TABLE I

BOILING POINTS, FREEZING POINTS AND CONSTANTS OF THE VAPOR PRESSURE EQUATION

| Substance | B. p., °C. Range | Calcd. | Prev. Obsd. | Ref. | F. p., °C. obsd. | Dep. °C. | Prev. obsd. | Ref. | A | B | C |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Benzotrifluoride | 102.01-102.02 | 102.04 | 102.3 | 10 | −29.14 | 0.02 | −29.05 | 10 | 7.0202 | 1335.5 | 220.58 |
| *p*-Bis-(trifluoromethyl)-benzene | 116.23-116.24 | 116.28 | | | 2.78 | .02 | | | 7.0375 | 1351.6 | 208.89 |
| *o*-Fluorotoluene | 114.35-114.36 | 114.40 | 114.48-114.53 | 11 | −62.0 | .4 | −60 | 12 | 6.9732 | 1356.8 | 217.15 |
| *m*-Fluorotoluene | 116.52-116.53 | 116.55 | 116.27-116.30 | 11 | −87.7 | .3 | −87 | 12 | 7.0095 | 1382.7 | 218.34 |
| *p*-Fluorotoluene | 116.58-116.59 | 116.59 | 116.62-116.65 | 11 | −56.8 | .05 | −53 | 12 | 7.0574 | 1410.8 | 221.19 |
| *o*-Chlorobenzotrifluoride | 152.32-152.33 | 152.31 | 152.8 | 10 | − 6.37 | .04 | − 7.4 to 7.6 | 10 | 7.0144 | 1490.4 | 208.24 |
| *m*-Chlorobenzotrifluoride | 137.69-137.72 | 137.63 | 138.4 | 10 | −56.7 | .76 | −55.4 | 10 | 7.0555 | 1458.9 | 211.82 |
| *p*-Chlorobenzotrifluoride | 138.69-138.71 | 138.63 | 139.3 | 10 | −33.2 | .14 | −34.0 | 10 | 7.1640 | 1536.3 | 220.08 |

measurements were made on each compound from 10 to 760 mm. The experimental data were fitted by the method of least squares to the equation

$$\log p = -\frac{B}{t+C} + A$$

where $p$ is the pressure in mm. and $t$ is the temperature in degrees centigrade.

The mean deviation between the observed pressures and those calculated from the equation varied from ±0.24 mm. for *o*-fluorotoluene and *p*-chlorobenzotrifluoride to ±0.10 mm. for *o*-chlorobenzotrifluoride.

Table I gives the boiling point ranges corrected to one atmosphere, the boiling points calculated from the vapor pressure equation, the freezing points, the freezing point depressions, and the values of the three constants in the above equation.

The agreement of the data for the three fluorotoluenes with that of Stull[13] is not very good. The present data for benzotrifluoride agree fairly well with that of Stull[13] and Field[14] but do not agree very well with that of Booth, Elsey and Burchfield.[15]

(10) H. S. Booth, THIS JOURNAL, **57**, 2066 (1935).
(11) Deal, Thesis, Duke University, 1944.
(12) Klemm, Klemm and Schiemann, *Z. physik. Chem.*, **A165**, 379 (1933).

## Summary

The vapor pressures and the freezing points of benzotrifluoride, *p*-bis-(trifluoromethyl)-benzene, *o*-, *m*- and *p*-fluorotoluene and *o*-, *m*- and *p*-chlorobenzotrifluoride have been measured.

The vapor pressure data have been fitted to a suitable equation.

(13) Stull, *Ind. Eng. Chem.*, **39**, 517 (1947).
(14) Field, THIS JOURNAL, **68**, 2649 (1946).
(15) Booth, Elsey and Burchfield, *ibid.*, **57**, 2066 (1935).

DURHAM, NORTH CAROLINA RECEIVED JUNE 26, 1950

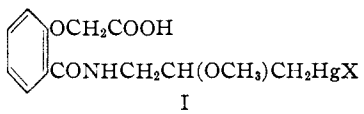
---

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF LAKESIDE LABORATORIES, INC.]

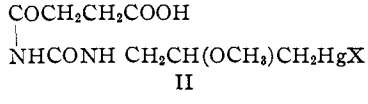
# Mercurial Diuretics. II. Methoxymercuration of N-Allyl Amides

BY R. L. ROWLAND, WENDELL L. PERRY AND SAMUEL GERSTEIN

The organic mercurials which have been investigated as diuretics have generally been those obtained by methoxymercuration of the monoallylamide of a dibasic acid. Thus Salyrgan, I, and Mercuhydrin, II, contain a free carboxyl radical.



I



II

The increased diuretic potency of $NH_2CONHCH_2CH(OCH_3)CH_2HgX$, (III), X = Cl, Br, $SCH_2COOH$, etc.,[1] which is a simplification of II by removal of the β-carboxypropionyl radical, has been noted. The possibility that a similar simplification of I might result in a compound with improved diuretic properties prompted the investigation of $C_6H_5CONHCH_2CH(OR)CH_2HgCl$ (IV) where R = $CH_3$. The methoxymercuration products of other simple aliphatic and aryl allyl amides were also of interest in the course of an exploratory study of variation of diuretic potency and toxicity with chemical structure. Although the preparation of mercurated allylacetamide has been claimed,[2] its physical and pharmacological properties have not been reported. No other reports are available on the preparation or properties of the mercurials obtained by the addition of mercuric acetate and alcohols to the allyl amides of unsubstituted aliphatic or aryl monocarboxylic acids. Perhaps the most nearly related compound is the isostere of IV, R = H, formed by the addition in water of mercuric acetate to the allyl amide of pyridine-3-carboxylic acid.[3]

A representative group of allyl amides was prepared. With the exception of allylacetamide and allylbenzamide, these compounds are new. Addition of mercuric acetate to the allyl amides was accomplished in methyl alcohol and, for convenience, the product was isolated as the chloromercuri derivative. The locations of the acetoxy-

(1) Rowland, Perry, Foreman and Friedman, THIS JOURNAL, **72**, 3595 (1950).
(2) Tabern, U. S. Patent 2,163,296 (1939).
(3) Hartmann and Panizzon, U. S. Patent 2,136,501 (1938).

TABLE I

$RCONHC_6H_5$

| R | Formula | Yield, % | B. p. °C. | Mm. | M. p., °C. | $n^{25}D$ | Nitrogen, % Calcd. | Found |
|---|---|---|---|---|---|---|---|---|
| $C_2H_5$ | $C_9H_{11}ON$ | 70 | 105–106 | 8 | .... | 1.4553 | 12.38 | 12.41 |
| $n$-$C_3H_7$ | $C_7H_{13}ON$ | 70 | 103–104 | 6 | 17–18 | 1.4560 | 11.01 | 11.09 |
| $n$-$C_4H_9$ | $C_8H_{15}ON$ | 90 | 116–117 | 2 | .... | 1.4557 | 9.92 | 9.92 |
| $(H_3C)_3C$ | $C_8H_{15}ON$ | 55 | 97.5–98 | 8 | 25–26 | 1.4538 | 9.92 | 9.92 |
| $\alpha$-$C_{10}H_7$ | $C_{14}H_{13}ON$ | 65 | ..... | .. | 85–86[a] | .... | 6.63 | 6.56 |

[a] Crystallized from an ethyl alcohol–water mixture.

TABLE II

$RCONHCH_2CH(OCH_3)CH_2HgX$

| No. | R | X | Formula | Yield, % | M. p., °C. | Recryst. solv. | Mercury,[a] % Calcd. | Found | Nitrogen, % Calcd. | Found |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $CH_3$ | Cl | $C_6H_{12}O_2NHgCl$ | 65 | 142–143 | EtOH | 54.78 | 55.04 | 3.82 | 3.80 |
| 2 | $C_2H_5$ | Cl | $C_7H_{14}O_2NHgCl$ | 25 | 94–95 | $i$-$Pr_2O$ | 52.75 | 52.38 | 3.68 | 3.81 |
| 3 | $n$-$C_3H_7$ | Cl | $C_8H_{16}O_2NHgCl$ | 20 | 89–90 | $i$-$Pr_2O$ | 50.88 | 50.56 | 3.55 | 3.58 |
| 4 | $n$-$C_4H_9$ | Cl | $C_9H_{18}O_2NHgCl$ | 40 | 94–95 | $i$-$Pr_2O$ | 49.13 | 49.53 | 3.43 | 3.47 |
| 5 | $(H_3C)_3C$ | Cl | $C_9H_{18}O_2NHgCl$ | 55 | 104–105 | $i$-$Pr_2O$ | 49.13 | 48.67 | 3.43 | 3.41 |
| 6 | $C_6H_5$ | $OCOCH_3$ | $C_{13}H_{17}O_4NHg$ | 80 | 89–90 | ... | 44.39 | 43.70 | 3.10 | 3.20 |
| 7 | $C_6H_5$ | Cl | $C_{11}H_{14}O_2NHgCl$ | 10 | 111–112 | EtOH | 46.83 | 46.45 | 3.27 | 3.26 |
| 8 | $\alpha$-$C_{10}H_7$ | $OCOCH_3$ | $C_{17}H_{19}O_4NHg$ | 35 | 158–160 | EtOH | 39.96 | 41.35 | 2.79 | 2.99 |
| 9 | $\alpha$-$C_{10}H_7$ | Cl | $C_{15}H_{16}O_2NHgCl$ | 40 | 161–162 | EtOH | 41.94 | 41.43 | 2.92 | 3.01 |

[a] Mercury was determined on a macro scale by precipitation as mercuric sulfide from hydrochloric acid solution.

mercuri and methoxy radicals in the addition product were assumed to be those presented in V since the study of other mercurated amides[4] indicated that the acetoxymercuri radical is attached to the terminal carbon atom.

$$RCONHCH_2CH{=}CH_2 + Hg(OOCCH_3)_2 + CH_3OH \longrightarrow$$
$$RCONHCH_2CH(OCH_3)CH_2HgOCOCH_3 \xrightarrow{NaCl}$$
$$RCONHCH_2CH(OCH_3)CH_2HgCl \quad (V)$$

**Pharmacology.**—Investigation of the pharmacology of these compounds by Mr. P. A. Nuhfer of these laboratories was not encouraging. With the exception of the naphthamide derivatives, the mercurials were soluble in dilute aqueous alkali. Diuretic response was studied in dogs at a dosage of 0.006 millimole/kg. In this series of methoxymercurated allyl amides, compounds 2, 3, 4, 5 and 7 produced diuretic responses which were of the same order of magnitude as or less than that produced by I or II. Only N-(3-chloromercuri-2-methoxypropyl)-acetamide produced a response greater than I or II. The increased diuretic response from this compound was counterbalanced by the increased toxicity mentioned below. The mercury excretion *via* the urine during the six-hour period following intravenous injection ranged from 20 to 40% of the injected mercury.

The fourteen-day toxicities were unfavorable. The $LD_{50}$'s at 14 days following a single intravenous dose in rats ranged from 0.03 to 0.04 millimole/kg. as compared to 0.07 millimole/kg. for II.

From the study of compounds of the type $NH_2CONHCH_2CH(OR)CH_2HgX$[5] wherein considerable variation of R($CH_3$, $C_2H_5$, $i$-$C_3H_7$, $C_4H_9$) and of X ($OOCCH_3$, OH, Cl, Br, $SCH_2COOH$, $N(COCH_2)_2CO$) resulted in no appreciable improvement of the 14-day toxicity or of the diuretic response over that compound when R = $CH_3$ and X = Cl, it appears improbable that variation of R′ or X in the series $RCONHCH_2CHOR'CH_2HgX$ would result in any betterment of pharmacological properties.

(4) Pearson, Sigal, and Krug *J. Org. Chem.*, **15**, 1048 (1950).

(5) Nuhfer, to be published.

## Experimental[6]

**N-Allyl Amides.**—The preparations of N-allylacetamide and N-allylbenzamide have been reported previously.[7] N-Allylpropionamide was prepared similarly to N-allylacetamide utilizing the acid anhydride. N-Allyl-$\alpha$-naphthamide was prepared by the Schotten–Baumann reaction. The other amides were prepared by the reaction of the acid chloride with allylamine in ether. The amine hydrochloride was removed and the amide obtained by distillation of the ethereal solution. The yields and properties of the new compounds are listed in Table I.

**Preparation of N-(3-Chloromercuri-2-methoxypropyl) Amides.**—The methoxymercurations of the allyl amides were all accomplished in similar fashion. The method is exemplified by the addition of mercuric acetate and methyl alcohol to N-allylacetamide: To a hot solution of 10 g. (0.10 mole) of N-allylacetamide in 50 cc. of methyl alcohol was added a hot solution of 31.9 g. (0.10 mole) of mercuric acetate and 10 cc. of glacial acetic acid in 150 cc. of methyl alcohol. After the mixture had been heated under reflux for two hours, it was allowed to stand twenty hours. The insoluble material was removed by filtration and an aqueous solution of 8 g. (0.14 mole) of sodium chloride was added to the filtrate. The solution was concentrated to dryness at room temperature and the residue was crystallized to a constant melting point.

With the mercurials obtained by mercuration of the amides of aromatic acids, it was possible to isolate, by concentration of the addition reaction mixture, solids which would appear to be the acetoxymercuri compounds. The methoxymercuration product of allyl benzamide was not crystallized, but was washed with isopropyl ether prior to analysis.

The yields and properties of the mercurials are listed in Table II.

**Acknowledgment.**—We are indebted to Mr. H. C. Krahnke and his staff for the mercury and nitrogen analyses and to Drs. H. L. Daiell and H. L. Friedman for their interest and encouragement.

(6) All melting points over 80° are corrected.

(7) Chiari, *Monatsh.*, **19**, 572 (1898); Bergman, Dreyer and Radt, *Ber.*, **54**, 2143 (1921).

## Summary

A series of compounds has been prepared by the addition of mercuric acetate and methyl alcohol to N-allyl amides. The high toxicity of these mercurials lessens their possible usefulness as diuretics.


MILWAUKEE 1, WISCONSIN RECEIVED JUNE 30, 1950

---

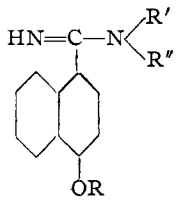
[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

# N,N-Disubstituted Amidines. III. 4-Alkoxy-α-naphthamidines[1]

BY EMIL LORZ AND RICHARD BALTZLY

Physiological examination of the amidines previously reported from these laboratories[2] has shown that the type possesses considerable potency in topical anesthesia. This potency increases within certain limits with the size of the attached groups, N,N-di-*n*-butyl-α-naphthamidine being thrice as active as cocaine whereas the corresponding benzamidine is one-half as active. Alkoxyl substitution in the benzamidines increases potency and, except in the ortho-position, diminishes toxicity. It thus seemed probable that 4-alkoxy-α-naphthamidines, readily obtainable from the appropriate 4-alkoxy-α-naphthonitriles, would be powerful local anesthetics. In agreement with this hypothesis, N,N-di-*n*-butyl-4-methoxy-α-naphthamidine hydrochloride was found to have a potency about twenty-five times that of cocaine, as tested on the cornea of guinea pigs.

A considerable series of analogous and homologous amidines, representable by Formula A, was then prepared by the addition of the appropriate bromomagnesium dialkylamides to 4-alkoxy-α-naphthonitriles.




A

These compounds are listed in Table I, the numbering being consecutive with our earlier papers.[2] Only one 4-butoxyamidine, Compound LX (A, R = R′ = R″ = *n*-butyl) was prepared since this substance proved too irritant for testing. Except for LX and LIX (A, R = *n*-propyl; NR′R″ = 4-methylpiperazino) R was ethyl or methyl. In these main series the N,N-dialkyl amidines having N-alkyl groups of four to five carbon atoms consistently showed a high potency—more than twenty times that of cocaine. The diethyl- and diisopropylamidines (XXXVI and XXXVIII) were relatively impotent. The di-*n*-hexyl derivative (XLIV) produced a film on the eye and could not be assayed. Replacement of one N-alkyl group by benzyl or by an aryl group (Compounds XLV-XLIX, and LVI) had a rather erratic but not especially beneficial effect. Replacement of –NR′R″ by heterocyclic radicals gave compounds of lowered toxicity but of no great potency. Local anesthetic activity is indicated in Table I by +, ++ and +++. Compounds marked + are less than ten times as active as cocaine; those marked ++ are ten to twenty times as active and +++ indicates activity over twenty times that of cocaine.[3] The N,N-dialkylamidines were two to four times as toxic as cocaine. Substances marked T in Table I could not be tested because of local irritant action.

Electrometric titrations in 50% methanol[2b] were run on some representative compounds. The basicities (expressed as $pK_a$) were very close to those of benzamidines having similar substitutions although the N,N-dialkyl-α-naphthamidines appear slightly less basic than the corresponding benzamidines and the N-alkyl-N-aryl-α-naphthamidines slightly more basic. It is tempting to assign this latter phenomenon to steric inhibition of resonance (in the aniline moiety) but the deviations may not be significant. The dissociation constants are presented in Table II.

## Experimental

The additions of bromomagnesium secondary amides to the appropriate nitriles were carried out by the methods described previously.[2] The yields and properties of the resultant amidines are shown in Table I, the methods of isolation (A, A′, B, etc.) referring to the procedures of our earlier papers.[2]

**Nitriles.**—Of the four nitriles employed, only 4-ethoxy-α-naphthonitrile has been reported previously.[4] All were prepared by a modification of the method of Newman[5] which consists of doubling the proportion of pyridine and halving the reflux time. Under these circumstances yields of 75–80% were obtained consistently whereas the original method gave very poor results—the yield of nitrile was poor and that of tars was large. The effect of the increased quantity of pyridine is to lower the reaction temperature. Examination of Newman's experimental details indicates that the exchange reaction with α-bromonaphthalene must require much less than 15 hours to reach completion (Newman records a 70% yield from α-chloronaphthalene after 6 hours) but α-naphthonitrile is not affected by the longer and more drastic treatment. Since there is no reason for suspecting exaltation of the activity of the bromine atom from the presence of a para alkoxyl group and since the nitrile func-

(1) The work here reported is part of a joint research carried out in collaboration with a pharmacological group in these laboratories.

(2) Lorz and Baltzly, THIS JOURNAL, (a) **70**, 1904 (1948); (b) **71**, 3992 (1949).

(3) Pharmacological results are to be published separately. Precise evaluation of activities, always difficult in animal experiments, is complicated in this series by the presence of very steep dose-response curves. Many of these amidines will produce anesthesia lasting several hours in 0.03% concentration (anesthesia from 1% cocaine is found to last 40–50 minutes in control experiments) but 0.02% solutions may produce no anesthesia at all. The general behavior of the amidines suggests that local anesthetic potency in this series is a function of partition coefficients and diffusion speeds in the penetration of the tissues rather than of the inherent properties of the compounds toward the nervous tissues. In agreement with this is the fact that as injection anesthetics the α-naphthamidines differ relatively little among themselves in potency and are not especially active.

(4) Karrer, Rebmann and Zeller, *Helv. Chim. Acta*, **3**, 261 (1920).

(5) Newman, THIS JOURNAL, **59**, 2472 (1937); *Org. Syntheses*, **21**, 89 (1941).