

THE METHOXYMERCURATION OF N-ALLYLPHTHALIMIDE

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It is generally accepted that the products obtained in the methoxymercuration of an unsaturated compound can be predicted from knowledge of the dipole direction of the unsaturated grouping, the entering mercury group being considered the positive fragment (1). However, no proof of the structure of the methoxymercurial derived from an N-allylamide compound has ever been reported. Since the basic organic structure of almost all the mercurial diuretics (Mercurhydrin, Salyrgan, etc.), employed in the clinical therapy of congestive heart failure, is of the N-allylamide type, it is important that this proof be sought. The purpose of the work was to seek the proof using some simple structure (N-allylphthalimide) which would yield readily crystallized derivatives and then to apply the experience and knowledge gained to a study of the structure of Mercurhydrin.² For that matter, the methoxymercurial derived from N-allylphthalamic acid is employed in Italy as a diuretic (2).

Carrara and Mori (3) apparently were the first to study the addition of mercuric acetate in methanol to N-allylphthalimide. They reported a yield of 60% and arbitrarily assigned structure II, N-(2-acetoxymercuri-3-methoxypropyl)phthalimide, to the compound. The isomeric structure (I) was reported by Tabern (4) in the patent literature for the addition compound of mercuric acetate in methanol to N-allylphthalamic acid. No proof of structure was offered in either reference, though general considerations would favor the orientation proposed by Tabern.

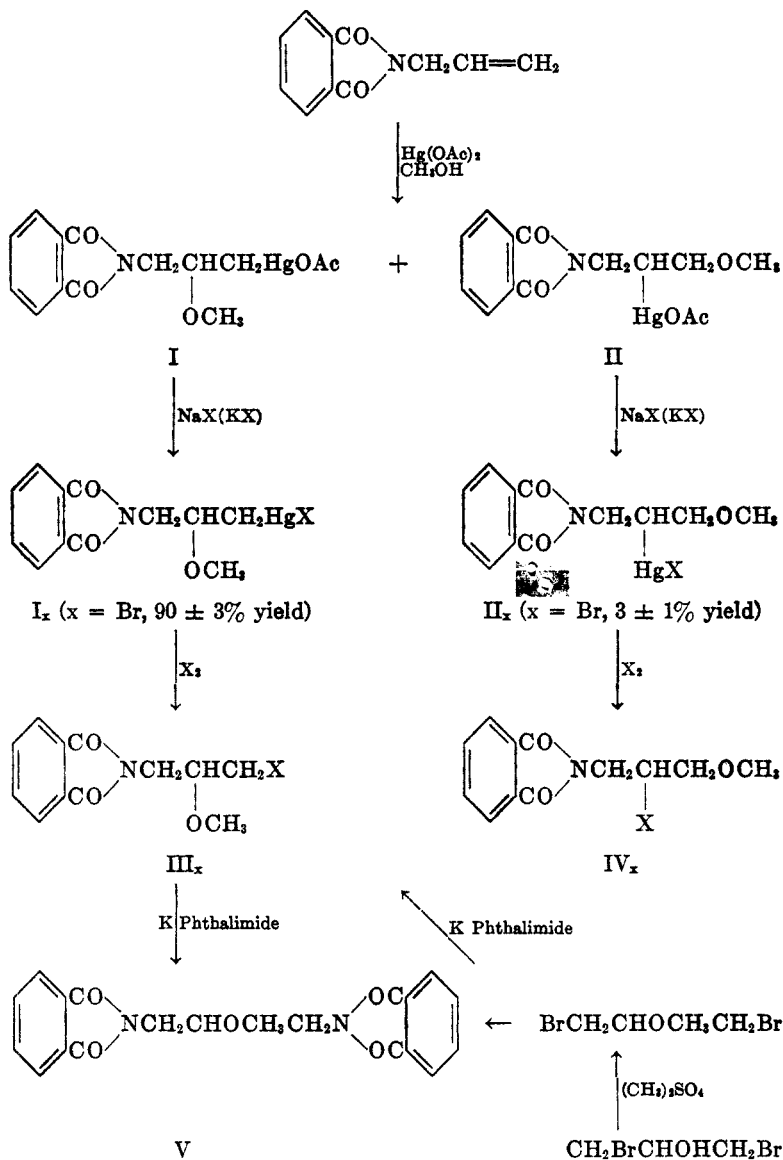
In more precise work of this laboratory, it was found that the addition of mercuric acetate in methanol to N-allylphthalimide actually gave *both* isomers—the predominant one in yields of $90 \pm 3\%$, the minor one in yields of $3 \pm 1\%$.³ This is the first conclusive example of the isolation of both isomers from a methoxymercuration reaction. It is true that Connor and Wright (5) have indicated the formation of such a mixture in the methoxymercuration of oleic acid, but the properties of the mercurials were such as not to warrant separation and identification.

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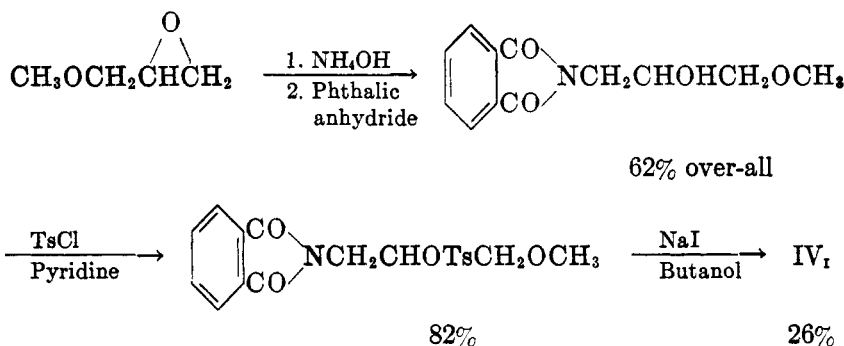
² The authors acknowledge the financial support of Lakeside Laboratories, Inc., who suggested the work on Mercurhydrin and have given their fullest cooperation on all phases of the problem.

³ Since the acetates were too soluble in most solvents for semi-quantitative isolation work, the yields were actually based on the mercuric bromides obtained from the acetates by treatment with potassium bromide.

FLOW CHART



The structure of I, the predominant isomer, was proved to be N-(2-methoxy-3-acetoxymethyl)phthalimide by the series of reactions given in the Flow Chart and described in the Experimental. The structure of II, the less predominant isomer, was proved to be N-(2-acetoxymethyl-3-methoxypropyl)phthalimide by its degradation to IV₁, which was identical with the synthetic compound made as follows:



EXPERIMENTAL

A. *The methoxymercuration of N-allylphthalimide.* To a hot solution of mercuric acetate (127.2 g., 0.40 mole) in 1100 cc. of absolute methanol, a solution of N-allylphthalimide (75.5 g., 0.403 mole, m.p. 69–70°⁴) in 500 cc. of hot methanol was added all at once. The resulting solution was refluxed for three hours, filtered hot, and allowed to crystallize. The methoxyacetoxymercurial (I) thus formed was washed with 200 cc. of cold methanol and air-dried (149 g., 78%, m.p. 138–139.5°).

Anal. Calc'd for C₁₄H₁₅HgNO₅: Hg, 41.97. Found: Hg, 41.58, 41.72, 41.83.⁵

The mother-liquor was concentrated to about 700 cc. and then treated with a hot solution of aqueous potassium bromide (10.6 g., 0.09 mole) in 75 cc. of water. The methoxybromomercurial (I_{Br}) crystallized slowly. After standing for 24 hours, the crystals were collected and air-dried (24.1 g., 12%, m.p. 165–171°).⁶ The filtrate, on standing for another day, deposited the isomeric methoxybromomercurial (II_{Br}), which, when dried, weighed 8.6 g. (4.3%, m.p. 122–124.5°; recrystallized from methanol, m.p. 124–125.5°).

Anal. Calc'd for C₁₂H₁₃BrHgNO₅: Hg, 40.23; Br, 16.03.

Found: Hg, 39.91, 40.07; Br, 15.96, 15.95.

This procedure was repeated several times and the yields duplicated, *i.e.*, I and/or I_{Br}, 90±3%; II_{Br}, 3±1%.

B. *Halides of the predominant isomer (I_x, x = Cl, Br, and I).* To a hot solution of I (108 g., 0.226 mole) in 1200 cc. of methanol, a hot solution of potassium halide (0.24 mole) in 250 cc. of water was added. I_x began to crystallize immediately and, on cooling, filtering, and air-drying, gave the following results:

METHOXYHALO-MERCURIAL	M.P., °C.	YIELD, %	Hg		HALOGEN	
			Calc'd	Found	Calc'd	Found
I _{Br}	173 -174	93	40.23	40.09 (Avg.)	16.03	15.9 (Avg.)
I _{Cl}	171.2-172	96	44.16	43.91	7.81	7.7
I _I	159 -160.2	97	36.76	36.75	23.25	23.4

⁴ All melting points were taken with a partial immersion thermometer, 0–300°, corrected by comparison with U.S.P. reference standards.

⁵ The mercury and halogen determinations of the methoxymercurials were done in this laboratory by the method of Rauscher (6). All other determinations were done by Clark Microanalytical Laboratory, Urbana, Ill.

⁶ The wide melting point range of this I_{Br} crop indicated contamination with some II_{Br}, to be described.

The halides were so insoluble in methanol and other solvents (except acetic acid), that recrystallization of large batches was not practical. The analytical results were obtained with original crops. The halides were quite stable but darkened over a period of months, if they were not protected from light.

C. *The halogenation of the methoxyhalomercurials.* 1. *Iodination of the predominant isomer, N-(2-methoxy-3-bromomercuriopropyl)phthalimide (I_{Br}).* A well-stirred suspension of I_{Br} (5 g., 0.01 mole) in 100 cc. of methanol containing iodine (2.6 g., 0.01 mole) was refluxed until the color of iodine had practically disappeared (20 min.). The solution was then concentrated at water-pump vacuum to about 20 cc. and diluted with 50 g. of 20% aqueous potassium iodide solution. The demercurated product separated as an oil, but solidified on standing in the refrigerator. It was filtered, washed with more aqueous iodide solution, with water, and then air-dried (3.6 g., more than quantitative). Recrystallization from 50 cc. of methanol gave a first crop (2.75 g., m.p. 107.5–108.5°) and a second crop (0.3 g., m.p. 106–107.5°), representing a total yield of 88% N-(2-methoxy-3-iodopropyl)phthalimide (III_I).

A similar iodination of I_I, using carbon tetrachloride in place of methanol, gave a yield of 87% of III_I, m.p. 103–105°; recrystallization from methanol m.p. 108–109°; identical with first iodination compound.

Anal. Calc'd for C₁₂H₁₂INO₃: I, 36.77; C, 41.76; H, 3.51.

Found: I, 37.23; C, 42.15; H, 3.48.

The two experiments showed that iodine replacement was independent of solvent effect, and either the bromomercurial or iodomercurial could be converted to the demercurated iodo compound (III_I).

2. *Iodination of the less predominant isomer, N-(2-Bromomercuri-3-methoxypropyl)phthalimide (II_{Br}).* The iodination of II_{Br} (1.35 g., 0.0027 mole) gave 0.80 g. (86%, m.p. 70–71°) of N-(2-iodo-3-methoxypropyl)phthalimide (IV_I). IV_I had unusual properties. When recrystallized from petroleum ether (b.p. 69–70°), the m.p. was 71–72°. When heated above its m.p., allowed to resolidify, and then recrystallized from petroleum ether, the m.p. was 79.5–80°. When the low-melting form was dissolved in petroleum ether and seeded with the high-melting form, the resultant recrystallized product melted at 78.7–80°.

Anal. Calc'd for C₁₂H₁₂INO₃: I, 36.77; C, 41.76; H, 3.51.

Found: I, 37.22; C, 42.22; H, 3.78.

3. *Bromination of I_{Br}.* The bromination of I_{Br} in ethyl acetate, catalyzed by bright sunlight, was erratic and yielded an inferior demercurated product (III_{Br}, average yield 55%; m.p. 101–102.5° after recrystallization from methanol). The bromine analysis was slightly high, indicative of some uncontrolled bromination which is apparently inherent in this process (7); however, the mixed melting point showed no depression with the authentic sample to be described. III_{Br} was obtained in a better state of purity *via* the phthalamic acid route. I_{Br} (121 g., 0.243 mole) was dissolved in 500 cc. of a warm 5% aqueous solution of sodium hydroxide. The solution was diluted to 1 liter, mixed with several grams of Supercel and filtered. The filtrate was acidified with acetic acid and the white solid, N-(2-methoxy-3-bromomercuriopropyl)phthalamic acid (VI_{Br}), washed with water and air-dried (116 g., 92.5%, m.p. 135–136° with dec.; recrystallization of 3 g. of VI_{Br} from 65 cc. of methanol, m.p. 136° sharply with dec.). Crude VI_{Br} (108 g., 0.21 mole) was redissolved in 500 cc. of water containing sodium hydroxide (8.5 g., 0.215 mole). After filtration of the solution to remove an insoluble residue (5.6 g.), potassium bromide (38.5 g.) was added. To this stirred solution, cooled in an ice-bath and exposed to bright sunlight, a solution of bromine (33.5 g., 0.21 mole) in 250 cc. of water containing 38.5 g. of potassium bromide was added over a period of 45 minutes. The solution was acidified with hydrobromic acid (litmus), allowed to stand in the refrigerator for one hour, filtered to remove a small amount of fore-precipitation, and refrigerated overnight. N-(2-Methoxy-3-bromopropyl)phthalamic acid (VII_{Br}) formed (29.7 g., 45%, m.p. 113–115.5°). The filtrate, on continued refrigeration, deposited a further amount of VII_{Br} (10 g., 15.3%, m.p. 118–120°). Recrystallization of the

first crop from 350 cc. of chloroform yielded pure VII_{Br} (18.5 g., m.p. 118–119°, Neutral equivalent, calc'd: 316. Found: 317.8, 315.5). VII_{Br} was converted to the phthalimide (III_{Br}) by refluxing for one hour in glacial acetic acid. After recrystallization from methanol, III_{Br} was obtained in a good state of purity (m.p. 102.5–103.5°).

Anal. Calc'd for C₁₂H₁₂BrNO₃: Br, 26.81; C, 48.34; H, 4.04.

Found: Br, 26.73; C, 48.79; H, 4.06.

D. *The synthesis of reference compounds and comparison with the degradation products of the mercurials.* 1. *1,3-Dibromo-2-methoxypropane.* Glycerol-1,3-dibromohydrin (8) was converted to 1,3-dibromo-2-methoxypropane by the method of Krantz and Foreman (9). In a 1-liter, round-bottomed flask, glycerol-1,3-dibromohydrin (408 g., 1.87 moles) and freshly distilled methyl sulfate (276 g., 2.2 moles) were heated by means of a water-bath for 12 hours. The reaction mixture was then cooled and neutralized with sodium bicarbonate solution (180 g. in 2 liters of water). The oily layer was separated, washed consecutively with cold, 50% aqueous sodium hydroxide, cold concentrated ammonium hydroxide, diluted with chloroform, washed further with water, and dried. The crude product (143 g.) distilled at 82–94° at 17 mm. Redistillation yielded pure 1,3-dibromo-2-methoxypropane (b.p. 89.5–92.5° at 22 mm., n_D^{25} 1.5100; 124 g.; 28.5%.)

2. *The Gabriel reaction with 1,3-dibromo-2-methoxypropane.* A mixture of potassium phthalimide (37 g., 0.2 mole), 1,3-dibromo-2-methoxypropane (60 g., 0.26 mole), xylene (75 cc.), and sodium iodide (0.5 g.) was refluxed for 10 hours with considerable darkening. After steam-distilling to remove the excess 1,3-dibromo-2-methoxypropane, the diphtalimido compound was separated by reason of its insolubility in petroleum ether (b.p. 69–70°). To remove phthalic acid, it was suspended in 2% sodium hydroxide and washed with water (6.2 g., 17%, m.p. 200–205°). Two recrystallizations of 3.2 g. of crude V from 150-cc. portions of ethyl acetate yielded pure 1,3-diphtalimido-2-methoxypropane (V, 1.2 g., m.p. 208.5–209°).

Anal. Calc'd for C₂₆H₁₆N₂O₈: C, 65.93; H, 4.43.

Found: C, 65.79; H, 4.27.

A mixed melting point of V with the diphtalimido compound obtained from III_I by the Gabriel reaction (62% yield) showed no depression.

Anal. Calc'd for C₂₆H₁₆N₂O₈: C, 65.93; H, 4.43.

Found: C, 66.20; H, 4.34.

The petroleum ether extract yielded 14 grams of crude N-(2-methoxy-3-bromopropyl)-phthalimide (23%, m.p. 95–100°). Two recrystallizations from methanol (1 g. per 10 cc.) raised the melting point to 102.5–103.5° (9.2 g.). Further recrystallization gave the pure compound (m.p. 103.2–104°).

Anal. Calc'd for C₁₂H₁₂BrNO₃: Br, 26.81; C, 48.34; H, 4.04.

Found: Br, 27.01; C, 48.57; H, 4.04.

A mixed melting point of synthetic N-(2-methoxy-3-bromopropyl)phthalimide with III_{Br}, derived from the mercurial, showed no depression, thus establishing the structure of III_{Br}.

3. *The synthesis of N-(2-iodo-3-methoxypropyl)phthalimide (IV_I).* (a). *1-Chloro-3-methoxy-2-propanol.* The general procedure of Koelsch (10) was used, and the properties of the compound compared well with that of Flores-Gallardo and Pollard (11), (b.p. 170–171° at 748 mm., n_D^{25} 1.4422, 72% yield).

(b). *1,2-Epoxy-3-methoxypropane (Methyl glycidyl).* The basic procedure of Clark and Hartman (12) was used, and the properties of the methyl glycidyl obtained compared well with those of Flores-Gallardo and Pollard (11). (b.p. 112–117° at 750 mm., 71% yield.)

(c). *2-Hydroxy-3-methoxypropylamine.* The method of Knorr and Knorr (13) was used to make this new compound [62% yield; b.p. 90–91° at 10 mm., n_D^{25} 1.4536–38, d_{25}^{25} 1.0591; Neutral equiv. Calc'd: 109; Found, 105; *urea derivative* (14), m.p. 92.5–94° after recrystallization from ethylene chloride].

(d). *N-(2-Hydroxy-3-methoxypropyl)phthalimide.* The method of Cope, *et al.* (15) was used to make this new compound. The yield of crude product was quantitative (m.p. 57–61°).

Crystallization of a small amount from petroleum ether (b.p. 69–70°; 0.5 g. from 100 cc.) gave the pure compound, m.p. 61.5–62.5°.

Anal. Calc'd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.7.

Found: C, 61.24; H, 5.54.

(e). *The tosyl ester of N-(2-Hydroxy-3-methoxypropyl)phthalimide and other less successful derivatizations.* Attempts were first made to convert the hydroxy compound directly to the corresponding halogen derivative. Treatment of N-(2-hydroxy-3-methoxypropyl)phthalimide with phosphorus triiodide gave an unknown iodo derivative which did not give the correct analysis; 15% yield; m.p. 118–120°.

Anal. Calc'd for $C_{12}H_{12}INO_3$: C, 41.76; H, 3.51.

Found: C, 42.7; H, 3.17.

Treatment of the hydroxy compound with thionyl chloride gave a poor yield of the *sulfite ester*, m.p. 139–139.5°;

Anal. Calc'd for $C_{24}H_{24}N_2O_9S$: C, 55.80; H, 4.68.

Found: C, 55.87; H, 4.73.

Treatment of N-(2-hydroxy-3-methoxypropyl)phthalamic acid (prepared as an oil from the amine and phthalic anhydride) with excess thionyl chloride yielded N-(2-chloro-3-methoxypropyl)phthalimide (20%, m.p. 71–72.5° from methanol and water).

Anal. Calc'd for $C_{12}H_{12}ClNO_3$: Cl, 14.0. Found: Cl, 13.5.

The tosylation of N-(2-hydroxy-3-methoxypropyl)phthalimide was accomplished as follows: the phthalimide (14 g., 0.06 mole) and *p*-toluenesulfonyl chloride (11.3 g., 0.06 mole) were mixed in 25 cc. of dry pyridine and allowed to stand overnight. The tosyl ester which crystallized was washed with 50% methanol-water. The filtrate on dilution with water deposited a further amount of the tosyl ester. The combined crude yield was 19 g., 82%, m.p. 150–156°. Recrystallization from ethanol gave 15 g. of tosyl ester m.p. 157–157.6°. The analytical sample melted at 157.2–157.8°.

Anal. Calc'd for $C_{19}H_{19}NO_6S$: S, 8.23. Found: S, 8.44.

(f). *N-(2-Iodo-3-methoxypropyl)phthalimide.* Attempts to replace the chlorine group of N-(2-chloro-3-methoxypropyl)phthalimide by sodium iodide in acetone at 110° (sealed tube) and by sodium iodide in refluxing butanol failed. On the other hand, the replacement of the tosyl ester by iodine using sodium iodide and refluxing butanol was successful as described (16): the tosyl ester (6 g., 0.015 mole) and sodium iodide (6.75 g., 0.04 mole) were dissolved in 90 cc. of dry *n*-butanol and refluxed for several hours. By this time, the sodium-*p*-toluenesulfonate, which had separated out, caused considerable bumping. It was removed and the filtrate refluxed for four more hours. After a second filtration, the butanol was removed by distillation at reduced pressure (water aspirator). The residue was extracted with two 50-cc. portions of petroleum ether (b.p. 69–70°) and the remaining product dissolved in hot methanol. On cooling the methanol, some unreacted tosyl ester crystallized which was removed by filtration. The methanol filtrate was diluted with water, whereupon the iodo derivative crystallized. The iodo compound from the petroleum ether extract and from the methanol-water weighed 1.3 g. (26%). Recrystallization from petroleum ether gave pure N-(2-iodo-3-methoxypropyl)phthalimide, m.p. 79–80°; repeated recrystallizations, m.p. 80–80.2°.

Anal. Calc'd for $C_{12}H_{12}INO_3$: C, 41.76; H, 3.5; I, 36.77.

Found: C, 41.54; H, 3.46; I, 36.23.

A mixed melting point of the synthetic sample and of IV₁, the iodo derivative of the methoxymercuration product, showed no depression. Furthermore, when the low-melting form of IV₁ (m.p. 70–71°) was seeded in petroleum ether with the synthetic sample, the melting point was raised to 79–80°. When the synthetic sample (m.p. 79–80°) was recrystallized from methanol-water, the melting point was again lowered (m.p. 70–80°).

E. *An alternate procedure for the methoxymercuration of N-allylphthalimide (17).* A mixture of mercuric chloride (10.3 g., 0.0375 mole) and mercuric acetate (12 g., 0.0375 mole) in hot methanol was added to N-allylphthalimide (14.2 g., 0.075 mole) dissolved in 100 cc. of hot methanol. After refluxing for three hours, it was allowed to cool overnight, and the

crystals obtained were washed with 50 cc. of methanol, and air-dried (29.7 g., 87%, m.p. 169–170.5°). The identity of this product was established as N-(2-methoxy-3-chloromercuripropyl)phthalimide (I_{C1}) by iodination to III_I (81%, m.p. 107–108°; mixed m.p. with III_I showed no depression). By concentration of the filtrate, the isomeric chloromercurial was obtained in an impure state (2 g., m.p. 110–120°). Repeated recrystallization from methanol gave 0.3 g., m.p. 128–129°. The identity of this product was established as N-(2-chloromercuri-3-methoxypropyl)phthalimide by iodination to IV_I (quantitative yield, m.p. 79.5–80°, mixed m.p. with IV_I showed no depression).

SUMMARY

The methoxymercuration of N-allylphthalimide yielded two position isomers whose structures were proved to be N-(2-methoxy-3-acetoxymmercuripropyl)phthalimide, the predominant isomer, and N-(2-acetoxymmercuri-3-methoxypropyl)phthalimide, the less predominant isomer.

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