Reversible Cyclization of *N*-(3-Hydroxy-1-Alkenyl)Pyridinium Salts to Pyridooxazines

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Partially hydrogenated pyrido[2,1-*b*][1,3]oxazine, cyclopenta[*d*]pyrido[2,1-*b*][1,3]oxazine and pyrido[1,2-*a*]-[3,1]benzoxazine ring systems were easily formed in the reaction of 3-hydroxy-2-(2-hydroxy-1,3-dioxo-2-indanyl)-2-alken-1-one derivatives with tosyl chloride and pyridine bases. A facile interconversion between pyridooxazines and the corresponding pyridinium salts was also realized.

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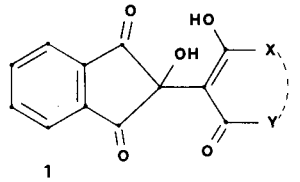
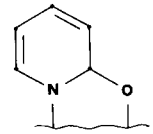
We have recently reported on the dehydration of adducts from 1,2,3-indanetrione with acyclic CH-acid compounds by two different dehydrating systems (1,2). During that investigation strong resistance of the analogous adducts with cyclic CH-acid compounds (1) towards the elimination reaction was observed.

Studies were continued by trying tosyl chloride in pyridine as a further dehydrating system on adducts **1a-e** (3), and the following results were obtained. Adducts **1b** and **1e** afforded nitrogen products directly, the spectroscopic data of which, especially uv and nmr (reported in Figures 1 and 2 for the compound derived from **1b**), suggested the presence of the type **2** dihydropyridine ring moiety (4,5). Adducts **1a** and **1d** produced a pyridinium salt and a pyridinium betaine, respectively. The betaine from **1d** was unaffected by treatment with aqueous bicarbonate solution, whereas pyridinium salt from **1a** yielded a product, the spectroscopic properties of which indicated a structure very close to that of the products obtained from **1b** and **1e**.

The dihydropyridine ring **2**, in the products from **1a,b,e**, could be formed *via* the following reaction



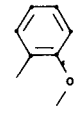
1



2

a : x ... y = $-CH_2-CH_2-$; b : x ... y = $-CH_2-CH_2-CH_2-$

c : x ... y = $-CH_2-C(CH_3)_2-CH_2-$; d : x ... y =



e : x = y = H

sequence: tosylation of the hydroxyl group (enolic or alcoholic); nucleophilic substitution by pyridine; and intramolecular ring closure of the resulting pyridinium salt. Nevertheless, careful examination of physical and spectroscopic data of the three cyclization products did not allow

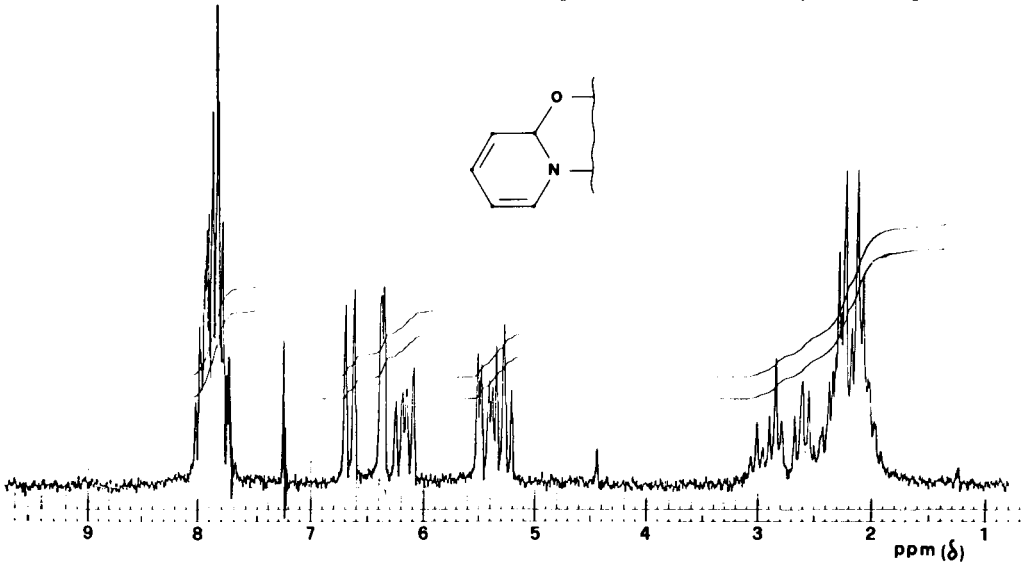


FIG. 1 : 100 - MHz nmr spectrum of compound 3b (R=H) in $CDCl_3$

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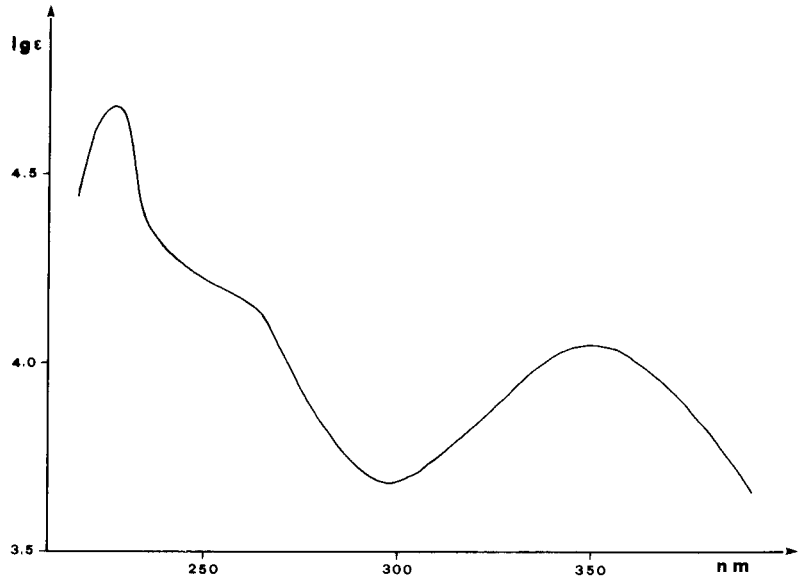
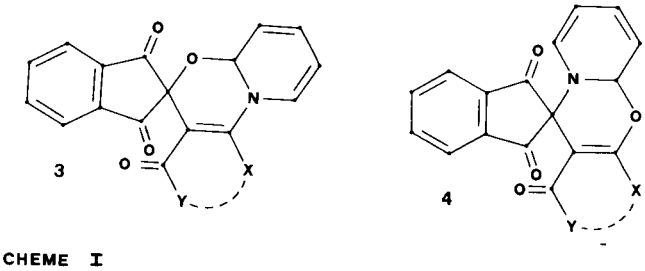


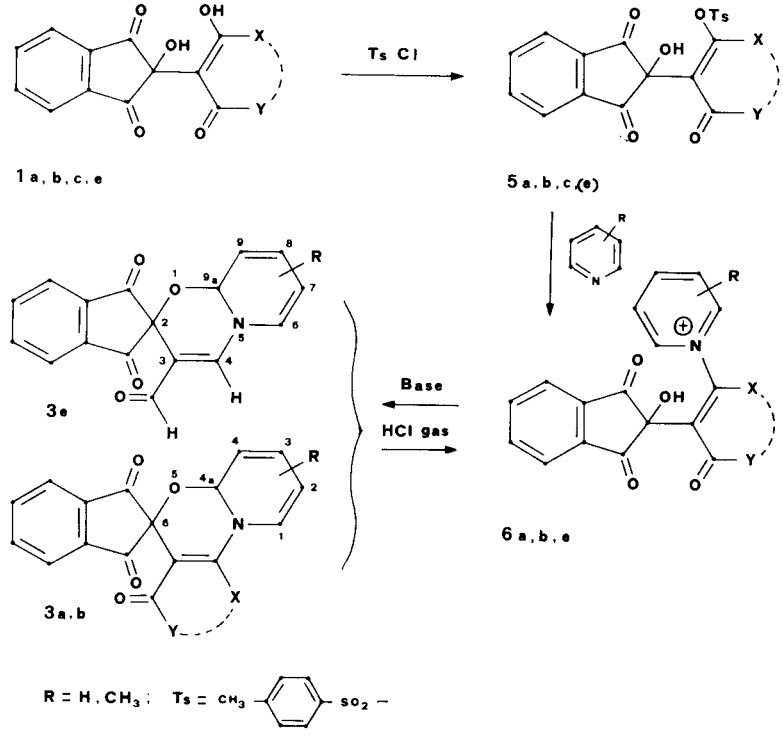
FIG. 2: UV spectrum (CH_3CN) of compound 3b (R = H)

any conclusive structure differentiation between the two possible isomeric pyridooxazine structures **3** and **4**, derived from tosylation of enolic or alcoholic hydroxyl group, respectively.

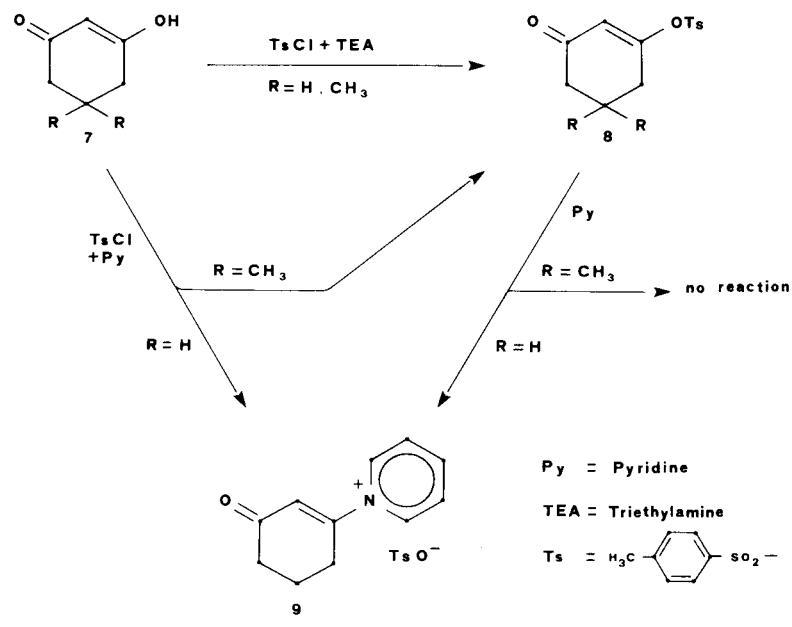
To achieve an unambiguous structure assignment we then synthesized a *p*-toluenesulfonate derivative of **1b** by using tosyl chloride and the more hindered base triethylamine instead of pyridine; the spectroscopic data clearly



SCHEME I



SCHEME II



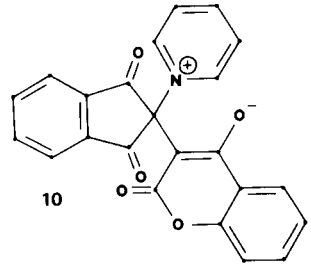
demonstrated that tosylation had occurred at the enolic function giving **5b**. Treatment of **5b** with pyridine gave the same product as the one formed directly in the reaction of **1b** with tosyl chloride and pyridine.

This result definitely proved that **5b** was an intermediate and that the true structure of the cyclized compound from **1b** was **3b**, 4a*H*,8*H*-9,10-dihydropyrido[1,2-*a*]-[3,1]benzoxazine-6-spiro-2′-indane-7,1′,3′-trione. By analogy that from **1a** was **3a**, 4a*H*-8,9-dihydrocyclopenta-[*d*]pyrido[2,1-*b*][1,3]oxazine-6-spiro-2′-indane-7,1′,3′-trione and the one from **1e** was **3e**, 3-formyl-2*H*,9a*H*-pyrido-[2,1-*b*][1,3]oxazine-2-spiro-2′-indane-1′,3′-dione. The formation of these products occurred according to Scheme I (R = H).

As indicated in Scheme I, the annulation reaction in the last step was reversible: when treated with hydrogen chloride, pyridooxazines **3** produced pyridinium salts **6**, which in turn could be converted back to **3** by simple treatment with aqueous sodium bicarbonate solution. This facile interconversion, similar to others already known (6,7), was especially interesting because of the significant analogy with the biological behaviour of pyridine coenzymes (8) and with the reaction sequence leading to the *in vivo* conversion of nicotinamide to nicotine (9).

Unlike **1a,b,e**, adduct **1c**, upon treatment with tosyl chloride in pyridine, only produced tosylate **5c**, which remained unchanged even under more drastic experimental conditions. The conversion of enolic tosylates **5** into pyridinium salts **6** is a vinylic substitution, a well known reaction that easily takes place only on activated substrates (10-12). In the case of **5c**, this process apparently suffered strong steric hindrance by geminal methyl groups. Similar steric effects have already been observed in many other six-membered cyclic structures bearing methyl groups in suitable positions (13-16), but in our case the complete inhibition of substitution in **5c** as compared with **5b** was rather surprising. However, it was observed that this behaviour was retained also by enolic tosylate of dimedone **8** (R = CH_3), which proved to be unreactive towards pyridine, whereas the enolic tosylate of 1,3-cyclohexanedione **8** (R = H) gave the normal substitution product **9**, as can be seen in Scheme II.

The anomalous behaviour of adduct **1d**, giving a pyridinium betaine unable to cyclize to pyridooxazine structure, was consistent with the intermediate formation of an alcoholic tosylate which after substitution gave betaine structure **10**. Both the different tosylation site and



10

the failure to cyclize could be related to the lesser nucleophilic character of the enolic oxygen in **1d** with respect to that of the other adducts, due to the stronger acidity of the 4-hydroxycoumarine moiety.

The extension of the tosylation reaction on adducts **1a,b,e**, to picoline bases gave the following results. 2-Methylpyridine yielded a pyridooxazine derivative **3e** (R = 6-CH_3) only from adduct **1e**, whereas the enolic tosylates **5a** and **5b** were obtained from adducts **1a** and **1b**, respectively. This different behaviour could again be ascribed to stronger steric interactions arising in the approach of the base to the nucleophilic substitution site in cyclic enolic tosylates **5a** and **5b** with respect to the acyclic enolic tosylate **5e**, a supposed intermediate that was not isolated. Reaction with 3-methylpyridine afforded pyridooxazine derivatives **3a** (R = 4-CH_3), **3b** (R = 4-CH_3), and **3e** (R = 9-CH_3), derived from a nucleophilic attack of the alcoholic group at the 2-position of the intermediate 3-methylpyridinium salts **6**. Small amounts (13-15%) of isomers derived from an attack at the 5-position could be detected by careful analysis of the nmr spectra of the crude products (17). A similar isomeric ratio was also observed in the cyclization of 3-methylpyridinium salts **6** to give pyridooxazines **3** by aqueous bicarbonate solution. This remarkable regioselectivity of the nucleophilic attack was in good agreement with previous findings concerning other nucleophilic reactions on 3-methylpyridinium cations (18-21). Finally, 4-methylpyridine led to the expected pyridooxazine derivatives **3a** (R = 3-CH_3), **3b** (R = 3-CH_3) and **3e** (R = 8-CH_3).

Further studies are in progress in our laboratory to apply this facile annulation reaction to the synthesis of new heterocyclic ring systems of chemical and pharmaceutical importance.

EXPERIMENTAL

Melting points were determined by capillary method on a Dr. Tottoli apparatus (Buchi) and are uncorrected. Ir spectra were recorded as potassium bromide pellets on a Perkin Elmer model 283 spectrophotometer. Uv spectra were recorded on a Cary 15 spectrophotometer. Nmr spectra were taken on Varian EM-360 instrument using TMS or DSS as internal standards; the following abbreviations were used: s, singlet; dd, double doublet; t, triplet; dt, double triplet; q, quartet; m, multiplet(s); br, broad signal. Exchange with deuterium oxide was used to identify hydroxyl protons. Chromatographic separations were carried out on silica gel columns (0.06-0.2 mm, Merck).

Preparation of Adducts **1a-d**.

A solution of ninhydrin (1.78 g., 10 mmoles) and the appropriate β-dicarbonyl compound (cyclopentanedione, cyclohexanedione, dimedone (22), 4-hydroxycoumarine, 10 mmoles) in 25 ml. of ethanol was stirred at room temperature for 3-6 hours. The solid product which formed was collected and crystallized from ethanol (Table I).

2-Hydroxy-2-(bisformylmethyl)-1,3-indanedione (**1e**).

Malonaldehyde bisdimethylacetal (1.80 g., 11 mmoles) was added dropwise to a stirred aqueous solution (30 ml.) of ninhydrin (1.78 g., 10 mmoles) heated at 50-55°. After 2 hours the reaction mixture was cooled and the precipitate was collected and crystallized from acetone-hexane to give 2.20 g. of **1e** (Table I).

Reaction of Adducts **1** with Tosyl Chloride in Pyridine and in Methyl Pyridines (23).

Tosyl chloride (0.63 g., 3.3 mmoles) was added to a stirred ice-cooled solution of the adduct **1** (3 mmoles) in 4-5 ml. of anhydrous pyridine or methyl pyridine. The reaction mixture was then allowed to warm to room temperature and was stirred for another 2 hours; different work-up procedures were used as specified for single adducts.

Adduct **1a**.

A precipitate was formed. It was collected, washed with a few drops of anhydrous dioxane and crystallized.

Reaction in pyridine and 4-methylpyridine gave pyridinium chlorides **6a** in 80% and 40% (24) yield, respectively, whereas reaction in 3-methylpyridine afforded the cyclopenta[*d*]pyrido[2,1-*b*][1,3]oxazine derivative **3a** (R = 4-CH_3) (25) (Tables II-IV) directly.

Reaction with 2-methylpyridine produced the enolic tosylate **5a** in 40% yield, m.p. 132-136° dec., uncrystallized (26); ir: ν max 3360, 1750, 1710, 1685, 1640 cm^{-1}; nmr (27) (dimethyl sulfoxide-d_6): δ 2.43 (s, 3H, CH_3, partially masked by solvent signal), 2.2-2.5 (m, 2H, CH_2-CO-, partially masked by solvent signal), 2.95 (m, 2H, CH_2-C=C), 3.80 (s, 1H, -OH),

Table I

Physical, Analytical and Spectroscopic Data of Adducts **1** (22)

Compound No.	Yield %	M.p. °C	Formula	Analysis Calcd./Found % C	H	Ir (cm^{-1}) (Potassium Bromide Discs)	Nmr (Dimethyl Sulfoxide-d_6) δ (ppm); J, Hz
1a	92	201-203 dec.	$C_{14}H_{10}O_5$	65.12 65.41	3.90 3.88	3500, 1760, 1750, 1720, 1640, 1600,	2.40 (s, 4H, CH_2), 7.98 (s, br, 4H aromatics), 8.04-8.60 (br, 2H, OH)
1b	95	170-172 dec.	$C_{15}H_{12}O_5$	66.17 65.90	4.44 4.20	3360, 1730, 1710, 1640, 1610	1.82 (m, 2H, CH_2-CH_2-CH_2), 2.25 (s, br, 4H, CH_2-CH_2-CH_2), 7.80 (s, 4H, aromatics), 8.02-8.70 (br, 2H, OH)
1d	90	197-199 dec.	$C_{18}H_{10}O_6$	67.08 67.40	3.13 3.06	3440, 3360, 1755, 1710, 1660, 1630 1610	6.80-7.60 (br., partially masked, 2H, -OH), 6.42 (m, 2H), 6.70 (m, 2H), 8.07 (s, br, 4H, indane)
1e	95	143-145 dec.	$C_{12}H_8O_5$	62.07 62.39	3.47 3.46	3540, 3440, 3160, 1735, 1665, 1650, 1600	4.30-6.50 (br, 2H, -OH), 7.94 (s, 4H, aromatics), 8.60 (s, 2H, -CHO and =CHOH)

Table II

Physical and Analytical Data of Compounds **3**

Compound No.	R	Yield %	M.p. °C Solvent(s)	Formula	Analysis Calcd./Found % C	H	N
	H	– (a)	170-172 dec.	$C_{19}H_{13}NO_4$	71.47	4.10	4.39
			benzene		71.78	3.99	4.15
3a	4-CH_3	75	169-171 dec.	$C_{20}H_{15}NO_4$	72.06	4.54	4.20
			chloroform-hexane		72.37	4.46	3.86
	3-CH_3	– (a)	153-155 dec.	$C_{20}H_{15}NO_4$		as above	
			benzene		72.42	4.37	4.17
	H	72	189-191 dec.	$C_{20}H_{15}NO_4$		as above	
			benzene		72.35	4.40	4.02
3b	4-CH_3	76	187-189 dec.	$C_{21}H_{17}NO_4$	72.61	4.93	4.03
			benzene		72.92	4.64	3.88
	3-CH_3	58	176-178 dec.	$C_{21}H_{13}NO_4$		as above	
			benzene		72.41	4.84	3.96
	H	72	114-116 dec.	$C_{17}H_{11}NO_4$	69.62	3.78	4.78
			chloroform-hexane		69.98	3.74	4.43
	6-CH_3	65	129-130 dec.	$C_{18}H_{13}NO_4$	70.35	4.26	4.56
3e			benzene		69.99	4.14	4.33
	9-CH_3	77	115-117 dec.	$C_{18}H_{13}NO_4$		as above	
			benzene		70.59	4.28	4.24
	8-CH_3	52	103-105 dec.	$C_{18}H_{13}NO_4$		as above	
			chloroform-hexane		70.01	4.06	4.29

(a) Yield not reported because the product was not obtained directly by treatment of **1a** with tosyl chloride and pyridine bases but only by cyclization of pyridinium chloride **6a** with sodium bicarbonate solution (see Experimental).

Table III

Ir (a), Uv (b) and Nmr (c) Data of Compounds **3**

Compound No.	R	Ir (Potassium Bromide Discs), ν cm^{-1}	Uv, λ max Log ϵ	Nmr, δ (ppm), J = Hz
	H	1750, 1710, 1675, 1660, 1610, 1570	229 (4.71), 251 (4.36), 340 (4.04)	2.42 (m, 2H, CH_2), 2.85 (m, 2H, CH_2), 7.94 (m, 4H, aromatics)
3a	4-CH_3	1750, 1715, 1670, 1660, 1615, 1580	229 (4.73), 251 (4.43), 342 (4.09)	1.78 (s, 3H, CH_3), 2.42 (m, 2H, CH_2), 2.86 (m, 2H, CH_2), 7.96 (m, 4H, aromatics)
	3-CH_3	1750, 1715, 1685, 1670, 1620, 1580	229 (4.75), 252 (4.42), 331 (4.10)	1.83 (s, 3H, CH_3), 2.43 (m, 2H, CH_2), 2.89 (m, 2H, CH_2), 7.98 (m, 4H, aromatics)
	H	1750, 1715, 1635, 1600,1570	227 (4.67), 243 sh (4.28), 258 sh (4.18), 349 (4.05)	1.90-2.40 (m, 4H, CH_2-CH_2), δ_A = 2.55, δ_B = 2.91 (2H, CH_2, AB system (d) J_{AB} = 16 Hz) 7.90 (m, 4H, aromatics)
3b	4-CH_3	1750, 1715, 1635, 1605, 1570	227 (4.71), 242 sh (4.33), 258 sh (4.22), 352 (4.14)	1.78 (s, 3H, CH_3), 1.90-2.40 (m, 4H, CH_2-CH_2), δ_A = 2.50, δ_B = 2.88 (2H, CH_2, AB system (d), J_{AB} = 16 Hz), 7.93 (m, 4H, aromatics)
	3-CH_3	1750, 1715, 1675, 1635, 1600, 1570	227 (4.75), 242 sh (4.37), 260 sh (4.29), 348 (4.14)	1.82 (s, 3H, CH_3), 1.90-2.40 (m, 4H, CH_2-CH_2), δ_A = 2.54, δ_B = 2.91 (2H, CH_2, AB system (d) J_{AB} = 16 Hz), 7.88 (m, 4H, aromatics)
	H	1745, 1710, 1645, 1615, 1565	228 (4.70), 243 sh (4.35), 350 (4.16)	8.06 (s, 4H, aromatics), 8.40 (s, 1H, *CH*=C-CHO), 9.11 (s, 1H, CHO)
	6-CH_3	1750, 1710, 1640,	228 (4.67), 246 sh (4.31),	2.10 (s, 3H, CH_3), 7.97 (m, 5H, 4 aromatics + *CH*=C-CHO),
3e		1615, 1580	351 (4.12)	9.13 (s, 1H, CHO)
	9-CH_3	1745, 1710,1640, 1620, 1580	228 (4.82), 247 sh (4.47), 351 (4.24)	1.60 (s, 3H, CH_3), 8.11 (s, 4H, aromatics), 8.43 (s, 1H, *CH*=C-CHO), 9.12 (s, 1H, CHO)
	8-CH_3	1745, 1710, 1645, 1620, 1580	228 (4.70), 249 sh (4.32), 348 (4.14)	1.77 (s, 3H, CH_3), 7.72 (s, 1H, *CH*=C-CHO), 7.95 (m, 4H, aromatics), 9.10 (s, 1H, CHO)

(a) Only absorption bands in the more significant range 1800-1500 cm^{-1} were reported. (b) Uv spectra were recorded in acetonitrile solution. (c) Nmr parameters of the dihydropyridine ring protons are reported separately in Table IV. Spectra were recorded in deuteriochloroform except for **3e** (R = H, 9-CH_3) for which dimethylsulfoxide-d_6 was used. (d) Further split into triplets.

7.52 (d, 2H, aromatics, tosyl), 7.97 (s, 4H, aromatics, indane), 8.00 (d, 2H, aromatics, tosyl, partially masked).

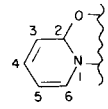
Anal. Calcd. for $C_{21}H_{16}SO_7$: C, 61.16; H, 3.91. Found: C, 60.88; H, 4.10.

Adduct **1b**.

The reaction mixture from pyridine, 3-methylpyridine and 4-methylpyridine, was poured on ice and the precipitate was collected, washed with water and crystallized to give pyrido[1,2-*a*][3,1]benzoxazine derivatives **3b** (R = H, 4-CH_3 (25), 3-CH_3, respectively) (Tables II-IV) directly.

The reaction mixture from 2-methylpyridine, after 24 hours of stirring, was poured on ice cooled 2*N*-hydrochloric acid and rapidly extracted with chloroform. The organic phase, dried on sodium sulfate and evaporated to dryness under vacuum without heating, afforded a moderately unstable enolic tosylate **5b** (28) in 35% yield, m.p. 103-105° from anhydrous acetone-hexane; ir: ν max 3250, 1750, 1715, 1650, 1615 cm^{-1}; nmr (27) (dimethyl sulfoxide-d_6): δ 1.85 (m, 2H, -CH_2-CH_2-CH_2), 2.0-2.5 (m, 4H, CH_2-CH_2-CH_2), 2.28 (s, 3H, CH_3), 7.13 (d, 2H, aromatics, tosyl), 7.56 (d, 2H, aromatics, tosyl), 7.78 (s, 4H, aromatics, indane), OH, masked in the range 1.5-2.5.

Table IV

Nmr (a) Parameters of Dihydropyridine Ring Protons  of Compounds **3**

Compound No.	R	H-2	H-3	H-4	H-5	H-6	J_{2-3} (b)	J_{3-4}	J_{4-5}	J_{5-6}
	H	6.80	5.49	6.15	5.26	6.48	3	10	6	7.5
3a	3-CH_3	6.65	—	5.91	5.24	6.40	—	—	6	7.5
	4-CH_3	6.79	5.33	—	5.21	6.53	3	—	—	8.
	H	6.40	5.46	6.18	5.29	6.67	3	10	6	7.5
3b	3-CH_3	6.26	—	5.94	5.26	6.58	—	—	6	7.5
	4-CH_3	6.31	5.22	—	5.18	6.62	3	—	—	8
	H	6.40	5.49	6.22	5.37	6.87	3	10	6	7.5
3e	6-CH_3	6.53	5.45	6.13	5.17	—	2.5	10	6	—
	3-CH_3	6.28	—	6.05	5.37	6.83	—	—	6	7.5
	4-CH_3	6.48	5.20	—	5.13	6.38	3	—	—	7

(a) Spectra were recorded in the solvents indicated in Table III. Numbering of the dihydropyridine ring protons and methyl groups refers to that indicated in the head of the table and does not correspond to the correct one of the pyridooxazine structures **3** shown in Scheme I. (b) Approximate values due to further allylic splitting.

Table V

Physical and Analytical Data of Pyridinium Chlorides **6** (a)

Compound No.	R	M.p., °C (b,c)	Formula (b)	Analysis Calcd./Found % C	H	N	Cl
	H	196-198 dec.	$C_{19}H_{14}ClNO_4$	64.14	3.97	3.94	9.96
				64.47	4.08	3.71	9.65
6a	3'-CH_3	163-165 dec.	$C_{20}H_{16}ClNO_4$	64.96	4.36	3.79	9.59
				64.68	4.56	3.51	9.26
	4'-CH_3	204-206 dec.	$C_{20}H_{16}ClNO_4$		as above		
				65.29	4.47	3.55	9.29
	H	176-178 dec.	$C_{20}H_{16}ClNO_4$		as above		
				65.25	4.58	3.49	9.24
6b	3'-CH_3	184-186 dec.	$C_{21}H_{18}ClNO_4$	65.71	4.73	3.65	9.24
				65.40	5.04	3.35	8.97
	4'-CH_3	234-236 dec.	$C_{21}H_{18}ClNO_4$		as above		
				66.01	4.57	3.55	9.56
	H	136-138 dec.	$C_{19}H_{18}ClNO_5$	60.72	4.83	3.73	9.82
				60.79	4.89	3.49	9.53
6e	2'-CH_3	145-147 dec.	$C_{20}H_{20}ClNO_5$	61.62	5.17	3.59	9.19
				61.95	5.19	3.36	9.09
	3'-CH_3	134-136 dec.	$C_{20}H_{20}ClNO_5$		as above		
				61.97	5.38	3.33	9.09

(a) Pyridinium chloride **6e** (R = 4'-CH_3) has not been isolated (29). (b) Pyridinium chlorides **6e** were obtained as ethyl hemiacetals from absolute ethanol. (c) Pyridinium chlorides **6a,b** were crystallized from ethanol-ethyl ether.

Anal. Calcd. for $C_{22}H_{18}SO_7$: C, 61.96; H, 4.25. Found: C, 61.70; H, 4.50.

Adduct **1c**.

Enolic tosylate **5c** was isolated in 65% yield as a precipitate by pouring the reaction mixture on ice, m.p. 161-162° from acetone-hexane; ir: ν max 3330, 1760, 1730, 1625, 1600 cm^{-1}; nmr (27) (dimethyl sulfoxide-d_6): δ 0.98 (s, 6H, CH_3), 2.18 (s, 2H, CH_2-CO), 2.37 (s, 3H, CH_3), 2.77 (s, 2H, -CH_2-C=C), 3.40 (br, 1H, OH), 7.38 (d, 2H, aromatics, tosyl), 7.88 (d, 2H, aromatics, tosyl), 7.90 (s, 4H, aromatics, indane).

Anal. Calcd. for $C_{24}H_{22}SO_7$: C, 63.42; H, 4.88. Found: C, 63.70; H, 4.82.

Adduct **1d**.

Pyridine betaine **10** was obtained in 85% yield by the above work-up procedure, m.p. 208-210° dec. (not sharp) from dioxane-hexane; ir: ν max 1745, 1705, 1670, 1600 cm^{-1}; nmr (dimethyl sulfoxide-d_6): δ 6.95-7.25 (m, 2H, aromatics, coumarine) 7.43 (dt, 1H, aromatic, coumarine, J = 8, J = 2 Hz), 7.62 (dd, 1H, aromatic, coumarine, J = 8, J = 2 Hz), 7.97 (m, 4H, aromatics, indane), 8.10 (m, 2H, β-pyridinium), 8.62 (m, 1H, γ-pyridinium), 9.05 (m, 2H, α-pyridinium).

Adduct **1e**.

Pyrido[2,1-*b*][1,3]oxazine derivative **3e** (R = H, 6-CH_3, 9-CH_3 (25), 8-CH_3) were obtained from reaction in pyridine, 2-methyl, 3-methyl and 4-methylpyridine, respectively (Table II-IV) by using the same workup procedure described for pyrido-oxazines **3b**.

Conversion of Pyridooxazines **3** to Pyridinium Chlorides **6**.

The pyridooxazine derivative **3** was dissolved in the minimum amount of anhydrous methylene chloride at room temperature and dry hydrogen chloride was gently bubbled through the solution. The precipitate (29) was collected and crystallized to give **6** in 85-90% yield (Tables V-VI).

Cyclization of Pyridinium Chlorides **6** to Pyridooxazines **3**.

A saturated aqueous bicarbonate solution (2 ml.) was added at room temperature to a solution of pyridinium salts **6** (1 mmole) in 4-5 ml. of water. The precipitate was filtered and crystallized to give pyridooxazine derivative **3** in 90-95% yield.

3-*p*-Toluenesulfonyloxy-5,6-dimethyl-2-cyclohexen-1-one (**8**) (R = CH_3) and *N*-(3-Oxo-1-cyclohexenyl)pyridinium *p*-Toluenesulfonate (**9**).

Tosyl chloride (2.28 g., 12 mmoles) was added to a stirred ice-cooled solution of **7** (10 mmoles) in anhydrous pyridine (5 ml.). The reaction mixture was then allowed to warm to room temperature and stirred 2 hours for **7** (R = H) and 10 hours for **7** (R = CH_3). The precipitate from **7** (R = H) was collected, washed with anhydrous dioxane and crystallized from ethanol-ethyl ether to give 2.5 g. of **9** (72% yield), m.p. 173-175° dec.; ir: ν max 1680, 1625, 1210, 1195, 1030, 1010 cm^{-1}; nmr (27) (deuterium oxide): δ 2.25 (m, 2H, -CH_2-CH_2-CH_2), 2.32 (s, 3H, CH_3), 2.53 (m, 2H, CH_2-CO), 2.94 (m, 2H, CH_2-C=C), 6.39 (s, br, 1H, CH), 7.15 (d, 2H, aromatics, tosyl), 7.57 (d, 2H, aromatics, tosyl), 8.10 (m, 2H, β-pyridinium), 8.63 (m, 1H, γ-pyridinium), 8.90 (m, 2H, α-pyridinium).

Anal. Calcd. for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.05. Found: C, 62.86; H, 5.62; N, 3.71.

The reaction mixture from **7** (R = CH_3) was diluted with chloroform and extracted with 2*N* hydrochloric acid and water. The organic layer was dried (anhydrous sodium sulfate), the solvent eliminated under vacuum, and the residue gave, after chromatographic purification on a silica gel column (50-50 ethyl acetate-hexane as eluent), 2.50 g. of **8** (R = CH_3) (85% yield), m.p. 52-53° from hexane; ir: ν max 1680, 1640, 1600, 1375, 1360, 1190, 1175 cm^{-1}; nmr (30) (deuteriochloroform): δ 1.06 (s, 6H, gem-CH_3), 2.20 (s, 2H, CH_2-CO), 2.37 (s, 2H, CH_2-C=C), 2.47 (s, 3H, CH_3), 5.74 (s, 1H, -CH), 7.33 (d, 2H, aromatics), 7.79 (d, 2H, aromatics).

Anal. Calcd. for $C_{15}H_{18}SO_4$: C, 61.20; H, 6.16. Found: C, 61.47; H, 6.08.

Table VI

Spectroscopic Data of Pyridinium Chlorides **6**

Compound No.	R	Ir (Potassium Bromide Discs), ν cm^{-1}	Uv (a) λ max nm, (log ϵ)	Nmr (b), δ (ppm), J = Hz
	H	3510, 3440 1760, 1725, 1715, 1665, 1635, 1600	233 (4.71), 250 sh (4.30)	3.03 (m, 2H, CH_2-CO), 3.62 (m, 2H, CH_2-C=C), 8.34 (s, 4H, aromatics indane), 8.63 (m, 2H, β-pyridinium), 9.07 (m, 1H, γ-pyridinium), 9.59 (m, 2H, α-pyridinium)
6a	3'-CH_3	3490, 3440, 1760, 1730, 1715, 1665, 1635, 1600	233 (4.68), 252 sh (4.22)	3.08 (s, 3H, CH_3), 3.19 (m, 2H, CH_2-CO), 3.78 (m, 2H, CH_2-C=C), 8.57 (s, 4H, aromatics indane), 8.59 (m, 1H, β-pyridinium, partially masked), 9.05 (m, 1H, γ-pyridinium), 9.58 (m, 2H, α-pyridinium)
	4'-CH_3	3440, 3400, 1750, 1710, 1640, 1600	233 (4.70), 251 sh (4.34)	3.04-3.20 (m, 2H, CH_2CO, partially masked), 3.16 (s, 3H, CH_3), 3.75 (m, 2H, CH_2-C=C), 8.48 (s, 4H, aromatics indane), 8.49 (m, 2H, β-pyridinium), 9.54 (m, 2H, α-pyridinium)
	H	3440, 3350, 3210, 1750, 1715, 1680, 1625, 1600	228 (4.43), 242 sh (4.17)	2.56 (m, 2H, CH_2-CH_2-CH_2, J = 6 Hz), 2.98 (t, 2H, CH_2-CO), 3.53 (t, 2H, CH_2-C=C), 7.90-8.35 (m, 1H, aromatic indane), 8.42 (s, 3H, aromatics indane), 8.60 (m, 2H, β-pyridinium), 9.14 (m, 1H, γ-pyridinium) 9.65 (m, 2H, α-pyridinium)
6b	3'-CH_3	3340, 1755, 1715, 1680, 1630, 1600	227 (4.48), 243 sh (4.18)	2.68 (m, 2H, CH_2-CH_2-CH_2, J = 6 Hz), 2.97 (t, 2H, CH_2-CO, J = 6 Hz, partially masked), 3.01 (s, 3H, CH_3), 3.50 (t, 2H, CH_2-C=C, J = 6 Hz), 7.95-8.35 (m, 1H, aromatic indane), 8.41 (s, 3H, aromatics indane), 8.46 (m, 1H, β-pyridinium, partially masked), 8.92 (m, 1H, γ-pyridinium), 9.54 (m, 2H, α-pyridinium)
	4'-CH_3	3440, 1750, 1710, 1675, 1635, 1600	230 (4.56), 246 sh (4.27)	2.69 (m, 2H, CH_2-CH_2-CH_2, J = 6 Hz), 2.98 (t, 2H, CH_2-CO, J = 6 Hz), 3.12 (s, 3H, CH_3), 3.50 (t, 2H, CH_2-C=C, J = 6 Hz), 8.40 (m, 2H, β-pyridinium partially masked), 8.45 (s, 4H, aromatics), 9.42 (m, 2H, α-pyridinium)
	H	3140, 1725, 1635, 1605	234 (4.08), 256 (4.24)	0.56 (t, 3H, CH_3, J = 7 Hz), 3.23 (q, 2H, CH_2, J = 7 Hz), 5.68 (s, 1H, O-CH-O), 5.90-7.10 (br, 2H, -OH), 7.50-8.50 (m, 7H, 4H aromatics indane + 2-H, β-pyridinium + 1H olefinic), 8.80 (m, 1H, γ-pyridinium), 9.53 (m, 2H, α-pyridinium)
6e (c)	2'-CH_3	3150, 1725, 1630, 1605	235 (4.10), 260 (4.33)	0.55 (t, 3H, CH_3-CH_2, J = 7 Hz), 2.95 (s, 3H, CH_3), 3.18 (q, 2H, CH_2, J = 7 Hz), 5.77 (s, 1H, O-CH-O), 6.10-7.30 (br, 2H, OH), 7.50-8.40 (m, 7H, 4H aromatics indane + 2H, β-pyridinium + 1H olefinic), 8.67 (m, 1H, γ-pyridinium), 9.53 (m, 1H, α-pyridinium)
	3'-CH_3	3100, 1730, 1630, 1605	230 (4.10), 256 (4.24)	0.55 (t, 3H, CH_3-CH_2, J = 7 Hz), 2.58 (s, 3H, CH_3), 3.21 (q, 2H, CH_2, J = 7 Hz), 5.68 (s, 1H, O-CH-O), 5.90-7.20 (br, 2H, -OH), 7.50-8.30 (m, 6H, 4H aromatics indane + 1H, β-pyridinium + 1H olefinic), 8.65 (m, 1H, γ-pyridinium), 9.30 (m, 2H, α-pyridinium)

(a) Spectra were recorded in methanol-0.1*N* hydrochloric acid. (b) Spectra were recorded in deuterium oxide except for compounds **6e** for which dimethyl sulfoxide-d_6 was used. (c) Spectroscopic data refer to ethyl hemiacetal forms; nmr spectra show partial elimination of free ethanol with appearance of a feeble -CHO singlet δ 9.75-9.85.

3-*p*-Toluenesulfonyloxy-2-cyclohexen-1-one (**8**) (R = H).

A solution of tosyl chloride (1.14 g., 6 mmoles), **7** (R = H, 0.56 g., 5 mmoles) and anhydrous triethylamine (0.84 ml., 6 mmoles) in anhydrous dioxane (8 ml.) was stirred for 3 hours at room temperature. Triethylamine hydrochloride was filtered off and the dioxane solution was rapidly chromatographed on silica gel column (ethyl acetate-hexane 50-50 as eluent) to give 1.13 g. (85% yield) of **8** (R = H), m.p. 44-45° from hexane; ir: ν max 1675, 1630, 1600, 1380, 1360, 1190, 1180 cm^{-1}; nmr (deuteriochloroform): δ 1.97 (m, 2H, CH_2-*CH_2*-CH_2), 2.2-2.7 (m, 4H, *CH_2*-CH_2-*CH_2*), 2.45 (s, 3H, CH_3), 5.80 (s, br, 1H, CH), 7.40 (d, 2H, aromatics), 7.77 (d, 2H, aromatics).

Anal. Calcd. for $C_{13}H_{14}SO_4$: C, 58.23; H, 5.30. Found: C, 58.40; H, 5.46.

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(22) Adduct **1c** from dimedone had been previously prepared by A. Schönberg and R. Singer, *Chem. Ber.*, **103**, 3871 (1970).

(23) Only adducts leading to pyridooxazine structures (**1a,b,e**) were submitted to reaction with methylpyridines.

(24) The yield was increased to 70% carrying out the reaction in anhydrous dioxane (3 ml.) and 4-methylpyridine (2 ml.) solution.

(25) Small amounts (13-15%) of the isomeric product (2- or 7-CH_3) can be detected in the nmr spectrum of the crude product.

(26) Efforts to crystallize **5a** led to partial decomposition of the product; however, several washings of crude **5a** with anhydrous dioxane gave a product of sufficient analytical purity.

(27) Assignment of signals to the methylene groups are tentatively made by analogy with that in the model compound **8** (R = CH_3), for which signs of allylic splitting were observed in the lower field signal of methylene protons.

(28) Compound **5b** can also be obtained by the same procedure as described for **8** (R = H).

(29) In the case of pyridooxazine derivative **3e** (R = 8-CH_3) no precipitate was obtained. Tlc analysis of the methylene chloride solution showed a complex reaction mixture which was not investigated further.

(30) Signals at δ 2.37 and 5.74 showed signs of allylic coupling.