ml. portions of 5% hydrochloric acid. The acid extracts were treated with an excess of 10% aqueous potassium hydroxide, and extracted with chloroform; the chloroform extracts were dried, concentrated and distilled to give 16.1 g. of **10-(2-hydroxy-3-diethylaminopropyl)-1-azaphenothiazine.** The *base*, 11.5 g. (0.035 mole), 12.6 g. (0.14 mole) of anhydrous oxalic acid and 200 ml. of methyl ethyl ketone was refluxed until a clear solution formed: the oxalate separated from the cooled solution.

NEW BRUNSWICK, N. J.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, RESEARCH DIVISION, AMERICAN CYANAMID CO., LEDERLE LABORATORIES]

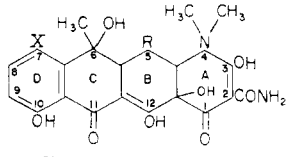
Chemistry of the Tetracycline Antibiotics.[1] I. Quaternary Derivatives

BY JAMES H. BOOTHE, GUIDO E. BONVICINO, COY W. WALLER, JOSEPH P. PETISI, RAYMOND W. WILKINSON AND ROBERT B. BROSCHARD

RECEIVED NOVEMBER 11, 1957

The quaternary methiodides of the antibiotics tetracycline and chlorotetracycline have been prepared and some of their chemical properties are described. In general the quaternary compounds are more reactive and less stable than the corresponding tertiary amines. The quaternary amines are reduced with extreme ease to the dedimethylaminotetracyclines.

During investigations of the chemistry and of the preparation of derivatives of the tetracycline antibiotics, the conversion of the tertiary amine which occurs in these compounds to a quaternary amine was studied. This is a report on the formation and subsequent reactions of these quaternary compounds.



tetracycline, X = R = H; chlorotetracycline, X = Cl, R = H; oxytetracycline, X = H, R = OH

The first attempts to quaternize these antibiotics were by heating with methyl iodide at 95° in a sealed vessel using tetrahydrofuran as a solvent. Each of the three antibiotics chlorotetracycline, tetracycline and oxytetracycline reacted differently. Chlorotetracycline yielded the corresponding methiodide in good yield, but tetracycline was dehydrated at the 5a–6-position. No pure product was isolated from this reaction, but the ultraviolet absorption spectra showed conclusively that the product was an anhydrotetracycline[2] derivative. Because of its insolubility in tetrahydrofuran, oxytetracycline was allowed to react using 1,2-dimethoxyethane as a solvent. The only recognizable product from this reaction was tetramethylammonium iodide. This probably resulted from an initial quaternization of the antibiotic followed by elimination of trimethylamine which then further reacted with methyl iodide.

A more practical method of preparing the methiodides of tetracycline and chlorotetracycline is to allow the reaction to proceed at room temperature for about a week during which time the methiodides slowly crystallize. Quaternization experiments on oxytetracycline again demonstrated the instability of oxytetracycline methiodide, even at room temperature. A solution of oxytetracycline and excess methyl iodide in methyl Cellosolve at room temperature yielded tetramethylammonium iodide as a white crystalline deposit. The dark filtrate from the tetramethylammonium iodide was not worked up further; however, this reaction is discussed in some detail by Conover.[3]

The methiodides are readily converted to the corresponding betaines (III) by raising the *p*H of their solutions to about 4–5. The betaines are crystalline compounds which are somewhat unstable even as solids especially in the presence of light at room temperature. They can be stored satisfactorily at 5° in the dark for several months, but always have a slight odor of trimethylamine. The betaines can be reconverted to the quaternary salts by treatment with strong acids such as hydriodic acid.

These quaternary derivatives are relatively inactive as antibacterial agents as compared to the antibiotics from which they are prepared.

The quaternary derivative of chlorotetracycline is more labile in neutral or alkaline solution than chlorotetracycline; for example in 0.1 *M* sodium borate the latter compound is fairly stable while its methiodide breaks down rapidly. Also under alkaline conditions which would convert chlorotetracycline to isochlorotetracycline,[4] much more extensive changes occur with the methiodide. If oxygen is carefully excluded, the mild alkaline treatment of chlorotetracycline methiodide yields dedimethylaminoaureomycinic acid (VII, X = Cl).[5] The treatment of chlorotetracycline with 5 *N* sodium hydroxide to yield dedimethylaminoaureomycinic acid already has been described.[5] This transformation involves at least three separate steps, and the probable sequence is as follows: (1) the cleavage of the C ring to form the phthalide, isochlorotetracycline[4]; (2) a Hofmann-type elimination of dimethylamine to form a double bond at position 4–4a; and (3) cleavage of the B ring be-

(1) The trademarks of the American Cyanamid Co. for chlorotetracycline and tetracycline are Aureomycin and Achromycin, respectively, and the trademarks of Charles Pfizer and Co. for oxytetracycline and tetracycline are Terramycin and Tetracyn, respectively.

(2) C. W. Waller, B. L. Hutchings, R. W. Broschard, A. A. Goldman, W. J. Stein, C. F. Wolf and J. H. Williams, THIS JOURNAL, **74**, 4981 (1952).

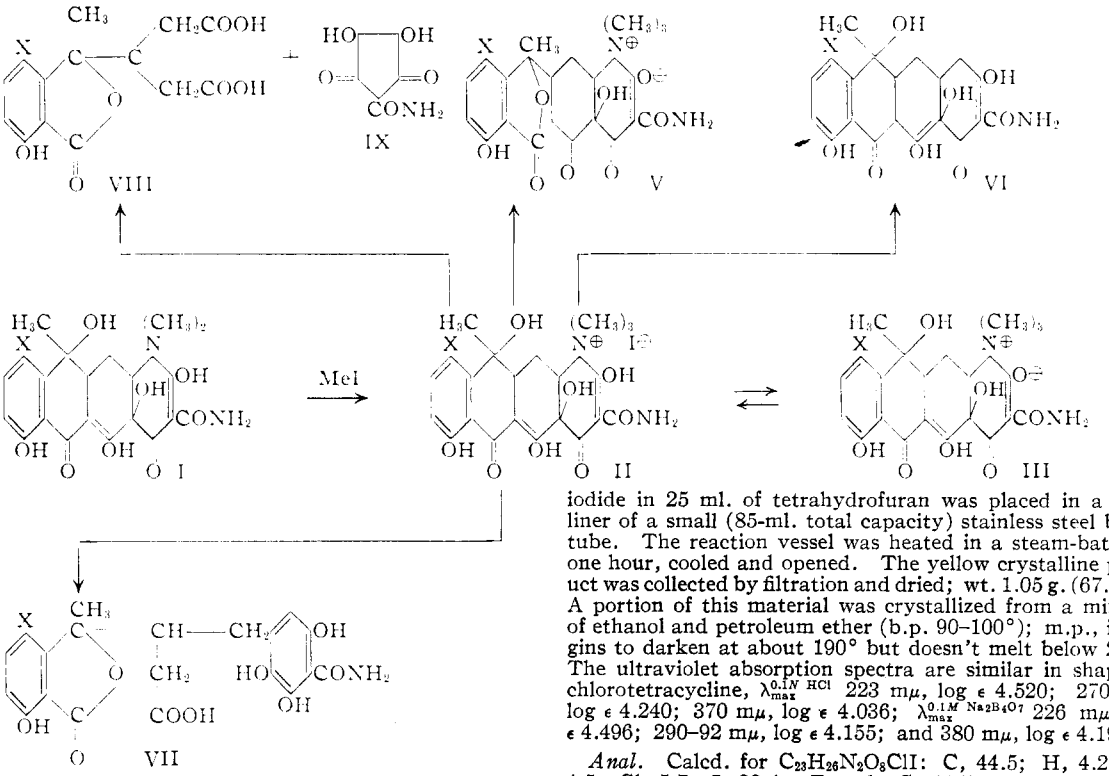
(3) L. H. Conover, Symposium on Antibiotics and Mould Metabolites, The Chemical Society, Special Publication No. 5, 1956, pp. 72–74.

(4) C. W. Waller, B. L. Hutchings, C. F. Wolf, A. A. Goldman, R. W. Broschard and J. H. Williams, THIS JOURNAL, **74**, 4981 (1952).

(5) C. W. Waller, B. L. Hutchings, A. A. Goldman, C. F. Wolf, R. W. Broschard and J. H. Williams, *ibid.*, **74**, 4979 (1952).

tween positions 12–12a. The second reaction in this sequence, the amine elimination, should be greatly facilitated by the presence of quaternary rather than a tertiary amino group. It is therefore not surprising that this series of reactions can be carried out under less drastic conditions when chlorotetracycline methiodide rather than chlorotetracycline is the starting material.

The conversion of dedimethylaminoaureomycinic acid to β-(4-chloro-7-hydroxy-3-methylphthalide-3)-glutaric acid (VIII, X = Cl)[6] and 3,4-dihydroxy-2,5-dioxocyclopentane-1-carboxamide (IX)[7] by treatment with *N* sodium hydroxide has been described. It was therefore not unexpected to find that treatment of chlorotetracycline methiodide with *N* sodium hydroxide in the presence of oxygen also yielded these same two compounds, the phthalide derivative (VIII X = Cl) and the substituted cyclopentane X.



Isochlorotetracycline methyl betaine (V) can be prepared readily either by treatment of isochlorotetracycline with methyl iodide and subsequent neutralization to the betaine or by treating chlorotetracycline methiodide with sodium acetate in boiling methanol.

One of the most useful properties of the quaternary compounds is their ready reduction with zinc and acetic acid to the corresponding dedimethylamino compounds.[8] The previously described methods of preparation of these dedimethylaminotetracycline compounds involved reduction of the parent antibiotic with zinc and acetic acid for 6–8 hours.[9,10] Under these conditions the parent antibiotics yielded dedimethylamino compounds contaminated with 12a-deoxydedimethylamino compounds. In our hands this led to difficult purifications and low yields. Fortunately, the quaternary compounds were found to be reduced extremely rapidly, only 10–15 minutes being required to obtain complete reduction of tetracycline or chlorotetracycline methiodides. This short reaction time minimizes the removal of the 12a-hydroxyl group and gives good yields of the dedimethylamino compounds.

Acknowledgment.—The authors wish to thank Mr. L. Brancone and associates for the microanalyses and Mr. W. Fulmor and associates for the spectral data contained herein.

Experimental

Chlorotetracycline Methiodide (II, X = Cl).—A solution of 1.2 g. of chlorotetracycline (I, X = Cl) and 3 ml. of methyl iodide in 25 ml. of tetrahydrofuran was placed in a glass liner of a small (85-ml. total capacity) stainless steel bomb tube. The reaction vessel was heated in a steam-bath for one hour, cooled and opened. The yellow crystalline product was collected by filtration and dried; wt. 1.05 g. (67.3%). A portion of this material was crystallized from a mixture of ethanol and petroleum ether (b.p. 90–100°); m.p., it begins to darken at about 190° but doesn't melt below 275°. The ultraviolet absorption spectra are similar in shape to chlorotetracycline, $\lambda_{max}^{0.1N\ HCl}$ 223 mμ, log ε 4.520; 270 mμ, log ε 4.240; 370 mμ, log ε 4.036; $\lambda_{max}^{0.1M\ Na_2B_4O_7}$ 226 mμ, log ε 4.496; 290–92 mμ, log ε 4.155; and 380 mμ, log ε 4.191.

Anal. Calcd. for $C_{23}H_{26}N_2O_8ClI$: C, 44.5; H, 4.2; N, 4.5; Cl, 5.7; I, 20.4. Found: C, 44.7; H, 4.7; N, 4.6; Cl, 5.8; I, 20.3.

The identical methiodide results from allowing a solution of 2.4 g. of chlorotetracycline and 6 ml. of methyl iodide in 50 ml. of tetrahydrofuran to stand at 24° for seven days; wt. 3.0 g. (96.5%).

Chlorotetracycline Methyl Betaine (III, X = Cl).—A solution of 2 g. of chlorotetracycline methiodide (II, X = Cl) in 5 ml. of dimethylformamide was clarified by centrifuging and the clear solution was poured into 50 ml. of water containing 5 ml. of 20% sodium acetate. A crystalline product was deposited slowly which was filtered off after 16 hours at 5°; wt. 0.87 g. This product was redissolved in 25 ml. of water by adding 5–6 drops of 6 *N* sulfuric acid. The solution was treated with charcoal, clarified by filtration, and sodium acetate solution was added to bring the *p*H to 4.5–

(6) B. L. Hutchings, C. W. Waller, S. Gordon, R. W. Broschard, C. F. Wolf, A. A. Goldman and J. H. Williams, THIS JOURNAL, **74**, 3710 (1952).

(7) C. W. Waller, B. L. Hutchings, C. F. Wolf, R. W. Broschard, A A. Goldman and J. H. Williams, *ibid.*, **74**, 4978 (1952).

(8) J. R. D. McCormick, *et al.*, *ibid.*, **79**, 2849 (1957).

(9) F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, P. N. Gordon, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, *ibid.*, **75** (1953).

(10) C. R. Stephens, L. H. Conover, R. Pasternack, F. A. Hochstein, W. T. Moreland, P. P. Regna, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, *ibid.*, **76**, 3568 (1954)

5. The crystalline product which was deposited was filtered off and dried at 60° *in vacuo* for 2 hours. When the compound was placed in a m.p. bath at 160° and the temperature was raised at the rate of 3°/minute, darkening began to occur at 195° followed by melting with blackening at 205°. The ultraviolet absorption spectra are the same as the methiodide except that they lack the maxima at about 223–226 mμ due to the iodide ion.

Anal. Calcd. for $C_{23}H_{25}N_2O_8Cl$: C, 56.0; H, 5.1; N, 5.7; Cl, 7.2. Found: C, 55.7; H, 5.4; N, 5.8; Cl, 7.3.

Tetracycline Methiodide (II, X = H).—To a solution of 100 g. of tetracycline (I, X = H) in 2 l. of tetrahydrofuran was added 240 ml. of methyl iodide. The solution was allowed to stand at about 25° and after 10–20 hours, crystals of the methiodide began to form. After six days the mixture was cooled to 5° for two days and the product was filtered off, washed with tetrahydrofuran and ether and dried; wt., 128.5 g. (97%). This material was identical to tetracycline methiodide.[8]

Tetracycline Methyl Betaine (III, X = H).—Five hundred mg. of tetracycline methiodide (II, X = H) was stirred in 25 ml. of water and a small amount of insoluble material was removed by filtration. The filtrate on standing at 5° overnight deposited some crystalline material which presumably was the betaine. However when a solution of sodium acetate was added to the mixture to raise the *p*H from about 2.5 to about 4.5, considerably more material crystallized in a short time. The product was filtered off and washed with water and methanol. The product was slurried in methanol which did not dissolve it, but the crystalline form changed. This material was removed by filtration and dried at 60° *in vacuo* for a short time. It can be crystallized by dissolving in hot methanol, but the odor of trimethylamine indicates some decomposition. The analysis indicates that a molecule of methanol is retained in the compound. When a sample was placed in the m.p. bath at 160° and heated at the rate of 3°/min. the compound darkened and melted at 180–186°. The ultraviolet absorption spectra are the same as tetracycline methiodide except that they lack the absorption maxima at 223–226 mμ due to the iodide ion.

Anal. Calcd. for $C_{23}H_{26}N_2O_8 \cdot CH_3OH$: C, 58.8; H, 6.1; N, 5.7. Found: C, 58.5; H, 6.2; N, 5.5.

A suspension of 500 mg. of tetracycline methyl betaine in 10 ml. of tetrahydrofuran was treated dropwise with hydriodic acid until all dissolved. After treating with charcoal and filtering, the solution slowly deposited crystals of tetracycline methiodide.

Chlorotetracycline Methochloride.—A solution of 1.2 g. of chlorotetracycline methiodide (II, X = Cl) in 50 ml. of ethanol was shaken with 5 g. of silver chloride in the dark for 8 hours at 25°. At this point it was partially worked up and found to still contain some methiodide. Fresh silver chloride was added and the mixture was shaken for an additional 6 hours. The insolubles were filtered off and the ethanol was concentrated to 15 ml. and diluted with ether until cloudy. After several hours the crystalline product was filtered off and dried; wt. 0.949 (90.3%).

Anal. Calcd. for $C_{23}H_{26}N_2O_8Cl_2$: C, 52.1; H, 5.0; N, 5.3; Cl, 13.4. Found: C, 51.5; H, 5.6; N, 5.9; Cl, 12.8.

Reaction of Oxytetracycline with Methyl Iodide.—To a solution of 500 mg. of oxytetracycline base in 9 cc. of methyl Cellosolve was added 1.2 cc. of methyl iodide. After 22 hours at 25° a light colored crystalline material was observed in the reaction. An aliquot of the reaction mixture was removed for microbiological assay which showed that 284 mg. (57%) of the oxytetracycline remained unreacted in the reaction mixture. The crystalline precipitate was collected by filtration, washed with ether and dried; wt. 50 mg. This product was identified as tetramethylammonium iodide by its infrared absorption spectrum. The 50 mg. represents a 53.6% yield based on the 47% of oxytetracycline which was unaccounted for by the microbiological assay.

Isochlorotetracycline Methyl Betaine (V, X = Cl).—(a) A solution of 5 g. of isochlorotetracycline in 150 ml. of tetrahydrofuran, 25 ml. of methanol and 25 ml. of methyl iodide was allowed to stand at 25° for three days and then was evaporated to dryness. The residue was dissolved in 50 ml. of water and 5 ml. of 12 *N* hydrochloric acid by heating on a steam-bath. To the hot solution was added a boiling solution of 20 g. of sodium acetate in 50 ml. of water. The resulting crystalline product was collected after cooling, washed with water, methanol and boiling methanol, and dried *in vacuo* at 78°; wt. 4.6 g. (86%), m.p. 270–284° with dec. The material is a monohydrate. The ultraviolet absorption spectra are similar in shape to isochlorotetracycline, $\lambda_{max}^{0.1N\ HCl}$ 242 mμ, log ε 4.123; 273 mμ, log ε 4.139; 310 mμ (shoulder), log ε 3.729; $\lambda_{max}^{0.1M\ Na_2B_4O_7}$ 255 mμ, log ε 4.114; 292 mμ, log ε 4.140; 345 mμ, log ε 3.838.

Anal. Calcd. for $C_{23}H_{25}N_2ClO_8 \cdot H_2O$: C, 54.0; H, 5.3; N, 5.5; Cl, 6.95. Found: C, 54.4; H, 5.6; N, 5.5; Cl, 7.1.

(b) A solution of 20 g. of chlorotetracycline methiodide (II, X = Cl), 20 g. of sodium acetate trihydrate, 400 ml. of methanol and 40 ml. of water was refluxed for 45 minutes. The crystalline product which had formed was filtered off, washed and dried; wt. 9.0 g. (55%). This product was identical with the methyl betaine described above.

Alkaline Cleavage of Chlorotetracyclinemethiodide (II, X = Cl).—(a) In absence of oxygen: To a suspension of 500 mg. of chlorotetracycline methiodide in 24.6 ml. of water containing 10.20 mg. of sodium hydrosulfite was added 5.4 ml. of *N* sodium hydroxide. The resulting solution was kept under an atmosphere of nitrogen for one hour and then acidified to *p*H 1–2. The gummy precipitate was removed and crystallized from a mixture of water and methanol; weight 150 mg. This material was dedimethylaminoaureomycinic acid (VII, X = Cl), identical with that already described[7] and having ultraviolet absorption spectra as follows: $\lambda_{max}^{0.1N\ HCl}$ 268 mμ, log ε 4.216; 310 mμ (broad), log ε 3.785; $\lambda_{max}^{0.1M\ Na_2B_4O_7}$ 258 mμ, log ε 4.353; 350 mμ, log ε 3.932.

(b) In presence of oxygen: Oxygen was bubbled through a suspension of 1.0 g. of chlorotetracyclinemethiodide in 45 ml. of water, and 5 ml. of 10 *N* sodium hydroxide was added. The resulting solution after oxygenating for one hour was acidified and extracted with two 100-cc. portions of ethyl acetate. The water phase was saved to work up later and the ethyl acetate extracts were concentrated to dryness, and the residue was boiled with 50 ml. of chloroform. A dark insoluble material was filtered off and the filtrate was concentrated to dryness. The residue was boiled with 5 ml. of ethyl acetate until crystallization occurred. In two crops, 310 mg. of β-(4-chloro-7-hydroxy-3-methylphthalide-3)-glutaric acid (VIII, X = Cl) was obtained identical with that already described.[6] The ultraviolet absorption spectra show $\lambda_{max}^{0.1N\ HCl}$ 268 mμ, log ε 4.222; 310 mμ, log ε 3.801; $\lambda_{max}^{0.1M\ Na_2B_4O_7}$ 258 mμ, log ε 4.354; 350 mμ, log ε 3.934.

The water phase which had been extracted with ethyl acetate was now concentrated to 8 ml. and adjusted to *p*H 6–7. In a few minutes a sodium salt began to crystallize, and after cooling well it was filtered off and dried; wt. 120 mg. This material was crystallized from a few ml. of 0.1 *N* hydrochloric acid to give pure 3,4-dihydroxy-2,5-dioxocyclopentane-1-carboxamide[7] (IX).

Dedimethylaminochlorotetracycline[9] (VI, X = Cl).—A solution of 24.8 g. of chlorotetracycline methiodide in 200 ml. of acetic acid and 140 ml. of water was stirred vigorously with 12.0 g. of freshly opened zinc dust (Merck) for 15 min. The temperature rose a few degrees and a solid precipitated with the zinc. The solids were filtered off and 50 ml. of dimethylformamide was used to dissolve the product from the zinc. On adding about 100 ml. of methanol and 5 ml. of 6 *N* hydrochloric acid, 6.15 g. of crystalline product was obtained. The filtrate on concentrating to dryness and crystallizing from dimethylformamide and methanol gave 3.08 g. of additional material. The original filtrate of acetic acid and water was diluted with more water, extracted with ethyl acetate and the residue from this extract was crystallized from methanol to give 3.46 g. of product; total wt. 12.69 g. (73%). This material melted at about 156–159° and was otherwise identical with that already described.[9]

Dedimethylaminotetracycline[8] (VI, X = H).—A solution of 20 g. of tetracycline methiodide (II, X = H) in a mixture of 300 ml. of acetic acid and 300 ml. of water was stirred rapidly and 10 g. of zinc dust was added. The mixture was stirred for about 15 minutes during which time the temperature rose from 24 to 28°. The zinc dust was filtered off and the filtrate was diluted with 2 l. of water containing 20 ml. of concentrated hydrochloric acid. After cooling the solution for one hour in ice, the product separated as small round aggregates of crystals which were collected and dried; wt. 10.43 g. (77.4%). This material was crystallized by dissolving 500 mg. in 40 ml. of boiling ethyl acetate

and diluting with an equal volume of petroleum ether (b.p. 90–100°). The product, after drying at 60° *in vacuo* for one hour, melted with decomposition at about 195–200°. All other properties of this compound were identical to those already described.[8]

PEARL RIVER, N. Y.

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES]

Synthesis of Some Substituted Benzimidazolones

BY ROBERT L. CLARK AND ARSENIO A. PESSOLANO

RECEIVED NOVEMBER 2, 1957

A number of benzimidazolones, substituted in the aromatic ring and on the nitrogen atoms, and the necessary intermediates, were synthesized. Some of them possessed anti-convulsant, antimitotic and anti-leukemic activity.

This paper deals with the synthesis of substituted benzimidazolones. Although a number of benzimidazolones are reported in the literature, very few data are available on their pharmacological activity. It has now been found that many of them protect rats from convulsions due to electro shock, one of the better ones being 5-tetradecylbenzimidazolone.[1] Also, some, especially 5-*t*-butylbenzimidazolone, have an anti-mitotic effect.[1] Several of the compounds showed activity against mouse leukemia; one of the best compounds was 1,3-dimethyl-5-*t*-butylbenzimidazolone.[2]

The benzimidazolone ring was formed from substituted *o*-diaminobenzene derivatives by one of two methods, either the diamine was allowed to react with phosgene, or heated with urea. In the former case phosgene was bubbled into an aqueous acid solution of the diamine. In most cases the benzimidazolone separated almost immediately and could be washed free of impurities. A solution resulting from a stannous chloride reduction of an *o*-nitroamine could be used directly with phosgene, without isolation of the diamine.

In the latter case an intimate mixture of the *o*-diamine (or acid salt) and urea was heated slowly to 140°. At this temperature a melt usually resulted. With continued heating the liquid solidified to give the benzimidazolone which could be purified by crystallization.

The diamine intermediates, listed in Table II, were prepared by more or less standard procedures from the most available starting materials. All other intermediates leading up to the *o*-diamine are listed in Table III along with their method of preparation.

The N-alkylated derivatives were prepared by the use of the method Kloetzel[3] developed for alkylating amides. A suspension of the benzimidazolone, powdered potassium hydroxide and the alkyl halide in acetone was heated under reflux to give, in most cases, a good yield of the dialkylated benzimidazolone.

To prepare monoalkylbenzimidazolones it was necessary to form first the N-alkylnitroamine. This was done by tosylating an *o*-nitroaniline and then alkylating the nitrogen of the sulfonamide. The tosyl group was then hydrolyzed and the nitro group reduced to give the monoalkylated *o*-diamine.

Acylation of the benzimidazolone nitrogen was readily carried out using acid anhydrides at elevated temperatures.

The benzene ring of benzimidazolone can be acylated by a Friedel–Crafts reaction using an acid chloride in carbon disulfide in the presence of aluminum chloride.[4] These acyl compounds can then be reduced to give the alkyl derivatives.

All of the benzimidazolones prepared, along with their method of preparation and physical constants, are listed in Table I.

Experimental[5]

A. **Reaction of *o*-Diamines with Phosgene.**—Phosgene was bubbled into an aqueous hydrochloric acid solution of the *o*-diamine. In some cases the product precipitated in a very short time, while others required several hours. After precipitation was complete the benzimidazolone was collected and washed well with water. This product was fairly pure but generally could be recrystallized if desired. The phosgene method was superior to the urea method in that a whiter, purer product was obtained in better yields (75–95%).

B. **Reaction of *o*-Diamines with Urea.**—A mixture of 1.0 mole of aromatic *o*-diamine, or its hydrochloride, and 1.1 moles of urea was heated in an oil-bath at 140° or higher, depending upon the melting point of the mixture. A clear melt formed which was followed by effervescence. Heating was continued, and in most cases the substituted benzimidazolone soon solidified. After heating 15 minutes more the solid mass was cooled and dissolved in 2.5 *N* sodium hydroxide. After filtration it was reprecipitated with concentrated hydrochloric acid. The benzimidazolone was then crystallized or purified further by repetition of the base–acid treatment. The yields ranged from 40 to 75%.

C. **Catalytic hydrogenation of nitro groups** was accomplished by shaking an alcohol solution of the nitro compound under hydrogen at 40 p.s.i. in the presence of 5% palladium-on-charcoal. After removing the catalyst by filtration the filtrate was either evaporated to give the free amines, or hydrogen chloride was passed into the solution. Often the hydrochloride separated immediately but sometimes ether had to be added to precipitate it.

(1) These biological results will be presented in more detail in a publication from the Merck Institute for Therapeutic Research by Drs. J. Hawkins, Jr., and H. Stoerk.

(2) Private communication from the Division of Chemotherapy of Sloan-Kettering Institute.

(3) I. J. Pachter and M. C. Kloetzel, THIS JOURNAL, **74**, 1321 (1952).

(4) J. R. Vaughan and J. Blodinger, *ibid.*, **77**, 5757 (1955).

(5) We are indebted to Mr. R. N. Boos and his associates for the microanalyses, and to Dr. W. H. Jones and his associates for the hydrogenations.