[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, VANDERBILT UNIVERSITY]

STUDIES CONCERNING THE STRUCTURE OF MERCUHYDRIN[1]

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Mercuhydrin is a widely used diuretic, composed of a complex of theophylline and the methoxymercuration product of β-carboxypropionylallylurea (1, 2). Most of the work of this problem was concerned only with the structure of the methoxymercuration product which will be called M. When this work was begun, little was known of the precise structure of M or other methoxymercurials of a similar nature. It had been demonstrated that Salyrgan, another diuretic, contained a methoxyl grouping (3). The mercury atom had usually been assigned the 3-position in the allylamide fragment, although no proof of this orientation was recorded in the literature (4). In fact, it was not even certain whether M was a homogeneous substance. With this background and with the results of the work described in the preceding paper, the following studies on the structure of M were made.

It was not certain whether the starting material possessed structure (I) or (II):

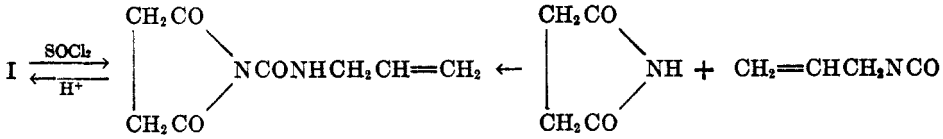
$$HOOCCH_2CH_2CONHCONHCH_2CH{=}CH_2$$

I

$$HOOCCH_2CH_2CON(CH_2CH{=}CH_2)CONH_2$$

II

though structure I was favored by analogy to the amide obtained by the acetylation of methylurea (5). The problem was solved by smooth conversion of I to N-succinyl-N′-allylurea:



Mild hydrolysis regenerated I. Since I was also synthesized from the reaction product of succinimide and allyl isocyanate, there could be no doubt that the structure of the starting material was N-(β-carboxypropionyl)-N′-allylurea (I).

The methoxymercuration of I gave M in good yield. As agreed with other observers, the structure of this product (or others with free carboxyl groups or complexing groups) was uncertain and perhaps variable (6). Analyses and chemical behavior of M indicated the general structure:

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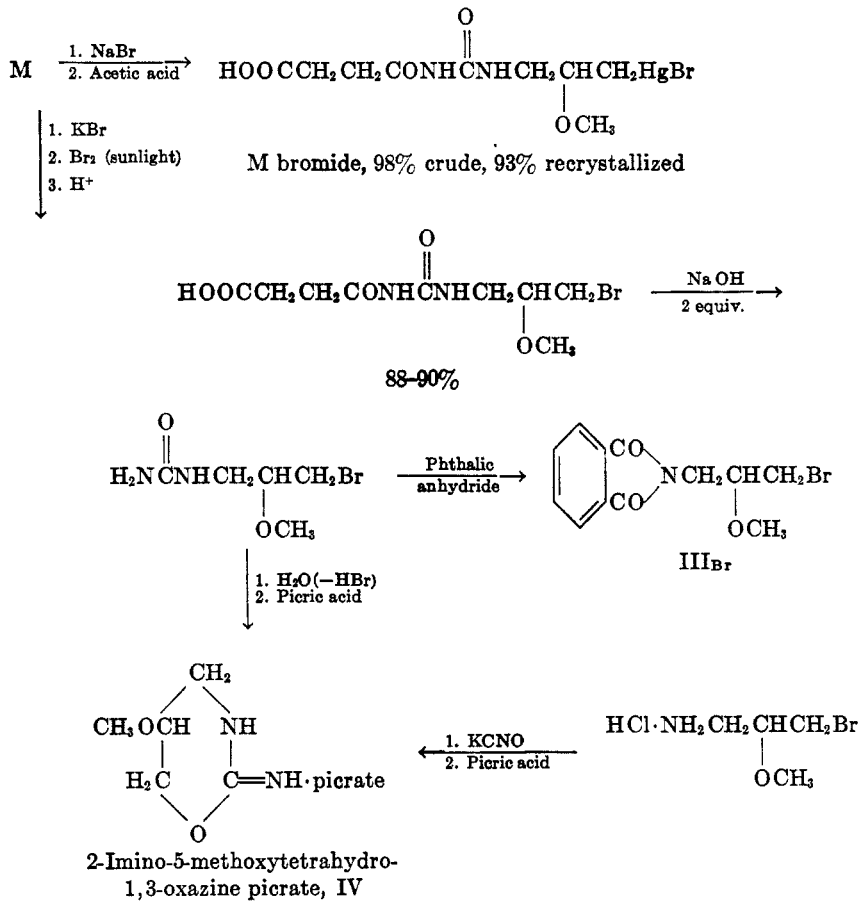
$H(OOCCH_2CH_2CONHCONHCH_2CHOCH_3CH_2Hg)_xOOCCH_3$. Van Loon and Carter (7) have encountered similar compounds. Analyses of M purified by solution in sodium bicarbonate and reprecipitation with acetic acid indicated the structure: $HOOCCH_2CH_2CONHCONHCH_2CHOCH_3CH_2HgOH$. The recalcitrant nature of M, as ascertained by its insolubility in water and other solvents and by its non-crystalline characteristics, was overcome by converting it to the crystalline M halides, using the appropriate potassium or sodium halide, thus facilitating the investigation of the homogeneity of M, itself. Intensive investigation of the M halides prepared from M both of this laboratory and of plant batches indicated that, within the limits of detection, the M halides were perfectly homogeneous substances (8).

The structure of M bromide was proved by the following series of reactions:



N-(2-Methoxy-3-bromopropyl)urea was unstable, decomposing in hot aqueous solutions or on standing to the tetrahydroöxazine (IV). A similar tetrahydrooxazine has been prepared by Gabriel and Lauer (9) from 3-bromopropylamine

and potassium cyanate.[3] The identical compound was prepared from potassium cyanate and 2-methoxy-3-bromopropylamine hydrochloride, the latter having been obtained from the acid hydrolysis of the N-(2-methoxy-3-bromopropyl)-phthalamic acid. Further confirmation of the identity of the urea was obtained by its conversion to the corresponding phthalimide by the method of Smith and Emerson (10).

Thus, it has been shown that the methoxymercuration of the N-allylamide type structure, which is possessed by the starting material of most diuretics, leads predominantly (in the case of N-allylphthalimide) or apparently exclusively (in the case of N-(β-carboxypropionyl)-N′-allylurea) to 2-methoxy-3-acetoxy (or hydroxy)-mercuripropyl derivatives.

EXPERIMENTAL

A. *The structure of β-(carboxypropionyl)allylurea* (I or II). I (or II) (m.p. 143.5–145°, 25 g., 0.125 mole) was suspended in a solution of thionyl chloride (9.2 cc., 0.125 mole) in benzene (150 cc.). Evolution of gas began at 40° and continued for four hours while the mixture was brought gradually to 78°. During this period, I (or II) had dissolved, and on cooling a solid product crystallized; this was washed with 40 cc. of benzene and air-dried (19 g., 83%, m.p. 87.5–89°). Pure succinylallylurea was obtained by recrystallization from isopropyl alcohol (m.p. 90–92°, hydrolysis equiv. Calc'd: 182; Found: 180). It (1 g.) was reconverted by dilute sulfuric acid (0.5 g. in 12 cc. of water) to β-carboxypropionylallylurea (74%, m.p. 142–144°; mixed m.p. the same).

Attempted synthesis of succinylallylurea from allyl isocyanate (11) and succinimide by the method of Menschutkin (12) yielded the impure compound which could not be separated from succinimide. However, hydrolysis of this impure compound with dilute sulfuric acid yielded a small amount of β-carboxypropionylallylurea (m.p. 142–144°; mixed m.p. with authentic sample 143–145°). This series of reactions is compatible only if the original urea structure is considered to be N-(β-carboxypropionyl)-N′-allylurea (I).

B. *M—The methoxymercuration product of* I. To a hot solution of mercuric acetate (15 g., 0.048 mole) in 200 cc. of methanol, a hot solution of I (10 g., 0.05 mole) in 150 cc. of methanol was added all at once. A white solid separated immediately, and the resulting suspension was refluxed for three hours, cooled to room temperature overnight, filtered, and the solid obtained washed with 100 cc. of methanol (20 g., 91%, m.p. 177–178.5° dec.). The mercury analysis was considerably higher than that calculated for an acetoxy derivative (Hg found: 44.3; Hg calc'd for acetoxy derivative: 40.9).

The purification of M, as prepared here or from plant batches, was carried out by slow solution in aqueous sodium bicarbonate and reprecipitation with acetic acid (average yield 90%, m.p. 188.5–190.5° dec.). The mercury analyses corresponded to the hydroxy compound N-(β-carboxypropionyl)-N′-(2-methoxy-3-hydroxymercuripropyl)urea.

Anal. Calc'd for (M) $C_9H_{16}HgN_2O_6$: Hg, 44.8. Found: Hg, 44.7, 44.9, 44.75.

Purification by solution in aqueous sodium hydroxide gave smaller yields due to the hydrolysis of the succinyl grouping.

C. *The M halides.* The halides were prepared from M (crude or purified; 0.05 mole) by slow solution in 50 cc. of water containing 0.052 mole of sodium or potassium halide. A slight amount of fore-precipitate was removed by filtration, and the filtrate acidified with three cc. of acetic acid. The M halide which precipitated was washed with water and

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[3] IV is isomeric with 5-methoxyhexahydro-2-pyrimidone. The burden of proof of the correct structure rests on the work of Gabriel and Lauer (9). However, this does not affect the proof of structure of M.

M HALIDE	M.P., °C. (dec.)	Hg		N (Kjeldahl)	
		Calc'd	Found	Calc'd	Found
Chloride	161 -162.5	42.93	43.13	6.0	5.96
Bromide	163 -164	39.20	39.21	5.47	5.43
Iodide	144.8-145.5	Unstable			

recrystallized from methanol (1 g. per 50 cc. for I and Cl; 1 g. per 80 cc. for Br). The yields were 98% (crude) and 92–93% (recrystallized from methanol).

Intensive investigation of the mother liquors of M bromide or fractional acetic acid precipitation of the sodium salt solution failed to disclose the presence of any isomeric M bromide (8).

D. *The degradation of M bromide.* Crude M (43 g., 0.096 mole) was dissolved in 150 cc. of water containing 18 g. of potassium bromide. To the filtered solution, cooled in an ice-bath and exposed to strong sunlight, a solution of bromine (16 g., 0.1 mole) in 85 cc. of water containing 20 g. of potassium bromide was added with stirring as rapidly as the color of bromide disappeared. The mixture was filtered and acidified with hydrobromic acid. The solid was washed with water (26.2 g., 88%, m.p. 134–136.5°). Recrystallization of 22 g. from 100 cc. of methanol gave pure N-(β-carboxypropionyl)-N′-(2-methoxy-3-bromopropyl)urea; m.p. 135.5–137°.

Anal. Calc'd for $C_9H_{15}BrN_2O_5$: Neutral equiv., 311; N, 9.01; Br, 25.69; CH_3O, 9.97.
Found: Neutral equiv., 310.5; N, 8.83; Br, 25.56; CH_3O, 10.28.

The above compound (15 g., 0.048 mole) was hydrolyzed overnight in the refrigerator by aqueous sodium hydroxide (3.9 g., 0.1 mole in 40 cc. of water) to N-(2-methoxy-3-bromopropyl)urea (5.1 g., 50%, m.p. 94–95°). Wasteful crystallization from water gave the pure compound, m.p. 98–98.8°.

Anal. Calc'd for $C_5H_{11}BrN_2O_2$: Br, 37.86. Found: Br, 37.7.

The pure compound, on standing or preferably on boiling with water, cyclized to 2-imino-5-methoxytetrahydro-1,3-oxazine (IV, 87% yield as the picrate; picrate m.p. 196–197° after recrystallization from water).

Anal. Calc'd for $C_5H_{10}N_2O_2 + C_6H_3N_3O_7$: N, 19.5; C, 36.78; H, 3.65.
Found: N, 19.96; C, 36.85; H, 3.55.

N-(2-Methoxy-3-bromopropyl)urea was further characterized by its conversion to N-(2-methoxy-3-bromopropyl)phthalimide using the procedure of Smith and Emerson (10) [25% crude yield; m.p. after crystallization from petroleum ether (b.p. 69–70°) and then from methanol, 102.5–103.5°].

E. *The synthesis of reference compounds and comparison with M degradation products.* N-(2-Methoxy-3-bromopropyl)phthalamic acid (4.4 g., 0.014 mole), whose structure had been proved in the preceding paper, was refluxed with 100 cc. of 2.4 *N* hydrochloric acid for four hours. The mixture was cooled, the phthalic acid which crystallized removed by filtration, and the filtrate evaporated to dryness at water-aspirator pressure. The crude 2-methoxy-3-bromopropylamine hydrochloride remaining was dissolved in 10 cc. of water, filtered, and mixed with potassium cyanate (1.0 g.). After standing briefly, the mixture was filtered, evaporated almost to dryness, redissolved in 5 cc. of water and treated with a saturated aqueous picric acid solution. IV was obtained (28% yield, m.p. 194–195°; recrystallized from water m.p. 196–197°).

Anal. Calc'd for $C_{11}H_{13}N_5O_9$: N, 19.5; C, 36.78; H, 3.65.
Found: N, 19.7; C, 37.0; H, 3.79.

A mixed melting point of this picrate and the picrate of the cyclized product obtained from M by bromination and hydrolysis showed no depression.

Furthermore, the mixed melting point of N-(2-methoxy-3-bromopropyl)phthalimide, whose structure was proved in the first paper, and of the phthalimide prepared from M by bromination, hydrolysis, and phthalation was undepressed.

F. *The preparation of M bromide from Mercuhydrin.* The commercial diuretics, such as Mercuhydrin, can be freed from the complexing reagents by treatment with aqueous potassium bromide. Mercuhydrin (2 g.) was suspended in 20 cc. of 20% aqueous potassium bromide solution. After standing overnight, the theophylline which precipitated was collected (0.3 g., 58%). Treatment of the filtrate with acetic acid yielded M bromide (0.85 g., 51%, m.p. after recrystallization 163–163.5°).

SUMMARY

The methoxymercuration of N-(β-carboxypropionyl)-N′-allylurea, followed by treatment of the product with aqueous potassium bromide, yielded N-(β-carboxypropionyl)-N′-(2-methoxy-3-bromomercuripropyl)urea (M bromide). No other isomer could be found. The structure of M bromide was proved by degradation to N-(2-methoxy-3-bromopropyl)urea from which two derivatives were made and shown to be identical to known reference compounds.

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