obtained by raising the bath temperature slowly to 150°. The residue from the distillation was a dark, tough glass. The distillate was redistilled onto the cold finger in the sublimation apparatus; but this time the mixture was kept at room temperature. The distillate was washed from the cold finger with ether, the ether was removed, and the distillation at room temperature was repeated. Again the product was washed from the cold finger with ether. The ether was removed under diminished pressure and the residual liquid (0.5 g., 29%) was nitrated by means of a procedure identical with that described in part A. The crude nitration product was divided into fractions by recrystallization from acetic acid, and the first fraction, having a m. p. of 226–229°, was chromatographed in the manner described in part A. From the second quarter of the chromatogram a compound was obtained which, after recrystallization from benzene–petroleum ether, formed small, pale yellow needles, m. p. 235–237°. A mixture of this substance and that of m. p. 237–238° described in part A had a m. p. of 236–237°.

Action of Potassium Acid Sulfate on the Carbinol (XVI).—A mixture of 21 g. of XVI and 268 mg. of freshly fused potassium acid sulfate was heated in an oil-bath under a pressure of 70–85 mm. until slow distillation of a milky liquid occurred. The temperature of the oil-bath was so regulated that the temperature of the distilling vapors was maintained between 190 and 200°. The distillate was dissolved in ether, and the solution was dried over Drierite. The ether was removed, and the dehydration procedure was repeated, using 200 mg. of potassium acid sulfate. This time, the distillate was clear and colorless. It was dissolved in ether, and the ether solution was washed with 5% sodium hydroxide and with water and dried over Drierite. After removal of the ether, the residual liquid was distilled under diminished pressure. Although there was some lower-boiling material, the only constant-boiling portion, which comprised most of the product, had a b. p. of 122–123° (3 mm.); $n^{25}D$ 1.5322. This substance had the composition of the unchanged carbinol.

Anal. Calcd. for $C_{16}H_{24}O$: C, 82.69; H, 10.42. Found: C, 82.63; H, 10.37.

The action of boiling acetic anhydride on XVI had similar results.

Summary

1. The products of the rearrangement of 3,3′,5,5′-tetramethylhydrazobenzene (VII) in 10% hydrochloric acid have been shown to be 2,2′,6,6′ - tetramethyl - 4,4′ - diaminobiphenyl (VIII) and 2,2′,4,6′-tetramethyl-6,4′-diaminobiphenyl (IX).

2. The only abnormality of this rearrangement which might be attributed to the hindering effect of the methyl groups is the low benzidine (VIII) to diphenyline (IX) ratio in the product.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF MIZZY, INC.]

Esters of β-Alkylaminoethanols

BY JULIAN R. REASENBERG AND SAMUEL D. GOLDBERG[1]

Since the discovery that esters of β-monoalkylaminoethanols were suitable local anesthetics,[2] a considerable amount of work has been done on compounds of this type. Goldberg and Whitmore prepared the β-monoalkylaminoethyl and γ-monoalkylaminopropyl esters of *p*-aminobenzoic acid in which the alkyl group varied from ethyl to amyl in size. Goldberg, Ringk and Spoerri[3] prepared the α-alkyl substituted analogs of the above and Pierce, Salsbury and Frederickson[4] prepared the alkoxybenzoates of these amino alcohols. Kremer and Waldman[5] prepared the β-mono alkylamino β,β-dimethylethanols and attempted to esterify these. Pierce and his coworkers successfully esterified the last mentioned amino alcohols with alkoxybenzoic acids and obtained local anesthetics.[6] Since then, Ringk and Epstein[7] have prepared the *p*-aminobenzoates which Kremer and Waldman failed to prepare and in addition have extended some of the other series previously described.

In a recent patent and subsequent comprehensive series of papers, issued since this work was completed, Cope and Hancock have described aromatic esters of 2-alkylaminoethanols, monoalkylaminopropanols, and monoalkylaminobutanols.[8] The present paper deals with the esterification of β-monoalkylaminoethanols and β-monoalkylamino β,β-dimethylethanols with a number of aromatic acids to give esters. Also, since there is some confusion about the mechanism of the Schotten–Baumann reaction involved, an attempt has been made to elucidate the course of the reaction.

Ringk and Epstein[7] show that for the reaction of one mole of acyl chloride with one mole of β-monoalkylaminoethanol in aqueous alkali, two products are possible, namely, the β-hydroxy amide and the β-amino ester. Hancock and Cope[8d] have demonstrated that in the Schotten–Baumann reaction between an acid chloride and a β-alkylaminoalcohol, the main product is the amide. Our present work leads to a complete and independent agreement with the work of Cope. When the condensation is carried out by the method of Goldberg and Whitmore[2] only the β-hydroxy amide is formed, and, under the influence of strong acid, this amide undergoes a rearrangement to form the acid salt of the corresponding amino ester.

This rearrangement, or acyl shift, is more or

(1) Present address: Graham Chemical Co., Jamaica 2, N. Y.

(2) Goldberg and Whitmore, THIS JOURNAL, **59**, 2280 (1937).

(3) Goldberg, Ringk and Spoerri, *ibid.*, **61**, 3562 (1939).

(4) Pierce, Salsbury and Frederickson, *ibid.*, **64**, 1691 (1942).

(5) Kremer and Waldman, *ibid.*, **64**, 1089 (1942).

(6) Pierce, Salsbury, Haden and Willis, *ibid.*, **64**, 2884 (1942).

(7) Ringk and Epstein, *ibid.*, **65**, 1222 (1943).

(8) (a) Cope, U. S. Patent 2,339,914, Jan. 25, 1944; (b) Cope and Hancock, THIS JOURNAL, **66**, 1448 (1944); (c) Cope and Hancock, *ibid.*, **66**, 1453 (1944); (d) Hancock and Cope, *ibid.*, **66**, 1738 (1944).

less reversible. Thus, when the amino group is primary, the reverse reaction takes place spontaneously when an attempt is made to liberate the free base.[9] When the amino group is secondary (as it is in the β-monoalkylaminoethanols), then several factors influence the degree of lability of the alkylamino alkyl ester. If the N-alkyl group is small (methyl or ethyl), the stability of the free base of the anesthetic is low. Also, the nature of the acyl group exerts a strong influence on the stability of the product. The presence of a nitro group on the benzoic acid part of the molecule tends to labilize the amino ester with the consequent formation of hydroxy amide. Thirdly, if the carbon atom to which is linked the alkylamino group is primary as in β-alkylaminoethanols, the rearrangement from amide to ester in the presence of acid is more difficult than if the carbon atom in question were tertiary as in the 2-alkylamino-2-methylpropanols.

In two of the anesthetics described in this paper the entire series of intermediates were solid products and were isolated and characterized. Figure 1 illustrates the cycle of reactions which occur. Thus the condensation of *p*-nitrobenzoyl chloride with the monoalkylaminoethanol forms the nitro amide A and not the nitro ester F as had been postulated previously. This compound (A) is insoluble in dilute acid indicating

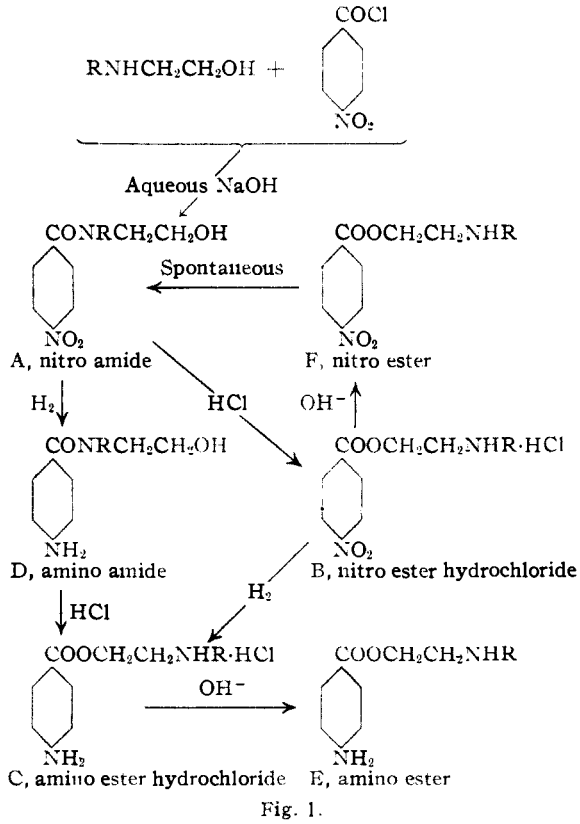

Fig. 1.

(9) Reasenberg and Smith, THIS JOURNAL, 66, 991 (1944).

that there is no basic amino group present. However, on treatment with strong acid and warming, an exothermic reaction occurs and the nitro ester hydrochloride B is formed by a migration of the acyl part of the molecule. This compound exhibits some solubility in water. On treatment with dilute alkali, the free base F is formed. This compound is slightly soluble in dilute acid but is unstable and on standing reverts to the more stable nitro amide A. The instability of F is presumably caused, as mentioned previously, by the presence of the nitro group since the same compound without the nitro group or with an amino group (E) is stable under these conditions.

The nitro group on A can be reduced to give D. This compound is soluble in cold dilute acid and can be reprecipitated by alkali. On heating with strong acid, however, it is converted into Compound C, thus again affording an illustration of the acyl migration. C can, of course, also be prepared by the reduction of B and is water soluble. On treating a water solution of C with alkali, the free base E is liberated as a water insoluble product which is stable and does not rearrange to form D. This again seems to point to the fact that the *p*-nitro group of compound F exerts a labilizing effect on the molecule.

All of the anesthetics listed in the tables were prepared by one of two general methods. The first method (D in experimental section and tables) is the classical Schotten–Baumann method. The second method (E in experimental section and tables) is the condensation of the acid and amino alcohol in the presence of concentrated sulfuric acid. This is a modification of an old method which has been used to esterify β-dialkylaminoethanols. However, with the monoalkyl aminoethanols, the yields are much better and it is presumed that perhaps instead of a direct esterification, as must occur with the dialkylaminoethanols, a dehydration to form the hydroxy amide occurs first and under the influence of strong acid and heat this rearranges to form the desired amino ester. This method enabled us to esterify acids such as *p*-ethylamino- and *p*-methylaminobenzoic acids.

Table I describes the amino alcohols used in this work. Three different methods were used to prepare these compounds and representative illustrations for their preparation are described in the experimental section. Except as noted, the 2-alkylamino, 2-methyl propanols listed in Table I were made by the method of Kremer and Waldman.[5] The exceptions were made by a modification, as described under B in the experimental section. Tables II, III, and IV list the anesthetic compounds and intermediates prepared during the course of this investigation. The tables with their footnotes are self-explanatory and the general methods of preparation are described in the experimental section. The yields of the preparations described in the experimental

section are in general representative of the various methods. A description of the pharmacology of these compounds will be reported elsewhere.

TABLE I

β-MONOALKYL AND MONOALICYCLYLAMINOETHANOLS

R	B. p., °C.	Pressure, mm.	M. p., °C.	Picrate, m. p., °C.
Amino alcohols of type $RNHCH_2CH_2OH$				
n-Octyl[a,c]	128–129	8	Liquid	71–72[b]
Cyclopentyl[d]	101	5	Liquid	116–117[e]
Amino alcohols of type $RNHC(CH_3)_2CH_2OH$				
n-Propyl[f,g,h]	182–184	760	58–59	121–122
n-Butyl[f,g,h]	195–198	760	70–71	134–135
i-Butyl[f,g,h]	185–190	760	46–47	145–146
n-Amyl[f,g,h]	215–218	760	58–59	109–110
n-Octyl	127–128	8	57–59	96–97[i]
2-Octyl[h]	114–116	5	Liquid	
Cyclohexyl[j,k]	238	760	77–78	167–169[l]
4-Methylcyclohexyl[j]	253	763	95–96	136–137[m]

[a] Ethyl and *n*-butylaminoethanol, courtesy of Sharples Solvents Corp.; *i*-butyl- and *n*-amylaminoethanol, courtesy of Benzol Products Corp.; amyl-2, (4-methylamyl)-2, 2-methylcyclohexyl, and 4-methylcyclohexylaminoethanols were prepared by method B (previously reported by ref. 19); cyclohexylaminoethanol (ref. 19) was prepared by methods B and C; *n*-hexyl, 2-ethylhexyl (ref. 18), *n*-heptyl, and octyl-2-aminoethanol (ref. 19) were prepared by method A. [b] Calcd. for $C_{16}H_{26}N_4O_8$: N, 13.94; Found: N, 13.74. [c] Prepared by method C. [d] Prepared by method B. [e] Calcd. for $C_{12}H_{18}N_4O_8$: N, 15.65. Found: N, 15.51. [f] Also prepared by Kremer and Waldman.[5] [g] Also prepared by Pierce, Salsbury, Haden and Willis.[6] [h] Also prepared by Ringk and Epstein.[7] [i] Calcd. for $C_{18}H_{30}N_4O_8$: N, 13.03. Found: N, 13.01. [j] Prepared by a modification of the method of Cope and Hancock (ref. 19). See Method B. [k] Also prepared by Hancock and Cope (ref. 8d). [l] Calcd. for $C_{16}H_{24}N_4O_8$: N, 14.00. Found: N, 13.93. [m] Calcd. for $C_{17}H_{26}N_4O_8$: N, 13.54. Found: N, 13.48.

Experimental

The following acids and acid chlorides were obtained from Eastman Kodak Co.: *p*-aminobenzoic acid, *p*-nitrobenzoyl chloride, *m*-nitrobenzoyl chloride, benzoyl chloride, cinnamoyl chloride and *p*-toluic acid.

3-Nitro-4-methylbenzoic acid was prepared by the method of Kloppel.[10] The corresponding acid chloride was made by the method of H. Meyer,[11] using thionyl chloride on the free acid. The product, *m*-nitro-*p*-toluyl chloride, boiled at 150–1° (6 mm.). The reduction of the nitro acid to *m*-amino-*p*-toluic acid was effected by the method of Kloppel.[10] *p*-Ethylbenzoic acid was prepared by the haloform reaction from *p*-ethylacetophenone.[12] *p*-Toluyl chloride and *p*-ethylbenzoyl chloride, b. p. 245–50°, were prepared by the method of Meyer.[11] 3-Nitro-4-ethylbenzoic acid was prepared by the method of Aschenbrandt[12] and was converted into its acid chloride, b. p. 150–153° (6 mm.), by the method of Meyer.[11]

Cuminic acid was prepared from cuminic aldehyde by the Cannizzaro reaction[13] and this was converted into its acid chloride according to Cahours.[14] *p*-Methylamino and *p*-dimethylaminobenzoic acid were obtained by the action of dimethyl sulfate on *p*-aminobenzoic acid,[15] while *p*-ethylamino and *p*-diethylaminobenzoic acid were prepared in a similar manner.[16] *p*-Diethylaminomethylbenzoic acid was prepared according to Einhorn.[17]

(10) Kloppel, *Ber.*, **26**, 1773 (1893).
(11) H. Meyer, *Monatsh.*, **22**, 425 (1901).
(12) Aschenbrandt, *Ann.*, **216**, 221 (1883).
(13) Baker, Dippy and Page, *J. Chem. Soc.*, 1774 (1937).
(14) Cahours, *Ann.*, **70**, 45 (1870).
(15) Houben and Schottmuller, *Ber.*, **42**, 3739 (1909).
(16) Houben and Freund, *ibid.*, **42**, 4822 (1909).
(17) Einhorn, *ibid.*, **29**, 1594 (1896).

Amino Alcohols

Method A. Preparation of *n*-Hexylaminoethanol.—A mixture of 300 g. of *n*-hexyl bromide (1.8 moles), 329 g. of ethanolamine (5.4 moles), and 250 ml. of isopropanol was placed in a 1.5 liter round-bottom flask equipped with a reflux condenser. The flask was warmed cautiously until the reaction commenced (50°) and the course of the exothermic reaction was controlled by a cooling bath so that a gentle reflux was obtained. When the reaction had subsided, the mixture was refluxed for an additional two hours. The alcohol was then removed by distillation and the residue was poured into 2 liters of water containing 75 g. of sodium hydroxide (1.8 moles). The oily layer which formed was removed in a separatory funnel and the water layer was extracted twice with ether which was then combined with the oil. The ethereal layer was washed with five successive 75-ml. portions of water and then dried over solid sodium hydroxide. The ether was removed from the solution by distillation and the residue was vacuum distilled. The product was collected as a water white liquid boiling at 108–109° (6 mm.) and weighed 208 g. The boiling point at atmospheric pressure was 232–234°.[18]

Method B. Preparation of β-Cyclohexylamino-β,β-dimethylethanol.—The method was essentially that of Cope and Hancock[19] except that Raney nickel promoted with platinic chloride was used as the catalyst[20] and the hydrogenation was performed at 60–80°. It was found that the catalyst could be used over and over again with very little diminution of activity. It was observed that the method of Cope and Hancock worked very well for derivatives of ethanolamine but not for derivatives of 2-amino-2-methylpropanol. In one of their later papers[8d] they have confirmed this observation and have utilized a very similar method of preparation of the amino alcohols. For these preparations a modification of the method was utilized as follows:

A mixture of 178 g. of 2-amino-2-methylpropanol (2.0 mole) and 500 ml. of anhydrous toluene was placed in a distilling flask and slowly distilled through an efficient column. When the distillate was no longer cloudy, 196 g. of anhydrous cyclohexanone (2.0 moles) was added and the distillation was continued. The distillate was collected in a water separator and the separated toluene was returned to the distilling flask. When 36 ml. of water (2.0 mole) had been collected the toluene was removed completely by distillation and the residue was vacuum distilled. The product was a water-white non-viscous liquid boiling at 74–75° (8 mm.) and weighed 204 g. The anhydro product (for discussion of structure see refs. 8d, 19) was then hydrogenated as follows:

A mixture of 33.8 g. of the spiro-oxazolidine just described (0.20 mole), 100 ml. of glacial acetic acid, and 0.5 g. of Adams PtO_2 previously reduced to Pt was hydrogenated at 2–3 atmospheres and room temperature. A total of 0.2 mole of hydrogen was absorbed in six hours. The reductates of three such experiments were combined (0.6 mole of reactant) and filtered free of catalyst. Fifty ml. of concentrated hydrochloric acid (0.6 mole) was added and the solvent removed by distillation under diminished pressure. The residue was dissolved in 500 ml. of water and the clear solution was treated with 160 g. of sodium hydroxide dissolved in 250 ml. of water. The oil which formed soon solidified to a waxy solid and was separated by filtration and washed with water. This was placed in a beaker and warmed to melt the solid. On cooling, it solidified and the aqueous layer was poured off and the residue subjected to distillation. The main fraction of β-(cyclohexylamino)-β,β-dimethylethanol boiled at 238° with virtually no forerun or residue and weighed 84 g., m. p. 77–78°, picrate m. p. 167–169°, yield 82%.

Anal. of picrate. Calcd. for $C_{16}H_{24}N_4O_8$: N, 14.00. Found: N, 13.93.

Method C. Preparation of *n*-Octylaminoethanol.—A mixture of 349 g. of *n*-octylamine (2.7 mole) and 250 ml. of

(18) Matthes, *Ann.*, **315**, 114 (1901).
(19) Cope and Hancock, THIS JOURNAL, **64**, 1503 (1942).
(20) Reasenberg, Lieber and Smith, *ibid.*, **61**, 384 (1939).

TABLE II

R	Nitro ester HCl, m. p., °C.	a	Amino ester HCl, m. p., °C.	b	Empirical formula	Cl Analyses, % Calcd.	Found
Esters of type *p*-$H_2NC_6H_4COOCH_2CH_2NHR\cdot HCl$							
Ethyl[c,f]	.....	..	170–171	*m*	$C_{11}H_{17}N_2O_2Cl$	14.50	14.33
n-Hexyl	149–150	*m*	162–163[g]	*o*	$C_{15}H_{25}N_2O_2Cl$	11.79	11.67
n-Heptyl[d,h]	139–140	*m*	157–158[i]	*p*	$C_{16}H_{27}N_2O_2Cl$	11.26	10.98
n-Octyl[j]	123–126	*m*	132[k,l]	*p*	$C_{17}H_{29}N_2O_2Cl$	10.78	10.65
Cyclopentyl[f]	.....	..	194–195	*m*	$C_{14}H_{21}N_2O_2Cl$	12.44	12.38
Cyclohexyl[d,r,dd]	232-235	*n*	178–179[s]	*p*	$C_{15}H_{23}N_2O_2Cl$	11.87	11.82
2-Methylcyclohexyl[d]	227–229	*n*	202–203	*o*	$C_{16}H_{25}N_2O_2Cl$	11.33	11.52
4-Methylcyclohexyl[d]	202–204	*n*	182–183[t]	*p*	$C_{16}H_{25}N_2O_2Cl$	11.33	11.30
Esters of type *p*-$H_2NC_6H_4COOCH_2C(CH_3)_2NHR\cdot HCl$							
n-Propyl[e]	113–115	*m*	235–237	*p*	$C_{14}H_{23}N_2O_2Cl$	12.36	12.23
n-Butyl[e,u]	148–149	*q*	207–209[w]	*x*	$C_{15}H_{25}N_2O_2Cl$	11.79	11.67
i-Butyl[e]	153–154	*m*	218	*o*	$C_{15}H_{25}N_2O_2Cl$	11.79	11.75
n-Amyl[e]	155–156	*m*	211–213	*o*	$C_{16}H_{27}N_2O_2Cl$	11.26	11.32
n-Octyl	144–145	*m*	137–139	*p*	$C_{19}H_{33}N_2O_2Cl\cdot{}^1/_2H_2O$	9.69	9.67
Octyl-2[e]	Liquid	..	137–140	*p*	$C_{19}H_{33}N_2O_2Cl\cdot{}^1/_2H_2O$	9.69	9.61
Cyclohexyl[y]	209–211	*o*	142–144	*p*	$C_{17}H_{27}N_2O_2Cl$	10.82	10.71
4-Methylcyclohexyl	200–201	*m*	205–206	*p*	$C_{16}H_{29}N_2O_2Cl$	10.40	10.18
Esters of type *m*-$H_2NC_6H_4COOCH_2CH_2NHR\cdot HCl$							
n-Butyl	127–128	*m*	129	*m*	$C_{13}H_{21}N_2O_2Cl$	12.99	12.88
i-Butyl	171–172	*m*	177–178	*m*	$C_{13}H_{21}N_2O_2Cl$	12.99	12.91
n-Amyl	127–128	*v*	120	*m*	$C_{14}H_{23}N_2O_2Cl$	12.39	12.39
Octyl-2	160–161	*m*	120–122	*m*	$C_{17}H_{29}N_2O_2Cl$	10.79	10.76
Esters of type *m*-$H_2NC_6H_4COOCH_2C(CH_3)_2NHR\cdot HCl$							
n-Butyl[e]	173	*o*	205–206	*n*	$C_{15}H_{25}N_2O_2Cl$	11.79	11.67
i-Butyl[e]	154–155	*m*	187	*o*	$C_{15}H_{25}N_2O_2Cl$	11.79	11.77
n-Amyl	147–149	*m*	147–148	*m*	$C_{16}H_{27}N_2O_2Cl$	11.26	11.17
Esters of type 4-CH_3-3-$NH_2C_6H_3COOCH_2CH_2NHR\cdot HCl$							
n-Butyl[dd]	147–149	*m*	137–138	*m*	$C_{14}H_{23}N_2O_2Cl$	12.39	12.22
i-Butyl[dd]	180	*m*	187–188	*o*	$C_{14}H_{23}N_2O_2Cl$	12.39	12.33
n-Amyl[dd]	145–147	*m*	122–123	*m*	$C_{15}H_{25}N_2O_2Cl$	11.79	11.88
n-Hexyl	159–160	*m*	128[aa]	*p*	$C_{16}H_{27}N_2O_2Cl$	11.26	11.22
Octyl-2	118–119	*m*	157–158[bb]	*p*	$C_{18}H_{31}N_2O_2Cl$	10.34	10.15
2-Ethylhexyl	133–135	*z*	86–88	*p*	$C_{16}H_{31}N_2O_2Cl\cdot{}^1/_2H_2O$	10.09	10.04
Esters of type 4-CH_3,3-$NH_2C_6H_3COOCH_2C(CH_3)_2NHR\cdot HCl$							
n-Butyl	169–170	*n*	190–192	*o*	$C_{16}H_{27}N_2O_2Cl$	11.26	11.19
i-Butyl	193–195	*m*	175–176	*n*	$C_{16}H_{27}N_2O_2Cl$	11.26	11.21
n-Amyl	144–145	*m*	182–184	*m*	$C_{17}H_{29}N_2O_2Cl$	10.78	10.89
Octyl-2	Liquid	..	158–159	*cc*	$C_{20}H_{35}N_2O_2Cl$	9.57	9.64
Esters of type 4-C_2H_5-3-$NH_2C_6H_3COOCH_2CH_2NHR\cdot HCl$							
n-Butyl	117–119	*v*	137–138	*m*	$C_{15}H_{25}N_2O_2Cl$	11.79	11.74
i-Butyl	150–152	*v*	117–119	*m*	$C_{15}H_{25}N_2O_2Cl$	11.79	11.76

[a] Solvent for recrystallization of the nitro ester hydrochlorides. [b] Solvent for recrystallization of the amino ester hydrochlorides. [c] Unless specified otherwise, the esters were prepared by method D. [d] Previously reported by Cope (ref. 8b). [e] Previously reported by Ringk and Epstein (ref. 7). [f] Prepared by method E. [g] Free base, m. p. 81–84°. [h] Nitro amide m. p. 88–89°, calcd. for $C_{16}H_{24}N_2O_4$: N, 9.09. Found: N, 9.37. Amino amide m. p. 81–82°. Calcd. for $C_{16}H_{26}N_2O_2$: N, 10.07. Found: N, 10.11. [i] Free base m. p. 70–71°. Calcd. for $C_{16}H_{22}N_2O_2$: N, 10.07. Found: N, 10.02. [j] Nitro amide m. p. 91–92°. [k] The compound crystallizes from water as the monohydrate m. p. 113–114°. Calcd. for $C_{17}H_{29}N_2O_2Cl\cdot H_2O$: Cl, 10.22; H_2O, 5.23. Found: Cl, 10.05; H_2O, 5.72. [l] Free base, m. p. 62–64°. [m] Isopropanol. [n] 95% ethanol. [o] Absolute ethanol. [p] Water. [q] Alcohol–ether. [r] Nitro amide m. p. 121°. Calcd. for $C_{15}H_{20}N_2O_4$: N, 9.58. Found: N, 9.86. Amino amide m. p. 170–171°. Calcd. for $C_{15}H_{22}N_2O_2$: N, 10.68. Found: N, 10.77. Amino amide picrate m. p. 146–148°. Calcd. for $C_{21}H_{25}N_5O_9$: N, 14.25. Found: N, 14.23. [s] Crystallizes from water as the monohydrate. Calcd. for $C_{15}H_{23}N_2O_2Cl\ H_2O$: H_2O, 5.60. Found: H_2O, 5.66. Picrate m. p. 166–167°. Calcd. for $C_{21}H_{25}N_5O_9$: N, 14.25. Found: N, 14.32. [t] Crystallizes from water as the monohydrate. Calcd. for $C_{16}H_{25}N_2O_2Cl\cdot H_2O$: Cl, 10.72. Found: Cl, 10.59. [u] Nitro amide m. p. 162–163. Kremer and Waldman (ref. 5) report 162.5–163.5°. [v] Alcohol–ether. [w] There is a hydrate which melts at 190°. [x] Alcohol–water. [y] Nitro amide m. p. 64.5°. The nitro and amino ester hydrochlorides were previously reported by Hancock and Cope (ref. 8d). Three dimorphous forms of the amino ester hydrochloride have been isolated. The low melting form (142–144°, softens at 135° rapid heating) is obtained from water. On slow heating this resolidifies and remelts at 205° (dec.). On recrystal-

lization from isopropanol it melts at 188°. When a small sample of the highest melting form is ground up with the lowest melting form, the entire sample melts at 205° (dec.). When a sample of the highest melting form isolated by Cope and Hancock is ground with the authors' 142–144° form, it all reverts to the 205° form proving the identity of the two samples obtained in the two laboratories. (Private communication. The m. p. comparisons were performed by Dr. Hancock.) [a] Benzene. [aa] The amino ester hydrochloride crystallizes from water as a hydrate, m. p. 113–114° (softens at 106°). On drying overnight at 75°, it loses its water and melts sharply at 127°. [bb] The dihydrochloride melts at 223–225° (dec.). [cc] Ethyl acetate–ligroin. [dd] Also prepared by method E.

isopropanol was placed in a liter round-bottom flask and gently refluxed. To this was added 113 g. of ethylene chlorohydrin over a period of ten hours. The mixture was refluxed for an additional fourteen hours and the alcohol was then removed by distillation. The residue was poured into 2 liters of water and a solution of 60 g. of sodium hydroxide in 100 ml. of water (1.5 moles) was added. The oil which formed was extracted with ether and the aqueous layer was removed. The ether layer was washed several times with water and then dried over solid sodium hydroxide. The ether was removed in a water-bath and the residue was distilled. The first fraction consisted of 154 g. of *n*-octylamine b. p. 174–175°. The residue was then vacuum distilled and the main fraction boiled at 128–129° (9 mm.) and consisted of 120 g. of β-(*n*-octylamino)-ethanol.

Method D. Preparation of N-(*n*-Heptyl)-N-(β-hydroxyethyl)-*p*-nitrobenzoamide (A of Fig. 1).—To a mixture of 15.9 g. of *n*-heptylaminoethanol (0.1 mole) suspended in 200 ml. of water containing 5.0 g. of sodium hydroxide (0.12 mole) was added slowly with stirring a solution of 18.6 g. of *p*-nitrobenzoyl chloride (0.1 mole) dissolved in 300 ml. of ether. When the reaction was complete the aqueous layer was removed in a separatory funnel and the ether layer was washed rapidly in succession with water, 5% hydrochloric acid, and water. On standing, the ether solution deposited crystals. These were separated by filtration and were dried to give 24.5 g. of yellow nitroamide. A portion was purified by recrystallization from hot isopropyl ether to give slightly yellowish crystals, insoluble in dilute hydrochloric acid, m. p. 88–89°.

Anal. Calcd. for $C_{16}H_{24}N_2O_4$: N, 9.09. Found: N, 9.37.

For the preparation of amides of β-(alkylamino)-β,β-dimethylethanols the ethereal solution was not washed with dilute hydrochloric acid because the product reacted with the acid and then dissolved in it.

Preparation of β-(*n*-Heptylamino)-ethyl-*p*-nitrobenzoate Hydrochloride (B of Fig. 1).—To 19.5 g. of nitro amide was added 1.1 equivalents of concentrated hydrochloric acid. The mixture was gently warmed to 80° for about one minute when a clear homogeneous solution resulted. On further heating (five minutes) an exothermic reaction occurred and a two-phase system resulted. This was allowed to cool and the solid which formed was recrystallized from 250 ml. of isopropanol to give 15.2 g. of soft yellow needles, m. p. 139–140°.

Anal. Calcd. for $C_{16}H_{25}N_2O_4Cl$: Cl, 10.28. Found: Cl, 10.10.

A portion of the nitro ester hydrochloride was dissolved in water and made alkaline with ammonium hydroxide. A yellow oil formed which was washed with water by decantation several times. The oil was soluble in dilute hydrochloric acid and was reprecipitated by dilute alkali. On standing overnight the yellow oil solidified to a slightly yellowish solid which was insoluble in dilute acid. When recrystallized from isopropyl ether it melted at 87–89°. A mixed melting point determination with a known sample of nitro amide (A of Fig. 1) had an m. p. of 87–89°.

Preparation of β-(*n*-Heptylamino)-ethyl *p*-Aminobenzoate Hydrochloride (C of Fig. 1).—A paste of 25 g. of iron powder and 50 ml. of water was prepared and to it was added slowly 11.0 g. of nitro ester hydrochloride (B of Fig. 1). The mixture was stirred vigorously and the temperature of the reaction was kept below 60° by the rate of addition of the solid. When the reduction was complete, the mixture was made ammoniacal and extracted four times with 50-ml. portions of hot benzene. The benzene was clarified by filtration, washed with water, and extracted twice with 100-ml. portions of 5% hydrochloric acid. The aqueous layer was warmed and purified with Darco to give a colorless solution. This was made ammoniacal and the oil was dissolved in alcohol and titrated with alcoholic hydrochloric acid. On standing a thick white precipitate formed. This was filtered and dried to give 7.4 g. of crude β-(*n*-heptylamino)-ethyl *p*-aminobenzoate hydrochloride. On recrystallization from hot water several times white needles were obtained, m. p. 157–158°.

Anal. Calcd. for $C_{16}H_{27}N_2O_2Cl$: Cl, 11.26. Found: Cl, 10.98.

Preparation of β-(*n*-Heptylamino)-ethyl *p*-Aminobenzoate (E of Fig. 1).—A solution of 2.0 g. of the amino ester hydrochloride just described was dissolved in 100 ml. of water and treated slowly with stirring with an excess of

TABLE III

R	Ester HCl m. p., °C.	Solvent	Empirical formula	Cl Analyses, % Calcd.	Found
Esters of type $C_6H_5COOCH_2CH_2NHR \cdot HCl$					
n-Butyl[a]	135	*j*	$C_{13}H_{20}NO_2Cl$	13.75	13.81
i-Butyl	141–142	*k*	$C_{13}N_{20}NO_2Cl$	13.75	13.74
n-Amyl	151–152	*k*	$C_{14}H_{22}NO_2Cl$	13.04	12.99
Amyl-2[d]	149	*j*	$C_{14}H_{22}NO_2Cl$	13.04	12.92
n-Hexyl	162–163	*j*	$C_{15}H_{24}NO_2Cl$	12.40	12.29
(4-Methyl-amyl)-2	171–172[b]	*j*	$C_{30}H_{48}N_2O_6S$	*c*	*c*
n-Heptyl	165–166	*k*	$C_{16}H_{26}NO_2Cl$	11.82	11.92
n-Octyl	161–162	*l*	$C_{17}H_{28}NO_2Cl$	11.24	11.25
Octyl-2[d]	130–131	*j*	$C_{17}H_{28}NO_2Cl$	11.24	11.41
2-Ethylhexyl	45–48	*m*	$C_{17}H_{28}NO_2Cl$	11.24	11.05
Cyclopentyl	144–145	*j*	$C_{14}H_{20}NO_2Cl$	13.18	13.23
Cyclohexyl[d]	189–191	*n*	$C_{15}H_{22}NO_2Cl$	12.48	12.37
2-Methylcyclo-hexyl	193–194	*l*	$C_{16}H_{24}NO_2Cl$	11.91	11.89
4-Methylcyclo-hexyl	145–146	*l*	$C_{16}H_{24}NO_2Cl$	11.91	11.91
Esters of type $C_6H_5COOCH_2C(CH_3)_2NHR \cdot HCl$					
n-Butyl	150–151	*k*	$C_{15}H_{24}NO_2Cl$	12.40	12.49
i-Butyl	175–176	*k*	$C_{15}H_{24}NO_2Cl$	12.40	12.43
n-Amyl	137–138	*k*	$C_{16}H_{26}NO_2Cl$	11.82	11.90
n-Octyl	117–119	*o*	$C_{19}H_{32}NO_2Cl$	10.37	10.40
Octyl-2	118–120[d]	*p*	$C_{19}H_{32}NO_2Cl$	10.37	10.37
Cyclohexyl	213–214	*q*	$C_{17}H_{24}NO_2Cl$	11.37	11.25
4-Methylcyclo-hexyl	213–214	*j*	$C_{18}H_{26}NO_2Cl$		
Esters of type $C_6H_5CH{=}CHCOOR \cdot HCl$					
β-(Isobutyl-amino)-ethyl[e]	182–184[f]	*p*	$C_{15}H_{22}NO_2Cl$	12.48	12.70
β-(*n*-Amylamino)-β,β-dimethylethyl	125–127	*p*	$C_{19}H_{32}NO_2Cl$	10.88	11.02
β-(Cyclohexyl-amino)-ethyl[g]	182–183[h]	*m*	$C_{17}H_{24}NO_2Cl$	11.44	11.32

[a] The esters were prepared by method D. All of the resulting amides were oils. [b] The compound was isolated as the normal sulfate $(C_{15}H_{23}NO_2)_2H_2SO_4$. [c] Calcd. for $C_{30}H_{48}N_2O_8S$: S, 5.37. Found: S, 5.16. [d] Mixed m. p with the *n*-octyl analog 95–112°. [e] The amide is a solid, m. p. 89–91° from isopropyl ether. [f] The free base is an oil. [g] The amide melts at 148–149°. The free base (amino ester) is an oil. [h] The cpd. melts at 182–183 and immediately resolidifies and melts again at 193–194°. [i] Previously reported by Cope and Hancock (ref. 8b). [j] Isopropanol. [k] Ethyl acetate. [l] Acetone. [m] Water. [n] 95% ethanol. [o] Benzene–ligroin. [p] Dilute HCl. [q] Water–ethanol.

TABLE IV

ESTERS OF TYPE p-R'$C_6H_4COOCH_2CH_2NHR''$·HCl

Unless specified otherwise the esters were prepared by method E.

R'	R''	Ester HCl m. p., °C.	Solvent	Empirical formula	Cl Analyses, % Calcd.	Found
Methyl	Ethyl	172–174	*g*	$C_{12}H_{18}NO_2Cl$	14.56	14.47
Methyl	*n*-Butyl	164–165	*h*	$C_{14}H_{22}NO_2Cl$	13.04	12.84
Methyl	*i*-Butyl	195–197	*h*	$C_{14}H_{22}NO_2Cl$	13.04	12.86
Ethyl	*n*-Butyl[e]	144–145	*i*	$C_{15}H_{24}NO_2Cl$	12.40	12.32
Ethyl	*i*-Butyl[e]	138	*j*	$C_{15}H_{24}NO_2Cl$	12.40	12.44
Isopropyl	Ethyl	100–101	*g*	$C_{14}H_{22}NO_2Cl$	13.04	13.12
Isopropyl	*n*-Butyl	134–136	*g*	$C_{16}H_{26}NO_2Cl$	11.32	11.72
Isopropyl	*i*-Butyl[f]	126	*g*	$C_{16}H_{26}NO_2Cl$	11.32	11.70
Isopropyl	*n*-Amyl[e]	140–142	*k*	$C_{17}H_{28}NO_2Cl$	11.24	11.24
Methylamino	Ethyl	165–167	*l*	$C_{12}H_{19}N_2O_2Cl$	13.81	13.76
Methylamino	*n*-Butyl	137–138	*h*	$C_{14}H_{23}N_2O_2Cl$	12.36	12.37
Methylamino	*i*-Butyl	129–131	*m*	$C_{14}H_{23}N_2O_2Cl$	12.36	12.33
Methylamino[a]	*n*-Butyl	115–117	*h*	$C_{14}H_{23}N_2O_2Cl$	12.36	12.46
Methylamino[a]	*i*-Butyl	132–134	*h*	$C_{14}H_{23}N_2O_2Cl$	12.36	12.25
Dimethylamino	Ethyl	193–194	*h*	$C_{13}H_{21}N_2O_2Cl$	13.00	13.10
Dimethylamino	*n*-Butyl	161–162	*h*	$C_{15}H_{25}N_2O_2Cl$	11.79	11.79
Dimethylamino	*i*-Butyl	215–216	*l*	$C_{15}H_{25}N_2O_2Cl$	11.79	11.77
Ethylamino	Ethyl	176–178	*h*	$C_{13}H_{21}N_2O_2Cl$	13.00	13.14
Ethylamino	*n*-Butyl	145–146	*h*	$C_{15}H_{25}N_2O_2Cl$	11.79	11.81
Ethylamino	*i*-Butyl	145–146[b]	*h*	$C_{15}H_{25}N_2O_2Cl$	11.79	11.78
Diethylamino	Ethyl	170–171	*h*	$C_{15}H_{25}N_2O_2Cl$	11.79	11.70
Diethylamino	*n*-Butyl	135–136[c]	*g*	$C_{17}H_{29}N_2O_2Cl$	10.78	10.91
Diethylamino	*i*-Butyl	132–133	*n*	$C_{17}H_{29}N_2O_2Cl$	10.78	10.76
Diethylaminomethyl	*i*-Butyl	173–174[d]	*m*	$C_{18}H_{32}N_2O_2Cl_2$	18.68	18.48

[a] Substituted in the meta position. [b] Mixed m. p. with the *n*-butyl analog, 130–135°. [c] On recrystallization from water a hydrate forms which melts at 80°, but on drying at 65° it melts at 135–136°. [d] Isolated as the dihydrochloride. [e] Prepared by method D. [f] Also prepared by method D. [g] Ethyl acetate. [h] Isopropanol. [i] Benzene. [j] Toluene–isopropanol. [k] Ethyl acetate–ether. [l] Absolute ethanol. [m] Methanol–ethyl acetate. [n] Isopropanol–benzene.

ammonium hydroxide. A curdy white precipitate formed. This was filtered, washed with water and recrystallized several times from methanol to give white needles, m. p. 70–71°.

Anal. Calcd. for $C_{16}H_{26}N_2O_2$: N, 10.07. Found: N, 10.02.

Preparation of N-(*n*-Heptyl)-N-(β-hydroxyethyl) *p*-Aminobenzoamide (D of Fig. 1).—A solution of 23.0 g. of nitroamide (A of Fig. 1, 0.075 mole) dissolved in 125 ml. of isopropanol was subjected to catalytic hydrogenation at 2–3 atmospheres in the presence of 0.25 g. of Adams platinum oxide catalyst. Three moles of hydrogen was absorbed in fifteen minutes, after which no further reduction occurred. The solution was filtered free of catalyst and most of the solvent was removed by distillation *in vacuo*. The colored residue was poured into water and the orange oil which formed soon solidified. This was removed by filtration, washed with water and dissolved in cold 3% hydrochloric acid. The slightly colored solution was purified with Darco in the cold three times to give a colorless solution which was then made ammoniacal, when a white precipitate formed. This was separated by filtration and air dried to give 17 g. of product. On recrystallization from benzene glistening plates of amino amide were obtained, m. p. 81–82°

Anal. Calcd. for $C_{16}H_{26}N_2O_2$: N, 10.07. Found: N, 10.11.

Attempts to prepare the hydrochloride of this product resulted in the formation of an oil: 10 g. of this amino amide was treated with 4.5 ml. of concentrated hydrochloric acid (1.5 equivalents) and the resulting clear solution was warmed for five minutes at 80°. On cooling the mixture solidified to a white mass which was dissolved in 350 ml. of hot water and treated with Darco to give a colorless solution. The excess acid was neutralized and on standing overnight the clear solution deposited crystals. These were separated by filtration and air dried to give 8.5 g. of product. On recrystallization from hot water, white needles were obtained, m. p. 157–158°; mixed m. p. with known sample of amino ester hydrochloride (C of Fig. 1), m. p. 157–158°.

Method E: Preparation of β-Isobutylaminoethyl *p*-Diethylaminobenzoate Hydrochloride.—A mixture of 19.3 g. of *p*-diethylaminobenzoic acid (0.10 mole) and 23.4 g. of β-isobutylaminoethanol (0.20 mole) was warmed for one hour at 90–100° to give a clear viscous liquid. After cooling this was carefully treated with 50 ml. of concentrated sulfuric acid and the resulting solution was heated at 110° for one hour and then cooled. This was dissolved in 800 ml. of water and the resulting clear solution was neutralized with sodium bicarbonate. The neutralized solution was made ammoniacal when an oil formed. This was extracted with ether and the ethereal solution was washed with water and then extracted with 200 ml. of dilute hydrochloric acid. The warm acid solution was decolorized with Darco and made ammoniacal. The oil was dissolved in ether and titrated with alcoholic hydrochloric acid. A white precipitate formed which was removed by filtration and air dried to give 18.8 g. of crude product. This was recrystallized twice from isopropanol–benzene to give white crystals, m. p. 132–133°.

Anal. Calcd. for $C_{17}H_{29}N_2O_2Cl$: Cl, 10.78. Found: Cl, 10.76.

The ammoniacal aqueous solution from which the anesthetic oil had been extracted with ether was acidified with acetic acid and allowed to stand overnight when 9 g. of crude *p*-diethylaminobenzoic acid was recovered.

Summary

1. Several series of anesthetic esters of mono-

alkylaminoethanols and monoalkylamino-β,β-dimethylethanols with various organic acids have been prepared.

2. The reaction of a monoalkylaminoethanol with an aromatic acid chloride in the presence of aqueous alkali results in the formation of an N-alkyl-N-(β-hydroxyethyl) amide.

3. The β-hydroxyamides formed can be rearranged to corresponding β-alkylaminoethyl esters by treatment with strong acid.

4. A new method for the preparation of mono-alkylaminoethyl esters has been described, which consists in allowing the corresponding amino alcohol and aromatic acid to react in the presence of concentrated sulfuric acid.

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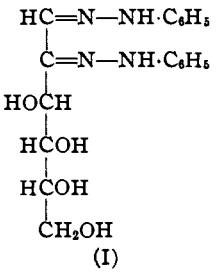
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

The Action of Copper Sulfate on the Phenyl Osazones of the Sugars. II. Some New Osotriazoles

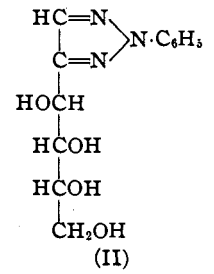
BY W. T. HASKINS, RAYMOND M. HANN AND C. S. HUDSON

Recently[1] it was shown that phenyl D-glucosazone (I) was readily decomposed in hot aqueous copper sulfate solution with the formation of a compound (II) to which the common name phenyl D-glucosotriazole was given. Because



(I)

Phenyl D-glucosazone



(II)

Phenyl D-glucosotriazole

of its great stability, low solubility, spontaneity of crystallization, high specific rotation ($[\alpha]^{20}D$ −81.6° in pyridine) and sharp melting point (195–196°) this osotriazole proves to be a valuable reference substance in confirming the identity of phenyl D-glucosazone.

The transformation of sugar phenyl osazones to phenyl osotriazoles by copper sulfate is apparently a general reaction, as is evident from the conversion of typical phenyl osazones of the pentose (D-xylose), hexose (D-galactose, D-altrose and L-sorbose) and compound sugars (lactose, cellobiose, maltose and turanose) to the corresponding phenyl osotriazoles. The ready formation from phenyl turanosazone of crystalline phenyl D-turanosotriazole[2] (m. p. 193–194°; $[\alpha]^{20}D$ +74.5° in water) and the acid hydrolysis of the latter derivative, as well as that of phenyl D-maltosotriazole, to form D-glucose and phenyl D-glucosotriazole (II) constitute proof that the phenyl osazones of turanose and maltose have an atom of nitrogen attached to each of their carbon atoms at positions 1 and 2 and are accordingly osazones of normal structure.

In the present communication we describe the preparation of the phenyl osotriazoles from xylose, galactose, sorbose, altrose, lactose and cellobiose and some of their acetyl and benzoyl derivatives. Thanks are expressed to Mr. Harry W. Diehl for assistance in the experimental work and to Dr. A. T. Ness for carrying out the microchemical analyses.

(1) Hann and Hudson, THIS JOURNAL, 66, 735 (1944).

(2) Hudson, *J. Org. Chem.*, 9, 470 (1944).

Experimental

Phenyl D-Xylosotriazole (III).—A solution of 20.0 g. of phenyl D-xylosazone and 16.7 g. (1.1 molecular equivalents) of copper sulfate pentahydrate in 1200 cc. of water was heated to boiling under a reflux condenser for thirty minutes, allowed to cool to room temperature and filtered to separate the fine red precipitate which had deposited. The filtrate was concentrated *in vacuo* to a volume of 25 cc., diluted with 10 cc. of absolute alcohol, and allowed to stand at 5° for eighteen hours; the crystalline precipitate which had formed was separated by filtration and recrystallized several times from 100 parts of warm ether. The yield was 5.8 g. (40%). The pure phenyl D-xylosotriazole melted at 88–90°, showed $[\alpha]^{20}D$ −32.3° in aqueous solution (*c*, 0.81), and crystallized as colorless, glistening plates; it is soluble in cold methyl and ethyl alcohols, acetone and acetic acid, warm ether, chloroform and benzene, and nearly insoluble in cold ether, chloroform, benzene and petroleum ether.

Anal. Calcd. for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57. Found: C, 56.13; H, 5.46.

Phenyl D-Xylosotriazole Triacetate.—A solution of 1.0 g. of phenyl D-xylosotriazole in a mixture of 5 cc. of pyridine and 5 cc. of acetic anhydride was allowed to stand at 20° for forty-eight hours and then poured upon crushed ice. The mixture was extracted with chloroform and the washed extract was concentrated by a current of air to a sirup which was crystallized by cooling, with ether and Dry Ice, its solution in a mixture of ether and petroleum ether. The compound was recrystallized from 5 parts of alcohol; it formed small elongated plates which melted at 57–58° and rotated $[\alpha]^{20}D$ −62.4° in chloroform (*c*, 0.83). The yield of pure product was 2.4 g. or 77%. It is readily soluble in cold methyl and ethyl alcohols, acetone, acetic acid and benzene and nearly insoluble in petroleum ether.

Anal. Calcd. for $C_{17}H_{19}N_3O_6$: C, 56.50; H, 5.30; CH_3CO, 35.7. Found: C, 56.57; H, 5.33; CH_3CO, 35.6.

Phenyl D-Xylosotriazole Tribenzoate.—To an ice-cold solution of 1.0 g. of phenyl D-xylosotriazole in 10 cc. of pyridine, 2.5 cc. of benzoyl chloride was added and the mixture was allowed to stand for twenty-four hours at 20° and then poured upon crushed ice. The reaction product was extracted with chloroform and the washed chloroform extract was evaporated to a sirup and dissolved in 10 cc. of absolute alcohol. The tribenzoate crystallized as small irregularly shaped prisms which after