aniline was present in a similar experiment the 2,4-dinitrophenylhydrazone of acetaldehyde began to form only after 30 hours of refluxing. No acetaldehyde was produced when U.O.P. nickel catalyst was substituted for the Raney nickel.

Distillation of 100 ml. of isopropyl alcohol from 5 g. of Raney nickel through a 50-cm. Vigreux column at a take-off rate of about 0.1 ml. per minute gave a distillate from which the 2,4-dinitrophenylhydrazone of acetone was prepared; m.p. 124–125° after recrystallization from 95% ethanol (lit. value[4] 126°).

N-Benzylaniline from N-Benzylideneaniline.—The procedure of the standard synthesis was followed using 25 g. (0.138 mole) of N-benzylideneaniline and 100 ml. of benzyl alcohol, giving 20.5 g. (81% yield) of N-benzylaniline, b.p. 164–167° (7 mm.), m.p. 34–36° (lit. value[4] 37°).

In a similar experiment using 25 g. (0.138 mole) of N-benzylideneaniline and 100 ml. of ethanol, there was obtained 5.30 g. (32% yield) of N-ethylaniline, b.p. 85–89° (12 mm.), $n^{22}D$ 1.5519, and 12.80 g. (51% yield) of N-benzylaniline.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS & COMPANY]

Some Compounds Related to Chloromycetin[1]

BY MILDRED C. REBSTOCK AND CHARLOTTE D. STRATTON

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Several types of compounds related to Chloromycetin were synthesized. These included 1-(2,5-dimethoxy-4-nitrophenyl)-, 1-(4-thiazolyl)-, 1-*p*-cyclohexylphenyl- and 1-*p*-isopropylphenyl-2-dichloroacetamido-1,3-propanediols. The preparation of α-acetamido- and α-dichloroacetamido-α-hydroxy and α-alkyloxy-*p*-nitroacetophenones is described together with a group of DL-*threo*-1-*p*-nitrophenyl-2-α-aminoacylamido-1,3-propanediols.

Several considerations have prompted the preparation of compounds related to Chloromycetin. During a systematic study of the effect of structural variations in the Chloromycetin molecule on activity against microörganisms sensitive to the antibiotic, compounds also were screened against several groups of less sensitive pathogenic organisms. In the process, Hillegas found that β-hydroxy-α-dichloroacetamido-*p*-nitropropiopheneone, a compound described by Long and Troutman,[2] was somewhat more active than Chloromycetin in inhibiting the growth of certain fungi. Other derivatives of the antibiotic have been prepared with specific product formulations in mind. Still other types of compounds were synthesized for use in studies to elucidate the mechanism of action of the antibiotic and its fate in experimental animals. A number of Chloromycetin related compounds falling into these several categories are described below.

Recently Phillips[3] reported that N-(2,5-dimethoxy-4-nitrophenethyl)-dichloroacetamide had activity against the Rift Valley Fever virus and prepared a number of similar compounds which did not include 1-(2,5-dimethoxy-4-nitrophenyl)-2-dichloroacetamido-1,3-propanediol. Aside from the possibility that the latter compound might have activity against the smaller virus group, it was of interest to synthesize this derivative of Chloromycetin for studies to determine the effect of the methoxyl groups in the 2- and 5-positions of the phenyl ring on the ability of the substance to inhibit the growth of bacteria sensitive to the antibiotic. The method of Long and Troutman[4] for the synthesis of Chloromycetin and Chloromycetin-related compounds provided a straightforward route to the desired product. Dimethoxyquinacetophenone[5] which served as starting material was obtained by the methylation of quinacetophenone.[6] The latter compound was brominated and the substituted phenacyl bromide product converted to the hexamethylenetetramine complex. The amino ketone hydrochloride obtained from this intermediate by acid hydrolysis was dichloroacetylated without purification, as described in a preceding paper.[7] Introduction of the hydroxymethyl group by condensation with formaldehyde followed by the Meerwein–Verley–Ponndorf reduction of the carbonyl group gave the desired 1-(2,5-dimethoxyphenyl)-2-dichloroacetamido-1,3-propanediol intermediate. The latter product was acetylated and the nitro group was then introduced by treatment with a mixture of concentrated nitric and glacial acetic acids. The protective acetyl groups were removed selectively using the Kunz hydrolysis,[8] and the desired 1-(2,5-dimethoxy-4-nitrophenyl)-2-dichloroacetamido-1,3-propanediol product was isolated. The assignment of the nitro group to the "4"-position was indicated by theoretical considerations and by direct comparison of the ultraviolet absorption spectrum[9] with the absorption spectra of 4-nitro-2,5-dimethoxyphenyl alkanes. The absorption maxima for the compound related to Chloromycetin were found at λ 218, 240, 273 and 372, in water solution.

The preparation of 1-(5-nitro-2-thienyl)-2-dichloroacetimido-1,3-propanediol was first described in the scientific literature by Carrara, *et al.*[10] The 1-(4-pyridyl)-2-dichloroacetamido-1,3-propanediol was reported by Van Der Meer, *et al.*,[11] and Gentry[12] and Clark[13] in H. S. Mosher's laboratory have

(1) Parke, Davis and Company trademark for chloramphenicol.

(2) L. M. Long and H. D. Troutman, THIS JOURNAL, **73**, 481 (1951).

(3) A. P. Phillips, *ibid.*, **74**, 6125 (1952); **75**, 621 (1953).

(4) L. M. Long and H. D. Troutman, *ibid.*, **71**, 2469 (1949).

(5) G. C. Amin and N. M. Shah, *Org. Syntheses*, **28**, 42 (1948).

(6) G. C. Amin and N. M. Shah, *Org. Syntheses*, **31**, 91 (1951).

(7) M. C. Rebstock, C. D. Stratton and L. M. Bambas, THIS JOURNAL, **77**, 24 (1955).

(8) A. Kunz and C. S. Hudson, *ibid.*, **48**, 1982 (1926).

(9) We are indebted to Dr. J. M. Vandenbelt and Miss Carola Henrich and co-workers for the ultraviolet absorption studies described in this paper.

(10) G. Carrara and G. Weitnauer, *Gazz. chim. ital.*, **81**, 142 (1951).

(11) S. Van Der Meer, H. Kofman and H. Veldstra, *Rec. trav. chim.*, **72**, 236 (1953).

(12) R. E. Gentry, Jr., Ph.D. Thesis, Stanford University, Dec. 1953.

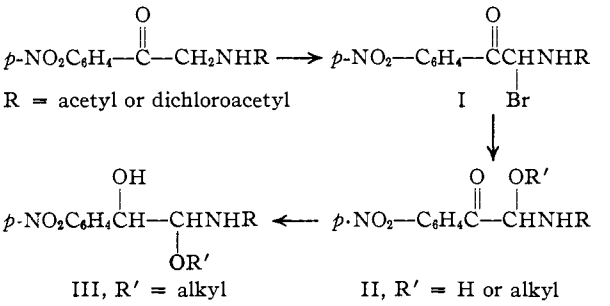
(13) D. E. Clark, Doctoral Dissertations No. 20, 38 (1952–1953).

synthesized the 2- and 3-pyridyl compounds. Among other heterocyclic aromatic compounds, the thiazole derivatives were of interest. The "4"-isomer, 1-(4-thiazolyl)-α-dichloroacetamido-1,3-propanediol, which is described here also was obtained conveniently from 4-acetylthiazole by a synthetic procedure based on the method of Long and Troutman.[4,7] The starting material was prepared by the method of Erlenmeyer and Ueberwasser[14] which involves condensing thioformamide with bromodiacetylmonoxime and hydrolyzing the resulting ketoxime with acetic acid in the presence of sodium bisulfite.

In continuing studies of compounds related to 1-biphenylyl-2-dichloroacetamido-1,3-propanediol, 1-*p*-cyclohexylphenyl- and 1-*p*-isopropylphenyl-2-dichloroacetamido-1,3-propanediol were prepared. Both compounds were also of interest in connection with studies designed to determine the effect on antibacterial activity of replacing the nitro group in the Chloromycetin molecule with other organic radicals. α-Bromoacetyl derivatives of cyclohexylbenzene and cumene were prepared by the Friedel–Crafts reaction. These intermediates then were taken through the remaining steps of the above synthetic procedure[4,7] to yield the desired compounds.

Although certain of these 1-aryl-2-dichloroacetamido-1,3-propanediols showed *in vitro* antibacterial activity, none had biological activity comparable to that of Chloromycetin. The 1-(2,5-dimethoxy-4-nitrophenyl)-2-dichloroacetamido-1,3-propanediol was relatively inactive in antibacterial and in antivirus tests.[15] Both 1-*p*-isopropyl- and 1-*p*-cyclohexylphenyl-2-dichloroacetamido-1,3-propanediols had low *in vitro* antibacterial activity, while the thiazole compound was relatively inactive against a group of six bacteria. In each of the examples described, only one isomer was isolated as a pure crystalline entity from the Meerwein–Verley–Ponndorf reductions, although two diastereoisomeric pairs are theoretically possible. The exact configuration of these compounds has not been established, but is thought to be *threo* since in all the examples reported to date where the configuration of the isomers is known, the *threo* isomer has been the major product of such reductions.

In addition to studying the effect of the nitrophenyl portion of the Chloromycetin molecule on antibacterial activity, a study has been made of a variety of acetophenone derivatives related to β-hydroxy-α-dichloroacetamido-*p*-nitropropiophenone since the latter compound was found to have marked activity against certain fungi. Among these compounds were the reaction products, II, obtained by treatment of α-bromo-α-dichloroacetamido-*p*-nitroacetophenone (I) with alcohols or water. The latter unique compound was prepared by the light-catalyzed bromination of α-dichloroacetamido-*p*-nitroacetophenone. In determining the structure of the product, the intact nature of the *p*-nitroacetophenone skeleton was indicated by characteristic absorption in the ultraviolet. Since the above alkoxy derivatives were obtained under the mildest of conditions, an extremely reactive bromine was indicated. Finally, reduction of the alkoxy compounds under Meerwein–Verley–Ponndorf conditions yielded the anticipated alcohol III.



Fleisher and Kendall[16] have described a reaction somewhat analogous except that the group on the carbon atom adjacent to the aryl ketone was acetoxy. In this case the compound brominated was 3,3-diacetoxy-11,20-diketo-12α-bromopregnane. The product contained an extremely reactive bromine which was shown to be on the 21-carbon atom.

α-Acetamido-*p*-nitroacetophenone readily underwent bromine substitution in the same manner as did the α-dichloroacetamido derivative, but when β-hydroxy-α-acylamido-*p*-nitropropiophenones were treated in this manner an N → O shift of the acyl group occurred, and the product isolated was an amine hydrobromide acyloxy derivative. Reversion to starting material occurred with the addition of an equivalent of base. Due to the ease of reaction of α-bromo-α-acylamido-*p*-nitroacetophenones with simple alcohols, the use of these compounds for preparing derivatives of alcohols in identification problems is indicated. Because of rather poor stability the bromo derivatives must be prepared shortly before use.

The possibility that phenylalanine may compete with Chloromycetin in enzyme acceptor systems has been considered by Woolley.[17] In a search for other substances more closely related to the antibiotic which might function in this manner, several derivatives differing from Chloromycetin by the substitution of simple amino acids for the dichloroacetyl group of the antibiotic were prepared for study. These compounds were also of interest in the light of Gale's observation that protein synthesis is impaired in Chloromycetin-sensitive bacteria treated with the antibiotic.[18]

Aside from the possibility that such compounds might compete with Chloromycetin as normal metabolites in an enzyme system, an equally attractive but opposite alternative was considered. The idea that these amino acid amides might be more effective antimetabolites than Chloromycetin by virtue of more efficient incorporation in the strategic enzyme system was entertained. Compounds were prepared in which glycine, alanine, phenylalanine and dichloroacetamidoglycine were substituted for

(14) H. Erlenmeyer and H. Ueberwasser, *Helv. Chim. Acta*, **23**, 197 (1940).

(15) We are indebted to Drs. A. S. Schlingman and J. Ehrlich and co-workers for antibacterial tests, to Dr. A. B. Hillegas and co-workers for the antifungal tests and to Dr. I. W. McLean and co-workers for the antivirus tests.

(16) G. A. Fleisher and E. C. Kendall, *J. Org. Chem.*, **16**, 573 (1951).

(17) D. W. Woolley, *J. Biol. Chem.*, **185**, 293 (1950).

(18) E. F. Gale and J. P. Folkes, *Biochem. J.*, **53**, 493 (1953).

TABLE I

1-ARYL-2-DICHLOROACETAMIDO-1,3-PROPANEDIOLS AND INTERMEDIATES USED IN PREPARING THESE COMPOUNDS

Structure, Ar =	Formula	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$ArCOCH_2Br$								
1-(2,5-Dimethoxyphenyl)(a)[19]	$C_{10}H_{11}BrO_3$	84–85	46.35	46.40	4.28	4.54		
1-*p*-Cyclohexylphenyl(b)	$C_{14}H_{17}BrO$	43–44	59.80	60.00	6.09	6.22		
$ArCOCH_2NHCOCHCl_2$								
1-(2,5-Dimethoxyphenyl)(c)	$C_{12}H_{13}Cl_2NO_4$	132–132.5	47.07	47.20	4.28	4.37	4.58	4.49
1-*p*-Cyclohexylphenyl (d)	$C_{16}H_{19}Cl_2NO_2$	116–117.5	58.54	58.74	5.83	6.04	4.26	3.94
1-*p*-Isopropylphenyl (e)	$C_{13}H_{15}Cl_2NO_2$	109–110	54.18	54.31	5.25	5.22	4.86	4.92
1-(4-Thiazolyl) (f)	$C_7H_6Cl_2N_2O_2S$	119.5–120.5	33.21	33.32	2.39	2.42	11.08	11.20
$ArCOCH(NHCOCHCl_2)CH_2OH$								
1-(2,5-Dimethoxyphenyl) (g)	$C_{13}H_{15}Cl_2NO_5$	121–122	46.44	46.41	4.50	4.59	4.17	4.10
1-*p*-Cyclohexylphenyl (h)	$C_{17}H_{21}Cl_2NO_3$	137–138	56.98	56.80	5.91	5.92	3.91	3.81
1-*p*-Isopropylphenyl (i)	$C_{14}H_{17}Cl_2NO_3$	115–116	52.84	52.96	5.38	5.58	4.40	4.40
1-(4-Thiazolyl) (j)	$C_8H_8Cl_2N_2O_3S$	142.5–143.5	33.93	34.23	2.85	2.89	9.90	9.84
$ArCHOHCH(NHCOCHCl_2)CH_2OH$								
1-(2,5-Dimethoxyphenyl) (k)	$C_{13}H_{17}Cl_2NO_5$	156–157	46.17	46.12	5.07	5.21	4.14	4.32
1-(2,5-Dimethoxy-4-nitrophenyl) (l)	$C_{13}H_{16}Cl_2N_2O_7$	164–164.5	40.74	41.02	4.21	4.32	7.31	7.46
1-*p*-Cyclohexylphenyl (m)	$C_{17}H_{23}Cl_2NO_3$	147.5–148.5	56.66	56.86	6.43	6.40	3.89	3.90
1-*p*-Isopropylphenyl (n)	$C_{14}H_{19}Cl_2NO_3$	114–115	52.51	52.40	6.08	5.89	4.37	4.36
1-(4-Thiazolyl) (o)	$C_8H_{10}Cl_2N_2O_3S$	150–151.5	33.69	33.80	3.54	3.66	9.83	9.79

(19) Solvents used in recrystallization in the succession indicated were: (a) ethanol; (b) ethanol, ligroin; (c) ethanol; (d) ethyl acetate, ethanol; (e) ethylene dichloride, ethanol; (f) ethylene dichloride, isopropyl alcohol, ethylene dichloride; (g) *n*-butyl alcohol, ethylene dichloride; (h) ethylene dichloride, ethanol, ethylene dichloride; (i) ethylene dichloride; (j) ethylene dichloride; (k) ethylene dichloride; (l) ethylene dichloride; (m) ethylene dichloride, ethyl acetate, ethanol; (n) ethylene dichloride, benzene, ethylene dichloride; (o) ethylene dichloride.

TABLE II

AMINO ACID AMIDES OF DL-*threo*-1-*p*-NITROPHENYL-2-AMINO-1,3-PROPANEDIOL AND PHTHALYL INTERMEDIATES

p-$NO_2C_6H_4CHOH—\underset{\displaystyle NHR}{\underset{|}{CH}}—CH_2OH$

R =	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, Calcd.	Nitrogen, Found
Phthalylglycyl	218–220	$C_{19}H_{17}N_3O_7$	57.14	57.11	4.29	4.27	10.52	10.26
Phthalylalanyl	194–195	$C_{20}H_{19}N_3O_7$	58.11	58.31	4.63	4.72	10.17	10.05
Glycyl	172–173	$C_{11}H_{15}N_3O_5$	49.07	49.13	5.61	5.72	15.61	15.33
Alanyl	156–157	$C_{12}H_{17}N_3O_5$	50.88	51.29	6.05	6.22	14.83	14.56
Phenylalanyl	139–140	$C_{18}H_{21}N_3O_5$	60.16	59.98	5.89	5.77	11.69	12.01
Dichloroacetamidoglycyl	170–171	$C_{13}H_{15}Cl_2N_3O_6$	41.07	41.49	3.98	3.95	11.05	11.28

the dichloroacetyl group in the Chloromycetin molecule (Table II). Although these compounds did exhibit a low order of *in vitro* antibacterial activity, biological tests failed to provide supportive evidence for either of the above propositions.

Experimental

1-(2,5-Dimethoxy-4-nitrophenyl)-2-dichloroacetamido-1,3-propanediol.—Using dimethoxyquinacetophenone[5,6] as starting material, the procedure of Long and Troutman[4] was employed in the preparation of 1-(2,5-dimethoxyphenyl)-2-dichloroacetamido-1,3-propanediol. The details of this synthesis have been reported in numerous publications and will not be repeated here other than to mention that the modified approach reported for the synthesis of 1-*p*-bromo- and *p*-methylbiphenylyl-2-dichloroacetamido-1,3-propanediol was used.[7] The analytical data characterizing the intermediates are given in Table I.

1-(2,5-Dimethoxyphenyl)-2-dichloroacetamido-1,3-propanediol was acetylated by dissolving 17.9 g. of the compound in 54 ml. of pyridine at room temperature and adding 57.3 ml. of acetic anhydride. The reaction mixture was at once chilled to 0° in an ice-bath and left to stand overnight while the ice was allowed to melt. The solvents were removed on the high vacuum pump and the crystalline residue recrystallized from 110 ml. of absolute ethanol to yield 21.9 g. of product melting at 136–138°. An analytical sample was prepared by recrystallizing 0.5 g. twice from absolute ethanol (m.p. 137–138°).

Anal. Calcd. for $C_{17}H_{21}Cl_2NO_7$: C, 48.35; H, 5.00; N, 3.32. Found: C, 48.54; H, 5.03; N, 3.35.

Nine grams of the above diacetate was suspended in 45 ml. of glacial acetic acid in a 3-necked round-bottom flask equipped with a stirrer and thermometer. The mixture was cooled to 17° and 4.1 ml. of concentrated nitric acid was added rapidly. No rise in temperature occurred. The reaction mixture was kept at 16–18° for 40 min. then allowed to come to room temperature and to stand for 1.33 hr. longer. The product which had partially separated was completely precipitated by adding 100 ml. of cold water. The mixture was chilled and filtered and washed with cold water to yield 9.2 g. of a yellow solid melting at 143–143.7°. A sample was recrystallized for analysis from absolute ethanol (m.p. 142.5–143.2°).

Anal. Calcd. for $C_{17}H_{20}Cl_2N_2O_9$: C, 43.69; H, 4.31; N, 6.00. Found: C, 43.95; H, 4.41; N, 6.21.

The acetyl groups were removed by the method of Kunz.[8] Nine grams of the above nitration product was dissolved in 235 ml. of acetone. The solution was cooled to 0° and 555 ml. of 0.1 *N* sodium hydroxide at 0° was added, together with an additional 65 ml. of acetone when the starting material began to precipitate. After standing for 1.5 hours at 0°, the reaction mixture was neutralized with 1 *N* sulfuric acid and filtered to remove a small amount of solid. The solvents were partially evaporated at reduced pressure and the product was filtered from the chilled solution to give 6.5 g. (86%) of yellow crystals melting at 163–164.5°. A sample was recrystallized for analysis from ethylene dichloride (m.p. 164–164.5°). That the compound was observed to

change crystal form near the melting point may account for the fact that the same material melted at 168–169° on the Fisher–Johns block.

1-(4-**Thiazolyl**)-**2-dichloroacetamido**-1,**3-propanediol.**—4-Acetylthiazole was prepared by treatment of the corresponding ketoxime with acetic acid and sodium bisulfite as described by Erlenmeyer and Ueberwasser[14] who obtained the latter compound from the condensation of thioformamide and bromodiacetylmonoxime.

4-Acetylthiazole was brominated in carbon tetrachloride solution to give an unstable oily product which proved to be the desired α-bromomethyl ketone intermediate as shown in subsequent steps of the synthesis. The bromination procedure was similar to that used by Erlenmeyer, *et al.*, for the preparation of α-bromoacetylthiazole from the 2-acetyl derivative.[20] The hexamethylenetetramine salt was prepared from freshly brominated ketone. The product separated from chloroform solution in 78% yield and was hydrolyzed without purification. From 31.6 g. of the salt treated with 52 ml. of concentrated hydrochloric acid and 225 ml. of absolute ethanol stirred at room temperature overnight was obtained 26 g. of solid which consisted of a mixture of 4-α-aminoacetylthiazole hydrohalide and ammonium chloride. This material was converted to the dichloroacetamide by suspending in dimethylformamide solution and treating with dichloroacetyl chloride as described in a preceding publication.[7] The recrystallized product was hydroxymethylated without complication, but two products were obtained from the Meerwein–Verley–Ponndorf reduction of the 4-α-dichloroacetamido-β-hydroxypropionylthiazole. The major product of the reaction proved to be the desired 1-(4-thiazolyl)-2-dichloroacetamido-1,3-propanediol. The minor component appeared to be an isopropyl ether[21] of this compound. To 130 ml. of refluxing isopropyl alcohol containing 8.7 g. of aluminum isopropylate and 0.796 g. of aluminum chloride was added 5.63 g. of the ketone to be reduced. The reaction was carried out in a 300-ml. 3-necked flask equipped with a mechanical stirrer and a Hahn condenser. After refluxing for 2.75 hr. and removing the acetone formed by distillation, an additional 40 ml. of isopropyl alcohol and 1 g. of aluminum isopropylate was added. The reaction was allowed to proceed for 1.5 hr. longer, then 100 ml. of water and 2 g. of sodium bicarbonate were added. The hot solution was filtered with the aid of Filter-Cel and the residue was extracted three times with 250-ml. portions of hot isopropyl alcohol. The combined extracts were evaporated at reduced pressure and the residue was treated with 15 ml. of ethylene dichloride. After standing overnight in the refrigerator, 810 mg. of crystals (m.p. 124–129°) was filtered off. This material was recrystallized three times from ethylene dichloride to give 260 mg. of product (m.p. 150–151.5°) which analyzed satisfactorily for the 1-(4-thiazolyl)-2-dichloroacetamido-1,3-propanediol; see Table I.

The mother liquor from the original recrystallization of the 810 mg. was evaporated and the residue was recrystallized three times from isopropyl alcohol to give 95 mg. of product melting at 157–157.5°. The analytical data indicated that this compound could be an isopropyl ether of the above product.[21] The ultraviolet absorption spectrum gave no indication of unsaturation in conjugation with the thiazole nucleus. A comparison of the infrared absorption curves of the two products also supported the conclusion that the latter product was an isopropyl ether derivative of the former.

Anal. Calcd. for $C_{11}H_{16}Cl_2N_2O_3S$: C, 40.37; H, 4.93; N, 8.56. Found: C, 40.14; H, 4.97; N, 8.47.

An acetate derivative was prepared for more precise identification by dissolving 35 mg. in 0.4 ml. of pyridine, chilling to 0° and adding 0.5 ml. of acetic anhydride. After standing for 16 hr. at room temperature the solvents were removed on the high vacuum pump and the residue was recrystallized from aqueous ethanol. After two recrystallizations the product melted at 139.3–139.8°.

Anal. Calcd. for $C_{13}H_{18}Cl_2N_2O_4S$: C, 42.28; H, 4.91; N, 7.59. Found: C, 42.57; H, 5.06; N, 7.54.

(20) H. Erlenmeyer, O. Weber, P. Schmidt, G. Kunz, Chr. Zinsstag and B. Prijs, *Helv. Chim. Acta*, **31**, 1142 (1948).

(21) The formation of isopropyl ethers as by-products in aluminum isopropylate reductions has been reported to occur in a few instances. A discussion of this variation may be found in "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., Vol. II, p. 178.

1-*p*-**Cyclohexyl- and** 1-*p*-**Isopropylphenyl-2-dichloroacetamido-1,3-propanediol.**—Cyclohexylbenzene and isocumene were condensed with α-bromoacetyl bromide in carbon disulfide solution with the aid of aluminum chloride. The latter reagent was added in portions during 1.25 hours to the stirred and gently refluxing reaction mixtures. The products were worked up by pouring on ice containing concd. HCl to decompose the aluminum chloride complexes and extracted into ethyl acetate. The ethyl acetate extracts were washed with saturated sodium bicarbonate solutions and water, then dried and evaporated. *p*-Isopropylphenacyl bromide was obtained as an oil which was converted to the crystalline hexamethylenetetramine salt without purification. The *p*-cyclohexylphenacyl bromide melted at 43–44°. The analytical sample was recrystallized from ethanol and ligroin.

Anal. Calcd. for $C_{14}H_{17}BrO$: C, 59.80; H, 6.09. Found: C, 60.00; H, 6.22.

Although chloroform is generally useful as a solvent in the preparation of hexamethylenetetramine complexes of substituted phenacyl halides, this solvent was not practical since neither of the above salts would separate from solution. When the reaction was carried out in chlorobenzene, the products were obtained readily in crystalline form. The α-aminomethyl ketone hydrohalides were prepared by acid hydrolysis of the crude tetramine complexes and converted without purification to the dichloroacetamides by treating with dichloroacetyl chloride in dimethylformamide solution.[7] The amides were hydroxymethylated and finally reduced under Meerwein–Verley–Ponndorf conditions to give the desired 1-*p*-substituted phenyl-2-dichloroacetamido-1,3-propanediol products; see Table I. Only a single diastereoisomer was isolated in either case. Since each compound had a low order of antibacterial activity, it is likely that the configuration of the isomers is *threo*.

α-Bromo-α-**acylamido**-*p*-**nitroacetophenones.**—A 17.0-g. sample of α-dichloroacetamido-*p*-nitroacetophenone was suspended in 200 ml. of chloroform. The reaction mixture was stirred mechanically and illuminated with a 500-watt projector lamp at a distance of 3 to 4 inches while 10.25 g. of bromine was added dropwise. The rate of addition was controlled by the rate of reaction and required about 45 min. The solvents were removed at reduced pressure and the residue was crystallized from 200 ml. of carbon tetrachloride to yield 14.6 g. of product (m.p. 118–120°). An analytical sample was obtained by recrystallizing a sample twice more from carbon tetrachloride (m.p. 119–121°).

Anal. Calcd. for $C_{10}H_7BrCl_2N_2O_4$: C, 32.46; H, 1.99; N, 7.57. Found: C, 32.67; H, 2.02; N, 7.80.

When 4.4 g. of α-acetamido-*p*-nitroacetophenone was treated in this manner, an oily product was obtained which appeared to have the α-bromo-α-acetamido-*p*-nitroacetophenone structure. Treatment with ethanol or water gave crystalline ethoxy and hydroxy derivatives analogous to the products prepared from α-bromo-α-dichloroacetamidonitroacetophenone and described below.

α-**Hydroxy and** α-**Alkyloxy**-α-**acylamido**-*p*-**nitroacetophenones.**—A 500-mg.s ample of α-bromo-α-dichloroacetamido-*p*-nitroacetophenone was suspended in 40 ml. of water and warmed for a few minutes on the steam-bath until dissolved. Upon chilling the product crystallized. A final recrystallization from ethylene dichloride gave analytically pure material (m.p. 136–137°).

Anal. Calcd. for $C_{10}H_8Cl_2N_2O_5$: C, 39.10; H, 2.63; N, 9.12. Found: C, 39.17; H, 2.61; N, 8.93.

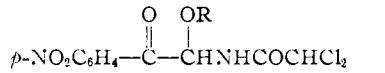
Treatment of α-bromo-α-acetamido-*p*-nitroacetophenone with water in this manner gave an analogous product which melted at 154–155° after recrystallizations from ethylene dichloride and ethyl acetate.

Anal. Calcd. for $C_{10}H_{10}N_2O_5$: C, 50.42; H, 4.23; N, 11.76. Found: C, 50.13; H, 4.33; N, 11.63.

When either α-acetamido or α-dichloroacetamido-α-bromonitroacetophenone was treated with an excess of one of the lower alcohols, the reaction mixture warmed spontaneously as the compound dissolved. The alcohol solutions were heated briefly on the steam-bath, then chilled, and the crystalline products isolated by filtration. Analytical samples were prepared by recrystallization from the same alcohol. In the case of the α-bromo-α-acetamidonitroacetophenone, only the ethoxy derivative was prepared (m.p. 149–150°).

Anal. Calcd. for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 54.19; H, 5.27; N, 10.67.

α-Bromo-α-dichloroacetamidonitroacetophenone was combined with several low molecular weight alcohols. The products crystallized readily and were obtained in good yield.



p-$NO_2C_6H_4$—C(=O)—C(OR)—CHNHCOCHCl$_2$

R =	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$-CH_3$	139.5–140	$C_{11}H_{10}Cl_2N_2O_5$	41.14	41.38	3.14	3.35	8.72	8.78
$-C_2H_5$	147–148	$C_{12}N_{12}Cl_2N_2O_5$	43.00	43.06	3.61	3.71	8.36	8.26
$-CH(CH_3)_2$	134.5–135.5	$C_{13}H_{14}Cl_2N_2O_5$	44.71	44.80	4.05	4.06		

Meerwein–Verley–Ponndorf Reductions of α-Alkoxy-α-dichloroacetamido-*p*-nitroacetophenones.—Both the ethoxy and isopropoxy compounds were reduced smoothly to the corresponding benzyl alcohols. In the case of the ethoxy compound it was necessary to use aluminum ethoxide with ethanol as the solvent. When the reaction was carried out in isopropyl alcohol with aluminum isopropylate, a mixture of ethoxy and isopropoxy products was obtained, presumably by interchange of alkoxy groups. The isopropoxy compound was reduced smoothly in isopropyl alcohol solution in the presence of aluminum isopropylate as indicated.

A sample of 4.15 g. of α-isopropoxy-α-dichloroacetamido-*p*-nitroacetophenone was added to a refluxing solution containing 4.86 g. of aluminum isopropylate and 0.05 g. of aluminum chloride in 200 ml. of dry isopropyl alcohol. The reaction mixture was allowed to reflux gently for 2 hours while the acetone produced was distilled off. At the end of this time, 100 ml. of water and 1 g. of $NaHCO_3$ were added and the hot solution was filtered on a Buchner funnel with the aid of Filter-Cel. The solid residue was extracted twice with 100-ml. portions of boiling isopropyl alcohol. The filtered extracts were combined and evaporated. The product was crystallized from ethylene dichloride to yield 2.86 g. of yellow solid. Color was removed by treating a hot ethanol solution with norite, filtering and adding water to turbidity. An analytical sample was prepared by a final recrystallization from ethylene dichloride (m.p. 156.5–158°).

Anal. Calcd. for $C_{13}H_{16}Cl_2N_2O_5$: C, 44.46; H, 4.59; N, 7.98. Found: C, 44.27; H, 4.65; N, 7.99.

The corresponding ethoxy derivative, prepared by carrying out the reduction in ethanol solution and using aluminum ethoxide, was crystallized for analysis from ethylene dichloride, ethanol, and finally ethylene dichloride to a melting point of 152–153°.

Anal. Calcd. for $C_{12}H_{14}Cl_2N_2O_5$: C, 42.71; H, 4.18; N, 8.31. Found: C, 43.11; H, 4.13; N, 8.25.

α-Amino Acid Amides of DL-*threo*-1-*p*-Nitrophenyl-2-amino-1,3-propanediol.—Phthalyl derivatives[22] of glycine, DL-alanine and DL-phenylalanine were converted to the acid chlorides by refluxing with excess thionyl chloride on the steam-bath for *ca.* 30 min. The excess thionyl chloride was evaporated and the products were crystallized from ligroin, benzene, and a ligroin–low boiling petroleum ether mixture, respectively. The acid chlorides reacted smoothly with DL-*threo*-1-*p*-nitrophenyl-2-amino-1,3-propanediol to give the desired amides. The phthalyl groups then were removed by treatment with hydrazine hydrate followed by adjustment of the *p*H with hydrochloric acid or acetic acid as is usual in the Sheehan peptide synthesis.[23,24] The preparation of the glycine amide is given as an example. Ten grams of DL-*threo*-1-*p*-nitrophenyl-2-amino-1,3-propanediol and 5 g. of sodium bicarbonate were suspended in a mixture of 100 ml. of ethyl acetate and water. To the rapidly stirred ice-cold solution was added 10.5 g. of phthalylglycyl chloride in portions during 30 min. The reaction was allowed to proceed for 1 hr. longer, then the solid amide product was filtered off (yield 18.5 g., m.p. 218–220°). An analytical sample was prepared by recrystallization from ethanol.

See Table II for data characterizing this compound and others in this series. To remove the phthalyl group, 2.2 g. of the above product was suspended in 40 ml. of absolute ethanol and refluxed for 2 hr. with 1.0 g. of 85% hydrazine hydrate. The solvents were removed under reduced pressure and the residue dissolved in 40 ml. of water. The *p*H was adjusted to 5 with glacial acetic acid, the mixture was chilled, and the solid phthalyl hydrazide was filtered off. The aqueous residue was made strongly alkaline with ammonia and extracted three times with ethyl acetate. The combined extracts were dried and evaporated and the product was crystallized from 15 ml. of ethylene dichloride. A second recrystallization from 15 ml. of absolute ethanol yielded 0.87 g. of product (m.p. 172–173°).

DL-*threo*-1-*p*-Nitrophenyl-2-azidoacetamido-1,3-propanediol.—Two grams of DL-*threo*-1-*p*-nitrophenyl-2-bromoacetamido-1,3-propanediol[25] was refluxed in a mixture of 25 ml. of ethanol and 5 ml. of water with 390 ml. of sodium azide for 3 hours. After standing overnight at room temperature the solvents were removed at reduced pressure. The residue was dissolved in 100 ml. of ethyl acetate and washed with 50 ml. of water. The ethyl acetate layer was dried over anhydrous magnesium sulfate and evaporated. The residue was recrystallized from 10 ml. of ethanol to give 0.9 g. The product was recrystallized once again from ethanol and finally from ethyl acetate for analysis (m.p. 121–122°).

Anal. Calcd. for $C_{11}H_{13}N_5O_5$: C, 44.75; H, 4.44; N, 23.72. Found: C, 44.82; H, 4.68; N, 23.81.

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(22) U. S. Patent 2,498,665.

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