Journal of Medicinal and Pharmaceutical Chemistry

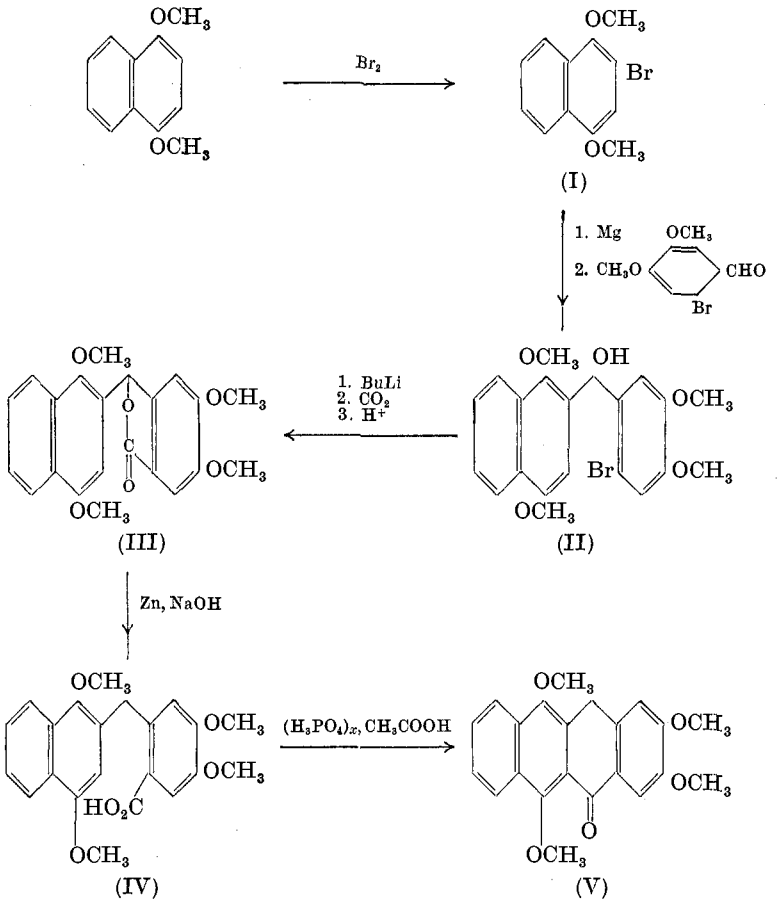
VOL. 4, No. 2 (1961)

Synthesis of 2,3,6,11-Tetramethoxy-5(12H)-naphthacenone as an Analogue of Tetracycline

JOHN B. DATA and RAYMOND D. BENNETT, *School of Pharmacy, Purdue University, Lafayette, Indiana*

The wide use of the tetracycline family of antibiotics has inspired the preparation of a number of modifications of the parent compound. Most of these have been made directly from one of the tetracyclines.[1-6] Recently several totally synthetic analogues of the tetracyclines have been reported.[7-14] Three of these are of special interest because they are identical with compounds previously prepared from the parent tetracyclines and have antibacterial activity, two being anhydrotetracyclines[11,12] and the other a 6-deoxytetracycline.[14] In our work it was decided to investigate the possibility of preparing relatively simple analogues containing the naphthacene nucleus present in tetracycline. Since only ring D of the tetracycline system is aromatic, the formation of such a system would involve considerable difficulty, as was shown in the three papers referred to above[11,12,14] published after this work was completed. Thus, it was thought desirable to make the A, C, and D rings aromatic; the compound prepared by Waller and Wolf[1] contains an aromatic A ring and the anhydrotetracyclines[2] contain an aromatic C ring. These compounds showed an activity comparable to that of the tetracyclines, so that it seemed reasonable to combine these two structural features into one compound.

The approach decided upon for the formation of the naphthacene ring system involved the reaction of a naphthalenic Grignard reagent with a substituted benzaldehyde, as illustrated. The aldehyde chosen was 6-bromoveratraldehyde, because this would give as a final product a compound having two hydroxyl groups in ring A; the compound prepared by Waller and Wolf[1] contains three hydroxyl groups in this ring. Several different bromonaphthalenic compounds were considered as the source of the C and D rings, with 2-bromo-1,4-dimethoxynaphthalene finally being



chosen, largely because it is much more easily prepared than the other possibilities.

The preparation of 2-bromo-1,4-dimethoxynaphthalene (I) by bromination of 1,4-dimethoxynaphthalene was carried out by a modification of the method reported by Ungnade and Hein.[15] The Grignard reagent of (I), prepared by entrainment with ethyl bromide, was reacted with 6-bromoveratraldehyde to give a 62 per cent yield of 6-bromo-α-(1,4-dimethoxy-2-naphthyl)-veratryl alcohol (II). Treatment of (II) with excess of butyllithium followed by carbonation of the organometallic compound formed

gave the lithium salt of 4,5-dimethoxy-α-(1,4-dimethoxy-2-naphthyl)-α-hydroxy-*o*-toluic acid, which upon acidification cyclized to the lactone, 5,6-dimethoxy-3-(1,4-dimethoxy-2-naphthyl)phthalide (III), isolated in 57 per cent yield. Reduction of (III) using zinc dust and sodium hydroxide solution yielded 52 per cent of 4,5-dimethoxy-α-(1,4-dimethoxy-2-naphthyl)-*o*-toluic acid (IV). Cyclization of (IV) was effected by treatment with a solution of polyphosphoric acid in glacial acetic acid to give a 33 per cent yield of 2,3,6,11-tetramethoxy-5(12H)-naphthacenone (V); the use of polyphosphoric acid alone or sulphuric acid gave dark amorphous material which resisted purification. The attempted demethylation of (V) with hydrobromic acid resulted in decomposition and no pure product could be isolated.

Experimental*

2-Bromo-1,4-dimethoxynaphthalene (I). To a stirred solution of 1,4-dimethoxynaphthalene (18·0 g, 0·096 mole) in chloroform (110 ml) containing iron filings (0·1 g) was added dropwise a solution of bromine (15·3 g, 0·096 mole) in chloroform (100 ml) while a slow stream of nitrogen was passed through the solution. Stirring was continued for 30 min after addition was complete, and then nitrogen was bubbled rapidly through the solution to expel the hydrogen bromide. The solution was filtered and poured into water (300 ml), the chloroform layer was separated, washed with potassium hydroxide solution (10 per cent) and dried over calcium chloride, and the solvent was removed in vacuum. The residue was dissolved in pentane (75 ml) and the solution was cooled to −15°. The solution was decanted from the crystalline material, concentrated to 30 ml, and again cooled to −15°. The crystals obtained were combined with the first crop and the total (18·4 g, 72 per cent) was recrystallized from methanol, using charcoal to decolourize, to give colourless needles (16·7 g, 65 per cent), m.p. 58–59°; reported,[15] m.p. 54–55°.

6-Bromo-α-(1,4-dimethoxy-2-naphthyl)veratryl alcohol (II). A nitrogen atmosphere was maintained throughout this preparation, and the ether was dried over lithium aluminium hydride and distilled into the dropping funnel under anhydrous conditions.

* Melting points are corrected.

A mixture of magnesium turnings (1·1 g, 0·046 mole), ground into fine pieces in a mortar, ethyl bromide (2 drops) and ether (4 ml) was stirred until the reaction was well under way. A solution of (I) (3·9 g, 0·014 mole) and ethyl bromide (2·2 g, 0·020 mole) in ether (12 ml) and benzene (6 ml) was added with vigorous stirring, using a Hershberg stirrer, at such a rate that rapid refluxing was maintained until addition was complete. The mixture was then heated under reflux for 20 min while dry benzene (12 ml) was added slowly. A hot solution of 6-bromoveratraldehyde[16] (9·0 g, 0·037 mole) in dry benzene (115 ml) was added rapidly with vigorous stirring, and refluxing and stirring were continued for 8 h. The cooled mixture was decomposed with water followed by dilute hydrochloric acid; the organic layer was separated, washed with water, dried over sodium sulphate, and evaporated to dryness in vacuum. The residue was extracted with dry ether (three 50-ml portions), the filtered extracts were evaporated to dryness and the oily residue was extracted with petroleum ether (300 ml) in small portions. The undissolved residue was recrystallized twice from ethanol to yield 3·9 g (62 per cent) of pale yellow crystals, m.p. 159–162°. Recrystallization from toluene raised the melting point to 164–165°.

Anal. Calcd. for $C_{21}H_{21}BrO_5$: C, 58·20; H, 4·90; Br, 18·46. Found: C, 58·33; H, 5·09; Br, 18·29.

5,6-Dimethoxy-3-(1,4-dimethoxy-2-naphthyl)phthalide (III). This experiment was performed in a nitrogen atmosphere using dry ether prepared as for (II).

A solution of *n*-butyllithium (0·05 mole) in ether (30 ml) was added slowly with stirring to a solution of (II) (3·3 g, 0·0076 mole) in ether (100 ml) and dry toluene (100 ml). The temperature was maintained at 0° during the addition and for 30 min longer. The white precipitate which first appeared quickly became bright pink and then gradually turned an orange colour. The suspension was transferred under nitrogen to a dropping funnel and added over a period of 15 min to a stirred slurry of powdered Dry Ice in ether. Stirring was continued until the mixture had reached room temperature, when water (150 ml) was added. The organic layer was extracted with sodium hydroxide solution (100 ml, 5 per cent) and the combined aqueous layers were shaken with ether and acidified. The oily precipitate was taken up in ether, shaken

with sodium bicarbonate solution (5 per cent) and dried over sodium sulphate, and the ether was evaporated. The residue was recrystallized from ethanol to give colourless crystals (1·66 g, 57 per cent), m.p. 192·5–194·5°. Recrystallization from benzene–petroleum ether raised the melting point to 198–199·5°.

Anal. Calcd. for $C_{22}H_{20}O_6$: C, 69·45; H, 5·32. Found: C, 69·18; H, 5·22.

4,5-Dimethoxy-α-(1,4-dimethoxy-2-naphthyl)-o-toluic acid (IV). A suspension of (III) (1·20 g) in a solution of sodium hydroxide (2·9 g in 35 ml of water) was stirred and refluxed until all the solid had gone into solution. Stirring and refluxing was continued for 17 h more while powdered zinc (4·0 g) was added in three portions at 1-h intervals during the first 3 h. The hot solution was filtered and the insoluble material was washed several times with hot water. The combined aqueous solutions were poured into excess hydrochloric acid (10 per cent) and the precipitate was filtered off, washed with water, and extracted exhaustively with sodium carbonate solution (10 per cent). Acidification of the combined extracts precipitated a light yellow powdery material (0·62 g, 52 per cent), m.p. 172–175°. Two recrystallizations from carbon tetrachloride raised the melting point to 177–179°.

Anal. Calcd. for $C_{22}H_{22}O_6$; C, 69·09; H, 5·81. Found: C, 68·77; H, 5·65.

2,3,6,11-Tetramethoxy-5(12H)-naphthacenone (V). A solution of (IV) (0·80 g) in glacial acetic acid (5 ml) was added to a solution of polyphosphoric acid in glacial acetic acid[17] (50 ml, 15 per cent). The solution was kept in a water bath at 50° for 10 min and then at room temperature for 20 min, after which it was poured into ice water (200 ml). The orange precipitate was filtered by suction and stirred for 30 min with sodium bicarbonate solution (50 ml, 5 per cent). After refiltering and washing with water it was crystallized from methanol to yield light orange needles (0·28 g, 33 per cent), m.p. 164–167°. Three more recrystallizations from methanol raised the melting point to 169–171°.

Anal. Calcd. for $C_{22}H_{20}O_5$: C, 72·50; H, 5·69. Found: C, 72·19; H, 5·54.

Attempted demethylation of (*V*). A solution of (V) (0·24 g) in glacial acetic acid (15 ml) and hydrobromic acid (6 ml, 48 per cent) was refluxed for 15 min and then cooled. When the mixture was

poured into water (100 ml), a dark brown resinous precipitate appeared. This could not be purified further by recrystallization or chromatography.

Microbiological Activity

With *Staphylococcus aureus* as the test micro-organism, 2,3,6,11-tetramethoxy-5(12H)-naphthacenone (D-1000-1, 5·0 μg per ml of medium) inhibited growth half maximally after 3 h incubation. The same degree of inhibition was effected by chlortetracycline hydrochloride (0·0045 μg per ml of medium). Thus, the product was less than 0·1 per cent as active as chlortetracycline.

Agar dilution streak plate tests were also performed using *Streptococcus faecalis* ATCC 8043, *Staphylococcus aureus* ATCC 6538P and *albus* No. 69, *Streptococcus sp.*, β-hemolytic No. 80, *Proteus vulgaris* ATCC 9484, and *Escherichia coli* ATCC 9637 as test organisms and chlortetracycline hydrochloride as the reference substance. Definite values could not be assigned for each organism because a conclusive study was restricted by the lack of the larger quantities of D-1000-1 needed to cope with its meagre activity. Limited tests indicate that D-1000-1 has a relatively low order of inhibitory property toward these micro-organisms.

Summary. 2,3,6,11-Tetramethoxy-5(12H)-naphthacenone was prepared as an analogue of the tetracycline antibiotics, specifically the anhydrotetracyclines. The method used for the formation of the naphthacene ring system involved reaction of a naphthalenic Grignard reagent with a substituted benzaldehyde followed by carboxylation and ring closure. This compound has a low order of microbiological activity.

Acknowledgements. The authors express their appreciation to Mr. A. C. Dornbush and his staff for the microbiological data, and they are grateful to Dr. Henry D. Piersma and others who helped to make arrangements for the test. Also, the authors are indebted to American Cyanamid Co., Lederle Laboratories Division, Pearl River, New York for having made available their facilities and personnel to make this microbiological study possible.

(*Received 12 January, 1961*)

References

[1] Waller, C. W. and Wolf, C. F. U.S. Patent 2,716,651, August 30, 1955
[2] Tatsuoka, S. *et al.* *J. pharm. Soc. Japan*, **75**, 1362 (1955); *Chem. Abstr.*, **50**, 10046 (1956)
[3] Stephens, C. R. 129th Meeting of the American Chemical Society, Dallas, 1956, Abstracts, p. 18M
[4] Stephens, C. R. *et al.* *J. Amer. chem. Soc.*, **80**, 5324 (1958)
[5] Beereboom, J. J., Ursprung, J. J., Rennhard, H. H. and Stephens, C. R. *J. Amer. chem. Soc.*, **82**, 1003 (1960)
[6] Boothe, J. H., Hlavka, J. J., Petisi, J. P. and Spencer, J. L. *J. Amer. chem. Soc.*, **82**, 1253 (1960)
[7] Smissman, E. E. and Gabbard, R. B. *J. Amer. chem. Soc.*, **79**, 3203 (1957)
[8] Mosfegh, A., Fallab, S. and Erlenmeyer, H. *Helv. chim. acta*, **40**, 1157 (1957)
[9] Pandit, A. L. and Kulkarni, A. B. *Curr. Sci.*, **27**, 254 (1958)
[10] Seshadri, S. and Kulkarni, A. B. *Curr. Sci.*, **28**, 65 (1959)
[11] Boothe, J. H. *et al.* *J. Amer. chem. Soc.*, **81**, 1006 (1959)
[12] Muxfeldt, H. *Chem. Ber.*, **92**, 3122 (1959)
[13] Yao-Tseng, H. *Tetrahedron*, **11**, 52 (1960)
[14] Fields, T. L., Kende, A. S. and Boothe, J. H. *J. Amer. chem. Soc.*, **82**, 1250 (1960)
[15] Ungnade, H. E. and Hein, H. *J. org. Chem.*, **14**, 913 (1949)
[16] Pschoor, R. *Liebigs Ann.*, **391**, 32 (1912)
[17] Brockmann, H. and Muxfeldt, H. *Chem. Ber.*, **89**, 1401 (1956)