Meso Heterocyclic Analogues of 9,10-Dihydroanthracene. XIII. On the Structure of the Products of Diacetylation of Phenoxathiin: A Correction (1)

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The diacetylation of phenoxathiin under the typical conditions for Friedel-Crafts reaction results in a mixture consisting of 2,7-diacetylphenoxathiin (**3**) and 2,8-diacetylphenoxathiin (**9**). The compound hitherto described in the literature as **9** proved to be in reality the mixture. For the first time, the compound **3** was isolated, purified and had its structure established. 3,4′-Diethyldiphenyloxide as well as 2,7- and 2,8-diethylphenoxathiins and their sulphones and sulphoxides have been synthesized.

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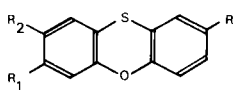
We have shown in our preceeding work (1) that the disucinoylation and diglutaroylation of phenoxathiin under the conditions of Friedel-Crafts reaction produce respectively a mixture of **1** and **2** with the major formation of product **1** having substitution on the 2 and 7 positions.



1 , R = R_1 = $-CO(CH_2)_nCO_2H$, R_2 = H

2 , R = R_2 = $-CO(CH_2)_nCO_2H$, R_1 = H

These results are in contradiction to the results of Tomita (2) as well as those of several others workers (3, 4,5) concerning the diacetylation of phenoxathiin.

A thorough inspection of this reaction, therefore, seemed necessary, particularly in view of the fact that several recent patents (6,7,8,9) claim pharmacological properties for diacetylphenoxathiin derivatives although convincing proof of the structures of these compounds have not yet been offered.

According to Tomita (2) the diacetylation of phenoxathiin results in a single product **9**. His reasoning was that both the diacids, obtained by the oxidation of the diacetylated product as well as the diethyl phenoxathiins resulting from its reduction, have melting points (> 300°) and boiling points in the same "range" as the authentic acidic products. The evidence seemed to be too meagre to ascribe an unambigous structure and a reopening of the whole problem was clearly warranted.

On reacting 2 moles of acetyl chloride with 1 mole of phenoxathiin in boiling methylene chloride in the presence of 2.2 moles of anhydrous aluminium chloride resulted, with overall yield of 85%, a product which consisted of several components. These were separated by column chromatography into 2-acetylphenoxathiin (10%) and a mixture of diacetyled product (85%). After several crystallizations from ethanol, benzene and dioxane, this mixture separated into compounds with m.p. = 187° and another with m.p. = 202-203°. High pressure liquid chromatography (10) has permitted us to give the proportion of each isomers as 80% and 20%, respectively. We have utilized a column of Lichrosorb Si 60 (10 μm) covered with bentone-34 and a mixture of hexane/ethyl/acetate (9:1) being used as eluent. The diacetylated product reported by Tomita (2) is, therefore, most probably the mixture of these two products. The proper elucidation of structures, however, has clearly shown that the major product which melts at 187° is actually the 2,7-diacetyl derivative **3** and not the isomeric 2,8-diacetyl derivative **10**, as has hitherto been claimed in the literature.

Although the uv and ir spectra of these two isomeric compounds were quite different, particularly the maxima of the uv absorption, they are not able to provide enough data necessary for assigning the structures. Chemical degradation was therefore necessary.

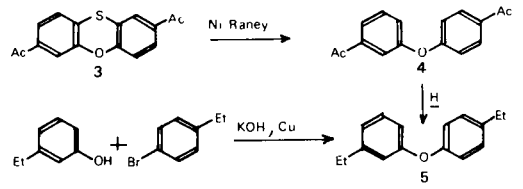
Raney Ni desulphurization of the product melting at

Table

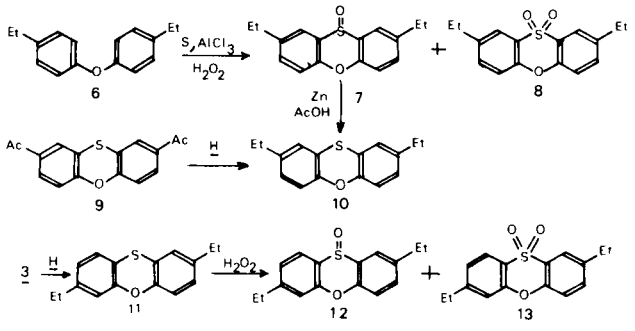
Analytical Data

Compounds	No.	Calcd. Percent C	Calcd. Percent H	Found Percent C	Found Percent H	Formula
2,7-Diacetylphenoxathiin	**3**	67.6	4.3	67.5	4.3	$C_{16}H_{12}O_3S$
2,8-Diacetylphenoxathiin	**9**	67.6	4.3	67.6	4.2	$C_{16}H_{12}O_3S$
3,4′-Diethyldiphenyloxide	**5**	84.9	8.0	85.0	8.0	$C_{16}H_{18}O$
4,4′-Diethyldiphenyloxide	**6**	84.9	8.0	84.8	8.1	$C_{16}H_{18}O$
2,8-Diethylphenoxathiin	**10**	75.0	6.3	74.9	6.2	$C_{16}H_{16}OS$
2,7-Diethylphenoxathiin	**11**	75.0	6.3	74.8	6.2	$C_{16}H_{16}OS$

187° following standard techniques (11,12,13) resulted in a diacetyldiphenyloxide characterized by microanalysis, ir and nmr. This product is different from the 4,4′-diacetyldiphenyloxide (14) which would have resulted if the two acetyl groups were in the 2 and 8 positions on phenoxathiin nucleus. That the acetyl groups were, on the other hand, on the 3 and 4 positions could be shown by its Wolff-Kishner reduction (17) which resulted in a compound having the identical spectral characteristics (uv, ir, nmr) as an authentic sample of 3,4-diethyldiphenyloxide, prepared (16) by the unambigous method of condensing 3-hydroxyethylbenzene with 4-bromoethylbenzene. These results are indicated in Scheme 1, and they, therefore, clearly indicate that the compound melting at 187° is 2,7-diacetylphenoxathiin.



Scheme 1



Scheme 2

The structure of the second compound had to be established by another pathway (Scheme 2).

Heating 4,4′-diethyldiphenyloxide (**6**), prepared from an authentic sample of diacetyl derivative of known structure, with sulphur in the presence of anhydrous aluminium chloride, resulted in the ring closure to the diethylphenoxathiin. Purification was rather difficult as its separation from the starting material was not easy. However, oxidation of the crude reaction product with hydrogen peroxide (15) led to a mixture of the sulphoxide **7** and the sulphone **8** which were quite easily separated by column chromatography. Oxidation of the diethyl derivative **11**, which in turn was obtained from **3** by reduction, led to slightly different products **12** and **13**. On subjecting the sulphoxide **7** to zinc/acetic acid reduction (19), pure 2,8-diethylphenoxathiin (**10**) was obtained, identical with the component obtained by reduction of the diacetylphenoxathiin (**9**). On subjecting the crude reduction product to vpc on a column of glass beads covered with a (1:1) mixture of OV-17 and Bentone-34 two distinct peaks with different Rf values were obtained which served to identify the two diethyl derivatives.

These experiments lead us to the conclusion that phenoxathiin undergoes diacetylation quite easily and the positions 2 and 7 are preferentially attacked. These observations have both practical and theoretical importance. Obviously, there is a competition between the two heteroatoms, oxygen and sulphur (18), as regards their directing influences. The *para*-directing influence of the former being slightly greater. The first substitution takes place on the 2-position. However, once the first acyl function enters the ring, it is the influence of sulphur which predominates and the second acyl group goes to position 7. In fact, subjecting the monoacetyl phenoxathiin with the acetyl group in the 2-position, to further acetylation resulted in the 2,7-diacetyl derivative, this clearly verifying the above proposition.

EXPERIMENTAL

Melting points were taken on a Köfler apparatus and are uncorrected. The nmr spectra were obtained on a Perkin Elmer R12 or on a Varian EM360. The chemical shifts are reported in parts per million (δ) downfield from an internal TMS reference. Ir were obtained in potassium bromide pellets on a Hitachi EPI-G2 or on Perkin Elmer 457. Uv spectra were recorded in 95% ethanol solutions on a Schimatzu 200. For glc we have used a Girdel 75 chromatograph and for hplc, a home-made apparatus. The authors express their thanks to Mr. Gilbert Jacques.

2,7- and 2,8-Diacetylphenoxathiin (**3**,**9**).

Sixteen g. (0.12 mole) of anhydrous aluminum chloride was added in small portions to a mixture of 10 g. (0.05 mole) of phenoxathiin and 8.7 g. (0.11 mole) of acetyl chloride in a reactor equipped with a reflux condenser and a mechanical stirrer, keeping the temperature at 0°. After allowing the temperature to rise to room temperature, the reaction was kept at that temperature overnight, followed by refluxing the reaction mixture for four hours. After hydrolysing the reaction mixture with ice and hydrochloric acid, the product was extracted with methylene chloride and evaporation of the organic layer, after drying, furnished 13.4 g. (94%) of the crude product. Two recrystallizations from dioxan followed by successive recrystallization from benzene and ethanol gave pure 2,7-diacetylphenoxathiin (**3**) in the form of fine, greenish-yellow needles m.p. 187°; uv λ max (95% ethanol): 252 and 287 nm; ir: ν max 1570 cm^{-1} (C = O), 890, 880, 850, 820, 805 cm^{-1} (CH aromatic); nmr (deuteriochloroform): δ 2.54 (s, 6H, CH_3CO), 7.25-7.70 (m, 6H, phenyl).

From the mother liquor of the ethanol recrystallization, the 2,8-diacetyl derivative (**9**) (m.p. 202°) was isolated in the form of shining, pale yellow plates; uv λ max (95% ethanol): 268 nm; ir: ν max 1670 cm^{-1} (C = O), 900, 850, 720 cm^{-1} (CH aromatic); nmr (deuteriochloroform) δ 2.54 (s, 6H, CH_3CO), 7.25-7.70 (m, 6H, phenyl).

Chromatography over a SE 30 (0.80 m) column in a Girdel 75 chromatograph gave 3 peaks corresponding respectively to the starting material (3%), 2-acetylphenoxathiin (7%) and the mixture of the two diacetylated products (90%).

On subjecting the mixture of the two diacetyl derivatives to hplc over a column of Lichrosorb Si 60 (10 μm) covered with bentone-34 and elution with a 9:1 mixture of hexane and ethyl/acetate the relative proportion of the components of the mixture was assesed to be 80% of the 2,7-diacetyl derivative and 20% of the 2,8-diacetyl product.

Acetylation of 2-Acetylphenoxathiin.

Fourteen g. (0.1 mole) of anhydrous aluminum chloride was added in small portions to 10 g. (0.04 mole) of 2-acetylphenoxathiin and 4 g. (0.05 mole) of acetyl chloride in 200 ml. of methylene chloride as in the preceding experiment. After stirring overnight and the usual work up, the crude product was twice recrystallized from ethanol to give 4 g. of 2,7-diacetylphenoxathiin, m.p. 187°, whose purity was verified with hplc.

Anal. Calcd. for $C_{16}H_{12}O_3S$: C, 67.80; H, 4.25. Found: C, 67.73; H, 4.00.

3,4'-Diacetyldiphenyloxide (**4**).

A solution of 10 g. of 2,7-diacetylphenoxathiin in 200 ml. of dioxan containing a catalytic amount of Raney Ni was stirred under reflux for 12 hours. At the end of this period the hot mixture was filtered and on cooling, unreacted starting material first crystallized out. On concentrating the mother liquor and leaving it for a few days 3,4'-diphenyloxide crystallized out which was purified by recrystallization from aqueous ethanol and cyclohexane, m.p. = 78°.

The purity was checked by vpc on a SE 30 (1.30 m) column; ir: ν max 1670 cm^{-1} (C = O), 805, 820, 730 cm^{-1} (aromatic CH); nmr (carbon tetrachloride): δ 2.57 (s, 3H, CH_3CO); 2.52 (s, 3H, CH_3CO); 6.22-7.24 (m, 8H, phenyl).

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.54; H, 5.30.

3,4'-Diethyldiphenyloxide (**5**).

Method a.

Twenty-one g. (0.17 mole) of 3-ethylphenol and 8 g. (0.14 mole) of potassium hydroxide was heated for 15 minutes at 150° on an oil bath under magnetic stirring. After allowing the temperature to drop to 90°, 18.5 g. (0.1 mole) of 4-bromoethylbenzene and 0.5 g. of Cu powder was added in one portion. After a further 15 to 20 minutes reflux the reaction mixture was cooled, treated with sodium hydroxide and extracted with chloroform. After drying on anhydrous magnesium sulphate, the organic layer was evaporated and the residue was chromatographed over a column of alumina using cyclohexane as eluent to give 14 g. (65%) of pure diethyl derivative. The purity was checked by vpc on a SE 30 (1.30 m) column; n_D^{21} = 1.5515; nmr (carbon tetrachloride): δ 1.23 (t, 6H, CH_3); 2.60 (q, 4H, CH_2), 6.5-7.32 (m, 8H, aromatic).

Method b.

One g. of **4** was dissolved in 100 ml. of diethylene glycol and after adding 1.2 g. of hydrazine hydrate the solution was heated under stirring. Potassium hydroxide (1.8 g.) was added and the stirring and heating was continued until the evolution of gases stopped. After cooling and hydrolysis on hydrochloric acid-ice, the solution was extracted with ether and the usual work up gave a product having identical Rf value, refractive index and spectral characteristics as that obtained by method a.

4,4'-Diethyldiphenyloxide (**6**).

On treating 13 g. of 4,4'-diacetyldiphenyloxide, 15 ml. of hydrazine hydrate and 22.4 g. of potassium hydroxide in 300 ml. of diethylene glycol in the same way as method b as described above an oil was obtained. On vacuum distillation 9.5 g. (93%) of 4,4'-diethyldiphenyloxide was obtained; b.p. = 176° (12 mm Hg. Vpc showed only one peak (SE 30 column, 1.30 m); nmr (carbon tetrachloride): δ 1.22 (t, 6H, CH_3); 2.60 (q, 4H, CH_2) 6.93 (m, 8H, aromatic).

Sulphoxide (**7**) and Sulphone (**8**) of 2,8-Diethylphenoxathiin.

In a 250 ml. three-necked flask, equipped with a mechanical stirrer, a reflux condenser and an arrangement for the evacuation of hydrogen sulphide, was placed 50 g. (0.22 mole) of 4,4-diethyldiphenyloxide, 5.5 g. (0.17 g.-atom) of sulfur and 7.36 g. (0.06 mole) of anhydrous aluminum chloride. The reaction mixture was heated under stirring at 100° for 7 hours after which it was hydrolysed in the usual way, extracted with chloroform and the chloroform layer washed with water until *p*H = 7, and dried over calcium chloride. Evaporation of the solvent gave a crude mixture of three products consisting of 3,6-diethyldibenzofuran, 2,8-diethylphenoxathiin, and the starting material. The mixture was dissolved in 350 ml. of absolute ethanol, 30 ml. of hydrogen peroxide added to it and the mixture refluxed for 6 hours, an additional 25 ml. of hydrogen peroxide being added at the end of the first 3 hours. After this period half the ethanol and an equal volume of water was added. The oil which separated was extracted with ether, the ethereal layer was washed with water to *p*H = 7, dried over anhydrous sodium sulphate and evaporated. The residue was chromatographed over alumina and elution with a (8:2) mixture of carbon tetrachloride-chloroform gave the sulphoxide **7**, m.p. = 97° (aqueous ethanol) which gave a blue-violet halochromy with sulphuric acid. Purity was checked with vpc; nmr (carbon tetrachloride): δ 1.26 (t, 6H, CH_3); 2.65 (q, 4H, CH_2); 6.85-7,80 (m, 6H, aromatic); ir: ν max 500 cm^{-1} (>S = O); 825, 840, 875, 900 cm^{-1} (aromatic); uv λ max (95% ethanol): 114,5 nm.

Anal. Calcd. for $C_{16}H_{16}O_2S$: C, 70.56; H, 11.74. Found: C, 70.43; H, 12.0.

The second component was 9 g. of sulphone **8**, m.p. = 100° (aqueous ethanol). Purity was checked with vpc; nmr (carbon tetrachloride): δ 1.28 (t, 6H, CH_3); 2.70 (q, 4H, CH_2); ir: ν max 540 cm^{-1} (>S$\overset{O}{\underset{O}{=}}$); 810, 890 (aromatic CH).

Anal. Calcd. for $C_{16}H_{16}O_3S$: C, 66.65; O, 16.65. Found: C, 66.30; O, 16.90.

2,8-Diethylphenoxathiin (**10**).

A catalytic amount of zinc dust was added to a solution of 4 g. of 2,8-diethylphenoxathiin sulphoxide in 100 ml. of acetic acid and the reaction mixture was boiled under stirring for three hours. The solvent was evaporated and the residue was treated with sodium bicarbonate and extracted with ether. The ethereal layer was washed with water to *p*H = 7 and dried over anhydrous sodium sulphate. The residue left after evaporation of the solvent was chromatographed over alumina. Two g. of pure 2,8-diethylphenoxathiin was obtained by elution with cyclohexane, the purity of the product being checked by vpc and hplc; nmr (carbon tetrachloride): δ 1.20 (t, 6H, CH_3); 2.53 (q, 4H, CH_2); 6.85 (s, 6H, aromatic); ir: ν max 790, 820, 870 cm^{-1} (aromatic CH); n_D^{25} = 1,607.

2,7-Diethylphenoxathiin (**11**).

2,7-Diethylphenoxathiin was obtained in the pure state following the same procedure as method b, from 2,7-diacetylphenoxathiin with a yield of 80%. The purity of the product was checked by vpc and hplc; nmr (carbon tetrachloride): δ 1.18 (t, 6H, CH_3); 2.52 (q, 4H, CH_2); 6.77 and 6.80 (d, 6H, aromatic).

Sulphoxide **12** and Sulphone **13** of 2,7-Diethylphenoxathiin.

A mixture of 4 g. of 2,7-diethylphenoxathiin, 12 ml. of hydro-

gen peroxide and 50 ml. of absolute ethanol was refluxed under magnetic stirring for 12 hours, an additional 6 ml. of hydrogen peroxide being added at the end of the first 3 hours. Half of the solvent was evaporated and an equal volume of water was added. The oil which separated was extracted with ether and the ethereal layer was washed with water to *p*H 7, dried and evaporated. The crude residue which weighed 3.55 g. (83%) was chromatographed over alumina and eluted with carbon tetrachloride to give 0.6 g. of sulphone **13**, m.p. 74° (50% aqueous ethanol); nmr (carbon tetrachloride): δ 1.28 (t, 6H, CH_3); 2.75 (q, 4H, CH_2); 6.90-8.00 (m, 6H, aromatic); ir: ν max 525, 550 cm^{-1} (>S$\overset{O}{\underset{O}{}}$); 815, 835, 860, 922 cm^{-1} (aromatic CH).

Anal. Calcd. for $C_{16}H_{16}O_3S$: C, 66.65; H, 5.59; O. 16.65. Found: C, 66.37; H, 5.62; O, 16.46.

The second component was 2.8 g. of sulphoxide **12** m.p. 63° (50% aqueous ethanol); nmr (carbon tetrachloride): δ 1.28 (t, 6H, CH_3); 2.73 (q, 4H, CH_2); 6.92-7.9 (m, 6H, aromatic); ir: ν 470, 490 cm^{-1} (>S = O); 750, 820, 870, 930 cm^{-1} (aromatic).

Anal. Calcd. for $C_{16}H_{16}O_2S$: C, 70.56; H, 5.92; O, 11.74. Found: C, 70.62; H, 6.01; O, 11.97.

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