

Studies on Analgesics

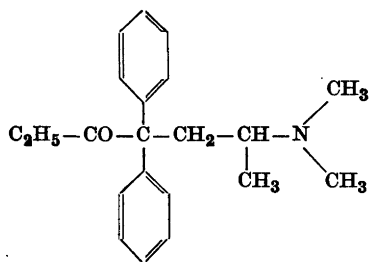
I. Synthesis of Ethyl 4-(N-Morpholinyl)-1,1-di-(α -thienyl)-butyrate and its Pharmacological Properties

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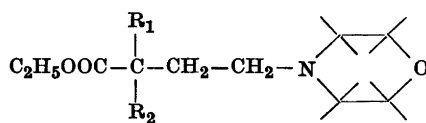
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Since the systematic work of Bockmühl and Erhardt¹ on amidone (I) and its derivatives, a number of other papers have been published on the synthesis of similar compounds. Speeter, Byrd, Cheney, and Binkley² prepared compound II, which has about the same analgetic effect as amidone and is ten times less toxic. Compound III, structurally very similar to II, was synthesized by Brown, Cook, and Heilbron³, and proved to be four times as effective as pethidine.

In this investigation compound IV has been prepared.



I



- II $R_1=R_2$ =phenyl-
 III R_1 =phenyl-, R_2 =thienyl-
 IV $R_1=R_2$ =thienyl-

Several attempts were made to obtain the starting material, di-(α -thienyl)-methane. This compound has already been described in the literature⁴, but the yield never exceeded 10%. Blicke and Burkhalter's method⁵ (in which dithienylmethane was obtained as a by-product on preparing α -(chloromethyl)-

thiophene) was first tried, but though several attempts were made, no dithienylmethane could be isolated. The second method of synthesis was *via* the ketone, thienone. By letting α -thienyllithium react with carbon dioxide we obtained a yield of 67 % of the ketone. However, the compound desintegrated and polymerised on reduction.

The final synthesis of dithienylmethane was carried out in accordance with Haubein's observation⁶ that no bibenzyl is formed when ArLi reacts with PhCH₂Cl. Thus, in the reaction between chloromethylthiophene and thienyllithium a 66 % yield of dithienylmethane was obtained. Ethyl 4-(N-morpholinyl)-1,1-di-(α -thienyl)butyrate was then made by the method used by Brown, Cook, and Heilbron³ for preparing compound II. Hence the monopotassium derivative of dithienylmethane, obtained by the action of potassium in liquid ammonia, was carbethoxylated with diethyl carbonate. The ester thus prepared was condensed with N-(2-chloroethyl)morpholine in the presence of sodamide in dry toluene, yielding the ethyl 4-(N-morpholinyl)-1,1-di-(α -thienyl)butyrate (IV).

The compound has an analgetic effect somewhat less than that of pethidine. The toxicity is remarkable low (LD₅₀ > 500 mg/kg white mouse subcut.), morphine and pethidine being more toxic. The local anaesthetic effect was compared with that of xylocaine. On rabbit cornea the compound has, under the same conditions (pH 3.7), a duration somewhat less than that of xylocaine and a much longer latency time. Further, the compound was tested for its spasmolytic and histaminolytic power. No appreciable effects were found.

EXPERIMENTAL *

Di-(α -thienyl)ketone (thienone). In a three-necked flask, equipped with a dropping funnel, a stirrer, a reflux condenser, and a gas inlet tube, was placed a mixture of 0.57 mole (48 g) of thiophene and 200 ml of absolute ether. A stream of dry nitrogen was used to expel the air. To the solution of thiophene was added 300 ml of a 1.35 N ethereal solution of butyllithium⁷. A vivid reaction took place immediately and the ether refluxed spontaneously. When all butyllithium had been added the solution was kept under gentle reflux for fifteen minutes, by means of a water bath. Then the stream of nitrogen gas was stopped, and carbon dioxide was allowed to bubble into the solution until test for organolithium compound⁸ was negative (10 hours). A reddish solution and a white fine grained precipitate that had settled at the bottom were obtained. The content of the vessel was decomposed with water, and the ethereal layer separated and washed completely with 2 N sodium hydroxide solution (to remove thiophenecarboxylic acid). The ethereal layer was dried (MgSO₄) and the solvent evaporated. Greyish green needles

*) All our melting points are corrected.

separated; yield 25 g (67 %). On recrystallization from isopropyl ether a constant melting point of 90–90.5° was obtained.

Several attempts to reduce this compound with sodium and alcohol or by Wulff-Kishner's method failed.

α -(Chloromethyl)thiophene. The compound was made by the method given by Blicke and Burkhalter⁵. As a by-product in the synthesis they reported dithienylmethane. We therefore carried out the synthesis at first chiefly to obtain this hydrocarbon (*cf.* above). However, we could obtain no isolable amounts of dithienylmethane. Fortunately we were able to use the chief product, chloromethylthiophene, for the synthesis of dithienylmethane (*cf.* below). However, chloromethylthiophene distilled at 72.5–73.5°/18 mm contrary to Blicke *et al.*'s⁴ statement that the boiling point is 81–82°/18 mm. We found the refractive index, n_D^{20} , to be 1.5638.

We also obtained a second fraction with the same boiling point as that reported by Blicke and Burkhalter⁵. They stated this fraction to be dithienylmethane with the correct m.p. 45–47°. After repeated recrystallizations from petroleum ether, we obtained the compound as small needles with m.p. 35–35.5°, which turned dark blue after a few days. On boiling with methanol the compound gave off hydrogen chloride. Further, our product was without smell, whereas dithienylmethane has a very characteristic odour. It is therefore evident that the second fraction could not be dithienylmethane.

Di-(α -thienyl)methane. As we could not find any useful method in the literature for preparing dithienylmethane we developed a synthesis using α -chloromethylthiophene. The apparatus used was the same as that previously described for α -thienylketone. To 150 ml of an ethereal solution of 0.37 mole (31 g) of thiophene was added 0.26 mole (400 ml of a 0.64 *N* solution of butyllithium) at such a rate as to cause gentle reflux. After 2 hours of heating on a water bath in order to complete the reaction the solution was allowed to cool. 0.32 mole (42 g) of chloromethylthiophene was then added slowly. The ethereal solution was boiled under reflux until test for organolithium compound⁸ was negative (40 hours). The content of the vessel was decomposed with water and the ethereal layer separated, washed with water and dried ($MgSO_4$). After filtering, the ether was driven off and the residue distilled. The compound was obtained as a faintly yellow oil which solidified rapidly; b.p. 128–130°/11 mm.; yield 31 g (66 %). After recrystallization from petroleum ether the dithienylmethane appeared as colourless needles; m.p. 44–45°.

Ethyl di- α -thienylacetate, $C_{12}H_{12}O_2S_2$ (252.3). Ammonia gas was introduced through a potassium hydroxide drying tube into a three-necked flask of 500 ml, equipped with a dropping funnel, a Hershberg stirrer and a condenser for cooling with freezing mixture (trichloroethylene and solid carbon dioxide). The condenser was kept at –50° and the flask at –35°. When the flask contained 300 ml of liquid ammonia the cooling bath was taken away and 0.18 mole (7.2 g) of potassium cut into pieces was added for a period of half an hour. After one hour the blue colour had disappeared. The condenser with freezing mixture was replaced by an ordinary water cooled reflux condenser and 0.17 mole (30 g) of dithienylmethane in 375 ml of ether was added drop by drop for one and a half hours. On the addition the solution turned brown. When half the volume of the dithienylmethane solution had been added the reaction mixture was heated to remove ammonia. After the solution had reached room temperature 0.084 mole (9.9 g) of diethyl carbonate was added. The solution was boiled for 12 hours under reflux. It was then decomposed with 300 ml of diluted acetic acid (5 %). The ethereal layer was separated and washed with water. The solution was dried ($MgSO_4$) and the ether driven off, leaving a reddish brown

viscous oil (35 g). On fractionating *in vacuo* a fore-run of 15 g of dithienylmethane was collected. The fraction of ethyl dithienylacetate had a boiling point of 124–125°/0.6 mm.; $n_D^{20} = 1.5728$; m.p. $\sim 7^\circ$; yield 12 g (28 %).

Calc.	C 57.1	H 4.80	S 25.4
Found	» 57.1	» 4.94	» 25.2

Ethyl 4-(N-morpholinyl)-1,1-di-(α -thienyl)butyrate, $C_{18}H_{23}NO_3S_2$ (365.5). To a 100 ml flask, equipped with a stirrer and a reflux condenser with a potassium hydroxide drying tube, was added 0.0284 mole (7.15 g) of the above mentioned ester, 0.0311 mole (4.65 g) of N-(2-chloroethyl)morpholine and 0.0310 mole (1.21 g) of sodamide suspended in 35 ml of dry toluene. On the addition of sodamide the solution turned brown, and on heating the colour deepened and ammonia was given off. The temperature of the mixture was kept at 120–130° for two hours, after which time the solution had turned light yellow. The toluene solution was shaken sufficiently with 2 N hydrochloric acid and from the combined extracts the base was liberated by addition of ammonia (1 : 1) and taken up in ether. After washing with water and drying (Na_2SO_4), the ether was driven off leaving a reddish brown oil (8.8 g), which was fractionated by distillation. The compound was obtained as a colourless oil; b.p. 164–164°/0.01 mm.; $n_D^{20} = 1.5676$; yield 5.85 g (57 %).

Calc.	C 59.1	H 6.34
Found	» 59.0	» 6.31

Nitrate, $C_{18}H_{24}N_2O_6S_2$ (428.5). Rhombic laths from propanol; m.p. 145–146°. The salt is slightly soluble in water.

Calc.	C 50.4	H 5.64
Found	» 50.3	» 5.60

SUMMARY

Ethyl 4-(N-morpholinyl)-1,1-di-(α -thienyl)butyrate was prepared and proved itself to have a distinctly analgetic effect and a remarkably low toxicity.

Acknowledgments are made to A.-B. Astra for financial support. We wish to express our sincere gratitude to Dr. S. Wiedling of the Biological Department of Astra and to Dr. L. Olsson of the Royal Veterinary College.

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Received July 25, 1951.