E- and *Z*-Isomerism of 2-Acetylthiophene Oximes

Santiago Conde, Carlos Corral* and Jaime Lissavetzky

Instituto de Química Médica (C.S.I.C), Juan de la Cierva, 3,
28006-Madrid, Spain

Recieved June 5, 1984

A study on the oximation of a number of 2-acetylthiophenes in order to ascertain the validity of contradictory results previously described is reported. The fact that the steric hindrance is smaller in 2-acetylthiophenes unsubstituted at position-3 than in acetylbenzenes allows in these cases the formation of *Z* oximes, which even can predominate on the *E* oximes in the case of a +M substitution at position-5. In the paper is also shown that the *E/Z* ratio of 2-acetylthiophene oximes can be deduced from the ^{1}H-nmr spectrum of the crude oxime mixture.

J. Heterocyclic Chem., **22**, 301 (1985).

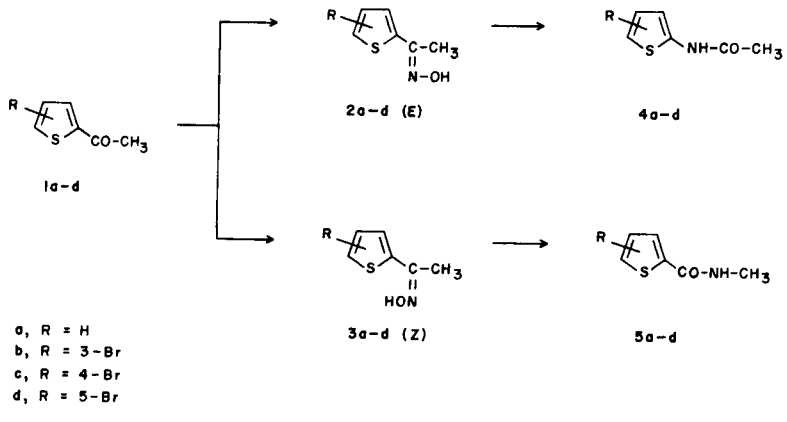
Oximation of acetylbenzene and its derivatives appears to yield exclusively *E* oximes [1-5]. Only by one indirect method the *Z*-oxime of acetylbenzene, a stable compound, has been prepared [6]. On the oximation reaction of 2-acetylthiophene and derivatives there are however contradictory reports. So whereas for 5-chloro-2-acetylthiophene a mixture of *E* and *Z* oximes has been described [7], for 2-acetylthiophene, 5-methyl-2-acetylthiophene and 5-bromo-2-acetylthiophene apparently pure *E* oximes are claimed [8]. On the other hand, without any reference to the configuration of the oximes, 4-nitro-2-acetylthiophene has been reported [5] to give only one oxime (mp 129°) and 5-nitro-2-acetylthiophene a mixture of the two oximes.

In the course of a research on β-adrenergic blocking agents, the supposed *E* and *Z* mixtures of the oximes of 2-acetylthiophene and its three monobromo derivatives were obtained by a classical method and quantitatively separated by hplc. The structural *E* and *Z* assignments of the oximes were established by their almost quantitative conversion into the corresponding amides by the improved Beckmann rearrangement method of Cymermann-Craig [9].

The results of the reaction of the Scheme are shown in Tables 1 and 2, as well as the physical data. Concerning these data for the oximes it should be noted that the ^{1}H-nmr signals of the protons of the methyl groups appear consistently at a higher field (≅ 0.1 ppm) in the *Z* than in the *E* oximes [10] and from the relative intensities of these signals in the ^{1}H-nmr spectrum of the crude oximation products, an *E/Z* isomer relation can be calculated which agrees closely with the experimental results of hplc separation. For compounds **1a** and **1c** the *E* isomer is predominant and for **1b** exclusively formed. This must be due to the unfavorable steric effect of the ring (hydrogen at position-3) upon the oximino group during the *Z* isomer formation, which is maximum for the 3-bromo derivative **1b**.

However for compound **1d** the *E/Z* isomer ratio is clearly inverted, the *Z* isomer being now the more abundant. This fact can only be explained on the basis of an interaction between the thiophenic sulfur atom and the N-OH group in the transition state lending to the *Z* isomer, while it is not possible in the transition state leading to the *E* isomer. This interaction is in this case strengthened by the +M mesomeric effect of the bromine atom next to the sulfur atom, whilst its -I inductive effect seems to have no influence whatsoever. In accordance with **1d**, the *E/Z*

Scheme



ratio, calculated by ^{1}H-nmr in the oximation reaction of 5-chloro-2-acetylthiophene is 38/62.

In order to know the influence on the *E/Z* isomer ratio of a -I-M group at position-5 and to ascertain the soundness of the reported formation of only one oxime in the oximation of 4-nitro-2-acetylthiophene, 2-acetylthiophene was nitrated and the isomer mixture was separated [5,11]. Oximation of both 2-acetyl-4-nitrothiophene and 2-acetyl-5-nitrothiophene and separation of their *E* and *Z* oximes as above yielded 65% of *E* oxime (mp 141-142°) and 35% of *Z* oxime (mp 155-156°) for the first one and 66% of *E* oxime and 34% of *Z* oxime for the latter [12].

Therefore, it appears that oximation of 2-acetylthiophene and derivatives yields a mixture of *E* and *Z* oximes except for the case of 3-substituted derivatives, which yield only *E* oximes and that the *E* isomer is always predominant in the mixture except for the case of +M 5-substituted derivatives, in which the sulfur atom is negatively charged, allowing a greater interaction with the -N-OH group in the transition state. This interaction seems to be present in all the *Z* oximes, since their ir spectra show no absorption band for the -OH stretching which is always present in the *E* oximes.

Table 1

Physical Data of the Oximes **2** and **3**

Compound	Rf [a]	% Isomer	Mp (°C)	NMR (DMSO-d_6, δ)
2a-*E* [b]	0.43	67	113-114	2.21 (s, 3H, CH_3), 7.05-7.65 (m, 3H, thiophenic protons), 11.3 (s, 1H, OH)
2b-*E*	0.4	100	111-112 [c]	2.31 (s, 3H, CH_3), 7.17 (d, 1H, H-4, thiophenic proton), 7.67 (d, 1H, H-5, thiophenic proton), 11.7 (s, 1H, OH)
2c-*E*	0.41	61	152-154	2.20 (s, 3H, CH_3), 7.43 (d, 1H, H-3 thiophenic proton), 7.64 (d, 1H, H-5 thiophenic proton), 11.5 (s, 1H, OH)
2d-*E*	0.46	35	135-137	2.18 (s, 3H, CH_3), 7.15 (s, 2H, thiophenic protons), 11.4 (s, 1H, OH)
3a-*Z* [d]	0.27	33	84-85	2.30 (s, 3H, CH_3), 7.15-7.85 (m, 3H, thiophenic protons), 11.6-11.8 (bs, 1H, OH)
3b-*Z*	—	—	—	—
3c-*Z*	0.24	39	143-145	2.30 (s, 3H, CH_3), 7.57 (d, 1H, H-3 thiophenic proton), 7.91 (d, 1H, H-5 thiophenic proton), 11.8-12.1 (bs, 1H, OH)
3d-*Z*	0.22	65	172-174	2.28 (s, 3H, CH_3), 7.38 (s, 2H, thiophenic protons), 11.8-12.1 (bs, 1H, OH)

[a] The Rf values were determined using ethylacetate/*n*-hexane 1:4 as eluent. [b] Lit mp 112-113° ref [9]. [c] Recrystallized from *n*-heptane. [d] Lit mp 81-84° ref [9].

Table 2

Physical Data and Yields of the Amides **4** and **5**

Compound	Yield %	Mp (°C)	NMR (DMSO-d_6, δ)
4a [a]	92	161-162 [b]	2.08 (s, 3H, CH_3), 6.66-7.00 (m, 3H, thiophenic protons), 10.9-11.2 (bs, 1H, NH)
4b [c]	91	95-96 [d]	2.20 (s, 3H, CH_3), 6.99 (d, 1H, H-5, thiophenic proton), 7.24 (d, 1H, H-4 thiophenic proton), 10.2-10.7 (bs, 1H, NH)
4c [e]	96	162-165 [f]	2.08 (s, 3H, CH_3), 6.60 (d, 1H, H-5, thiophenic proton), 7.00 (d, 1H, H-3, thiophenic proton), 11.1-11.6 (bs, 1H, NH)
4d	94	135-136 [g]	2.18 (s, 3H, CH_3), 7.1-7.2 (s, 2H, thiophenic protons), 11.2-11.4 (bs, 1H, NH)
5a [h]	87	113-114 [b]	2.73 (d, 3H, CH_3), 7.12-7.67 (m, 3H, thiophenic protons), 8.3-8.6 (m, 1H, NH)
5b	—	—	—
5c	96	154-155 [b]	2.75 (d, 3H, CH_3), 7.73 (d, 1H, H-5 thiophenic proton), 7.83 (d, 1H, H-3 thiophenic proton), 8.4-8.7 (m, 1H, NH)
5d	93	164-165 [b]	2.77 (d, 3H, CH_3), 7.34 (d, 1H, H-4 thiophenic proton), 7.63 (d, 1H, H-3 thiophenic proton), 8.4-8.9 (m, 1H, NH)

[a] Lit mp 161° ref [9]. [b] Recrystallized from benzene. [c] Lit mp 70-115° ref [17]. [d] Recrystallized from *n*-heptane. [e] Lit mp 160° ref [17]. [f] Recrystallized from acetonitrile. [g] Recrystallized from ethanol-water. [h] Lit mp 112-114° ref [9].

Table 3

Elemental Analyses

Compound	Formula	Calcd./Found C	H	N
2a	C_6H_7NOS	51.06	4.96	9.93
		51.24	5.03	9.81
2b	C_6H_6BrNOS	32.73	2.73	6.36
		32.91	2.59	6.41
2c	C_6H_6BrNOS	32.73	2.73	6.36
		33.01	2.61	6.49
2d	C_6H_6BrNOS	32.73	2.73	6.36
		32.58	2.67	6.58
3a	C_6H_7NOS	51.06	4.96	9.93
		51.13	4.83	9.75
3c	C_6H_6BrNOS	32.73	2.73	6.36
		32.88	2.79	6.54
3d	C_6H_6BrNOS	32.73	2.73	6.36
		32.57	2.85	6.57
4a	C_6H_7NOS	51.06	4.96	9.93
		50.93	4.87	9.85
4b	C_6H_6BrNOS	32.73	2.73	6.36
		33.01	2.48	6.51
4c	C_6H_6BrNOS	32.73	2.73	6.36
		32.95	2.61	6.59
4d	C_6H_6BrNOS	32.73	2.73	6.36
		32.84	2.77	6.54
5a	C_6H_7NOS	51.06	4.96	9.93
		50.98	5.15	9.77
5c	C_6H_6BrNOS	32.73	2.73	6.36
		32.98	2.78	6.47
5d	C_6H_6BrNOS	32.73	2.73	6.36
		32.85	2.64	6.54

EXPERIMENTAL

Melting points were determined on a Gallenkamp Capillary apparatus and are uncorrected. Proton nuclear magnetic resonance were recorded on a Varian EM-390 (90 MHz) Spectrometer (using TMS as internal standard). The separation of the oximes was made with a hplc Waters model 500 A. For all the compounds here described analyses of C, H and N are within ±0.3% of the theoretical values. 2-Acetylthiophene [13], 2-acetyl-3-bromothiophene [14], 2-acetyl-4-bromothiophene [15], 2-acetyl-5-bromothiophene [16], 2-acetyl-4-nitrothiophene [5,11] and 2-acetyl-5-nitrothiophene [5,11] were obtained according to the literature.

Oximes. General Procedure.

A solution of the corresponding acetylthiophene (0.1 mole), hydroxylamine hydrochloride (20 g) and pyridine (20 ml) in ethanol (200 ml) was heated under reflux for 2 hours and after cooling, the solvent was removed and water (500 ml) added. The mixture was stirred overnight and the precipitate filtered, washed with cold water and dried. The two isomers so formed were separated by hplc using ethyl acetate-*n*-hexane 1:4 as eluent except for **2b**. In this case only the *E* isomer was obtained and it was recrystallized from *n*-heptane. The yield of crude oxime mixture was *ca.* 90%. The ratio of isomers and their physical data for oximes **2** and **3** are shown in Table 1.

The ratio of isomers and their physical data of 4 or 5-nitro-2-acetylthiophene oximes are:

2-Acetyl-4-nitrothiophene *E*-Oxime.

This isomer was obtained in a yield of 65%, mp 141-142° (ethanol), Rf [ethyl acetate/*n*-hexane (1:4)], 0.42 ^{1}H-nmr (DMSO-d_6): δ 2.19 (s, 3H, CH_3), 7.95 (d, 1H, H-3, thiophenic proton), 8.83 (d, 1H, H-5, thiophenic proton), 11.4 (s, 1H, OH).

Anal. Calcd. for $C_6H_6N_2O_3S$: C, 38.71; H, 3.23; N, 15.05. Found: C, 38.96; H, 3.38; N, 14.93.

2-Acetyl-4-nitrothiophene *Z*-Oxime.

This isomer was obtained in a yield of 35%, mp 155-156° [ethyl acetate/*n*-hexane (1:1)], Rf [ethyl acetate/*n*-hexane (1:4), 0.25]; ^{1}H-nmr (DMSO-d_6): δ 2.29 (s, 3H, CH_3), 8.05 (d, 1H, H-3, thiophenic proton), 8.99 (d, 1H, H-5, thiophenic proton).

Anal. Calcd. for $C_6H_6N_2O_3S$: C, 38.71; H, 3.23; N, 15.05. Found: C, 38.88; H, 3.42; N, 14.96.

2-Acetyl-5-nitrothiophene *E*-Oxime.

This isomer was obtained in a yield of 66%, mp 190-191° (ethanol), Rf [ethyl acetate/*n*-hexane (1:3), 0.53]; ^{1}H-nmr (DMSO-d_6): δ 2.19 (s, 3H, CH_3), 7.55 (d, 1H, H-3, thiophenic proton), 8.05 (d, 1H, H-4, thiophenic proton).

Anal. Calcd. for $C_6H_6N_2O_3S$: C, 38.71; H, 3.23; N, 15.05. Found: C, 38.66; H, 3.52; N, 15.09.

2-Acetyl-5-nitrothiophene *Z*-Oxime.

This isomer was obtained in a yield of 34%, mp 186-188° (ethanol), Rf [ethyl acetate/*n*-hexane (1:3), 0.32]; ^{1}H-nmr (DMSO-d_6): δ 2.31 (s, 3H, CH_3), 7.63 (d, 1H, H-3, thiophenic proton), 8.25 (d, 1H, H-4, thiophenic proton).

Anal. Calcd. for $C_6H_6N_2O_3S$: C, 38.71; H, 3.23; N, 15.05. Found: C, 38.87; H, 3.27; N, 15.18.

Beckmann Rearrangement of 2-Acetylthiophene Oximes. General Procedure.

To a stirred solution of 0.015 mole of an oxime isomer in acetone (40 ml) cooled to 0°, a solution of sodium hydroxide (0.6 g, 0.015 mole) in water (16 ml) was added. This suspension was treated with *p*-soluenesulfonyl chloride (2.8 g, 0.015 mole) and the mixture was stirred until it became a clear solution. The solution was evaporated to dryness and the residue was extracted with benzene, dried over magnesium sulfate, concentrated to a minimum volume and applied to an alumina (75 g) column deactivated with water (1 ml). This column was eluted with 100 ml of *n*-hexane and after the portions of 100 ml of benzene/chloroform gradually increasing the amount of chloroform (5:0, 4:1, 3:2, 2:3, 1:4, 0:5). The intermediate fraction (2:3) afforded mainly a chromatographically pure solid.

Acknowledgements.

We thank Dr. J. Elguero for his advice and our Department of Analyses and Instrumental Techniques for all the analytical and spectroscopic data.

REFERENCES AND NOTES

[1] J. Meisenheimer, P. Zimmermann and U. v. Kummer, *Ann. Chem.*, **447**, 205 (1927).

[2] W. Brosche and W. Scriba, *Ann. Chem.*, **541**, 283 (1939).

[3] D. E. Pearson, H. W. Pope, W. W. Hargrave and W. E. Stamper, *J. Org. Chem.*, **23**, 1412 (1958).

[4] G. W. Buchanan and B. A. Dawson, *Can. J. Chem.*, **54**, 790 (1976).

[5] P. Fournari and J. P. Chane, *Bull. Soc. Chim. France*, 479 (1963).

[6] J. H. Smith and E. T. Kaiser, *J. Org. Chem.*, **39**, 728 (1974).

[7] A. Buzas and J. Teste, *Bull. Soc. Chim. France*, 359 (1960).

[8] O. Meth-Cohn and B. Narine, *Synthesis*, 133 (1980).

[9] J. Cymerman-Craig and A. R. Naik, *J. Am. Chem. Soc.*, **84**,

3410 (1962).

[10] Curiously, the chemical shift reported [6] for the methyl group of acetophenone *Z* oxime is 2.20 ppm and that for the *E* oxime is 2.28 ppm.

[11] P. J. Newcombe and R. K. Norris, *Aust. J. Chem.*, **32**, 2654 (1979).

[12] The *E* and *Z* configurations were assigned taking into account their ^{1}H-nmr spectra and Rf data.

[13] H. D. Hartough and A. I. Kosak, *J. Am. Chem. Soc.*, **69**, 3093 (1947).

[14] W. Steinkopf, H. Jacob and H. Penz, *Ann. Chem.*, **512**, 36 (1934).

[15] Ya. L. Gol'dfarb and Yu. B. Vol'kenshtein, *Dokl. Akad. Nauk SSSR*, **128**, 536 (1959).

[16] H. D. Hartough and L. G. Conley, *J. Am. Chem. Soc.*, **69**, 306 (1947).

[17] C. D. Hurd and H. M. Prestley, *J. Am. Chem. Soc.*, **69**, 859 (1947).