N-(3-Phthalidyl)-tetracycline, a New Carboxamido Derivative of Tetracycline

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Condensation reactions involving the carboxamido group of tetracycline have been reported by Gottstein, *et al.*[1] These workers describe an xanthydrol condensate of tetracycline as well as numerous derivatives prepared from amines and formaldehyde by the Einhorn reaction. One of these, N-(pyrrolidinomethyl)-tetracycline,[2] has proved superior to tetracycline when administered parenterally.[3,4]

The reactivity of the carboxamido moiety of tetracycline, and the interesting properties of its condensation products, has prompted us to evaluate the reaction of this amide with phthalaldehydic acid. Wheeler, *et al.*,[5] have shown that phthalaldehydic acid reacts with amines, amides, urethanes, alcohols and phenols giving rise to 3-substituted phthalides. It is believed that this acid reacts with the carboxamido group of tetracycline giving N-(3-phthalidyl)-tetracycline (I) as the reaction product. As noted with N-(9-xanthyl)-tetracycline,[6] I also failed to yield an Einhorn or Mannich derivative when it reacted with formaldehyde and morpholine or pyrrolidine. This is consistent with the proposed amide substitution for I. It also provides further evidence that the Einhorn rather than Mannich reaction normally occurs in aminoalkylations of tetracycline.

Using a turbidometric assay against *Micrococcus pyogenes var. aureus*, I was found to retain antibacterial activity equivalent to that contributed by the tetracycline portion of the molecule. It is soluble in water at pH 9 or greater but is virtually insoluble in 0.1 to 6.0 *N* hydrochloric acid. Unlike N-(pyrrolidinomethyl)-tetracycline, I gave no significant blood levels orally in dogs or intramuscularly in rabbits.

Experimental

Fifty grams (0.1 mole) of tetracycline base hydrate was slurried in 500 ml. of water and heated to 90 to 95°. This temperature was maintained throughout the course of the reaction. Phthalaldehydic acid (72 g., 0.48 mole) then was added rapidly with moderate agitation forming a yellow solution. In 5 min. a copious quantity of gum separated. After 15 min., heat and stirring were discontinued and the reaction mixture was allowed to cool to 25° for 2 hr. The gum was isolated by decantation and washed with 100 ml. of water. It then was dissolved in acetone at 50° from which it crystallized immediately. The crystals were removed by filtration, recrystallized from acetone and dried overnight at 90° under vacuum. A yield of 40 g. (71.3%) was obtained. I also was prepared by heating an equimolar mixture of the reactants at 120° for 0.5 hr. and crystallizing from acetone.

Anal. Calcd. for $C_{30}H_{25}N_2O_{10}$: C, 62.5; H, 4.90; N, 4.86. Found: C, 62.18, 62.5; H, 4.89, 5.03; N, 4.79, 4.9.

The compound had m.p. 191–193° dec., (capillary); $[\alpha]^{25}D$ −157° (*c* 1 in 0.1 *N* HCl in methanol); absorption maxima in 0.1 *N* HCl in methanol at 222 mμ (ε = 23,865), 272 mμ (ε = 20,867), 362 mμ (ε = 15,103); infrared absorption maxima (KBr pellet) 2.95, 3.25, 3.5, 5.6, 6.0, 6.2, 6.3 and 6.4 μ.

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Compounds Related to Carnitine: Derivatives of 4-Dimethylamino-3-hydroxybutyric Acid

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Carnitine (I) is an ubiquitous substance first extracted in 1905 from mammalian muscle tissue,[1] however, its structure was not fully elucidated until 1927 when Tomita and Sendju[2] succeeded in resolving synthetic *dl*-carnitine and showed that the *l*-isomer was identical with the naturally occurring material. Vitamin B_T, an essential factor to the mealworm (*Tenebrio molitor*), has been shown to be identical with carnitine.[3] The substance affects the oxidation of long chain fatty acids in liver homogenates[4] and its coenzyme A ester has been isolated from brain tissue and is reported to have an inhibitory action on neural transmission.[5] Recently[6] 4-dimethylamino-3-hydroxybutyric acid (II) and carnitine (I) have been tentatively identified as metabolites of 4-dimethylaminobutyric acid in the rat. Positive identification was not possible in the work cited, however, since a synthetic sample of II was lacking. As part of a study conducted in these laboratories designed partially to elucidate the possible function of carnitine and its derivatives in affecting the central nervous system and their part in mammalian lipid metabolism it became necessary to prepare II and several of its analogs, namely ethyl 4-dimethylamino-3-hydroxybutyrate (III), 4-dimethylaminobutane-1,3-diol (IV) and 4-dimethylamino-3-hydroxybutyramide (V).

$(CH_3)_3N^+CH_2CHOHCH_2COO^-$ I

$(CH_3)_2NCH_2CHOHCH_2Y$
II, Y = COOH
III, Y = $COOC_2H_5$
IV, Y = CH_2OH
V, Y = $CONH_2$

Compounds II, IV and V have been compared to carnitine in their ability to increase the oxidation of palmitate by incubated heart muscle particulates, and it was found that II was nearly as active as carnitine while IV and V were inactive by this test.[7] None of these

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