C.—A solution of I (3.29 g., 0.022 mole) in acetone (10 ml.) was treated dropwise during 10 min. with piperidine (1.9 g., 0.022 mole) in acetone (10 ml.) and stirring was continued 3.5 hr. The yellow powder (3.55 g., 70%) was extracted with hot ethanol to remove traces of IIf, then crystallized from ethanol; colorless prisms, m.p. 180–181°; R_f 0.88; in water, R_f 0.75.

Anal. Calcd. for $C_9H_{15}N_3S_2$ (Vf): C, 47.15; H, 6.70; N, 18.33; S, 27.92. Found: C, 46.80; H, 6.69; N, 18.28; S, 27.70.

Reactions of Ethylene Diisothiocyanate (I) with Diethylamine.—I was treated with diethylamine in water and in acetone according to runs A to B. The presence of both mono- and bisadducts was ascertained by chromatography (R_f values: 0.90 and 0.87, respectively). The products were not investigated further.

Hydrolysis.—All mono- and bisadducts were stable towards dilute acid. The substituted ethylenedithioureas were also stable towards alkali. The monoadducts, on the contrary, were hydrolyzed by dilute sodium hydroxide with formation of the known imidazolidine-2-thione (VII). This was collected in minute amount after refluxing 30 min. on the water bath Vf (100 mg.) with normal sodium hydroxide (10 ml.); in the other cases, VII was identified by chromatography of the alkaline solutions by comparison with a standard sample. In most cases, additional spots due to unidentified compounds appeared in the chromatograms. Acidification of the alkaline solution caused evolution of hydrogen sulfide.

Acknowledgment.—We gratefully acknowledge the support by Shell Internationale Research, Maatschappij N.V., The Hague, Holland, for the investigation.

Interaction of Phenyl Isocyanate and Related Compounds with Sodium Borohydride[1]

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Catalytic trimerization of phenyl, *p*-tolyl, and *p*-methoxyphenyl isocyanates has been observed with several complex metal hydrides, with and without solvent. Excess sodium borohydride in refluxing diglyme (diethylene glycol dimethyl ether) transforms phenyl isocyanate, its dimer and trimer, and *N*-formyl-*N*,*N'*-diphenylurea into a mixture of aniline, *N*-methylaniline, tris(*N*-methylanilino)borine, and formanilide. The latter compound is itself converted into aniline, *N*-methylaniline, and the aminoborine under the same conditions. Phenyl isothiocyanate yields only *N*-methylaniline and traces of the aminoborine at high temperature, but at lower temperatures thioformanilide is formed. A mechanism for the formation of the observed products is proposed.

The reaction of phenyl isocyanate with lithium aluminum hydride in refluxing ether has been reported by several workers[3,4] to give *N*-methylaniline in high yield. In a careful quantitative study Finholt and coworkers[5] reported the following stoichiometry for the following reaction.

$$4PhNCO + 3LiAlH_4 \rightarrow (PhNCH_3)_4AlLi + 2LiAlO_2$$

Hydrolysis of the intermediate complex then gave *N*-methylaniline.

In addition, other reports[6,7] have appeared on the reduction to substituted methylamines of other isocyanates with lithium aluminum hydride.

Formanilide[3] and phenyl isothiocyanate[4,5] also yield *N*-methylaniline with lithium aluminum hydride while *sym*-diphenylurea[4] was recovered unchanged after thirty hours in contact with lithium aluminum hydride.

This investigation extends complex metal hydride reactions with aryl isocyanates to sodium borohydride.

Results and Discussion

In the presence of catalytic amounts of sodium borohydride phenyl, *p*-tolyl, and *p*-methoxyphenyl isocyanates are converted into the corresponding trimers (isocyanurates) in high yield. Identity of the products was established by mixture melting points and comparison of their infrared curves with those of authentic samples. The formation of trimers was exothermic in either dioxane or diglyme without external heating when as little as 0.01 mole of sodium borohydride per mole of isocyanate was present. When the catalyst concentration was one tenth this value moderate heating was required to initiate reaction. Treatment of phenyl isocyanate with a catalytic amount of lithium aluminum hydride in ether also afforded the trimer.

Bulk polymerization of phenyl isocyanate by a catalytic amount of sodium borohydride also afforded triphenyl isocyanurate, although in this case moderate heating was required. Lithium aluminum hydride, lithium tri-*t*-butoxyaluminohydride, and potassium borohydride are also effective catalysts in the bulk polymerization of phenyl isocyanate. The two lithium hydrides gave exothermic reactions while potassium borohydride, like sodium borohydride, required moderate heating to initiate a reaction.

The catalytic bulk or solution trimerization of phenyl isocyanate by lithium aluminum hydride is noteworthy in view of the several reports of the formation of *N*-methylaniline from the isocyanate and equivalent quantities of this hydride. An explanation may be that, in the presence of excess hydride, reduction is the predominant reaction. Alternatively, an equilibrium may exist between the isocyanate monomer and the initially formed trimer, with gradual catalytic detrimerization to the monomer as reduction of the latter proceeds. Purely thermal displacement of the equilibrium in favor of the monomer is an unsatisfactory explanation for the failure to isolate trimer in refluxing ether since triphenyl isocyanurate represents a structure which is very stable to thermal attack.

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[1] Presented before the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962.

[2] One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

[3] F. Wessely and W. Swoboda, *Monatsh. Chem.*, **82**, 621 (1951).

[4] W. Ried and F. Müller, *Chem. Ber.*, **85**, 470 (1952).

[5] A. E. Finholt, C. D. Anderson, and C. L. Agre, *J. Org. Chem.*, **18**, 1338 (1953).

[6] H. H. Zeiss and W. B. Martin, Jr., *J. Am. Chem. Soc.*, **75**, 5935 (1953).

[7] R. L. Dannley, R. G. Taborsky, and M. Lukin, *J. Org. Chem.*, **21**, 1318 (1956).

TABLE I

REACTIONS WITH EXCESS SODIUM BOROHYDRIDE IN REFLUXING DIGLYME

		Product and yield								
		Aniline[a]		N-Methylaniline[a]		Tris(N-methylanilino)-borine[b]		Formanilide[a,c]		
Compound	Moles	Mmoles	%	Mmoles	%	Mmoles	%	Mmoles	%	Total %
PhNCO	0.1	4.8	4.8	25.7	26	13.4	40	3.3	3.3	74
$(PhNCO)_2$	.025	3.4	6.8	11.0	22	5.6	34	...	...	63
$(PhNCO)_3$	.017	2.1	4.1	17.2	34	4.7	28	1.7	3.3	69
PhNHCHO	.1	15.2	15	21.4	21	11.2	34	5.7	5.7	76
PhN(CHO)CONHPh	.024	4.9	10	15.1	31	5.2	32	0.8	1.7	75
PhNCS	.05	..	..	45.3	91	0.3	1.8			93

[a] Yields determined by gas chromatography. [b] Crude product. [c] Minimum yield.

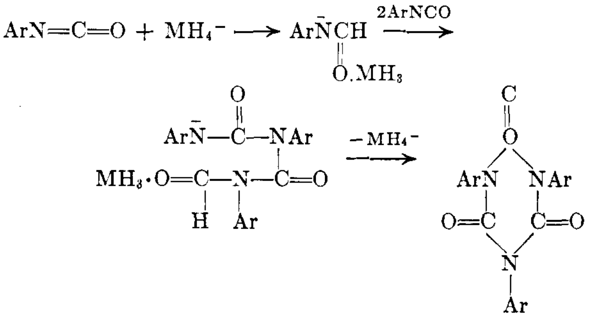
An example of detrimerization of an isocyanurate has been reported by Shapiro and co-workers[8] who found that tris(m-chlorophenyl) isocyanurate was converted to ethyl m-chlorophenylurethane upon reaction with ethanol for three hours at 120° in the presence of lithium ethoxide. The alkoxide was also a trimerization catalyst for the isocyanate.

When 0.5 mole of sodium borohydride per mole of phenyl isocyanate was employed in diglyme at temperatures up to 60°, triphenyl isocyanurate was isolated, irrespective of the order of addition of reagents. When the hydride was added to the isocyanate, however, a better yield of trimer was realized. In the case of reverse addition, reactions leading to reduction products probably predominated, although this possibility was not investigated fully.

No trimerization occurred with n-butyl, o-tolyl, and o-chlorophenyl isocyanates and catalytic amounts of sodium borohydride, even with heating. The unchanged isocyanates were recovered as the corresponding ureas after reaction with water. Steric factors may account for the lack of reaction in the case of the o-substituted phenyl isocyanates, although trimers have been obtained from these compounds using potassium acetate.[9] No reason for the lack of trimerization of n-butyl isocyanate is apparent, although the trimerization of alkyl isocyanates has been reported.[10]

Utilization of catalyst in the reduction of the nitro group[11] in p-nitrophenyl isocyanate may account for the color change noted when this isocyanate was treated with sodium borohydride. No trimer was obtained and the unchanged isocyanate was converted to urea.

Trimer formation catalyzed by complex metal hyhydrides may follow the path outlined in equation 1.



(1)

In refluxing diglyme (b.p. 162°) the reaction of phenyl isocyanate and excess sodium borohydride takes an entirely different course. After addition of dilute acetic acid to the cooled reaction mixture, aniline, N-methylaniline, and tris(N-methylanilino)borine were identified as reaction products, with yields of 4.8, 26, and 40%, respectively. No attempt was made to separate the small quantity of aniline from N-methylaniline and diglyme, but it was possible to analyze the mixture by gas chromatography on a silicone column. Reaction of the mixture with tosyl chloride and alkali afforded the p-toluenesulfonamides of the two amines. These derivatives were identified by mixture melting points and infrared spectra. In addition, the gas chromatogram of the amine mixture indicated the presence of a peak with the same retention time as formanilide. The yield of formanilide calculated by this analysis was 3.3%. This and the other values for formanilide reported in Table I probably represent only minimum yields of this product since its isolation from the reaction mixtures was not attempted in view of its high water solubility and because of the complex nature of the mixtures.

The identity of the aminoborine was established by mixture melting point with an authentic specimen and by comparison of infrared curves of the two samples.

In addition to phenyl isocyanate, several related compounds were subjected to the same reaction conditions with sodium borohydride, one mole of the hydride being used for each equivalent of compound. The same products were obtained from phenyl isocyanate dimer, trimer, and N-formyl-N,N'-diphenylurea as from phenyl isocyanate, except that no formanilide was detected in the amine fraction obtained from the dimer (although this was no doubt a product of the reaction). These derivatives of phenyl isocyanate probably function as phenyl isocyanate generators under the influence of heat and/or the catalytic activity of sodium borohydride. In addition to the isocyanate, thermal dissociation of the urea derivative yields formanilide. Formanilide gave the two amines and the aminoborine upon treatment with sodium borohydride in refluxing diglyme. Some formanilide was unchanged (Table I).

In contrast to the formation of trimer from phenyl isocyanate and excess sodium borohydride, at 15° phenyl isothiocyanate gave reasonable yields of thioformanilide, the primary reduction product expected from the isothiocyanate. The presence of aniline and N-methylaniline in the reaction mixture was not investigated. However, at 90° no thioformanilide was isolated, but the main product was N-methylaniline (74%), accompanied by aniline (6%), and a small amount of a solid, m.p. >200°, which was probably tris(N-methylanilino)borine. At still higher temperatures

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(8) S. L. Shapiro, V. Bandurco, and L. Freedman, **26,** *J. Org. Chem.*, 3710 (1961).

(9) I. C. Kogon, *J. Am. Chem. Soc.*, **78,** 4911 (1956).

(10) J. H. Saunders and R. J. Slocombe, *Chem. Rev.*, **43,** 203 (1948).

(11) C. E. Weill and G. S. Panson, *J. Org. Chem.*, **21,** 803 (1956).

(162°) the reaction gave predominantly *N*-methylaniline and a trace of the aminoborine, but no aniline (Table I).

No attempt was made to determine the actual hydride balance in the various reactions, but in all cases an excess of hydride was employed, as indicated by the gas evolution upon acidification of the reaction mixtures.

Several likely pathways can be considered for the formation of the observed products in the various reactions in refluxing diglyme. Initial attack by the hydride on phenyl isocyanate probably occurs at the carbon–oxygen bond since the form Ic makes the largest contribution to I. In the case of phenyl isothiocyanate, initial attack is more likely at the carbon–nitrogen bond since IIa would be expected to make the greatest contribution to II, in view of the greater electronegativity of nitrogen relative to sulfur. The sequences of equations 2 and 3 represent the proposed course of the reactions.

$$\underset{a}{\mathrm{Ph\overset{-}{N}{-}\overset{+}{C}{=}Y}} \longleftrightarrow \underset{b}{\mathrm{PhN{=}C{=}Y}} \longleftrightarrow \underset{c}{\mathrm{PhN{=}\overset{+}{C}{-}\overset{-}{Y}}}$$

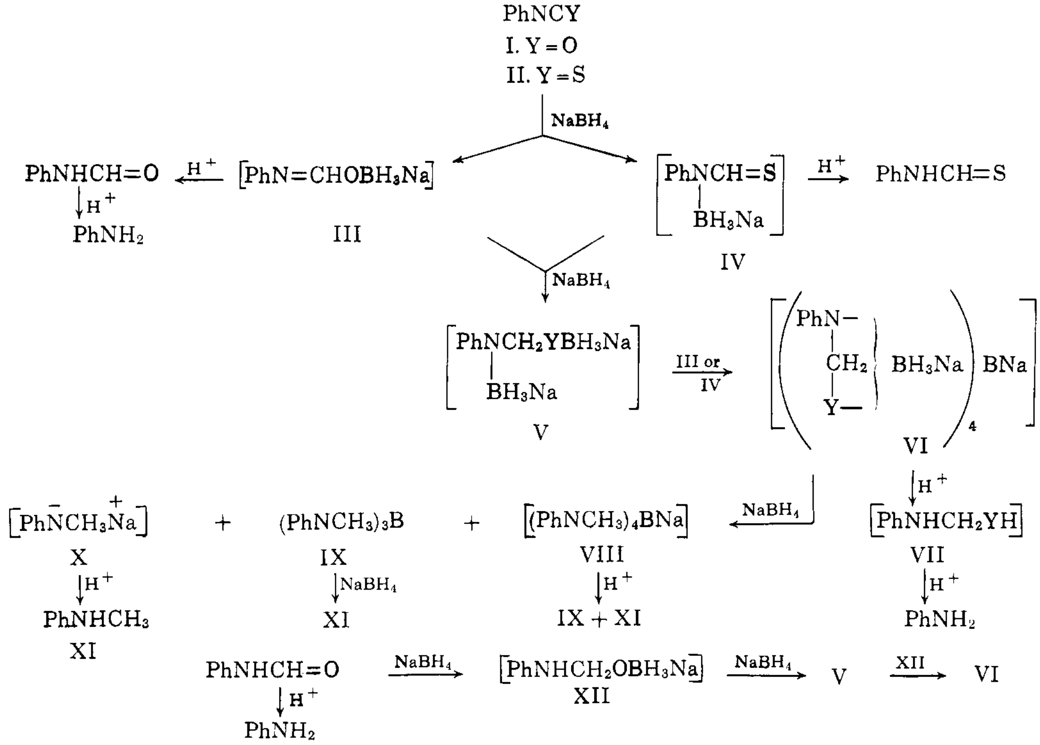
$$\begin{array}{l}\mathrm{I.\ \ Y = O}\\ \mathrm{II.\ \ Y = S}\end{array}$$

The intermediate VI may result from formanilide through reduction and salt formation.

An alternate route to aniline may involve hydrolysis *via* the route VI → VII.

It was determined that tris(*N*-methylanilino)borine was not appreciably hydrolyzed under the weakly acidic conditions used in working up the various reaction mixtures (85–96% recovery). Reaction of IX and sodium borohydride (1:3.5 molar ratio) in refluxing diglyme for one hour gave a 44% yield of XI and recovered IX (12%). The sequence VI → VIII → IX + XI cannot be the sole route by which *N*-methylaniline is formed since, in practice, the amount of the amine formed relative to the amount of the aminoborine isolated is much greater than that predicted by the above sequence. For these reasons it is likely that intermediates such as IX and X are precursors for most of the *N*-methylaniline.

The higher yield of the aminoborine from phenyl isocyanate compared to its sulfur analog would seem to indicate the formation in the former case of an intermediate VI in which many of the boron atoms are bound to three or four nitrogen atoms, while in the latter case most of the boron atoms are probably bound more or less equally to nitrogen and sulfur.



(2)

(3)

Hydrolysis of the intermediate III leads to formanilide (*via* its tautomeric form), which in turn is partly hydrolyzed to aniline (actually, aniline was found in about 10% yield when formanilide was subjected to the acidic conditions used in working up the various reactions). Further reduction by the hydride of III and IV would eventually lead to the (possibly polymeric) intermediate VI. Random distribution of nitrogen and oxygen (or sulfur) on boron in VI would be expected to furnish, following hydrogenolysis of carbon–oxygen (or carbon–sulfur) bonds by more hydride, intermediates such as VIII and X and tris(*N*-methylanilino)borine (IX). Acid hydrolysis of VIII and X leads to *N*-methylaniline (XI) and IX.

The formation of tris(*N*-methylanilino)borine by reaction of sodium borohydride and phenyl isocyanate, its generators, formanilide, and phenyl isothiocyanate is apparently the first case of the formation of a compound containing a stable boron–nitrogen bond from sodium borohydride and a compound containing a carbon–nitrogen double bond,[12] although the analogous formation of boron–oxygen[13] or boron–carbon[14] bonds

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(12) W. Gerrard, "The Organic Chemistry of Boron," Academic Press, Inc., New York, N. Y., 1961.

(13) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, p. 121.

(14) H. C. Brown, "Organometallic Chemistry," H. Zeiss, Ed., Reinhold Publishing Corp., New York, N. Y., 1960, p. 154.

from compounds containing carbon–oxygen or carbon–carbon double bonds, respectively, are known.

Reduction of amides by sodium borohydride apparently has not been reported previously.[15]

Experimental[16]

Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer using potassium bromide disks. Gas chromatographic analyses were made on the Aerograph Model A-700 gas chromatograph using acid-washed Chromosorb P coated with silicone high vacuum grease.[17]

Reagents and Solvents.—Liquid isocyanates were redistilled and *p*-nitrophenyl isocyanate was recrystallized before use. Sodium borohydride was purified according to Brown.[18] Diglyme was refluxed over sodium borohydride and redistilled. Dioxane was purified according to Fieser.[19]

Solution Trimerization of Phenyl Isocyanate.—A solution of 6.00 g. (0.05 mole) of phenyl isocyanate in 20 ml. of dioxane, protected with a calcium chloride drying tube, was cooled to 3° in an ice bath and 1 ml. (0.5 mmole) of sodium borohydride solution in diglyme (0.38 g. in 20 ml.) was added as the solution was stirred by a magnetic stirrer. Within 2 min. the temperature rose to 15° as a solid precipitated. After 15 min. in the ice bath, 50 ml. of ether was added to the mixture and the filtered solid was washed with ether. The weight of triphenyl isocyanurate, m.p. 279–280°, was 5.03 g. (84%). Recrystallization from a methylene chloride–petroleum ether (b.p. 30–60°) mixture gave white needles, m.p. 280–281° (lit.[9] m.p. 280–281°), m.m.p. with an authentic sample 278–279°. The infrared spectrum was identical with that of an authentic sample.

In a similar manner tris(*p*-methoxyphenyl) isocyanurate, m.p. 263–264° (lit.[9] m.p. 259–260°), and tris(*p*-tolyl) isocyanurate, m.p. 268–269° (lit.[9] m.p. 264–265°), were obtained in yields of 86 and 91%, respectively, from the corresponding isocyanates with catalytic amounts of sodium borohydride in dioxane. Identification of the isocyanurates was made by mixture melting points and comparison of infrared curves with authentic samples.

A phenyl isocyanate to catalyst molar ratio of 1:0.001 required heating for 45 min. at 70° in dioxane to obtain the trimer (93% yield).

Addition of sodium borohydride (0.05 mole) in diglyme to a solution of phenyl isocyanate (0.1 mole) in diglyme at room temperature caused of phenyl isocyanate (0.1 mole) in diglyme at room temperature caused the solution to heat up to 60°. After pouring the mixture into water and acidifying with 20% acetic acid, the trimer was recrystallized from 95% ethanol, m.p. 277–278° (69%). When the order of addition was reversed a much lower yield of trimer was obtained.

Unsuccessful attempts were made to trimerize *o*-chlorophenyl, (1 hr. at 70°), *o*-tolyl (1.5 hr. at 70°), *p*-nitrophenyl (0.5 hr. at 80°), and *n*-butyl (1 hr. at 70°) isocyanates in dioxane with catalytic amounts of sodium borohydride. In these cases the corresponding ureas were isolated and identified by mixture melting points and infrared data after the unchanged isocyanates were treated with water and acetone.

Trimerization of phenyl isocyanate by lithium aluminum hydride (0.01 mole per mole of isocyanate) in ether at room temperature was achieved in at least 60% yield (the odor of the reaction mixture indicated the presence of some unchanged isocyanate) within 5 min.

Bulk Trimerization of Phenyl Isocyanate.—Triphenyl isocyanurate was obtained by bulk polymerization of the isocyanate using a ratio of 1 mole of isocyanate to 0.01 mole of the following hydrides (% yields): lithium aluminum hydride (78%), lithium tri-*t*-butoxyaluminohydride (89%), potassium borohydride (74%), and sodium borohydride (74%). Trimerization with the first two hydrides was very exothermic while the latter two required heating to 70–80° to initiate reaction.

Bulk polymerization of *o*-tolyl and *o*-chlorophenyl isocyanates was unsuccessful when attempted at 80° for 2 hr.

Reaction of Phenyl Isocyanate with Excess Sodium Borohydride at High Temperature.—To a slurry of 3.78 g. (0.1 mole) of sodium borohydride in 50 ml. of diglyme at reflux was added over 15 min. with stirring a solution of 11.92 g. (0.1 mole) of phenyl isocyanate in 30 ml. of diglyme. The reaction mixture was protected by a calcium chloride tube. During the exothermic reaction most of the sodium borohydride dissolved. Stirring and refluxing was continued for 1 hr. after the addition was completed, and the yellow solution was cooled and poured into 750 ml. of ice and water. After carefully acidifying with 100 ml. of 20% acetic acid to decompose excess hydride, the mixture was left in a refrigerator overnight. Tris(*N*-methylanilino)borine was filtered and washed well with water, 4.42 g. (40%), m.p. 206–211°. The infrared spectrum of an ether-washed sample showed weak bands near 3 and 6 μ, indicating the presence of traces of *sym*-diphenylurea. Upon hydrolysis of the crude aminoborine with refluxing concentrated hydrochloric acid, 3% (based on the weight of crude sample) *sym*-diphenylurea was obtained in addition to 89% of the theoretical amount of *N*-methylaniline and a trace of aniline (probably from hydrolysis of the urea). The aminoborine was stable to hydrolysis by acetic acid of the concentration used in the work-up of the reaction mixture. Sublimation of the crude aminoborine at 185° (*ca.* 0.001 mm.) gave the pure product, m.p. 209–213° (lit.[20] m.p. 210°) and m.m.p. with an authentic sample 212–215°. Its infrared spectrum was identical with the infrared spectrum of an authentic sample.

Anal. Calcd. for $C_{21}H_{24}BN_3$: C, 76.60; H, 7.35; N, 12.76. Found: C, 76.81; H, 7.41; N, 12.73.

The boron-containing, water-soluble sublimation residue gave infrared peaks near 3 and 6 μ.

After filtration of the aminoborine, the acidic filtrate of the original reaction mixture was treated with concentrated hydrochloric acid and ether extracted. The water layer was made alkaline with sodium hydroxide and extracted with ether after saturating wth salt. After washing the extract with salt solution and drying over sodium sulfate, the ether was evaporated and the residue analyzed by gas chromatography. In addition to traces of ether and a large amount of diglyme, the residue contained 0.45 g. (4.8% yield) of aniline and 2.76 g. (26% yield) of *N*-methylaniline. Treatment of the mixture with tosyl chloride and sodium hydroxide allowed the isolation, after the usual work-up, of the *p*-toluenesulfonamides of aniline and *N*-methylaniline, m.p. 103–104° and 94–95°, respectively. In addition to the two amines the gas chromatogram indicated the presence of 0.40 g. (3.3% yield) of formanilide.

Phenyl isocyanate dimer, trimer, formanilide, *N*-formyl-*N*,*N'*-diphenylurea, and phenyl isothiocyanate were treated with sodium borohydride in the same way except that the solid compounds were mixed with the hydride prior to refluxing. One mole of borohydride was used for each mole of phenyl isocyanate equivalent. The yields of the various products are compared with those from phenyl isocyanate in Table I.

Thioformanilide.—To a suspension of 0.95 g. (0.025 mole) of sodium borohydride in 15 ml. of diglyme was added dropwise with stirring over 15 min. 6.75 g. (0.05 mole) of phenyl isothiocyanate while keeping the temperature near 10–15° with an ice bath. The yellow reaction mixture (odor of hydrogen sulfide) was then stirred another 1.5 hr. in the ice bath, poured into 250 ml. of ice-water, and acidified with 8 ml. of 6 *N* hydrochloric acid, heated to 70°, and then cooled in an ice bath. The yield of crude thioformanilide, m.p. 137°, was 4.80 g. (70%). Recrystallization from hot water gave white needles, m.p. and m.m.p. with an authentic sample 139–140° (lit.[21] m.p. 138°), 3.4 g. The product gave an infrared curve identical with that of an authentic sample. The presence of aniline and *N*-methylaniline in the reaction mixture was not investigated.

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[15] Ref. 13, p. 592.

[16] Melting points are uncorrected.

[17] Mention of trade names and firms does not imply their endorsement by the Department of Agriculture over similar products or firms not mentioned.

[18] H. C. Brown, E. J. Mead, and B. C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 6209 (1955).

[19] L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., D. C. Heath and Co., Boston, Mass., 1955, p. 284.

[20] A. Dornow and H. H. Gehrt, *Angew. Chem.*, **68**, 619 (1956).

[21] A. Reissert, *Ber.*, **37**, 3708 (1904).

A reaction time of 1 hr. at 25° (1:1 molar ratio of reactants) decreased the yield of thioformanilide to 49%; reaction for 1 hr. at 90° (1:1 molar ratio of reactants) gave only aniline (6%), *N*-methylaniline (74%), and a solid melting above 200° which was probably tris(*N*-methylanilino)borine (9%) but was not further investigated.

Acknowledgment.—The authors wish to thank Lawrence E. Brown and Ann L. Alford for microanalyses and Sylvia H. Miles, Gordon J. Boudreaux, and James S. Wittman, III, for infrared data and gas chromatographic analyses.

S-[ω-(Aminoöxy)alkyl]isothiuronium Salts, ω,ω'-Bis(aminoöxy)alkanes and Related Compounds[1]

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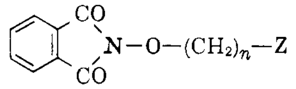
The reaction of N-hydroxyphthalimide with ω,ω'-dibromoalkanes yields ω-(phthalimidoöxy)alkyl bromides, Ia, and ω,ω'-bis(phthalimidoöxy)alkanes, Ib. Reaction of Ia with thiourea, followed by hydrolysis, leads to a facile synthesis of S-[ω-(aminoöxy)alkyl]isothiuronium salts, IIc. Hydrolysis of Ib makes available ω,ω'-bis(aminoöxy)alkanes which were characterized by their salts, amide and sulfonamide derivatives.

To continue our studies[2] on the synthesis of potential prophylactic agents capable of protecting animals from otherwise lethal doses of ionizing radiation, we turned our attention to the synthesis of S-[ω-(aminoöxy)alkyl]-isothiuronium salts, IIc. Such molecules are analogs and homologs of the active 2-aminoethanethiol and the corresponding isothiuronium salt, $H_3\overset{+}{N}\text{–}(CH_2)_2\text{–}S\text{–}C(\text{–}NH_2)\text{=}NH_2^+\ 2X^-$. Structure IIc meets the criteria seemingly essential for protective activity: a basic group, in this instance the aminoöxy moiety, in close vicinity of a thiol or potential thiol group, *viz.*, the isothiuronium group.

In designing these molecules, the aminoöxy function was to be liberated last by the acid hydrolysis of the corresponding phthalimidoöxy derivative.[3] The key intermediates in the synthesis of IIc were the ω-(phthalimidoöxy)alkyl bromides, Ia, which became readily available from the reaction of N-hydroxyphthalimide and ω,ω'-dibromoalkanes.



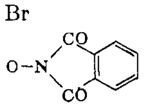
I

$H_3N^+\text{—}O\text{—}(CH_2)_n\text{—}Z\quad Br^-$

II

where the substituent Z is, in

(a) Br

(b) 

(c) $S\text{–}C(\text{–}NH_2)\text{=}NH_2^+\ Br^-$

(d) $S\text{–}SO_3^-\ Na^+$

(e) $O\text{–}NH_3^+\ Br^-$

(f) SH

Displacement of the bromo group in Ia with thiourea furnished the S-[ω-(phthalimidoöxy)alkyl]isothiuronium bromide, Ic, which was hydrolyzed readily by hydrobromic acid to the aminoöxy isothiuronium salt, IIc. This sequence of reactions was used to prepare five homologs of IIc (n = 2 to 6).

The formation of the ω-(phthalimidoöxy)alkyl bromide Ia, was invariably accompanied by some ω,ω'-bis(phthalimidoöxy)alkane, Ib The mixture was separated either by fractional crystallization or column chromatography. Hydrolysis with hydrobromic acid of Ib afforded the corresponding ω,ω'-bis(aminoöxy)-alkane dihydrobromides, IIe. The free bases were characterized by solid amide or sulfonamide derivatives.

These series of reactions are described somewhat in detail for one member of the series, *viz.*, when $n = 2$. N-Hydroxyphthalimide was treated with 1,2-dibromoethane in the presence of triethylamine at room temperature and gave a mixture of Ia and Ib ($n = 2$). The reaction of Ia with thiourea afforded the crystalline salt, Ic from which the phthaloyl moiety was readily cleaved off with hydrobromic acid to produce IIc (n = 2). A similar reaction of Ia with N-methylthiourea furnished the crystalline N-methyl analog of Ic (n = 2) but hydrolysis led to an oily salt, $H_3\overset{+}{N}\text{–}O\text{–}(CH_2)_2\text{–}S\text{–}C(\text{–}NH_2)\text{=}NHCH_3^+2Br^-$, which was characterized as a crystalline dipicrate. When Ib ($n = 2$) was hydrolyzed with hydrobromic acid, 1,2-bis(aminoöxy)-ethane was isolated as the crystalline dihydrobromide. The free base was characterized as its benzamide $(C_6H_5CONHOCH\text{–})_2$, its *p*-toluenesulfonamide, $(p\text{-}CH_3\text{–}C_6H_4SO_2NHOCH^{2-})_2$, and its *p*-acetamidobenzenesulfonamide. The last one of these was hydrolyzed further to the sulfanilamide analog, $(p\text{-}H_2N\text{–}C_6H_4SO_2\text{-}NHOCH_2\text{–})_2$.

It was also possible to remove the protective phthaloyl group from Ia ($n = 2$) with hydrobromic acid to give β-(aminoöxy)ethyl bromide hydrobromide (IIa. $n = 2$).

Benzoylation of this compound produced the crystalline derivative $C_6H_5CONHO(CH_2)_2Br$ which reacted further with thiourea to give the isothiuronium salt, $C_6H_5CONHO(CH_2)_2SC(\text{–}NH_2)\text{=}NH_2^+Br^-$. An attempt to prepare 2-(aminoöxy)ethanethiol, IIf (n = 2), from Ia ($n = 2$) by the following approach was un-

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[2] Our previous paper, L. Bauer and T. L. Welsh, *J. Org. Chem.*, **27**, 4382 (1962), summarizes the background in this field.

[3] The introduction of the aminoöxy group into a molecule *via* the phthalimidoöxy derivative was first described by A. F. McKay, *et al.*, *Can. J. Chem.*, **38**, 343 (1960), and presents certain advantages. The alkylation of N-hydroxyphthalimide is rapid and usually affords a crystalline derivative which is hydrolyzed with great ease by hydrobromic acid (3–5 min.). Other methods are available for the preparation of aminoöxyalkyl compounds *via* suitable derivatives of hydroxylamine. Recently, E. L. Schulmann, *et al.*, *J. Med. Pharm. Chem.*, **5**, 464 (1962), used acetoxime and benzohydroxamic acid to prepare a series of aminoöxy acids; R. M. Khomutov, *J. Gen. Chem. USSR* (Eng. Transl.), **31**, 1863 (1961), used ethyl N-hydroxyacetimidate, $CH_3\text{–}C(\text{=}NOH)OC_2H_5$, for the initial alkylation. The three references quoted here summarize this field.