The Reaction of Grignard Reagents with *t*-Butyl Hydroperoxide.—a. *t*-Butyl hydroperoxide (0.05 mole) in 50 ml. of ether was added slowly into a solution of the Grignard reagent (0.11 mole) in 50 ml. of ether maintained at 0–5°. Stirring was continued at this temperature for 2–3 hours and at room temperature for 10–16 hours. The reaction mixture was worked up by the regular procedure and the product was identified by its physical constants in comparison with an authentic sample. The yields given in parentheses were based on the amount of hydroperoxide consumed.

Thus, bromobenzene gave phenol (98%), m.p. 39–41°; 2-bromonaphthalene gave 2-naphthol (94%), m.p. 121–123°; *p*-bromotoluene gave *p*-cresol (90%), b.p. 92–94° (12 mm.), $n^{20}D$ 1.5397; benzyl chloride gave benzyl alcohol (90%), b.p. 100–101° (14 mm.), $n^{20}D$ 1.5395; 1-bromoöctane gave 1-octanol (92%), b.p. 97–98° (18 mm.), $n^{20}D$ 1.4290; bromocyclohexane gave cyclohexanol (96%), b.p. 69–71° (16 mm.), $n^{20}D$ 1.4658; and neopentyl bromide gave neopentyl alcohol (99%), b.p. 113–115°, m.p. 44°.

b. *t*-Butyl hydroperoxide (0.12 mole) in 50 ml. of ether was added during a one-hour period to an ethereal solution of ethylmagnesium bromide (70 ml. of a 2 *N* solution) which was stirred vigorously and cooled by means of a Dry Ice–acetone-bath (−70°). A solution of phenylmagnesium bromide, prepared from 0.1 mole of bromobenzene, then was added during the next 30 minutes into this cold suspension of magnesium *t*-butyl hydroperoxide. The mixture was stirred at −60° for an additional 30 minutes. At the end of this period, it was allowed to warm to 0°, and was maintained at this temperature for two hours. Vigorous stirring was required throughout the reaction in order to avoid caking. Following the usual procedure, there were obtained 7.5 g. (80%) of phenol and 0.7 g. (9%) of biphenyl.

The Reaction of Phenylmagnesium Bromide and Benzoyl Peroxide.—A solution of phenylmagnesium bromide (0.08 mole) in 110 ml. of ether was added over a period of 2.5 hours into a solution of benzoyl peroxide (19.4 g., 0.08 mole) in 175 ml. of benzene maintained at 0–5°. After 16 hours of stirring at room temperature, the resulting mixture gave a negative test for peroxide. Following the regular procedure, there was obtained benzoic acid (12.4 g., 0.102 mole), bromobenzene (2.6 g., 21%) and phenyl benzoate (5.6 g., 35%). The products were identified by comparison of physical constants and infrared spectra with the respective authentic samples.

In a parallel experiment, a portion of this Grignard reagent was hydrolyzed accordingly. With the exception of a small amount of biphenyl, no bromobenzene was detected.

The Reaction of Ethylmagnesium Bromide with Benzoyl Peroxide.—A solution of ethylmagnesium bromide (0.16 mole in 125 ml. of ether) was treated with a benzene solution of benzoyl peroxide (39.6 g., 0.16 mole in 200 ml. of benzene) at 0° by the regular procedure. There were obtained 28.8 g. (145%) of benzoic acid and 8.4 g. (35%) of ethyl benzoate. The recovered ether gave a positive Beilstein test for halogen indicating the possible presence of ethyl bromide.

The Reaction of Magnesium Bromide with Benzoyl Peroxide.—A filtered solution of magnesium bromide prepared from 5 g. (0.21 mole) of magnesium and 37.5 g. (0.20 mole) of ethylene bromide in 200 ml. of ether was added dropwise to a solution of benzoyl peroxide (24.2 g., 0.1 mole) in 20 ml. of cyclohexene and 200 ml. of benzene maintained at 0–5°. The mixture was allowed to warm to room temperature and was stirred at this temperature for two additional hours. Following the usual work-up, there was obtained benzoic acid (21 g., 86%) and *trans*-1,2-dibromocyclohexane (20.3 g., 83%), b.p. 37–39° (0.15 mm.), $n^{20}D$ 1.5529, identical in all respects with an authentic sample.

The Reaction of Diethylmagnesium with Benzoyl Peroxide.—A solution of diethylmagnesium (0.025 mole) in 125 ml. of ether–dioxane (1:1) was added dropwise to a solution of benzoyl peroxide (12.1 g., 0.05 mole) in 100 ml. of benzene. The mixture was refluxed for 11 hours after the addition, at the end of which period the supernatant solution gave a negative test for Grignard reagent but a positive test for peroxide. There was recovered from the alkaline extracts 4.0 g. of benzoic acid. The organic layer was washed thoroughly with an aqueous solution of sodium iodide in acetic acid until the washing remained colorless. Ethyl benzoate (2.5 g.), b.p. 97–99° (18 mm.), $n^{20}D$ 1.5065, was isolated from the organic layer by distillation.

The Reaction of Phenyllithium with Benzoyl Peroxide.—A solution of phenyllithium (0.143 mole) in 110 ml. of ether was added over a 40-minute period to a solution of benzoyl peroxide (34.2 g., 0.141 mole) in 250 ml. of benzene maintained at 0–5°. The mixture was stirred at 25° for 2 hours following the addition. The mixture then was hydrolyzed with water and extracted with alkaline. There was obtained from the alkaline extract 17.0 g. of benzoic acid. The organic layer was washed, dried and concentrated under reduced pressure to a semi-solid residue which was crystallized from benzene yielding 7.9 g. (61%) of triphenylcarbinol, m.p. 161–162°.

Reaction of Di-*t*-butyl Peroxide with Phenylmagnesium Bromide.—Di-*t*-butyl peroxide (0.2 mole) in 100 ml. of ether was added with stirring to an ethereal solution of phenylmagnesium bromide (0.21 mole in 200 ml.). Benzene (200 ml.) was added to the mixture and ether was removed by distillation until the boiling point of the mixture reached 80°. The mixture was then refluxed for 8 hours. After the usual work-up, di-*t*-butyl peroxide was recovered unchanged.

CHICAGO 37, ILL.

[CONTRIBUTION FROM THE WYETH INSTITUTE FOR MEDICAL RESEARCH]

Mercurial Diuretics. I. Addition of Mercuric Chloride and Secondary Amines to Allylamides[1]

BY GERHARD WENDT, B. VITHAL SHETTY AND WILLIAM F. BRUCE

RECEIVED JANUARY 29, 1959

A series of new mercurial diuretics have been prepared by treating a N-allylamide with a secondary amine and mercuric chloride.

Since the introduction of Salyrgan as an effective diuretic in 1924, all the mercurial diuretics have been made by alkoxymercuration of substituted allylamines, resulting in compounds of the basic structure[2]

$$RNHCH_2\underset{\displaystyle OY}{\underset{|}{C}}HCH_2HgX \qquad I$$

Many variations of groups R and X have been reported. However, little information has been published on the alteration of group Y[3] and these few investigations dealt with changes of the alkyl group in alcohols.[3,4] The use of hydroxylic sol-

(1) Presented before the Division of Medicinal Chemistry at the 134th Meeting of the American Chemical Society, Chicago, Ill., Sept. 7–12, 1958.

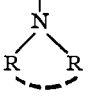
(2) In Salyrgan (Mersalyl) R = *o*-carbamylphenoxyacetic acid, Y = CH_3, X = OH.

(3) The various structures of groups R, Y and X and their effects on diuretic potency have been recently presented in a review by H. L. Friedman, *Ann. N. Y. Acad. Sci.*, **65**, 461 (1957).

(4) E. B. Robbins and K. K. Chen, *J. Am. Pharm. Assoc.*, **40**, 249 (1951); M. M. Best, W. F. Hurt, J. E. Shaw and J. D. Wathen, *Am. J. Med. Sci.*, **225**, 132 (1953); S. L. Shapiro, V. A. Parrino and L. Freedman, *J. Am. Pharm. Assoc.*, **46**, 689 (1957); C. W. Whitehead, THIS JOURNAL, **80**, 2178 (1958); C. W. Whitehead and J. J. Traverso, *ibid.*, **80**, 2182 (1958).

TABLE I

$NH_2CONHCH_2CHCH_2HgCl$ BASE

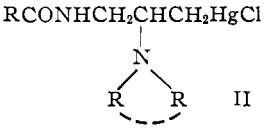


No.		Formula	Yield,[e] %	M.p. dec., °C.	Recrystn. solvent	Mercury, % Calcd.	Mercury, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
1	C_4H_8N[a]	$C_8H_{16}ClHgN_3O$	84	137–138	Methanol–ethanol	49.37	49.34	10.37	10.48	8.73	8.60
2	$C_5H_{10}N$[b]	$C_9H_{18}ClHgN_3O$	68	120–121	Ethanol–*i*-PrOH	47.73	47.73	10.00	10.07	25.72[f]	25.84[f]
										4.32[g]	4.46[g]
3	C_4H_8NO[c]	$C_8H_{16}ClHgN_3O_2$	84	138–139	Ethanol	47.51	47.60	9.95	10.01		
4	$C_5H_4N_2$[d]	$C_9H_{19}ClHgN_4O$	64	119–120	Acetone	46.08	45.90	12.87	12.60	8.15	7.91

[a] Pyrrolidino. [b] Piperidino. [c] Morpholino. [d] 1-Methylpiperazino. [e] Based on allylurea. [f] Carbon, %. [g] Hydrogen, %.

vents in the mercuration reaction will always result in an OY group at carbon atom 2, formula I. No solvents other than hydroxylic solvents have ever been applied to the synthesis of mercurial diuretics.

The object of our investigation is to make mercurials in which, instead of an OY group resulting from hydroxylic solvents, an (NRR) group from a secondary amine is present. The general structure of these compounds is shown in formula II.



II

A review of the literature revealed that this type of mercurial diuretic has not been described previously; therefore, it represents a new class of diuretics. However, one report is available on the preparation of organic mercurials by the addition of a mercuric salt to an olefin by using a non-hydroxylic solvent. In 1945, Freidlina and Kachetkova[5] published the synthesis of 1-(2-chloromercuri)-ethylpiperidine by treating piperidine and mercuric chloride with ethylene.

When we applied the addition reaction of mercuric chloride and piperidine to allylurea, 3-chloromercuri-2-piperidinopropylurea (III) was obtained in a 68% yield (Chart I). In this reaction, the piperidine[6] takes part in the same fashion as methanol in the methoxy-mercuration of the ethylene double bond.

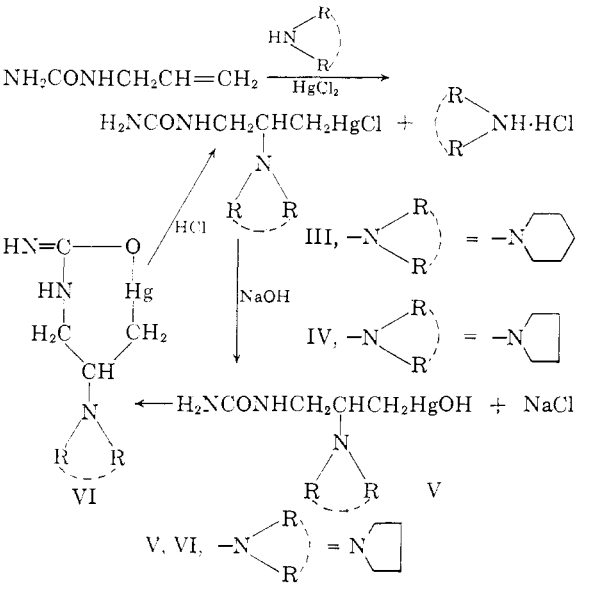
Compound III is only moderately soluble in the common solvents but it is dissolved readily by acids forming the corresponding salts. By using pyrrolidine as the secondary amine the yield of the corresponding pyrrolidino compound IV was even better. We obtained the crude mercurial in 84% yield.

Compound IV was resolved into its two optical antipodes, the (+)-isomer being separated as its salt with D-tartaric acid. The specific rotation observed for the D-tartrate was $[\alpha]^{25}D$ +25.25° and that for the hydrochloride was $[\alpha]^{24}D$ +19.20°.[7]

In experiments varying the proportions of pyrrolidine while keeping the ratio of mercuric chloride to allylurea constant we found it necessary to use an excess of pyrrolidine. By employing a ratio of 2.5:1:1 for pyrrolidine, mercuric chloride and allylurea, we isolated an impure product. However, satisfactory results were obtained by using a ratio 5:1:1. We also found that ethyl acetate and in some cases isopropyl alcohol are appropriate solvents for this type of reaction.

When the aqueous solution of the hydrochloride of IV was treated with two moles of sodium hydroxide a crystalline product was isolated in excellent yield. We expected 3-hydroxymercuri-2-pyrrolidinopropylurea (V) according to the reaction in Chart I, but analysis indicated that the anhydride

CHART I



VI of the hydroxy compound V was formed; VI is soluble in warm water and even more soluble in warm methanol. Molecular weight determinations were consistent with the empirical formula of the monomer. On the basis of these findings the anhy-

(5) R. Kh. Freidlina and N. S. Kachetkova, *Bull. acad. sci. U.R.S.S., Classe sci. chim.*, 128 (1945); *C. A.*, **40**, 3450[7] (1946).

(6) Piperidinomercuric chloride has been postulated as an intermediate in this type of reaction by G. F. Wright, *Ann. N. Y. Acad. Sci.*, **65**, 436 (1957), according to the scheme

$2\ C_5H_{10}NH + HgCl_2 \longrightarrow C_5H_{10}NHgCl + C_5H_{10}NH\cdot HCl$

(7) Since the diuretic effect of the (+)-isomer of IV was of the same magnitude as that of the racemic compound, no efforts were made to isolate the (−)-form.

TABLE II

$NH_2CONHCH_2CHCH_2HgCl$ HYDROCHLORIDES

No.	R	Formula	Yield,[d] %	M.p., °C. dec.,	Recrystn. solvent	Mercury, % Calcd.	Mercury, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	$N(CH_3)_2$	$C_6H_{16}Cl_2HgN_3O$	41	114–115	Water–acetone	48.14	48.20			17.02	17.32	17.30	17.58	3.63	3.67
2	$N(C_2H_5)_2$	$C_8H_{19}Cl_2HgN_3O$	48	98–99	Water–ethanol	45.10	45.10	9.45	9.35	15.94	15.87	21.60	21.58	4.31	4.32
3	$N(n\text{-}C_3H_7)_2$	$C_{10}H_{23}Cl_2HgN_3O$	45	106–107	Water	42.43	42.70	8.89	9.05	15.00	15.00				
4	C_4H_8N[a]	$C_8H_{17}Cl_2HgN_3O$	69	132–133	Water–*i*-PrOH	45.30	45.40	9.49	9.52	16.01	15.92	21.70	21.73	3.87	3.93
5	$C_5H_{10}N$[b]	$C_9H_{19}Cl_2HgN_3O$	54	125–126	Water–acetone	43.92	44.20	9.20	9.13	15.52	15.70	23.66	23.70	4.19	4.20
6	C_6H_{12}[c]	$C_{10}H_{21}Cl_2HgN_3O$	56	116–117	Water	42.61	42.60	8.93	8.82	15.06	15.02				

[a] Pyrrolidino. [b] Piperidino. [c] Hexamethylenimino. [d] Based on allylurea.

dride has been assigned the most probable structure VI. Rowland, *et al.*,[8] isolated an anhydride by treating 3-chloromercuri-2-methoxypropylurea, which is structurally related to IV, with sodium hydroxide. With two moles of hydrochloric acid the anhydride VI could be converted to the hydrochloride of the original chloromercuri compound IV. Melting points and infrared spectra of the original hydrochloride and that obtained from the anhydride VI were identical.

The successful synthesis of compounds III and IV prompted us to extend the investigation to other secondary amines. With various other amines, a total of eight new mercurials have been synthesized from allylurea.[9] A summary of these compounds along with other data is presented in Tables I and II. In Table I the data on the four purified bases are listed. With the exception of the last compound, purification of the free bases was found to be tedious. However, the crude bases were dissolved readily in dilute hydrochloric acid and the corresponding hydrochlorides were easily obtained in crystalline form from water or from the aqueous solutions upon addition of alcohol. In general, they were analytically pure without recrystallization. The data on the hydrochlorides are listed in Table II.

The successful synthesis of the new mercurials obtained from allylurea seemed to warrant an investigation of the reaction of mercuric chloride and secondary amines with other allylamides. Our studies with five amides of various acids revealed that the reaction is quite general. In Tables I and II, the ratio of amine to mercuric chloride to allylurea was 5:1:1. For the synthesis of four of the compounds listed in Table III, the corresponding ratio was 10:1:1 and 15:1:1, respectively.

Pharmacology.—Diuretic studies indicated that compounds of type $NH_2CONHCH_2CHN(\widehat{RR})CH_2HgCl$ (Tables I and II) were very effective oral diuretics.[10] The diuretic response of the dimethylamino compound (Table II, no. 1) in dogs at a dosage of 2 mg./kg. appeared to be the best. The diuretic activity of the *d,l*- and the *d*-forms of IV were observed to be of the same magnitude. It was not surprising to find that the anhydride VI was nearly as potent as IV, since the former compound was shown to be easily converted to the latter compound with dilute hydrochloric acid. Since these were tested orally, the same reaction no doubt took place in the animal organism. With increasing molecular weight for R a decrease of activity was noticed. Compound 3 in Table II, having the highest molecular weight for R, was the least effective in this series. The mercurials listed in Table III, while actively diuretic, were not better

(8) R. L. Rowland, W. L. Perry, E. L. Foreman and H. L. Friedman, THIS JOURNAL, **72**, 3595 (1950). For the anhydride, the authors discussed the possibility of two monomeric and one polymeric structure. No molecular weight determination supported their postulates.

(9) G. R. Wendt, U. S. Patent 2,800,471 (1957).

(10) Diuretic results on six compounds (3, Table I; 1–5, Table II) have been reported by H. Rosen, A. Blumenthal, M. H. Nead, R. Tislow and J. Seifter, *Proc. Soc. Exptl. Biol. Med.*, **95**, 635 (1957); J. H. Moyer, R. V. Ford, C. A. Handley, C. L. Spurr, C. P. Smith, J. Gaffney, C. Marsh, A. Alexander, C. House and A. Hall, *Antibiotic Med. Clin. Therapy*, **5**, 254 (1958).

TABLE III

RCONHCH$_2$CHCH$_2$HgX
N
R R

No.	R	N R R	X	Formula	Yield, %	M.p. dec., °C.	Recrystn. solvent	Mercury, % Calcd.	Mercury, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	$C_6H_5CONHCH_2$	$C_5H_{10}N$[c]	$C_5H_{10}N$[c]	$C_{22}H_{35}ClHgN_4O_2$[e]	74	121–122	Ethyl acetate	32.17	31.88	8.99	9.04
2	C_6H_5	$C_5H_{10}N$[c]	Cl	$C_{15}H_{21}ClHgN_2O$	53		Chloroform–ether	41.67	41.51	5.82	5.68
3	HOOC-o-C_6H_4	$C_5H_{10}N$[c]	Cl	$C_{16}H_{21}ClHgN_2O_3$	51	144–145		38.18	37.95	5.33	5.42
4	C_5H_4N[a]	$C_5H_{10}N$[c]	Cl	$C_{14}H_{22}Cl_3HgN_3O$[f]	83	113–114	Ethanol–water	36.12	36.16		
5	C_5H_4N[b]	C_4H_8N[d]	Cl	$C_{13}H_{19}Cl_2HgN_3O$[e]	31	151–152	Water	39.74	39.57		

[a] 3-Pyridyl. [b] 4-Pyridyl. [c] Piperidino. [d] Pyrrolidino. [e] Based on the analytical results, these compounds were isolated as monohydrochlorides. [f] Purified as dihydrochloride.

than those listed in Tables I and II. Toxicity studies in mice indicated that compounds 2 and 4 in Table II were about half as toxic as chlormerodrin. The diuretic activity of the compounds listed in Tables I, II and III decreased in the following order when compared with chlormerodrin: no. 1, Table II > IV > no. 2, Table II > VI > chlormerodrin > no. 3, Table III = no. 4, Table III > III = no. 3, Table I > no. 3, Table II > no. 5, Table III > no. 1, Table III > no. 2, Table III.

Several of the mercurials have been tested *in vitro* for antibacterial and antifungal activity. Their activity proved to be slight against fungi, moderate against yeasts but considerable against Gram positive and Gram negative bacteria. The ability of compounds 2 and 4 in Table II and of compounds 1, 4 and 5 in Table III to inhibit the growth of *M. tuberculosis* (Human type) strain H37Rv at a dose of 0.5 to 1.0γ/ml. is noteworthy.[11]

Experimental[12]

The synthetic procedures used for the preparation of the mercurials in Tables I, II and III are illustrated by the following examples.

3-Chloromercuri-2-pyrrolidinopropylurea (IV).—The solution of 30.0 g. (0.30 mole) of N-allylurea in 124 ml. (1.5 moles) of pyrrolidine was diluted with 150 ml. of ethyl acetate and cooled to 8–10° with an ice–water-bath. To this solution was added the solution of 81.5 g. (0.30 mole) of mercuric chloride in 360 ml. of ethyl acetate in small portions and with stirring over a period of one hour. Stirring was continued for 2 hours while still cooling and for another 20 hours at room temperature. After adding 300 ml. of isopropyl alcohol the reaction mixture was kept at 5° overnight. The precipitate was filtered off. The cake was slurried in 150 ml. of isopropyl alcohol and collected on a filter. The product, after drying, amounted to 103 g. One gram of the crude mercurial was recrystallized from a mixture of 200 ml. of methanol and 250 ml. of ethanol, yielding 850 mg. of analytically pure material.

Hydrochloride.—The remaining 102 g. of the product was dissolved in 550 ml. of 0.5 *N* hydrochloric acid preheated at 35–40° and filtered (filtrate *p*H 2.5). After adding 2200 ml. of isopropyl alcohol to the filtrate, 91 g. of hydrochloride crystallized at room temperature.

3-Chloromercuri-2-dimethylaminopropylurea.—To the solution of 5.0 g. (0.05 mole) of allylurea in 25 ml. of isopropyl alcohol was added at 5° 16.5 ml. of dimethylamine. To this mixture was added the solution of 13.6 g. (0.05 mole) of mercuric chloride in 140 ml. of isopropyl alcohol dropwise and with stirring over a period of one hour. The reaction mixture was placed on a shaker for 24 hours at 7° and thereafter for 70 hours at 25°. After filtering, the precipitate was suspended twice in 50 ml. of chloroform and vigorously stirred for 15 minutes. The product was filtered, yielding 14.2 g., m.p. 115–118° (crude product). The hydrochloride was prepared in a manner similar to that described for V.

Anhydride of 3-Hydroxymercuri-2-pyrrolidinopropylurea (VI).—To the solution of 13.3 g. (0.03 mole) of the hydrochloride of IV in 53 ml. of water was added 15 ml. of 4 *N* sodium hydroxide in small portions and with shaking. The precipitate, temporarily formed, was redissolved on shaking. On standing in the cold room the solution deposited crystals which after filtering and drying weighed 9.8 g. (88%). After recrystallizing from water the compound melted at 151–152°. *Anal.* Calcd. for $C_8H_{15}HgN_3O$: Hg, 54.24; mol. wt., 370. Found: Hg, 54.03; mol. wt., 334.

Resolution of IV.—Compound IV (20.3 g.) was dissolved in the solution of 75 g. of D-tartaric acid in 150 ml. of water at 50°, and the solution was filtered through charcoal. The filtrate deposited large crystals on standing for 3 days at room temperature. The salt was recrystallized twice from water and dried over anhydrous calcium chloride; yield 69 g. Exposing the material for 3 days to the atmosphere afforded the monohydrate, m.p. 118–120° dec. *Anal.* Calcd. for $C_{12}H_{22}ClHgN_3O_7 \cdot H_2O$: Hg, 34.92; H_2O, 3.14. Found: Hg, 34.48; H_2O, 3.53 (Karl Fischer); $[\alpha]^{25}D$ +25.25° (*c* 1, H_2O). The D-tartrate was converted by alkali to the insoluble base from which the *d*-HCl salt showed $[\alpha]^{24}D$ +19.20° (*c* 5, H_2O).

N-(3-Piperidinomercuri-2-piperidinopropyl)-benzamidoacetamide.—To a solution of 10.9 g. (0.05 mole) of N-allylhippuramide[13] in 75 ml. (0.75 mole) of piperidine was added dropwise with stirring a solution of 13.6 g. (0.05 mole) of mercuric chloride in 60 ml. of ethyl acetate. Stirring was continued for 20 hours. On standing for several days in the cold room, crystals of the monohydrochloride separated and were collected on a filter. The material was twice suspended in 120 ml. of water and vigorously stirred for 10 minutes. After filtering and drying, the material weighed 23.1 g.

N-(3-Chloromercuri-2-piperidinopropyl)-benzamide.—To a solution of 16.1 g. (0.10 mole) of N-allylbenzamide[14] in 99 ml. (1.0 mole) of piperidine was added 27.2 g. (0.10 mole) of pulverized mercuric chloride in small portions with shaking. Shaking was continued for 3 days. After filtering, the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in 100 ml. of warm ethanol. To the solution ether (680 ml.) was added to incipient turbidity. On standing at −5° for one day a precipitate was formed. Ether (170 ml.) was added and on standing for another day at −5° the precipitate increased. The ether layer was decanted and concentrated to about 400 ml. *in vacuo* and then added with stirring to 1600 ml. of ice-water forming a viscous precipitate which after triturating with four 400-ml. portions of water solidified. After drying, it weighed 25.3 g. (53%). The material is readily soluble in methanol, ethanol and chloroform. Addition of ether to a solution of the material in chloroform yielded an analytically pure compound. The softening point of material obtained by reprecipitation was indefinite and depended upon the solvents

(11) Private communication from Drs. G. Warren and S. Rosenman and associates.

(12) All melting points are uncorrected.

(13) O. Diels and E. Beccard, *Ber.*, **39**, 4125 (1907).

(14) M. Bergmann, F. Dreyer and F. Radt, *ibid.*, **54**, 2143 (1921).

used. For analysis a sample of the material was dried at 56°, 0.3 mm., for one hour.

N-(3-Chloromercuri-2-piperidinopropyl)-phthalamic Acid.—The procedure described for IV was followed for the reaction of 46.8 g. (0.25 mole) of N-allylphthalimide[15] and 124 ml. (1.25 mole) of piperidine with 67.9 g. (0.25 mole) of mercuric chloride. After the addition of the mercuric chloride, stirring was continued for 2 hours while the reaction mixture was attaining room temperature. After shaking for 4 days the solution was filtered and the filtrate was added dropwise while stirring to 2.5 l. of water, and thereafter stirring was continued for one day. The solution was clarified by filtration and the filtrate was extracted with 3 portions of 200 ml. of ether. The *p*H of the aqueous layer was adjusted to 6.5 by adding 350 ml. of 1 *N* acetic acid. After standing for a few days in the cold room the product separated in crystalline form.

N-(3-Chloromercuri-2-piperidinopropyl)-nicotinamide.—To a solution of 8.1 g. (0.05 mole) of N-allylnicotinamide[16] in 49.5 ml. (0.50 mole) of piperidine was added 13.6 g. (0.05 mole) of pulverized mercuric chloride in small portions and with shaking. After the addition of mercuric chloride was complete shaking was continued for one day. Then 200 ml. of ethyl acetate was added and the precipitate was filtered off. The filtrate was evaporated to dryness *in vacuo* (bath 25–30°) and the material was further dried over concd. sulfuric acid *in vacuo*. It was dissolved in 77 ml. of 2 *N* hydrochloric acid at 25° and filtered through charcoal. Addition of acetone to the filtrate yielded the crystalline hydrochloride, which was recrystallized from aqueous alcohol.

N-(3-Chloromercuri-2-pyrrolidinopropyl)-isonicotinamide.—The preceding procedure was employed using 8.1 g. (0.05 mole) of N-allylisonicotinamide,[17] 41.7 g. (0.50 mole) of pyrrolidine and 15.0 g. (0.055 mole) of mercuric chloride. Upon addition of 100 ml. of ether to the reaction mixture 2 layers were formed. The upper layer was decanted and the remaining oil was triturated 5 times with 50 ml. each of ether. The sirup was dried over phosphorus pentoxide. The product (25 g.) was dissolved in 84 ml. of 1 *N* hydrochloric acid and the solution clarified by filtration. The volume of the filtrate was reduced to 50 ml. *in vacuo*. When a solution of 29 g. of benzilic acid in 84 ml. of 1 *N* sodium hydroxide was added, a brown gum precipitated which was washed twice with 50 ml. of water. On triturating the gum with 100 ml. of acetone a white crystalline product was obtained. It was collected and washed with 100 ml. of acetone, yielding 7.9 g.

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(15) B. R. Baker, M. V. Querry, R. Pollikoff, R. E. Schaub and J. H. Williams, *J. Org. Chem.*, **17**, 74 (1952); it was recrystallized from *n*-heptane, m.p. 70–71°; [O. Wallach and I. Kamenski, *Ber.*, **14**, 162 (1881)].

(16) M. Hartmann and L. Panizzon, U. S. Patent 2,136,501 (1938).

(17) Since we had little success with the procedure described by J. H. Billman and J. L. Rendall (THIS JOURNAL, **66**, 540 (1944)), we synthesized the compound in good yields by treating isonicotinyl chloride hydrochloride in benzene with allylamine and triethylamine; b.p. 152–154° (0.25 mm.).

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, TULANE UNIVERSITY]

Aldoximes and Dinitrogen Tetroxide[1]

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Dinitrogen tetroxide nitrates and/or oxidizes aldoximes. With each oxime tested, nitration increases with temperature whereas oxidation is most effective at 0° and below. Nitrolic acids (II), the nitration products, are stable when R is alkyl but readily lose the elements of nitrous acid with furoxane (IV) formation when R is aryl or acyl. *aci*-Nitroalkanes (III), the oxidation products, are pyrolyzed readily into aldehydes when R is alkyl. *aci*-Nitroethane has been isolated.

The action of dinitrogen tetroxide upon aldoximes has been investigated heretofore with benzaldoxime[2] and isonitrosoacetone[3] from which diphenyl- and diacetylfuroxanes (IV), respectively, were obtained. The effect of this reagent upon acetaldoxime and propionaldoxime is described here together with a reinvestigation of the reaction with benzaldoxime.

From a 2:1 molar ratio of either α- or β-benzaldoxime and dinitrogen tetroxide from 36 to $-60°$, phenylnitrolic acid (II, R = C_6H_5), diphenylfuroxane (IV, R = C_6H_5), benzaldoxime anhydride N-oxide[4] (V, R = C_6H_5) and benzaldehyde are obtained. At the higher temperatures with short reaction times the best yields of II (R = C_6H_5) are observed, whereas at lower temperatures, product V (R = C_6H_5) predominates. Since phenylnitrolic acid upon standing at 0°, or more rapidly at its melting point, is transformed into benzoic acid (8%) and diphenylfuroxane (57%),[5] the best yield of IV (R = C_6H_5) was obtained from the reaction mixture stored at 0° for 72 hours. An excess of dinitrogen tetroxide converts the oxime into dinitrophenylmethane in high yield,[6] whereas a deficient amount of dinitrogen tetroxide allows appreciable recovery of oxime (Table I).

From acetaldoxime and dinitrogen tetroxide at $-60°$, a colorless solid, apparently the *aci*-form of nitroethane (III, R = CH_3) is obtained in 65% yield. In water, alcohol or ether it is converted into acetaldehyde. Careful neutralization of the reaction mixture at $-60°$ and subsequent acidification with carbonic acid affords nitroethane (V, R = CH_3). Other products obtained from the oxime and dinitrogen tetroxide under a variety of condi-

(1) Financial assistance under National Science Foundation grant NSF-G4240 is gratefully acknowledged.

(2) R. Scholl, *Ber.*, **23**, 3496 (1890).

(3) W. S. Mills, *Chem. News*, **88**, 228 (1903).

(4) Three structures have been proposed for V, formerly known as "benzaldoxime peroxide." R. Cuisa and E. Parisi, *Gazz. chim. ital.*, **55**, 416 (1925), suggested RCH=NOH·RC≡N→O. L. I. Smith, *Chem. Revs.*, **23**, 239 (1938), discusses two additional ones, RCH=NOON=CHR and V. Infrared absorption data (see Experimental) eliminate the first proposed structure as a result of no triple bond absorption in the 2200 to 2100 cm.$^{-1}$ region and contain many similarities with absorption data for diphenylfuroxane (IV, R = C_6H_5).

(5) H. Wieland and L. Semper, *Ber.*, **39**, 2522 (1906). Compare with N. Kornblum and W. M. Weaver, THIS JOURNAL, **80**, 4334 (1958), who found that phenylnitrolic acid in the presence of sodium nitrite in dimethylformamide at $-16°$ is changed into diphenylfuroxane (74%) and benzoic acid (8%), whereas at 25° the yields were diphenylfuroxane (3%) and benzoic acid (81%).

(6) L. F. Fieser and W. v. E. Doering, THIS JOURNAL, **68**, 2252 (1946).