The Reaction of Polyanhydrides with Thiophene

JOHN H. BILLMAN and FRANK H. TRAVIS, Indiana University

It was first shown by Steinkopf (1) and later confirmed by Tainter (2) and Barger (3) that it is possible to substitute the thiophene ring for a phenyl group, in a pharmacologically active compound, and obtain a compound of approximately equal activity. In no instance, however, did these workers find a thiophene-containing compound with an activity greater than the corresponding benzene isologue. Accordingly, it was decided to prepare some other thiophene-containing compounds to throw further light on this interesting observation.

Since acetophenone possesses a marked hypnotic activity, it was felt that the preparation of its thiophene isologue, acetothienone, would be an excellent starting point for this investigation. In addition propiothienone and butyrothienone were also synthesized (4) in order to see what effect an increase in the length of the carbon chain would have on hypnotic activity.

In contrast to the earlier observation made by Steinkopf, that thiophene isologues are analogous in physiological activity to the benzene derivatives, these three ketones proved to be quite toxic and were not hypnotics.

Because of this anomalous result, an attempt was made to synthesize some diketones of the type $C_4H_3SCO(CH_2)_x\ COC_4H_3S$ to see if they might possess anticonvulsant activity. As a basis for the preparation of these diketones reference was made to the work of Hill (5) who reports that polyadipic and polysebacic anhydrides react with benzene, in the presence of aluminum chloride, to give keto acids and diketones of the desired general structure. The only other reference found pertaining to the utilization of a polyanhydride in the Friedel-Crafts' reaction is in an article by Plant and Tomlinson (6) in which they report the formation of δ-anisoylvaleric acid and α, δ-dianisoylbutane from polyadipic anhydride and anisole. When phenetole was used they obtained δ-phenetoylvaleric acid and α, δ-diphenetoylbutane.

We have found that thiophene would react similarly with polyanhydrides but that it was essential to use stannic chloride instead of aluminum chloride to prevent excessive polymerization of the thiophene. The reaction may be shown in equation form by using sebacic anhydride as a typical example:

$$C_4H_4S + (CO(CH_2)_8CO_2)_x\ (+SCl_4) = C_4H_3SCO(CH_2)_8COC_4H_3S + C_4H_3SCO(CH_2)_8COOH$$

The polyanhydrides used were adipic, suberic, azelaic and sebacic. These were prepared by refluxing the corresponding dibasic acid with acetic anhydride and then removing by distillation under reduced pres-

sure the acetic acid, formed during the reaction, along with the excess acetic anhydride.

In addition to the above polyanhydrides, one cyclic anhydride, succinic anhydride, was allowed to react with thiophene (7). In the reactions involving succinic anhydride and polyadipic anhydride, only the keto acid could be isolated whereas with the other polyanhydrides it was possible to isolate the diketone as well as the keto acid.

The diketones and keto acids which have been tested show no anticonvulsant action except in the case of β-(α-thenoyl) propionic acid which was found to be approximately fifteen per cent as active as diphenylhydantoin.

The authors wish to thank Eli Lilly and Company and Dr. E. E. Swanson, of the same company, for running the pharmacological tests on these compounds.

Experimental

Preparation of Polyanhydrides.—The polyanhydrides were prepared by a procedure similar to that used for the synthesis of azelaic polyanhydride.

Azelaic Polyanhydride.—In a 250 ml. flask fitted with a reflux condenser were placed 37.6 g. of azelaic acid and 90 ml. of acetic anhydride. The oil-bath surrounding the reaction flask was heated to 170° and kept at that temperature for eight hours and then cooled. The upright condenser was then replaced by a condenser for downward distillation and the system evacuated by a water pump. The temperature of the bath was gradually raised to 120° C. and kept at that temperature until no more acetic anhydride came over. The azelaic polyanhydride remaining in the flask was cooled and then dissolved in 100 ml. of dry benzene.

The Reaction of Polyanhydrides with Thiophene.—The diketones and keto acids in Table I were prepared from thiophene and the proper polyanhydride in the presence of anhydrous stannic chloride. The procedure which follows is similar to that used for the synthesis of the other diketones and keto acids.

1,7 Di(α-thenoyl)heptane and 8(α-thenoyl)octanoic acid.—In a 500 ml. three-neck flask fitted with a mechanical stirrer, condenser, and a thistle tube with a stopper holding a burette, were placed 16.8 g. of thiophene and the benzene solution containing the azelaic polyanhydride. The mixture was cooled to 0° and 46.8 ml. of anhydrous stannic chloride dropped in over a period of one hour. The mixture was allowed to warm up to room temperature and stirred for an additional hour. The reaction mixture was cooled with ice and treated with 300 ml. of 10% hydrochloric acid. The benzene layer was separated from the acid solution and then extracted several times with a 5% sodium hydroxide solution. After washing with water the benzene solution was evaporated in vacuo to remove all of the benzene. The oily residue, on cooling, solidified to give light yellow crystals. Recrystallization from alcohol gave 8.7 g. (27% yield) of 1,7 di-(α-thenoyl) heptane melting at 66.5-67°.

Table I

Compounds prepared	M. P. °C.	Yield %	Carbon % Calcd.	Carbon % Found	Hydrogen % Calcd.	Hydrogen % Found
Keto Acids						
3-(α-Thenoyl) propanoic acid*	119-120	58.5				
5-(α-Thenoyl) pentanoic acid	76.5-77	3.8	56.50	56.73	5.65	5.88
7-(α-Thenoyl) heptanoic acid†			59.17	59.91	6.63	6.84
8-(α-Thenoyl) octanoic acid	63-65	24.5	61.41	61.40	7.08	6.90
9-(α-Thenoyl) nonanoic acid	54.5-55	8.3	62.68	62.60	7.51	7.66
Diketones						
1,6 Di(α-thenoyl) hexane	72.5-73	29.8	62.74	62.87	5.89	5.94
1,7 Di(α-thenoyl) heptane	66.5-67	27.0	63.75	64.25	6.25	5.98
1,8 Di(α-thenoyl) octane	66.5-67	21.2	64.67	64.64	6.69	6.79

* Previously prepared by Fieser (7).

† This keto acid melted in the region of room temperature and apeared to decompose during purification and on standing.

The alkaline solution was acidified with 10% hydrochloric acid and extracted with several 50 ml. portions of ether. The ether extract was evaporated in vacuo until all of the ether was removed. The remaining oil solidified when cooled and melted at 50-60°. Recrystallization from petroleum ether gave 6.3 g. (24.5% yield) of 8(α-thenoyl)octanoic acid melting at 63-65°.

Summary

1. It has been shown that suberic, azelaic, and sebacic polyanhydrides will react with thiophene in the presence of stannic chloride to give diketones and keto acids. Polyadipic anhydride gave only the keto acid.

2. None of the new ketones or keto acids tested for anticonvulsant activity were found to be active.

3. The 3-(α-thenoyl)propanoic acid, prepared from thiophene and succinic anhydride, was found to be approximately 15 per cent as active as diphenylhydantoin.

Bibliography

1. Steinkopf, 1924. Ann., **437**:14.
2. Tainter, 1930. Quart. J. Pharm. Pharmacol., **3**:584.
3. Barger, **1938**. J. Chem. Soc., 2100.
4. Raczynski, 1939. Senior Thesis, University of Illinois.
5. Hill, 1932. J. Am. Chem. Soc., **54**:4105-4106.
6. Plant and Tomlinson, **1935**. J. Chem. Soc., 1092-1094.
7. Fieser and Kennelly, 1935. J. Am. Chem. Soc., **57**:1611-1616.