Reactions of Isomeric Methyl Ethers of Triacetic Lactone.

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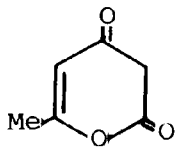
Summary: Reactions of isomeric methyl ethers (2a) and (3a) of triacetic lactone (1) with phosphorus pentasulphide have been found to yield the thiiderivative (2b) and (4a) respectively. Using aqueous solutions of secondary amines the methyl ether (2a) and its thioanalogue (2b) have been converted into 4-substituted 6-methyl-2H-pyrm-2-ones (2d-f) and 2H-pyran-2-thiones (2g-i) respectively. The 2H-pyrqn-2-tiones (2g-l) were isomerised into thiopyrm-2-ones (2j-l). In all these reactions the nucleophillic attack occurs at the 4 or 4,2-positions of the ethers. Thiopyram-2-ones (2j-l) on treatment with phosphorus pentasulphide gave the corresponding thiopyram-2-thiones (2m-o). The spectroscopic data of the compounds are recorded.

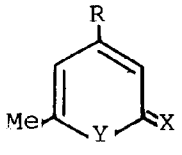
Methylation of triacetic lactone[1] (1) using diazomethane has been studied extensively to resolve the controversy about the formation of two isomeric methyl ethers (2a, 3a). The early work of Janiszewska-Drabarek[2] and later investigations of Djerassi et al[3]. and Bu'Lock[4] et al. have unambigously confirmed that diazomethane methylation of (1) gave methyl ether (2a) and (3a). During these investigations a thioether m.p. 106oC was reported by Arndt and Avan[5]. Although insufficient information was available for firm structural assignement the thioderivative was assigned structure (3b). Reactions of isomer (3a) has not been studied due to its less stability. Reactions of methyl ether (2a) include bromination[6] and nitration[5] at the 3-position; condensation of aldehydes[4,7] and acylation[8,9] at the 6-methyl position; Recently the methyl ether (2a) has also been used as precursor for the synthesis of natural products,[3,4,9] polypyrones[7,10] and polyketide type anthracene derivatives[11]. However, no reactions at the 2 or 4-positions of the ether (2a) have been reported. The present work describes the characterisation of the sulphurization products of isomeric ethers (2a, 3a) and the reactions of secondary amines with methyl ether (2a) and thioether (2a) and thioether (2b) which involve nucleophillic attacks at the 4 or 2,4-positions with subsequent formation of 4-substituted pyran-2-ones (2d-f) and their thioanalogue (2g-l).

The initial studies with isomeric ethers (2a, 3a) involved the sulphurization under the conditions described by earlier workers[5] because the structures of the resulting thioderivatives had not been firmly established. Diazomethane methylation of (1) yielded methyl ethers (2a) and (3a). Methyl ether (2a) on treatment with phosphorus pentasulphide in benzene gave the thioanalogue (2b). This is characterised by strong thiocarbonyl absorption[12] at 1180 cm^{-1} (Table-1), ultraviolet absorption maximum at 350nm (Table-1) and nmr spectrum (Table-II). The compound (2b) on boiling with 20% hydrochloric acid gave (2c). Hydrolysis of (2b) and (2c) using acetic acid and hydrogen peroxide yielded the methyl ether (2a) and triacetic lactone (1) respectively. these results conclusively prove structure (2b) for the thioanalogue.

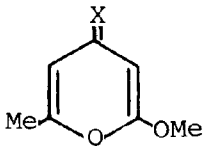
Methyl ether (3a) on treatment with phosphorus pentasulphide in benzene did not give the anticipated product (3b) as claimed by Arndt et al. but a bright yellow microcrystalline product m.p. 235°C, molecular formula $C_{12}H_{10}S_3O_2$ determined from elemental analysis and mass spectrum (m/e 282^+ M). The product shows negative ferric chloride test and does not react with dry or wet hydrochloric acid in the cold or hot state. Infrared shows a strong absorption at 1190 cm^{-1} (C=S conjugated with -C=C- of ring). On the basis of these evidence the product has been formulated as 4,4-bis(6-methyl-pyran-2-thione) sulphide (4a). This is further substantiated by the reaction of (4a) with hydrogen peroxide in acetic acid which gave bis-sulphone (4b), characterised by elemental analysis and infreared spectum (1720 cm^{-1} C=O of 2-pyrone, stron band at 1335, 1120-1160 cm^{-1} for sulphone group)[13a]. Formation of sulphone shows that the two pyran-2-thione rings in (4a) are linked with each other through a sulphur atom at their 4-positions. Bis-sulphide (4a) has also been obtained by the reaction of phosphourus



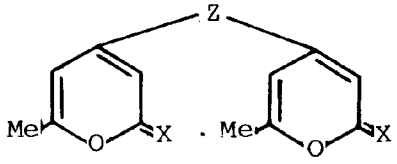
(1)



(2)



(3)
a X=O
b X=S



(4) X Z
a S S
b O SO_2

	R	X	Y				
a	OMe	O	O	i	NC_5H_{10}	S	O
b	OMe	S	O	j	$N(Me)_2$	O	S
c	OH	S	O	k	NC_4H_8	O	S
d	$N(Me)_2$	O	O	l	NC_5H_{10}	O	S
e	NC_4H_8	O	O	m	$N(Me)_2$	S	S
f	NC_5H_{10}	O	O	n	NC_4H_8	S	S
g	$N(Me)_2$	S	O	o	NC_5H_{10}	S	S
h	NC_4H_8	S	O				

pentasulphide with triacetic lactone (1) or 4-hydroxy-6-methyl-pyran-2-thione (2c). In the light of these reactions, the plausible explanation for the formation of (4a) seems to be the less stability[4] of the ether (3a) which under the reaction conditions decomposes to triacetic lactone (1) with subsequent sulphurization and dimerization to (4a).

In view of these observations the calim by Arndt[5] et al. for the formation of (3b) from (3a) is not acceptable. It may be pointed out that at that time the structural assignment of diazomethane methylation products of triacetic lactone (1) was not fully resolved and these workers[5] mistook the isomer (3a) as the sole product of methylation. Actually it was mixture of two isomeric ethers (2a, 3a) after sulphurization this gave a mixture of (2b) and (4a) to which these workers assigned structure (3b).

After having firmly established the structures of the sulphurization products, we carried out the reaction of secondary amines with methyl ether (2a) and its sulphur analogue (2b) Secondary amines[14] and other nucleophillic reagents15 have been known to decompose the pyrone ring. On the contrary, in the reaction of secondary amines with methyl ethers (2a, 2b), it has been observed that inspite of the availability of various points (2,4, and 6-position) for uncleophillic attack the initial target in all these reactions has exclusively been the replacement of the methoxy group at the 4-positon. However, in the reaction of (2b), the attack at the 4-position is followed by at the 2-position.

4-Methoxy-6-methyl-pyran-2-one (2a) on refluxing with 50% aqueous solutions of dimethylamine, pyrolidine and piperidine afforded (2d), (2e) and (2f) respectively. The striking similarity of ultraviolet (Table-I) of these compounds with that of (2a) indicates that the products have been formed with minimal structural change. The nmr data (Table-II) fits accurately and confirms the replacement of the methoxy group at the 4-position by dimethylamino pyrrolidino and piperidino groups. The carbonyl absorption bands of these compounds appear at 1690 cm^{-1} (Table-I) which is appreciably oower than expected of a 2-pyrone structure (i.e. above 1700 cm^{-1}). This is attributable to the conjugative effect[136] between thelone pair of the nitrogen of the substituent at the 4-position and the carbonyl of the ring.

4-Methoxy-6-methyl-pyran-2-thione (2b) on refluxing with 25% aqueous solution of the appropriate amine gave pyran-2-thiones (2g-i). Structures of these compounds are confirmed by the spectral data (Table-I, II). Further confirmation was obtained by converting the pyran-2-ones (2d-f) into (2g-i) by the action of phosphorus pentasulphide.

Conversion of (2b) into (2g-i) occurred very swiftly (0.25-0.5 hrs) but that of (2a) into (2d-f) required longer time (3-3.5 hrs) and higher concentration (50%) of secondary amines. This is presumably due to the greater aromatic and zwitterionic character of the pyran-2-thione (2b) ring which would be expected to facilitate the necleophilic displacement as compared to pyran-2-one (2a) ring.

Table-1. Infrared and Ultraviolet absorption data.

	ν max. cm^{-1}	λ max. nm	(log ξ)
2a	1736, 1722 (C=O); 1255 (-C-O)	281, -	3.97 -
2b	1650, 1540 (-C=C-); 1180 (C=S)	351, 277	4.07, 3.84
2c	1645, 1560 (-C=S-); 1180 (C=S)	352, 267	4.02, 3.7
2d	1690 (C=O); 1645 (-C=C-)	297, 267	4.13, 4.05
2e	1690 (C=O); 1650 (-C=C-)	297, 265	4.02, 4.03
2f	1690 (C=O); 1650 (-C=C-)	297, 265	4.05, 4.12
2g	1650 (C=C); 1180 (C=S)	350, 264	4.27, 4.36
2h	1650 (-C=C-); 1180 (C=S)	350, 267	4.33, 4.26
2i	1650 (-C=C-); 1180 (C=S)	352, 265	4.35, 4.24
2j	1615 (C=O); 1585 (C=C)	325, 264	4.13, 4.21
2k	1615 (C=O); 1585 (C=C)	325, 267	4.10, 4.12
2l	1615 (C=O); 1580 (C=C)	325, 265	4.05, 4.23
2m	1600, 1525 (-C=C-); 1180 (C=S)	392, 305	3.96, 4.15
2n	1600, 1525 (-C=C-); 1180 (C=S)	395, 305	3.96, 4.15
2o	1600, 1525 (-C=C-); 1180 (C=S)	395, 305	3.95, 4.25
4a	1630 (-C=C-); 1190 (C=S)	405, –	4.21, –
4b	1720 (C=O), 1335, 1305 (O=S=O)	340, 210	4.01, 4.31

Table-II. nmr spectra.

Compound	ppm Assignment (Position)									
2a	2.25	3H	(6)	5.82	1H	(3)		5.45	1H	(5),
	3.84	3H	(4).							
2b	2.35	3H	(6),	3.85	3H	(4)		6.1	1H	(5),
	6.73	1H	(3).							
*2c	2.3	3H	(6),	6.3	1H	(4),		6.4	1H	(3),
2d	2.3	3H	(6),	3.1	6H	(4),		5.0	1H	(5),
	5.8	1H	(3).							
2e	2.28	3H	(6),	3.4	4H	(Adj. to N in Pyrrolidine ring),				
	2.0	4H	(Pyrrolidine ring),			5.1	1H (5),	6.0	1H	(3).
2f	2.3	3H	(6),	3.5	4H	(Adj. to N in Piperidine ring),				
	1.7	6H	(Piperidine ring),			5.1	1H (5),	6.0	1H	(3).
2g	2.32	3H	(6),	3.1	6H	(4)		6.1	1H	(5),
	6.5	1H	(3).							
2h	2.31	3H	(6),	3.4	4H	(Adj. to N in Pyrrolidine ring)				
	2.04	4H	(Pyrrolidine ring),			5.8	1H (5),	6.35	1H	(3).
2i	2.31	3H	(6),	3.5	4H	(Adj. to N in Piperidine ring),				
	1.7	6H	(Piperidine ring),			6.1	1H (5),	6.6	1H	(3)
2j	2.32	3H	(6),	3.1	6H		(4),	5.57	1H	(5)
	6.6	1H	(3).							
2k	2.3	3H	(6),	3.5	4H	(Adj. to N in Pyrrolidine ring)				
	2.0	4H	(Pyrrolidine ring),			5.3	1H (5),	6.4	1H	(3)
2l	2.3	3H	(6)	3.5	4H	(Adj. to N in Piperidine ring),				
	1.7	6H	(Piperidine ring),			5.6	1H (5),	6.5	1H	(3).
2m	2.31	3H	(6),	3.18	6H	(4),		6.7	1H	(5),
	7.08	1H	(3).							
2n	2.3	3H	(6),	3.45	4H	(Adj. to N in Pyrrolidine ring)				
	2.0	4H	(Pyrrolidine ring),			6.4	1H (5),	7.0	1H	(3).
2o	2.31	3H	(6),	3.5	4H	(Adj. to N in Piperidine ring),				
	1.7	6H	(Piperidine ring),			6.6	1H (5),	7.1	1H	(3).

Pyran-2-thiones (2g), (2h) and (2i) when refluxed with 25% aqueous solution of appropriate secondary amine for a longer period of time gave thiopyran-2-ones (2j), (2k) and (2l) respectively. The same thiopyran-2-ones (j-l) were also obtained by prolonged refluxing of (2b) with 25% aqueous solution of the appropriate secondary amine. Structures of thiopyran-2-ones (2j-l) follows from elemental analysis, infrared (1615 cm^{-1} C=O of the ring[16]) and ultraviolet spectra (325 nm) which shows a hypsochromic shift of 25 nm as compared to (2g-i). The red shift is in agreement with the findings of El-Kholy[12c] et al. for similar types of compounds. The conversion of 4-substituted-6-methyl-pyran-2-thiones (2g-i) into 4-substituted 6-methyl-thiopyran-2-ones (2j-l) presumably involves the attack of secondary amines at the 2-position which results in the opening up of the ring to give intermediate thioamide (5) followed by hydrolysis to thioacid (6) and the latter finally cyclises to give 4-substituted 6-methyl-thiopyran-2-ones (2j-l).

Thiopyran-2-ones (2j-l) on refluxing with phosphorus pentasulphide in benzene gave thiopyran-2-thiones (2m-o) in good yields. The infrared spectra (table-I) of these compounds show a strong thiocarbonyl band at 1180 cm^{-1} while the carbonyl absorption[16] at 1615 cm^{-1} of the original thiopyran-2-ones (2j-l) disappears. Ultraviolet spectra (395 nm, Table-I) show a bathochromic shift[12c] of the order of 70nm as compared to (21-n) due to the transormation of carbonyl to thiocarbonyl group.

Experimental

Ultraviolet spectra were recorded on a Unicam SP 800 spectrophotometer in ethanol, infrared spectra Unicam SP 200 for mulls in Nujol and nuclear magnetic resonance spectra were measured wth Perkin-Elmer R 10 (60 MHZ) spectrophotometer, with deutero-chloroform as solvent, tetramethylsilane as internal reference and are quoted in ppm, unless otherwise stated. All melting points are uncorrected and were taken on Gallen-kamp melting point apparatus.

6-Methylpyran-2, 4-dione (Triacetic lactone) (I) was obtained by deacetylating the dehydroacetic acid as described by Collie[1]. m.p. 190°C.

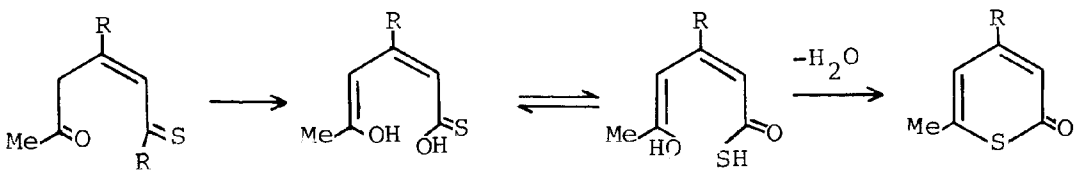
4-Methoxy-6-methyl-pyran-2-one (2a) and 2-methoxy-6-methyl-pyran-4-one (3a) were prepared by the diazomethane methylation of triacetic acid lactone. An improved yield (25%) of isomer (3a) was obtained by gradually adding the triacetic lactone to diazomethane solution in dry ether. Isomer (2a) on crystallisation from dry benezene and cyslohexane mixture (1:4) gave white needles (60%), m.p. 87°C (Lit[4]. m.p. 87°C) while isomer (3a) from cyclohexane gave white needles m.p. 92°C (Lit[4]. m.p. 92°C).

4-Methoxy-6-methyl-pyran-2-thione (2b): A solution of 4-methoxy-6-methyl-pyran-2-one (2a) (I g) in dry benzene was refluxed with phosphorus pentasulphide (I g) for two hours. After cooling the reaction mixture, benzene layer was decanted off. The residue was extracted with hot benzene(50ml). The combined extracts were washed with dilute solution of ammonium sulphide and then with water. After drying (Sodium sulphate) the extracts were evaporated to dryness. Residue on recrystallization from benzene-petroleum ether 60-80°C gave light yellow neddles m.p.125°C. (Found:- C, 53.52; H, 5.33; S, 20.49 $C_7H_8O_2S$ requires C, 53.84; H, 5.12; S,20.51%).

Compound (2b) on treatment with hydrogen peroxide in acetic acid gave back (2a). Identified by m.p., and comparison of spectral data.

4-Hydroxy-6-methyl-pyran-2-thione (2c):- Compound (2b) (0.3g) on refluxing with 20% hydrochloric acid (8ml) for 20 minutes and evaporation uder vacuo gave light yellow solid which on crystallization from benzene-petroleum ether (60-80°C) mixture (1:3) gave light yellow needles m.p. 162-164°C, m/e 142 (M^+) (Found:- C, 50.70: H, 4.22; S, 22.56 $C_6H_6O_2S$ requires C, 50.70; H, 4.22; S, 22.5%).

Compound (2c) on treatment with hydrogen per-



(5) (6) (2J-L)

oxide in acetic acid gave triacetic lactone (1). Identified by m.p. and mixed m p.

4, 4-Bis(6-methyl-pyran-2-thione) sulphide (4a):- A mixture of 2-methoxy-6-methyl-pyran-4-one (3a) (0.5g) and phosphorus pentasulphide (0.5g) in dry benzene (15ml) was refluxed for two hours. Benzene was decanted off Residue was extracted with benzene (20 ml) as well as with chloroform (20ml). Extracts on evaporation gave deep yellow solid, which on crystallization from chloroform-ethanol mixture (2:1) gave bright yellow microcrystalline solid, m.p. 235°C, mass spectrum m/e 282 (M^+); (Found:- C, 51.09; H, 3.98; S, 34.05; $C_{12}H_{10}O_2S_3$ requires C, 51.06; H, 3.54; S, 34.04%) *The same product (4a) was also obtained when triacetic lactone (1) or 4-hydroxy-6-methyl-pyran-2-thione (2c) was refluxed with phosphorus pentasulphide in dry benzene. The identify of the compound was established by m.p., mixed, m.p. and comparison of spectral data.

4, 4-Bis (6-methyl-pyran-2-one) sulphone (4b) :- A mixture of (4a) (0.5g) in glacial acetic acid (20ml) and hydrogen peroxide (10ml) was kept at room temperature for 8 days; Dilution with water gave light yellow solid which on crystallization from benzene-petroleum ether (60-80°C) mixture (4:1) gave faint yellow solid m.p., 190°C. (Found:- C, 51.00; H, 3.73; S, 10.95 $C_{12}H_{10}O_6S$ requires C, 51.06. H, 3.54. S, 11.34%).

General method for the preparation of compounds (2d-l):- A mixture of (2a) or (2b) (0.5g) in appropriate aqueous solution of secondary amine was refluxed for different periods of time. Reaction mixtures on evaporation under vacuum gave solid products which were crystallized from benezene-petroleum ether (60-80°C) mixture. For experimental conditions and analytical data see table III.

4-Substituted 6-methylthiopyran-2-thione (2m-o):- These compounds were obtained by refluxing (3 hrs.) the appropriate 4-substituted 6-methyl-thiopyran-2-one

Table -III. Experimental conditions and analytical data for compounds (2d-l)

* Compound	Pyrone/ Thiopyrone	Sec. Aq.	Amine Solution.	%	ml	Refl. time hr.	% Yield	m.p.
2d	2a	$HN(Me)_2$		50	10	3.5	50	150°C
2e	2a	HNC_4H_8		50	10	3.0	40	180°C
2f	2a	HNC_5H_{10}		50	10	3.0	50	170°C
2g	2b	$HN(Me)_2$		25	8	0.5	40	190°C
2h	2b	HNC_4H_8		25	8	0.25	50	215-17°C
2i	2b	HNC_5H_{10}		25	8	0.25	50	165°C
2j	2g	$HN(Me)_2$		25	15	3.0	40	160°C
2k	2h	HNC_4H_8		25	15	3.0	40	200°C
2l	2i	HNC_5H_{10}		25	15	3.0	40	150°C

	Calculated (%)				Formula	Found (%)			
	C	H	S	N		C	H	S	N
2d	62.74	7.18	–	9.15	$C_8H_{11}NO_2$	62.50	7.00	–	9.41
2e	67.04	7.26	–	7.82	$C_{10}H_{13}NO_2$	66.64	7.19	–	8.03
2f	68.39	7.77	–	7.25	$C_{11}H_{15}NO_2$	68.10	7.65	–	7.15
2g	56.80	6.50	18.93	8.28	$C_8H_{11}NOS$	56.51	6.38	18.84	7.89
2h	61.53	6.66	16.4	7.17	$C_{10}H_{13}NOS$	61.64	6.51	16.35	7.0
2i	63.15	7.17	15.31	6.69	$C_{11}H_{15}NOS$	63.0	7.30	15.12	6.51
2j	56.80	6.50	18.93	8.28	$C_8H_{11}NOS$	57.16	6.41	18.81	8.43
2k	61.53	6.66	16.4	7.17	$C_{10}H_{13}NOS$	61.64	6.7	16.29	7.17
2l	63.15	7.17	15.31	6.69	$C_{11}H_{15}NOS$	62.86	7.38	14.93	6.48

*(i) Compounds (2d-f) with phosphorus pentasulphide in benzene also gave (2g-i).

(ii) Compounds (2j-l) were also obtained by refluxing a mixture of (2b) and 25% aqueous solution of appropriate amine (10ml) for 3.5 hours.

(2j-l) (0.5g) with phosphorus pentasulphide (1 g) in dry benzene (15ml). Benzene was removed under vacuum. Residues were treated with 5% solution of ammonium sulphide (6ml). The products (80%) were filtered. All products were crystallized from benzene-petroleum ether (60-80°C) mixture (1:3) as bright yellow needles. Compound (2m). m.p. 197°C. (Found:- C, 51.68; H, 6.02; S, 34.77; N, 7.49 $C_8H_{11}S_2N$ requires C,51.89; H,5.94; S, 34.59; N, 7.5%). Compound (2n) m.p. 210°C (Found:- C,57.04; H; 6.0; S, 30.10; N, 6.52; $C_{10}H_{13}S_2N$ requires C, 56.87; H, 6.16; S, 30.33; N,6.63%) Compound (2b) m.p. 205°C. (Found: – C, 58.61: H, 6.66: S, 28.15: N, 6.20 $C_{11}H_{15}S_2N$ requires C, 58.66: H, 6.66: S, 28.44: N, 6.22%).

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