INVESTIGATION OF SOME NITROGEN COMPOUNDS OF 2,2'-DITHIENYL

V.* ACETYLATION AND FORMYLATION OF THE DITHIENYL ANALOG OF CINCHOPHEN

P. L. Trakhtenberg, A. E. Lipkin,
and Z. I. Nuzhdina

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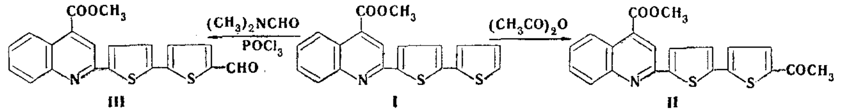
The acetylation and formylation of the methyl ester of the dithienyl analog of cinchophen gave 5'-acetyl- and 5'-formyl-5-(4-methoxycarbonyl-2-quinolyl)-2,2'-dithienyls.

In developing our previously described research on the electrophilic substitution of 2,2'-dithienyl derivatives [1], we carried out the acetylation of the methyl ester of the dithienyl analog (I) of cinchophen with acetic anhydride in polyphosphoric acid [2] and the formylation of I via the Vilsmeier reaction [3].



The position of the acetyl group in II was established by the condensation of II with isatin via the Pfitzinger reaction and by the synthesis from it of the previously described [4] 5,5'-bis(4-methoxycarbonyl-2-quinolyl)-2,2'-dithienyl (IV). The position of the formyl group in III was established from the identical character (melting points and IR spectra) of acids V, obtained by oxidation of II and III, and their esters (VI). These data make it possible to assign the 5'-acetyl and 5'-formyl-5-(4-methoxycarbonyl-2-quinolyl)-2,2'-dithienyl structures to acylation products II and III, respectively.

Thus, when the 5 position is blocked, electrophilic substitution occurs in the 5' position of 2,2'-dithienyl, which is in agreement with the observations made in [5-7].

EXPERIMENTAL

5-(4-Methoxycarbonyl-2-quinolyl)-2,2'-dithienyl (I). A total of 3.4 ml of concentrated H_2SO_4 was added with cooling and shaking to a mixture of 0.85 g (2.4 mmole) of 5-(4-carboxy-2-quinolyl)-2,2'-dithienyl and 26 ml of methanol, and the mixture was refluxed for 5-6 h. The excess methanol was removed by distillation, and the solution was filtered and poured over crushed ice. The aqueous mixture was neutralized with 10% Na_2CO_3 solution to give 97% of a product with mp 96° (from alcohol–acetone). IR spectrum: 1736 cm^{-1} (C=O). Found: S 18.1%. $C_{19}H_{13}NO_2S_2$. Calculated: S 18.2%.

5-(4-Methoxycarbonyl-2-quinolyl)-5'-acetyl-2,2'-dithienyl (II). A 9.5-g sample of P_2O_5 and 5.5 ml of 90% H_3PO_4 were mixed while cooling with ice water, and the mixture was gradually heated to 80-85° and stirred at this temperature for another 1-1.5 h. The polyphosphoric acid thus formed was cooled to 20°, and 1 ml of acetic anhydride was added. A 2-g (0.0057 mole) sample of powdered I was then added grad-

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*See [1] for communication IV.

V. V. Kuibyshev Kuibyshev Polytechnic Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 773-774, June, 1972. Original article submitted May 24, 1971.

ually to the mixture, during which the temperature rose to 34°. When the mixture had thickened considerably, 2-3 ml of glacial acetic acid was added, and the mixture was heated to 50° and stirred at this temperature for another 3.5 h. The hot mixture was poured over crushed ice, and the aqueous mixture was neutralized with 10% Na_2CO_3 solution until it was weakly acidic and allowed to stand overnight. The brown precipitate was removed by filtration and air-dried to give 1.1 g (50%) of a product with mp 210° (from alcohol–acetone). IR spectrum: 1728 cm^{-1} ($COOCH_3$), 1650 cm^{-1} ($COCH_3$). UV spectrum: λ_{max} 405 nm, log ε 4.58 (in dioxane). Found: S 16.4%. $C_{21}H_{15}NO_3S_2$. Calculated: S 16.3%. The semicarbazone had mp 253-254° (from alcohol–acetone). Found: S 14.3%. $C_{22}H_{18}N_4O_3S_2$. Calculated: S 14.2%. The thiosemicarbazone had mp 237-238° (from alcohol–acetone). Found: S 20.6%. $C_{22}H_{18}N_4O_2S_3$. Calculated: S 20.6%.

b,b'-Bis(4-methoxycarbonyl-2-quinolyl)-2,2'-dithienyl (IV). A mixture of 0.5 g (1.2 mmole) of II, 0.6 g (4 mmole) of isatin, 2.3 ml of 28% aqueous KOH, and 60 ml of ethanol was refluxed on a boiling-water bath and filtered. The cooled filtrate was acidified with dilute acetic acid, and the precipitated amorphous, claret-colored 5-(4-methoxycarbonyl-2-quinolyl)-5'-(4-carboxy-2-quinolyl)-2,2'-dithienyl was washed with hot water to remove the excess isatin to give 0.5 g (73%) of a product with mp 297-305° (from dioxane). The methyl ester was obtained by a method similar to that used to obtain I (except that the reaction time was 12 h) to give 10% of a product with mp 271-273° [from dioxane–acetone (1 : 1)] [4]. IR spectrum: 1728 cm^{-1} (C = O). UV spectrum: λ_{max} 429 nm, log ε 2.14 (in dioxane).

5-(4-Methoxycarbonyl-2-quinolyl)-5'-formyl-2,2'-dithienyl (III). A 25-ml sample of freshly distilled dimethylformamide was added dropwise with stirring and ice-water cooling to 10 ml (0.11 mole) of $POCl_3$. A 5-g (14 mmole) sample of finely ground I was added in small portions in the course of 10 min, during which the mixture took on a red color, darkened, and thickened. The mixture was then heated to 70-80° and stirred for another 3 h. When there was considerable thickening, 3-5 ml of dimethylformamide was added, and the mixture was then poured into cold water (a dark-brown precipitate formed), and the aqueous mixture was cooled and neutralized with 10% Na_2CO_3 solution. The yellow precipitate was removed by filtration and air-dried to give 5.2 g (92%) of a product with mp 187-188° (from alcohol–acetone). IR spectrum: 1669 cm^{-1} (CHO). UV spectrum: λ_{max} 401 nm, log ε 4.72 (in dioxane). Found: S 17.0%. $C_{20}H_{13}NO_3S_2$. Calculated: S 16.9%. The semicarbazone had mp 250-251° (from alcohol–acetone). Found: S 14.3%. $C_{21}H_{16}N_4O_3S_2$. Calculated: S 14.7%. The thiosemicarbazone had mp 224-225° (from alcohol–acetone). Found: S 20.8%. $C_{22}H_{18}N_4O_2S_3$. Calculated: S 20.6%.

5-(4-Methoxycarbonyl-2-quinolyl)-5'-carboxy-2,2'-dithienyl (V). A. A total of 20 ml of 15% aqueous KOH and 10 drops of bromine were mixed with ice-water cooling, and 0.5 g (1.3 mmole) of thoroughly ground powdered II was added. The reaction mixture was stirred and gradually heated to 70-80° and held at this temperature for 4-5 h until a homogeneous bright-yellow suspension formed. The mixture was diluted with water until all of the solid had dissolved, and the resulting solution was acidified with 10% hydrochloric acid to precipitate red flakes with mp 250° (dec.). The dimethyl ester (VI) was obtained in 30% yield by the method used to obtain III and had mp 143-145° (from alcohol–acetone). IR spectrum: 1706 cm^{-1} (C = O). Found: S 15.9%. $C_{21}H_{15}NO_4S_2$. Calculated: S 15.7%.

B. Compound III was similarly oxidized. Dimethyl ester VI was obtained in 30% yield by the method used to obtain I and had mp 145-147° (from alcohol–acetone).

The IR spectra of KBr pellets were measured by V. I. Pavskii with an IKS-14 spectrophotometer. The UV spectra of $2 \cdot 10^{-5}$-$2 \cdot 10^{-4}$ M solutions were measured with an SF-4 spectrophotometer.

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