of 1,1-bis(2-hydroxyethyl)hydrazone (0.226 mole) solution (A) prepared as described above was concentrated to a volume of 300 ml. on a steam bath under vacuum. To this solution was then added 10.6 g. (0.1 mole) of freshly distilled benzaldehyde and 100 ml. of methanol. After refluxing for 2 hr. and standing at room temperature overnight, the mixture was concentrated to 275 ml. on a steam bath under vacuum and extracted twice with 175-ml. portions of ether. The combined ether extracts were dried over magnesium sulfate. The ether was removed on a water bath and the residue distilled to give 11.55 g., 55.6% of the product, b.p. 161° at 0.1 mm.

Pyridine-2-carboxaldehyde 1,1-bis(2-hydroxyethyl)hydrazone. A solution of 1,1-bis(2-hydroxyethyl)hydrazone prepared as described above for solution (A) but with four times the quantities was concentrated to 400 ml. on a steam bath under vacuum and was made acidic to congo red with concd. hydrochloric acid. Seventeen and one-half grams of pyridine-2-carboxaldehyde were then added and the mixture heated to reflux for 15 min. Upon cooling to room temperature the solution was made basic to litmus and extracted twice with 200-ml. portions of chloroform. After drying 3 hr. over magnesium sulfate, the solvent was removed and the residue fractionated very slowly to yield 9.34 g., 27.3%, of the product, b.p. 188–193° at 0.5 mm. The viscous oil crystallized to give the solid product, m.p. 53–60°.

Attempted preparation of 4-acetamidobenzaldehyde 1,1-bis-(2-hydroxyethyl)hydrazone. A solution (A) of 1,1-bis(2-hydroxyethyl)hydrazine, prepared as described above, was concentrated on a steam bath under vacuum to 100 ml. The precipitated sodium chloride was then removed by filtration and the resulting liquid added to a solution containing 6.0 g. (0.0369 mole) of 4-acetamidobenzaldehyde in 100 ml. of ethanol. After refluxing gently for 1 hr. the mixture was cooled to room temperature and 200 ml. of water added. Upon standing 4 hr. in an ice bath the yellow crystals which had separated were collected by filtration and recrystallized from acetone-ethanol to give 0.2 g. of the product, m.p. 325°, with decomposition.

Benzaldehyde 1,1-bis(2-chloroethyl)hydrazone. Five and one-half grams (0.0263 mole) of benzaldehyde 1,1-bis(2-hydroxyethyl)hydrazone were mixed with 55 g. of phosphorus oxychloride and the mixture heated to reflux for 1 hr. The excess of liquid was removed by distillation on a steam bath under vacuum and the residue treated with 300 ml. of water. The solution was then extracted with 300 ml. of ether and the ether extract washed with 5% sodium bicarbonate solution. After drying over magnesium sulfate overnight the ether was removed on a steam bath and the product distilled carefully to yield 2.80 g., 43.5%, of product, b.p. 126° at 0.3 mm.

Infrared spectra were determined using a Baird double beam recording spectrophotometer against the 3.419 μ band for polystyrene and were run in carbon tetrachloride, chloroform, or potassium bromide as indicated in the Table. Ultraviolet spectra were made with a Beckman DK 3 recording spectrometer in spectral grade chloroform.

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Action of Grignard Reagents on Heterocyclic Compounds. IV.[1] Action of Grignard Reagents on Some Substituted Rhodanines

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Recently, substituted rhodanines that contain the toxiphoric dithiocarbamate chromophore —NCS$_2$— have received much attention as fungicides and mildew proofing agents,[2] and antimicrobal compounds.[3] It was thus of interest to prepare some differently substituted rhodanines which might be of use in this field. Mustafa, *et al.*[4] have allowed benzylidenerhodanine to react with Grignard reagents and they have stated that Grignard reagents add to the double bond of the lateral chain. The infrared measurements of their products (IId and IIe) are in favor of the constitution pro-

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