Attempted Syntheses of Tetracyclin Analogues. Part I.

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Diethyl- α -benzyl- α -(3-(3-methylphthalidyl))-malonate and diethyl- α -benzoyl- α -(3-(3-methylphthalidyl))-succinate as intermediates of aureomycinic acid analogues, and 2, 10-dibromo-1,4-dioxo-1,4,5,8,9,10-hexahydronaphthalene as intermediate of tetracyclin A. B ring analogue have been prepared.

The structure which is common to both terramycin and aureomycin have been named tetracyclin by C. R. Stephens et al.¹⁾

We attempted to prepare the analogues of this tetracyclin and in the course a few products as the intermediates of these analogues were synthesized.

Namely, with a view of synthesizing the an-

alogues of aureomycinic acid²⁾ which had been isolated as degradation product of aureomycin, the coupling reaction was first tried between 3-chloro-3-methylphthalide (acetophenon-o-carboxylic acid pseudo-acid chloride) (II) and diethyl benzoyl sodio malonate (III) and diethyl- α -benzyl- α -(3-(3-methylphthalidyl))-malonate (IV) was yielded.

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1) Stephens, *J. Am. Chem. Soc.*, **74**, 4977 (1952).

2) Hurchings, *ibid.*, **74**, 4980 (1952).

This pseudo-acid chloride (II) was highly anstable and decomposed at 45°C.

Reaction between the pseudo-acid chloride and diethyl benzoyl sodio succinate (V) yielded diethyl- α -benzoyl- α -(3-(3-methylphthalidyl))-succinate (VI).

Diethyl- α -benzoyl- α -(3-(3-methylphthalidyl))-malonate, however, was found to be quite stable to acid hydrolysis, and after twelve hours reflux in concentrated hydrochloric acid the two ester groups still retained.

Since these compounds (IV) and (VI) have two asymmetric centers, it exists in two racemic forms or diastere isomers, but we could not isolate them because the sample was very small in quantity.

As the first attempt to prepare a tetracyclin A. B ring analogue, we tried to use Diels-Alder reaction between butadien and some benzoquinone derivatives.

The reaction between 2,5-dimethoxy-benzoquinone and butadien did not proceed as expected and could not be obtained at all. But when 2,5-dibromo-benzoquinone (VII) and butadien had been heated in benzene at 100°C in sealed tube for six hours, a light yellow adduct (VIII)³⁾ was obtained in good yield.

This adducts (VIII) was somewhat unstable, discoloured after a long time at room temperature, and festered skin, the solution of this adduct in benzene was specially hard and proved toxic to house flies.

One bromine-atom of this adduct was very unstable, therefore the authors could not prepared 2,9-diacetoxy-1,4-dioxo-1,4,5,8,9,10-hexahydronaphthalen from this adduct with silver acetate.

As the studies are now in progress, they will

be published in future.

EXPERIMENTAL

3-Chloro-3-methylphthalide (II)

A mixture of 8.2 g of acetophenon-o-carboxylic acid⁴⁾ and 10.4 g of phosphorus pentachloride were stirred in 30 ml. of dry benzene for two hours below 40°C. The clear solution was filtered and the filtrate was evaporated *in vacuo* at room temperature and petroleum ether (50 ml.) was added. After cooling for one day the solid was filtered and washed with petroleum ether; yield 8.0 g. This product was not further purified but was used for the further reactions.

Diethyl- α -benzyl- α -(3-(3-methylphthalidyl))-malonate (V)

To a stirred dry benzene solution suspended with 0.9 g of sodium-sand was added 10 g of diethyl- α -benzyl-malonate⁵⁾ dissolved in the equal quantity of dry benzene. The mixture was refluxed for four hours.

After the sodium-sand was dissolved completely a suspension of 3 g of 3-chloro-3-methylphthalide in 20 ml. of dry benzene was added to the solution at room temperature.

Stirring was continued for one hour at room temperature then the mixture was refluxed until it became neutral, cooled, and the insolubles were removed by filtration. The clear benzene solution was concentrated to dryness *in vacuo* and the dark red residual oil was diluted with alcohol.

The crystalline product was filtered and dried, wt. 4.0 g, m.p. 141–143°. A portion of it was crystallized twice from acetic acid; m.p. 145–146°. *Anal.* Calcd. for $C_{23}H_{24}O_6$; C, 69.68; H, 6.10

Found: C, 69.33; H, 6.25

Diethyl- α -benzoyl- α -(3-(3-methylphthalidyl))-succinate (VI)

This was prepared using 0.5 g of sodium-sand, 6.1 g of α -benzoyl-succinate⁶⁾ and 4.1 g of 3-chloro-3-methylphthalide by the above described methods.

The crystalline product was 3.2 g, m.p. 220–221°C. *Anal.* Calcd. for $C_{23}H_{24}O_7$; C, 67.91; H, 5.70

Found: C, 67.88; H, 5.76

2,10-Dibromo-1,4-dioxo-1,4,5,8,9,10-hexahydronaphthalene (VIII)

Five and four tenth grams of 2,5-dibromo-*p*-benzoquinone⁷⁾ (m.p. 188°), 1.6 g of freshly distilled buta-

4) Gabriel, *Ber.*, **10**, 1553.

5) Leuchs, *Ber.*, **44**, 1509.

6) Perkin, *J. Am. Chem. Soc.*, **47**, 273 (1925).

7) Sarauw, *Ann.*, **209**, 112 (1881).

3) Matsui and Nishizawa, Jap. pat. No. 227,481.

dien; 40 ml. of benzene were shaken in sealed tube at 100°C for six hours. The light-yellow reaction mixture was filtered, and concentrated to dryness *in vacuo*.

The crude product was recrystallized from alcohol;

5.3 g, m.p. 94–95° *Anal.* Calcd. for $C_{10}H_8O_2Br_2$; C, 37.50; H, 2.5

Found: C, 37.38; H, 2.31

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The Effect of Riboflavin on Hypertension induced by High Salt Diet in the Rat

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The effect of riboflavin on development of hypertension in rats given a high salt diet was studied. Large doses of riboflavin prevented both elevation of blood pressure and rise of cholesterol levels in the serum. The increase in liver monoamine oxidase activity of the rats fed riboflavin was confirmed.

Calder¹⁾ reported that rats fed a vitamin B-deficient diet showed a higher level of blood pressure than those fed a similar diet supplemented with yeast or liver extracts and considered that the vitamin B group contained in the supplements may inhibit the elevation of blood pressure of the animals. The present study was designed to determine whether riboflavin is effective to inhibit the elevation of blood pressure in rats induced by a salt-rich diet.

EXPERIMENTAL AND RESULTS

The first experiment; A preliminary examination was performed to find the effect of riboflavin on salt-hypertension occurring in animals. In this study, ten two-month-old Wistar strain albino rats were divided into two groups; one of them was fed a basal diet

consisting of 91.8 g polished rice, 5 g casein, 0.5 g calcium carbonate, 2.5 g sodium chloride, 0.2 g dried carrot powder and 0.1 mg thiaminehydrochloride, the other was fed a basal diet plus 1 mg riboflavin. The basal diet contained 0.071 mg riboflavin. The diet which was pasted by heating with 100 ml water per 100 g was given *ad lib.* and drinking water was restricted according to the suggestion of Sapirstein²⁾ that the ratio of sodium chloride to water intake, rather than the amount of sodium chloride, is considered to be the determining factor for development of this type of hypertension.

After three months' feeding, systolic blood pressure of the rat was measured by the method of Williams *et al.*³⁾ and then, the animals were sacrificed by decapitation and their liver and kidney removed immediately so as to serve for the determinations of

2) L. A. Sapirstein, W. L. Brandt, and D. R. Drury, *Proc. Soc. Exp. Biol. Med.*, **73**, 82 (1950).

3) J. R. Williams, T. R. Harrison and A. Gollman, *J. Clin. Invest.*, **18**, 373 (1939).

1) R. M. Calder, *J. Exp. Med.*, **76**, 1 (1942); **79**, 215 (1944).