Chemistry of Dithienyl Diketones. I. Synthetic Explorations

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A series of dithienyl diketones (thenils) have been prepared by four routes: *via* the thenoin condensation followed by oxidation; by the reaction of thienyllithiums with dimethyl oxalate; by oxalylation of alkoxythiophenes; and by oxidation of the thenoins resulting from the reaction of thienyl Grignards with thienylglyoxals. All except the alkoxythenils **11**, **12**, and 3,3′-benzo[*b*]thenil (**3**) give the unstable thenilic acids upon treatment with hydroxide.

Dithienyl diketones, or thenils,[2] the thiophene analogs of benzils, have been scarcely investigated. Indeed, of the simple thenils, only 2,2′-thenil[3] (**1**), 3,3′-thenil[4] (**2**), and 3,3′-benzo[*b*]thenil[5] (**3**) have been reported. We were first attracted to this area by our efforts toward the synthesis of some dithienyl isosteres of JB 336, a pharmaceutical with demonstrated antispasmodic and psychotomimetic properties.[6,7] The thenilic acids needed to prepare those amino esters were to be prepared by the base-induced rearrangement of the thenils. Since we wished to have at hand many different substituted thenilic acids, this gave us an excellent opportunity to explore the rather neglected thenilic acid rearrangement on both a qualitative and a quantitative basis. By analogy, a study of this type would have much meaning in terms of the benzilic acid rearrangement as well.[8]

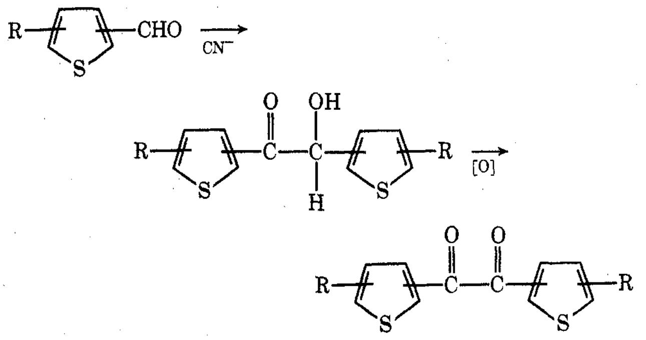
The most obvious means of preparing the thenils was by oxidation of the thenoins and here we could investigate the benzoin condensation of thienyl aldehydes, at least on a qualitative basis.

Discussion

All of the aldehydes needed in Scheme I for the thenil syntheses have been previously described.[9] They were formed either by Wilsmeier–Haack formylation of the appropriate substituted thiophene or by reaction of thienyllithiums with dimethylformamide.

There appears to be no simple method of predicting which aldehydes will undergo the benzoin or mixed benzoin condensation.[10] Present studies involving the thiophene aldehydes certainly supported this contention as well. Of the compounds listed in Table I, only **1–6** were accessible by Scheme I in which the intermediate thenoin was isolated. Thenils **7** and **8** were obtained by direct oxidation of the thenoin condensation reaction mixture with cupric sulfate and pyridine.

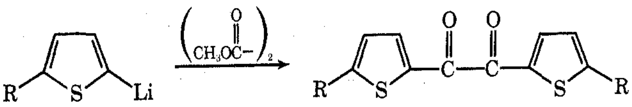
SCHEME I



The remaining aldehydes gave only recovered starting material or intractable tars upon treatment with cyanide and subsequent oxidation.

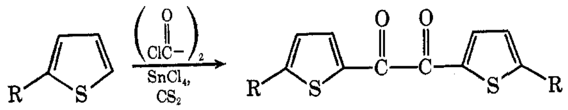
Nyberg[11] has shown that 2- and 3-thienyllithium give the corresponding thenils upon reaction with dimethyl oxalate. Thenils **9** and **10** were synthesized in this manner, thus extending the generality of this procedure (Scheme II).

SCHEME II



Advantage was taken of the strong electron-donating properties of the alkoxy group to obtain thenils **11** and **12** by the reaction of 2-methoxy and 2-isopropoxythiophene with oxalyl chloride. The yield of **12** was especially low since this compound probably suffers protolytic degradation to give the very unstable hydroxythienyl compound during the acylation (Scheme III).

SCHEME III



The H_3–H_4 coupling constant in **11** was 4.4 Hz and this falls outside the range reported for 3–4 coupling constants in thiophenes.[12] However, degradation of the thenil with ammonium cyanide followed by basic hydrolysis and acidification gave only 5-methoxy-2-thenoic acid, thereby confirming 2,5 substitution.

Thenil **13** was obtained by oxidation of the thenoin formed by the reaction of 5-methyl-2-thienylmag-

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[1] Abstracted, in part, from the Ph.D. dissertation of G. P. N.

[2] The name thenil for dithienyl diketone is a logical extension of IUPAC rule C 313.4. The name has been used previously for such compounds.[3,4]

[3] S. Z. Cardon and H. P. Lankelma, *J. Amer. Chem. Soc.*, **70**, 4248 (1948).

[4] E. Campaigne and R. C. Bourgeois, *ibid.*, **75**, 2702 (1953).

[5] E. Campaigne and E. S. Neiss, *J. Heterocycl. Chem.*, **3**, 46 (1966).

[6] J. H. Biel, L. G. Abood, W. K. Hoya, H. A. Lesser, and E. P. Kluchesky, *J. Org. Chem.*, **26**, 4096 (1961).

[7] G. P. Nilles and R. D. Schuetz, *J. Med. Chem.*, **13**, 1249 (1970).

[8] G. P. Nilles and R. D. Schuetz, *J. Org. Chem.*, **36**, 2489 (1971).

[9] (a) H. D. Hartough, "Thiophene and Its Derivatives," Interscience, New York, N. Y., 1952, Chapter 11; (b) H. D. Hartough and S. L. Meisel, "Compounds with Condensed Thiophene Rings," Interscience, New York, N. Y., 1954, p 109; (c) A. R. Dodson, Ph.D. Thesis, Michigan State University, East Lansing, Mich., 1961; (d) J. Sice, *J. Amer. Chem. Soc.*, **75**, 3697 (1953); (e) W. Hoek, H. Wynberg, and J. Strating, *Recl. Trav. Chem. Pays-Bas*, **85**, 1054 (1966); (f) R. D. Schuetz and G. P. Nilles, *J. Org. Chem.*, **36**, 2188 (1971).

[10] W. S. Ide and J. S. Buck, *Org. React.*, **4**, 269 (1948).

[11] K. Nyberg, *Acta Chem. Scand.*, **23**, 1087 (1969).

[12] S. Gronowitz, *Advan. Heterocycl. Chem.*, **1**, 8 (1963).

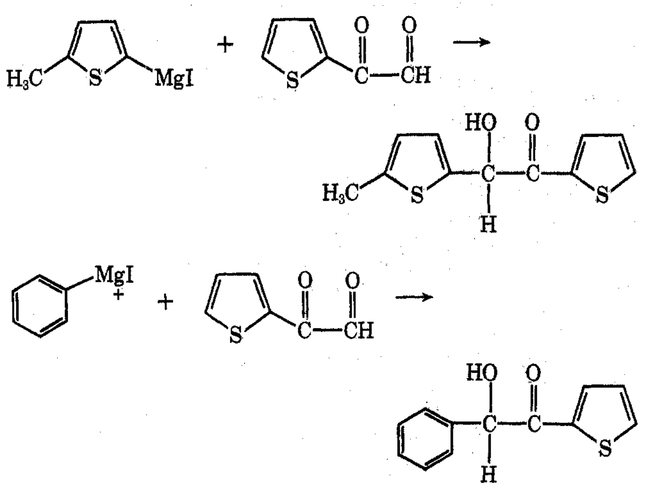
TABLE I
THENILS SYNTHESIZED

Thenil	R_1	R_2[a]	Scheme	% yield[a]	λ_{max} (log ϵ)[b]
1	H	H	I	23	310 (4.236)
2	3,3′-Thenil		I	36	273 (4.261)
3	3,3′-Benzo[*b*]thenil		I	14	316 (4.459)
4	2,2′-Benzo[*b*]thenil		I	83	336 (4.723)
5	2-Thienyl	2-Thienyl	I	64	397 (4.775)
6	2-Thienylphenyl diketone		IV	21	290 (4.014)
7	Cl	Cl	I	41	335 (4.278)
8	CH_3	CH_3	I	30	324 (4.282)
9	F	F	II	34	314 (4.482)
10	1-Adamantyl	1-Adamantyl	II	22	324 (4.577)
11	CH_3O	CH_3O	III	33	350 (4.335)
12	$(CH_3)_2CHO$	$(CH_3)_2CHO$	III	17	354 (4.631)
13	CH_3	H	IV	28	317 (4.236)

[a] Based on the starting material as illustrated in each scheme. [b] Of the principle band responsible for the color of the compound.

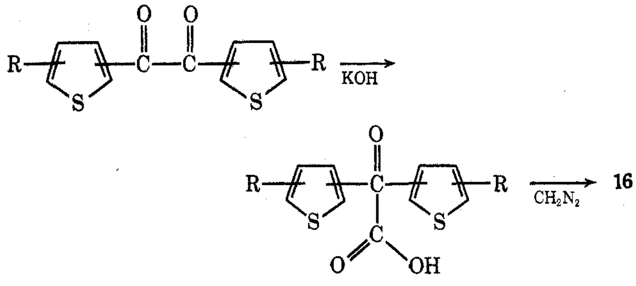
nesium iodide with 2-thienylglyoxal (Scheme IV). To our knowledge this is the first report of the reaction of a Grignard reagent with an arylglyoxal. While the yields are low, the method should be quite general for the synthesis of symmetrical and unsymmetrical benzoins. In a similar manner, the reaction of phenylmagnesium iodide with 2-thienylglyoxal gave 2-thenoylphenylcarbinol (**14**) which was identical with the compound obtained by cocondensation of benzaldehyde and 2-thenaldehyde. This synthesis serves to confirm the structure originally proposed for this compound.[13]

SCHEME IV



All of the new thenils were characterized by their satisfactory elemental analyses (see Table II), their low energy carbonyl absorptions $\nu_{C=O}$ = 1630 ± 30 cm^{-1}, visually by their yellow to rust orange color, and by their facile conversion, for the most part, to the corresponding thenilic acid **15** upon treatment with hydroxide.

The thenilic acids seem to be stable only in solution or in the solid state below −20°. They were all characterized by conversion to their methyl esters **16** upon treatment with diazomethane. The esters are stable indefinitely. The thenilic acids were the only products discovered upon base-induced rearrangement of the thenils, with three exceptions.



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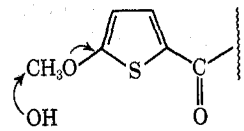
Treatment of the methoxythenil **11** with hydroxide failed to yield the corresponding methoxythenilic acid, or its methyl ester after treatment of the rearrangement reaction mixture with diazomethane. In addition, the rate of disappearance of hydroxide was much greater than that predicted on the basis of the substituent effect. Indeed, the rate was greater than for the unsubstituted thenil.[8]

We postulate that either S_N2 attack of the hydroxide on either or both of the methoxy carbons occurs, **17**, or direct attack by the hydroxide on the thiophene ring, possibly *via* a Meisenheimer type complex as in **18**, leads to a hydroxythiophene. The hydroxythiophenes are well noted for their instability[14] which could explain our failure to obtain the expected product.



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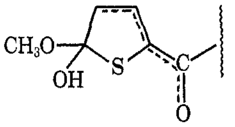

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Although insufficient amounts of the isopropoxythenil **12** prevented us from carrying out any synthetic investigations, the kinetics of the rearrangement indicate[8] the same type of behavior as for **11**. The decrease in the rate of disappearance of hydroxide for **12** *vs.* **11** tends to support, by steric arguments, the explanation for the anomolous behavior of the alkoxythenils.

The reaction of **3** with hydroxide yielded methyl 3-thianaphthoate[15] after the usual work-up rather than

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[13] J. H. Biel, E. P. Sprengler, H. L. Leiser, J. Horner, A. Drukker, and H. L. Friedman, *J. Amer. Chem. Soc.*, **77**, 2250 (1955).

[14] C. Frisell and S. O. Lawesson, *Org. Syn.*, **43**, 55 (1963).

[15] Identified on the basis of its mass spectrum. Peaks were found at *m/e* 192 (parent 35%), 161 (P − 31, loss of CH_3O–, 65%) and *m/e* 133 (loss of CO from *m/e* 161, 17%).

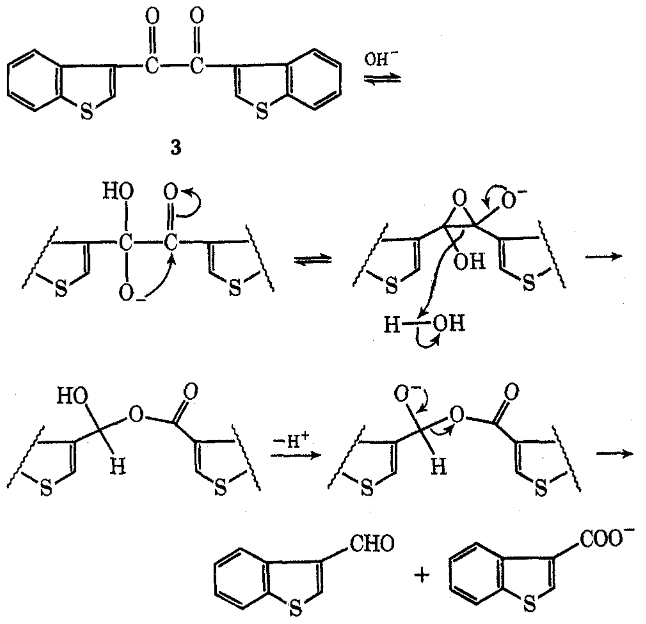
TABLE II

ELEMENTAL ANALYSIS FOR NEW COMPOUNDS

Thenil	Mp, °C	C, % Calcd	C, % Found	H, % Calcd	H, % Found	S, % Calcd	S, % Found	Thenilic ester from thenil	Registry no.	% yield[a]	Mp, °C	C, % Calcd	C, % Found	H, % Calcd	H, % Found	S, % Calcd	S, % Found
4	239–240	67.06	67.08	3.12	3.08	19.89	19.96	**1**	26447-85-8	69	93	51.95	51.86	3.96	3.80	25.22	25.02
5	177–179	55.93	55.80	2.61	2.83	33.18	33.04	**2**	28540-31-0	70	80–81	51.95	52.06	3.96	3.97	25.22	25.18
7	121–122	41.25	41.36	1.38	1.49	22.02	22.00	**4**	30202-68-7	62	103–104	64.38	64.15	3.98	3.95	18.09	17.98
8	86–87	57.57	57.44	4.03	4.01	25.62	25.60	**5**	30135-39-8	94	112–113	54.52	54.62	3.37	3.37	30.64	30.70
9	125–127	46.50	46.70	1.56	1.65	24.83	24.62	**7**	30202-67-6	92	Liquid	40.87	41.05	2.49	2.63	19.84	19.47
10	260–261	73.42	73.17	6.98	6.83	13.07	12.91	**8**	30135-41-2	80	57–58	55.29	55.60	5.00	4.95	22.71	21.47
11	140–142	51.05	51.08	3.57	3.56	22.72	22.79	**9**	30135-42-3	78	55–57	45.51	45.74	2.78	2.63	22.09	22.18
12	98–99	56.78	56.80	5.36	5.49	18.95	19.07	**13**	30226-74-5	56	95–96	53.91	53.71	4.15	4.22	23.99	24.10
13	44–45	55.91	55.74	3.41	3.41	27.14	26.97										

[a] Based on the thenil.

the expected thenilic acid ester. The cleavage of benzils, rather than the rearrangement, has been noted before only in the presence of alcohols.[16] We propose a mechanism to account for this behavior which is analogous to the one by Kwart[17] for the cyanide-catalyzed cleavage of benzils. The intermediate



aldehyde could be converted to 3-thianaphthoic acid and 3-hydroxymethyl thianaphthene by the Cannizzaro reaction.

Experimental Section[18,19]

Thenils 1–6 *via* **Scheme I.**—Thenils **1**, **2**, and **3** were prepared as described, ref 3–5, respectively. Thenils **4** and **5** were prepared as follows. A 0.100-mol quantity of the appropriate thiophene aldehyde and 3.25 g (0.050 mol) of potassium cyanide in 100 ml of 90% ethanol was refluxed for 30 min. The solution was cooled and neutralized with acetic acid, and 500 ml of water was gradually added. The precipitated thenoin was collected, air-dried, and dissolved in 100 ml of 80% aqueous acetic acid and 8.0 g (0.10 mol) of ammonium nitrate and 0.1 g of cupric acetate was added. After refluxing for 1 hr, the solution was cooled and the thenil crystallized and was collected. Purification was effected by sublimation at 120° (0.1 Torr).

Thenils 7 and 8 *via* **Scheme II.**—A solution of 14.7 g (0.100 mol) of 5-chloro-2-thenaldehyde and 2.5 g (0.051 mol) of sodium cyanide in 100 ml of dry THF containing 2% (v/v) of dimethyl sulfoxide was stirred under N_2 in a sealed flask for 30 hr. After neutralization with 2.4 ml of acetic acid, 25 g (0.10 mol) of cupric sulfate pentahydrate was added along with 100 ml of dry pyridine. This mixture was stirred 3 hr at room temperature and quenched in 750 ml of water. After standing 12 hr at 0°, the precipitate was collected, washed with water, air-dried, and continuously extracted with 30–50° petroleum ether until the yellow color was exhausted. The solvent was removed and the thenil was collected. Thenil **8** was prepared in the same manner except the reaction solvent was 50 ml of dimethyl sulfoxide instead of the THF–DMSO mixture.

Thenils 9 and 10 *via* **Scheme II.**—A solution of 0.02 mol of the appropriate substituted thiophene in 30 ml of dry ether under N_2 was stirred and treated in one portion with 0.025 mol of 1.6 *N* *n*-BuLi in hexane. After stirring 15 min, the thienyllithium solution was cooled to −60° and added dropwise to 0.018 mol of dimethyl oxalate in 100 ml of dry ether precooled to −60°. After an additional 1 hr of stirring, the reaction mixture was allowed to warm to room temperature and 50 ml of 2% HCl was added. The layers were separated, and the aqueous layer was extracted with ether (two 50-ml portions). The combined dried (Na_2SO_4) extracts were taken to dryness and the residue was continuously extracted with 30–50° petroleum ether. Further purification was by sublimation at 120° (0.1 Torr).

Thenils 11 and 12 *via* **Scheme III.**—A solution of 0.100 mol of the alkoxythiophene in 150 ml of carbon disulfide was cooled below 5° and 26.1 g (0.100 mol) of stannic tetrachloride in 30 ml of carbon disulfide was added with stirring. This solution was treated with 6.35 g (0.050 ml) of oxalyl chloride dropwise during 90 min, at 5° or lower. After stirring a further 15 min, the reaction mixture was poured into 100 ml of ice water and stirred well. The bulk of the product was removed by filtration. The ether layer was separated and the aqueous layer was extracted with ether (four 100-ml portions). The combined dried (Na_2SO_4) ether solutions were stripped of solvent, and the residue was combined with the previously isolated product. Further purification was by sublimation at 120° (0.1 Torr).

Thenils 6 and 13 *via* **Scheme IV.**—A Grignard solution prepared from 2.46 g (0.011 mol) of 5-methyl-2-iodothiophene and 0.267 g (0.011 g-atom) of magnesium in 20 ml of dry ether was added to 1.40 g (0.100 mol) of 2-thienylgyloxal in 25 ml of dry ether precooled to −50° with stirring and at such a rate that the temperature was maintained below −40° during the addition. After a further 1 hr of stirring, 10 ml of saturated ammonium chloride was added and the layers were separated. The aqueous layer was extracted with ether (two 25-ml portions), the combined ether solutions were dried (Na_2SO_4), and the solvent was removed in a rotary evaporator. The thenoin was oxidized to the thenil as in Scheme I. Thenil **6** was prepared in exactly the same manner using phenylmagnesium iodide in place of 2-

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(16) S. Selman and J. F. Eastham, *Quart. Rev., Chem. Soc.*, **14**, 221 (1960).

(17) H. Kwart and M. M. Baevsky, *J. Amer. Chem. Soc.*, **80**, 580 (1958).

(18) Infrared spectra were determined as KBr disks on a Perkin-Elmer 237B spectrophotometer. Nmr spectra were recorded on a Varian A-60 instrument with TMS as internal standard. Mass spectra were run by Mrs. L. Guile using a Hitachi Perkin-Elmer RMU-6 instrument at 70 eV. Ultraviolet spectra were taken on a Cary 14 spectrophotometer. Melting points were determined on an Electrothermal melting point apparatus calibrated with furnished standards. Elemental analyses were by Galbraith Laboratories, Knoxville, Tenn.

(19) The melting point reported[6] for 3,3′-benzo[*b*]thenil is in error. It should be as in Table II; E. Campaigne, Indiana University, personal communication, 1968.

thienylmagnesium iodide, to give **14** which was oxidized[20] to **6** as in Scheme I.

General Procedure for the Thenil–Thenilic Acid Rearrangement.—A 0.010-mol quantity of the thenil was suspended in 25 ml of water containing 2 g of potassium hydroxide. The solution was stirred and heated to reflux under N_2 until solution was effected. If solution was not complete in 1 hr, 10 ml of dioxane was added, and heating was continued an additional 2 hr. The cooled solution was acidified to congo red with concentrated HCl and immediately extracted with ether (two 25-ml portions). The combined dried (Na_2SO_4) extracts were treated with an excess of ethereal diazomethane. After stirring 1 hr at room temperature, the solvent was removed under reduced pressure, and the residue was recrystallized from 60–90° petroleum ether.

Registry No.—**1**, 7333-07-5; **2**, 7333-08-6; **3**, 5381-27-1; **4**, 30135-06-9; **5**, 30135-21-8; **6**, 30135-07-0; **7**, 30135-23-0; **8**, 30135-04-7; **9**, 30135-26-3; **10**, 30135-25-2; **11**, 30135-27-4; **12**, 30226-72-3; **13**, 30135-05-8.

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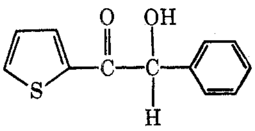
[20] The mass spectrum of **14** deserves further comment. It would appear that of the two possibilities for the condensation product between benzaldehyde and 2-thenaldehyde, namely, **14** and **19**, it should be possible



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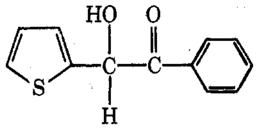

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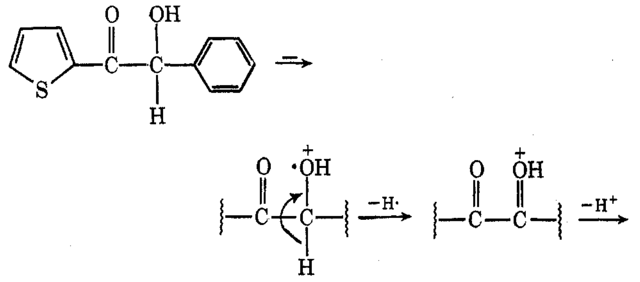
to distinguish between them on the basis of their mass spectra if cleavage occurred between the acyl and carbinol halves of the molecule. It appears, however, that the initial process upon electron impact is oxidation of the thenil, thus



with peaks observed at m/e 216 (P − 2, 5%), 111 (2-thenoyl, 55%), 105 (benzoyl, 100%), and 77 (phenyl, 36%). A literature search failed to uncover any reports concerning the mass spectra of benzoins. A mass spectrum of benzoin taken in these laboratories reveals the same behavior, that is, no apparent peak but only signals at m/e 210 (P − 2, 3%), 105 (benzoyl, 100%), and 77 (phenyl, 47%).

Chemistry of Dithienyl Diketones. II. Kinetic Investigations

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The kinetics and thermodynamic parameters of the thenilic acid rearrangement have been followed as a function of substituent effect in the temperature range of 15–80°. A reevaluation of the ionization constants of nine thenoic acids has been made in water at 49.5°. Improved Hammett type correlations are obtained basing a new set of σ values on these ionization constants. The deviation in the Hammett plot caused by the halo substituents is discussed in terms of the mechanism of the rearrangement.

Some years ago Smith[2] and Clark[3] proposed a mechanism for the benzilic acid rearrangement in which attack by hydroxide, 1,2 migration of the aryl group, and proton transfer all occurred simultaneously. This was in contrast to the earlier concept by Ingold[4] that a complex[5] between the diketone and hydroxide preceded rearrangement to the benzilate skeleton with the temporal location of the proton transfer being unspecified. It appeared to be of interest to investigate the existence of a linear free-energy relationship and whatever bearing this might have on the reaction mechanism.

In our preceding article[6] we have described the synthesis of a number of dithienyl diketones (thenils). It was shown that, with the exception of the alkoxy thenils and 3,3′-benzo[*b*]thenil, these compounds undergo the benzilic acid rearrangement to give the corresponding thenilic acids in good to excellent yields. Thusly, we were able to make a quantitative study of this rearrangement and, in addition, to further elucidate the electromeric nature of the thiophene ring.

Results

The potassium hydroxide induced rearrangement of the nine thenils in Table I was studied in the temperature range of 15–80°. Corrections were made for thenil consumed prior to t_0 and for the nonideality of the solvent, 2:1 (v/v) dioxane–water. The titrimetrically determined loss in hydroxide was used as basis to compute the observed second-order rate constants by the usual equation.[7a] In all cases, a plot of log [thenil/OH^-] *vs.* time was linear to at least 3 half-lives of the thenil, the minor component.[8]

Thermodynamic parameters for each reaction were calculated in the usual manner from the Arrhenius equation and the Eyring equation[9] and are presented in Table II. The entropy of activation, $\Delta S^{\ddagger}_{323°K}$, was

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[1] Abstracted, in part, from the Ph.D. dissertation of G. P. N.

[2] D. G. Ott and G. G. Smith, *J. Amer. Chem. Soc.*, **77**, 2325 (1955).

[3] M. T. Clark, E. G. Hendley, and O. K. Neville, *ibid.*, **77**, 3280 (1955).

[4] C. K. Ingold, *Annu. Rep., Chem. Soc.* (*London*), 124 (1928).

[5] A claim is made for the isolation of this intermediate complex which, depending on reaction conditions, can give benzilic acid or can be decomposed back to benzil and hydroxide: G. Scheuing, *Chem. Ber.*, **56**, 252 (1923).

[6] R. D. Schuetz and G. P. Nilles, *J. Org. Chem.*, **36**, 2486 (1971).

[7] (a) F. H. Westheimer, *J. Amer. Chem. Soc.*, **58**, 2209 (1936), has shown that the rearrangement is first order in base and first order in diketone. Thus, we employed the usual second-order equation as in S. W. Benson, "The Foundations of Chemical Kinetics," McGraw-Hill, New York, N. Y., 1960, p 18; (b) p 91.

[8] It became quite tedious with compounds such as 5,5,-dimethyl-2,2′-thenil to perform rate studies beyond 2 half-lives, since this would have required individual runs lasting longer than 3 days.

[9] J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, p 71.