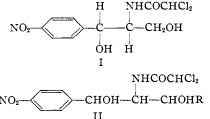
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS & COMPANY]

Chloromycetin (Chloramphenicol¹). The Synthesis of 3-Methyl and 3-p-Nitrophenyl Substituted Compounds

BY MILDRED C. REBSTOCK

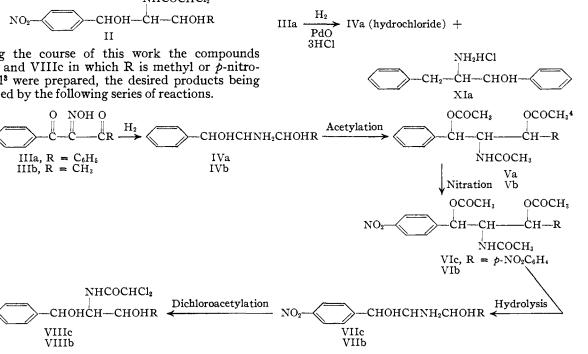
It was of interest to prepare compounds related to Chloromycetin in which a methyl group or p-nitrophenyl group was substituted in the side chain at the terminal carbon atom. Intermediates were obtained by the catalytic hydrogenation of isonitrosobenzoylacetone and isonitrosodibenzoylmethane. A study of the conditions of hydrogenation led to the characterization of certain other related compounds which were encountered as side products as well as the desired starting materials.

In preparing compounds related to Chloromyce $tin (I)^2$ it was of interest to synthesize certain ones in which the antibiotic structural pattern was preserved except for the lengthening of the side chain (II).



During the course of this work the compounds VIIIb and VIIIc in which R is methyl or \dot{p} -nitrophenyl³ were prepared, the desired products being obtained by the following series of reactions.

catalyst and the reduction was carried out in the presence of three equivalents of hydrochloric acid to prevent the formation of diphenylpyrazines. The hydrogenation of compounds IIIa and IIIb was carried out under virtually these conditions except that palladium oxide was used as the catalyst. The presence of a second ketone group was found to influence the course of the reaction. When R was phenyl (IIIa) an appreciable quantity of the related compound XIa was obtained in which hydrogenolysis of the benzyl hydroxyl group had occurred.



The reduction of β -isonitrosophenones has been studied extensively by Hartung and co-workers^{5,6,7,8} who found that the corresponding amino alcohols could be obtained by catalytic hydrogenation when palladium-on-Norite was used as the

(1) Chloramphenicol is the generic name for the antibiotic identified as Chloromycetin, a Parke, Davis & Company trademark.

(2) Rebstock, Crooks, Controulis and Bartz, THIS JOURNAL, 71, 2450 (1949).

(3) During the preparation of this paper one of the isomeric forms of compound VIIIc was reported by Huebner and Scholz, ibid., 78, 2089 (1951). This group obtained intermediate IVa by hydrogenating 1,3-diphenyl-2-phenylhydrazono-1,3-propanedione at neutral pH with Raney nickel catalyst.

(4) No specific configurational inference is intended.

(5) Hartung, THIS JOURNAL, **50**, 3370 (1928).
(6) Hartung, *ibid.*, **53**, 2248 (1931).

NO₂

(7) Hartung and Munch, ibid., 51, 2262 (1929).

(8) Hartung, Munch, Deckert and Crossley, ibid., 52, 3317 (1930).

The products of hydrogenation were separated by fractional crystallization of the free bases. The structure of compound XIa was confirmed by in-dependent synthesis. The series of reactions used by Algar, Hickey and Sherry⁹ who first prepared this compound were repeated to obtain a sample for mixed melting point determination. The synthesis involved hydrogenation of benzalacetophenone to form β -phenylpropiophenone,¹⁰ conversion of this compound to the isonitroso derivative, and reduction to the amino alcohol (XIa). There was no depression in melting point when the free bases or their corresponding dichloroacetamides were mixed.

When R was methyl (IIIb) the intermediate β (9) Algar, Hickey and Sherry, Proceedings of the Royal Irish Academy, **49**, 109 (1943). (10) "Organic Syntheses," Coll. Vol. I, p. 101.

TABLE	I
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INTERMEDIATES AND DERIVATIVES OF INTERMEDIATES IN THE SYNTHESIS OF VIIIb, VIIIc, XIIb AND XIIc

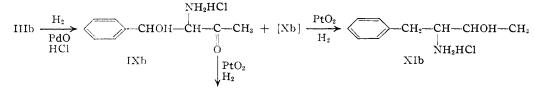
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Compound	R ==	Formula	M.p., °C.	Carbo Caled.	n, %ª Found						
NHCOCHCI?	$R = CH_{I}$	$C_{12}H_{15}NO_3Cl_2$	148 - 149	49.33	49.40	5.18	5.32	4.79	4.68		
CsHs—CHOH—CH—CHOHR NHCOCHCl:	$R = C_6 H_{5^{}}$ $R = C H_{5^{}}$	C17H17NO2Cl2 C12H18NO2Cl2	1 71– 172 132–133	$\begin{array}{c} 57.64 \\ 52.19 \end{array}$	57.83 52.39	$5.12 \\ 5.48$	$\begin{array}{c} 5.27\\ 5.75\end{array}$	3.95 5.08	3.88 5.07		
C6H6CH2CHCHOHR NHCOCHCl2	$R = C_6 H_{b} -$	C ₁₇ H ₁₇ NO ₂ Cl ₂	143-144	60.37	60.25	5.06	5.22	4.14	4.23		
C6H5CHOAc—CH—CHOAcC6H5 NHCOCHCl2	$R = CH_{a}$ -	C21H21NO5Cl2 C14H17NO8Cl2	147 - 148 98 - 99	$\begin{array}{c} 57.54 \\ 52.84 \end{array}$	57.65 52.84	$\frac{4.83}{5.38}$	$\frac{4.90}{5.38}$	3.13 4.40	3.34 4.60		
CeHe-CH2-CH—CHOAc—R NHAc	$R = C_8 H_{5^-}$ $R = C H_{3^{}}$	C19H19NO3Cl2 C16H21NO5	178179 130131	$\begin{array}{c} 60.01\\ 62.53 \end{array}$	$\begin{array}{c} 60.14 \\ 62.68 \end{array}$	5.04 6.89	5.28 6.92	3.68 4.56	3,81 4.59		
C6H6CHOAc—CH—CHOAcR NHAc	$R = C_6 H_{\delta} -$	$C_{21}H_{23}NO_{5}$	199-200	68.28	68.43	6.28	6.38	3.79	3,70		
C6H5CH2CH-CHOAcC6H5		$C_{19}H_{21}NO_2$	96 or 132b	73.28	73.23	6.80	6.57				
p·NO₂—C6H₄—CHOH—	$R = CH_3$	$C_{10}H_{14}N_2O_4$	144 - 145	53.09	53.39	6.24	6.32	12.39	12.47		
CHNH2-CHOHR	$R = p - NO_2C_8H_4-$	C15H15N3O8	196 - 197	54.01	53.84	4.54	4.71	12.61	12.83		
p-NO2C6H4—CH2—CHNH2—CHOHR	$R = CH_3 -$	$C_{10}H_{14}N_2O_3$	105 - 107	57.13	56.85	6.71	6.71	13.33	13.27		
	$\mathbf{R} = p \cdot \mathbf{NO}_2 \mathbf{C}_6 \mathbf{H}_4 -$	$C_{15}H_{16}N_{3}O_{5}$	166 - 167	56.77	57.21	4.77	4.73	13.24	13.15		
NHAc											
p-NO2C₀H₄CHOAcCH-CHOAcCH₃ NHAc		$C_{16}H_{20}N_2O_7$	153.5-154.5	54.54	54.41	5.72	5.97	7,95	7.54		
p-NO2C0H4CHOH-CH-CHOHCH3		$C_{12}H_{16}N_2O_5$	214 - 215	53.72	54.06	6.01	6.02	10.44	10.33		
NHCOCHCl2	$R = CH_{3}$ -	$\mathrm{C}_{12}\mathrm{H}_{14}\mathrm{N}_{2}\mathrm{O}_{5}\mathrm{C}\mathrm{l}_{2}$	191 - 192	42.75	43.02	4.19	4.25	8,31	8.14		
p-NO2C6H4CHOH-CH-CHOHR	$R = p - NO_2C_6H_4 -$	C17H15N3O7Cl2	217 - 219	45,96	46.08	3,40	3.40	9.46	9.70		
NHCOCHCl ₂	$R = CH_{8}$ -	$\mathrm{C}_{12}\mathrm{H}_{14}\mathrm{N}_{2}\mathrm{O}_{4}\mathrm{C}l_{2}$	185 - 186	44.87	44.96	4.39	4.42	8.72	8,59		
p-NO;—C ₆ H ₄ —CH ₂ CH—CHOHR	$R = p - NO_2C_6H_4 -$	$C_{17}H_{15}N_3O_6Cl_2$	252 - 253	47.68	47.66	3.53	3.60	9.81	9.73		

^a The analytical data were determined by Mr. C. E. Childs, Mrs. Geraldine Koch and Miss Virginia Pawlik of these laboratories. ^b The compound melting at 96° contains a molecule of water which can be removed by drying at 75° for 16 hours *in vacuo*. The dried product melts at 132-133°.

hydroxy ketone (IXb) was isolated. A further reduction in the presence of Adams platinum catalyst was necessary to obtain the desired aminodiol (IVb). The gummy residue (Xb) remaining after evaporation of the mother liquors from which IXb was crystallized was similarly hydrogenated in the presence of Adams catalyst. The free base of this product gave a crystalline derivative when treated with methyl dichloroacetate which proved to be the amide of XIb. The isolation of this compound demonstrated that again hydrogenolysis of the benzyl hydroxyl had occurred. precursor of XIa are formed by dehydration of the intermediate IXb or its phenyl compound to form dehydroamino ketones which are then hydrogenated has not been ascertained.

Compounds XIa and XIb were converted to Chloromycetin related compounds by nitration of the protected amino alcohols in the usual manner. These compounds were then hydrolyzed to remove the protecting groups and converted to the dichloroacetamides XIIb and XIIc.

Four stereoisomers of VIIIc can exist as a pair of enantiomorphs and two *meso* compounds. The



IVb (hydrochloride)

While it is to be expected that the carbonyl group next to the benzene ring in compound IIIb will be reduced more readily than the other carbonyl group, ultraviolet absorption studies of IXb established that this was the case.¹¹ The absorption spectrum of compound IXb was characteristic of that of a substituted benzyl alcohol and not a butyrophenone.

The fact that compound IXb can be isolated as an intermediate may have some bearing upon the mechanism of the reaction by which XIa and b are formed. Compound Xb was not characterized. Whether this precursor of XIb or the corresponding

(11) The author is greatly indebted to Dr. J. M. Vandenbelt for the ultraviolet absorption studies.

NO₂-CH₂-CH-CHOH--R
NHCOCHCl₂
XIIc, R =
$$p$$
-NO₂C₆H₄-
b, R = CH₃-¹²

asymmetric configuration of the structural type VIIIb provides for the existence of four pairs of enantiomorphs. In reducing the oximino ketones IIIa and IIIb only a single isomer was isolated. At the present time the configuration of these compounds is not known. Methods for obtaining the other isomers are being investigated.

(12) Compound XIIb was previously prepared by Dr. G. W. Moersch of these laboratories by another method which will be described elsewhere.

Experimental

Hydrogenation of Isonitrosobenzoylacetone.-The isonitroso derivative of benzoyl acetone was prepared by treatment of the diketone with sodium nitrite in the presence of glacial acetic acid as previously described by Wolff.18 Fifty grams of isonitrosobenzoylacetone dissolved in 440 ml. of absolute ethanol containing three equivalents of hydrogen chloride was hydrogenated in the presence of 3.0 g. of palla-dium oxide catalyst at 50 p.s.i. The hydrogen uptake was at first rapid with heat being evolved. After 22 hours the catalyst was removed although the uptake was only 64% of the theoretical and the solvent evaporated under reduced pressure. The crystalline residue was recrystallized from absolute alcohol, 33 g. of product melting at 158-161° being obtained. A second crop of 5.3 g. was combined with the above material. A sample recrystallized for analysis twice from ethanol melted at 165–166° with decomposition. Ele-mentary analysis and ultraviolet absorption studies indicated that the compound had the structure IXb.

Anal. Calcd. for $C_{10}H_{14}NO_2Cl$: C, 55.68; H, 6.54; N, 6.50. Found: C, 55.62; H, 6.74; N, 6.50.

A sample of 26.5 g. of the amino ketone IXb was hydrogenated to the aminodiol IVb using 600 mg. of Adams catalyst and carrying out the reduction in 300 ml. of 50% aqueous ethanol at room temperature and 46 p.s.i. When one equivalent of hydrogen had been absorbed in about seven hours, the catalyst was removed and the solvent evaporated at reduced pressure. The residue was dissolved in 250 ml. of water and the acid solution extracted twice with ether. The aqueous residue was then made alkaline with ammonia and the free base extracted four times with ethyl acetate. The combined extracts were dried over anhydrous magnesium sulfate and evaporated. The residue when recrystallized from hot ethylene dichloride yielded 15.8 g. of base melting at 105-108°. A sample recrystallized from chloroform for analysis melted at 109-110°.

Anal. Calcd. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.74. Found: C, 66.53; H, 8.54; N, 7.61.

The mother liquors from which IXb had separated were evaporated to a gummy residue amounting to 21.8 g. which was similarly hydrogenated over 400 mg. of Adams catalyst in 320 ml. of 60% aqueous ethanol for seven hours. The catalyst was then removed and the solvent evaporated. The residue was dissolved in water and the acid solution extracted twice with ether. Evaporation of the ether ex-tracts gave 7.8 g. of a gummy material which was discarded since it was not basic. The aqueous residue was then made alkaline with ammonia and extracted four times with ethyl The combined extracts were dried and evaporated acetate. to a yield of 9.2 g. of gummy basic material. This residue was refluxed for two hours on the steam-bath with a mixture of 20 ml. of methyl dichloroacetate and 35 ml. of absolute ethanol. The solvent was removed at reduced pressure and the residue triturated with low boiling petroleum ether to remove excess ester. The residue was then dissolved in 300 ml. of ethyl acetate, the acetate being washed with 0.1 N sulfuric acid, 5% sodium bicarbonate and water. The acetate solution was dried over anhydrous magnesium sulfate and evaporated. The crystalline residue was recrystallized from hot ethylene dichloride to a yield of 4.5 g. of amide (combined first and second crops) which melted at 124-126°. A sample recrystallized for analysis first from A sample recrystallized for analysis first from ethylene dichloride and finally benzene melted at 135-136° The analytical data were in agreement with the structure of a dichloroacetamide derivative of XIb.

Anal. Calcd. for $C_{12}H_{15}NO_2Cl_2$: C, 52.18; H, 5.47; N, 5.08. Found: C, 52.39; H, 5.75; N, 5.07.

Isonitrosodibenzoylmethane.— Neuville and Pechmann¹⁴ have prepared this compound by condensation of dibenzoylmethane with amyl nitrite. One lot of product was prepared in our laboratory in which butyl nitrite served as the nitrosating agent. However, the desired compound was more conveniently prepared by the conditions used by Wolff¹⁸ to prepare isonitrosobenzoylacetone. To a solution of 95 g. of dibenzoylmethane (Eastman Kodak Co.) in 1 1. of glacial acetic acid was added dropwise from a separatory funnel during one hour a solution of 54.9 g. of sodium nitrite in 100 ml. of water. The reaction mixture was stirred me-

chanically and the temperature kept at $12-15^{\circ}$ by means of an ice-bath. After stirring for one hour longer at room temperature, the reaction mixture was diluted with 1.5 l. of water. The mixture was chilled in ice to aid crystallization and the product finally isolated by filtration. After two recrystallizations from 500-ml. portions of chloroform a yield of 60.3 g. of the pure isonitrosodibenzoylmethane melting at 146-148° was obtained.

Hydrogenation of Isonitrosodibenzoylmethane.-Thirty grams of the above product dissolved in 470 ml. of absolute ethyl alcohol containing three equivalents of hydrogen chloride were hydrogenated in the presence of 3 g. of palladium oxide catalyst at 50 p.s.i. for 20 hours. After four hours a precipitate which had formed was dissolved by adding 170 ml. of water and the hydrogenation continued overnight. The uptake was 4.5 molecular equivalents or 75% of the theoretical. The catalyst was removed and solvents evaporated under reduced pressure. The crystalline residues combined from two such hydrogenation runs were suspended in 1 l. of water. To remove neutral by-products the aqueous solution was extracted twice with ether. Evaporation of these extracts gave 5 g. of a crystalline prod-uct which was not characterized. The aqueous residue was made strongly alkaline with ammonia and extracted three times with ether and once with ethyl acetate. The combined extracts were dried over magnesium sulfate and evap-The crystalline residue was dissolved in 300 ml. of orated. hot benzene and allowed to stand overnight at room temnot benzene and anowed to stand overnight at room tem-perature without disturbance. A crystalline base melting at $120-125^{\circ}$ was filtered off, 31.2 g, of product being ob-tained. Recrystallization from 200 ml. of benzene gave 27.1 g, melting at $132-134^{\circ}$, the base being isolated by fil-tration after standing for 1.5 hours at room temperature. A final crystallization from 200 ml. of benzene gave the pure income fuely the melting at $132-126^{\circ}$ isomer IVa, which melted at 135-136°

Anal. Caled. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.05; N, 5.76. Found: C, 74.14; H, 7.19; N, 5.87.

The residue obtained by evaporation of the mother liquor from which the first crop of 31.2 g. of product had been isolated was recrystallized twice from 105-ml. portions of ethylene dichloride and finally from benzene. In this way a yield of 10.8 g. of an amino alcohol melting at 116-117° was obtained. Reworking of the mother liquors from this product as well as from IVa above gave additional amounts of this isomer. The analytical data were in agreement with the structure XIa. There was no melting point depression when a sample was mixed with compound XIa prepared by the method of Algar, *et al.*,¹⁰ or between the corresponding dichloroacetamides of the two bases.

Anal. Calcd. for $C_{15}H_{17}NO: C, 79.26; H, 7.54; N, 6.16.$ Found: C, 79.44; H, 7.50; N, 6.00.

Acetylation of Intermediate Amino Alcohols.—Since the procedures used were the same throughout the series, the preparation of the intermediates used in the synthesis of dl-1-p-nitrophenyl-2-dichloroacetamido-1,3-butanediol only will be described. The acetylation was carried out by treating 20.0 g. of 1-phenyl-2-amino-1,3-butanediol with 50 ml. of acetic anhydride. When the reaction had subsided, the mixture was cooled to 15° and 45 ml. of pyridine was added to complete the acetylation. After standing at room temperature overnight the solution was evaporated *in vacuo*. The crystalline residue when recrystallized from 200 ml. of benzene yielded 28.0 g. of a product melting at 124–127°. An analytical sample prepared by recrystallizing from benzene, 95% alcohol and 50% aqueous alcohol melted at 130–131°.

Nitration of Intermediate Acetylated Amino Alcohols.— Twenty-eight grams of 1-phenyl-2-acetamido-1,3-acetoxybutane was added in portions during 15 minutes to 75 ml. of fuming nitric acid (sp. gr. 1.5) which had been previously decolorized by adding sulfamic acid. The temperature was kept at 5-10° during the addition by means of Dry Ice. The reaction mixture was allowed to stand at room temperature for 30 minutes longer after which it was quenched on ice. The excess acid was neutralized with solid sodium bicarbonate, a little ethyl acetate being added to control foaming and take up the solid. The faintly alkaline solution was extracted twice with ethyl acetate. The combined extracts were washed three times with water, then dried and evaporated to a crystalline residue. A sample was recrystallized several times from ethanol for analysis.

Hydrolysis of p-Nitrophenyl Acetylated Amino Alcohols.— The crude triacetate obtained in the above experiment was

⁽¹³⁾ Wolff, Ann., 325, 136 (1902).

⁽¹⁴⁾ Neuville and Pechmann, Ber., 23, 3380 (1890).

hydrolyzed without recrystallization by heating for four hours on the steam-bath in the presence of 500 ml. of 5% aqueous hydrochloric acid. In the case of compounds containing two nitrophenyl groups which were consequently quite insoluble in water, aqueous ethanol was used as the solvent. When the hydrolysis was complete, the reaction mixture was chilled and extracted once with ether and once with ethyl acetate. The aqueous residue containing the amine hydrochloride was evaporated at reduced pressure. The crystalline salt was then dissolved in 100 ml. of water and the free base liberated with ammonia. After standing overnight in the refrigerator a yield of 9.6 g. of base was isolated by filtration, the product melting at $137-140^{\circ}$. A

sample recrystallized for analysis from water melted at $144-145^\circ$

Dichloroacetamides of *p*-Nitrophenyl Amino Alcohols.— Dichloroacetamides of all bases were prepared by the method described recently for the preparation of α, α -dihaloacetamides of *dl-threo-p*-nitrophenyl-2-amino-1,3-propanediol.¹⁶ In bases where the benzyl hydroxyl group had been replaced by hydrogen it was necessary to reflux for at least two hours for the reaction to go to completion.

(15) Rebstock, This Journal, 72, 4800 (1950).

DETROIT, MICH.

RECEIVED JANUARY 29, 1951

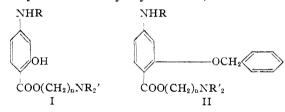
[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Derivatives of 4-Amino-2-hydroxybenzoic Acid. I

BY R. O. CLINTON, S. C. LASKOWSKI, U. J. SALVADOR AND MARY WILSON

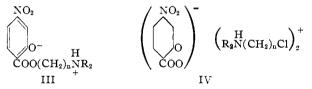
There is described the preparation of several series of new local anesthetics derived from the 4-aminosalicylic acid (PAS) nucleus. The majority of these compounds are very active, both topically and by infiltration procedures.

As part of a continuing investigation of new local anesthetics in these laboratories we have prepared several series of compounds derived from the 4amino-2-hydroxybenzoic acid nucleus. The present communication describes a number of dialkylaminoalkyl 4-amino- and 4-alkylamino-2-hydroxybenzoates, I, and dialkylaminoalkyl 4-amino- and 4-alkylamino-2-benzyloxybenzoates, II.



Although no compounds of the type presently discussed have appeared in the literature,¹ a few dialkylaminoalkyl salicylates have been described by McElvain.² The latter compounds did not show outstanding anesthetic properties. It would be expected, by analogy with other series, that the inclusion of a 4-amino group in this type of compound would greatly increase the local anesthetic activity, but no conclusions as to toxicity or irritation would be warranted.

Considerable experimental work was carried out in the determination of a suitable procedure for the preparation of the intermediate ω -dialkylaminoalkyl 2-hydroxy-4-nitrobenzoates. The direct Fischer esterification of 2-hydroxy-4-nitrobenzoic acid by means of a dialkylaminoalkanol and dry hydrogen chloride gave very poor results, as did the preparation of the basic esters *via* an intermediate ω haloalkyl 2-hydroxy-4-nitrobenzoate. Transesterification between a dialkylaminoalkanol and an alkyl 2-hydroxy-4-nitrobenzoate gave fair yields with dialkylaminopropanols and poor yields with dialkylaminoethanols. The Hörenstein-Pählicke³ reaction between 2-hydroxy-4-nitrobenzoic acid and a dialkylaminoalkyl chloride gave poor to excellent yields of the dialkylaminoalkyl 2-hydroxy-4-nitrobenzoate hydrochlorides, the best results being obtained from 2-dialkylaminoethyl chlorides. The products were somewhat difficult to purify, due to the properties inherent in the dialkylaminoalkyl 2hydroxy-4-nitrobenzoate bases. Because of the high "acidity" of the free phenolic group, it is probable that the bases exist in the form of the salts indicated by III. The bases are highly colored, high melting, and water soluble, although their solubility in non-polar solvents is very slight. Judging from



the experimental results, it seems likely that the "acidity" of the phenolic group could also interfere with the course of the Hörenstein–Pählicke reaction through the formation of semi-stable intermediates of the type shown in IV, although no evidence was obtained that alkylation of the phenolic group occurred to an appreciable extent.⁴

Because of the difficulties encountered in the above procedures, attention was turned to the utilization of a "blocked" 2-hydroxy-4-nitrobenzoic acid. Since it had been found in preliminary work that the catalytic reduction of an alkyl 2-acetoxy-4-nitrobenzoate in alcohol gave as sole product the alkyl 4-amino-2-hydroxybenzoate, due to acetyl group transference to the solvent, this route offered a possible source of the desired products. The Hörenstein–Pählicke reaction between 2-acetoxy-4-nitrobenzoic acid and a dialkylaminoalkyl chloride in isopropyl alcohol solution gave a mixture of compounds, the major product proving to be the

⁽¹⁾ Since the completion of this manuscript Drain, et al., J. Pharm. Pharmacol., 1, 784 (1949), have indicated their preparation of 2-diethylaminoethyl 4-amino-2-hydroxybenzoate. No experimental data or properties were recorded.

⁽²⁾ McElvain and Caruey, This JOURNAL, 68, 2595 (1946).

⁽³⁾ Hörenstein aud Pählicke, Ber., 71, 1644 (1938).

⁽⁴⁾ In the case of the related compound, 2-hydroxy-4-nitrobenzonitrile, phenolic alkylation does occur under the conditions of the Hörenstein-Pählicke reaction. Further, experiments in other series (unpublished) have indicated that phenolic alkylation can also be made to take place with the alkyl 2-hydroxy-4-nitrobenzoates.