The Quaternization of 2-(*p*-Dimethylaminophenyl)pyridines

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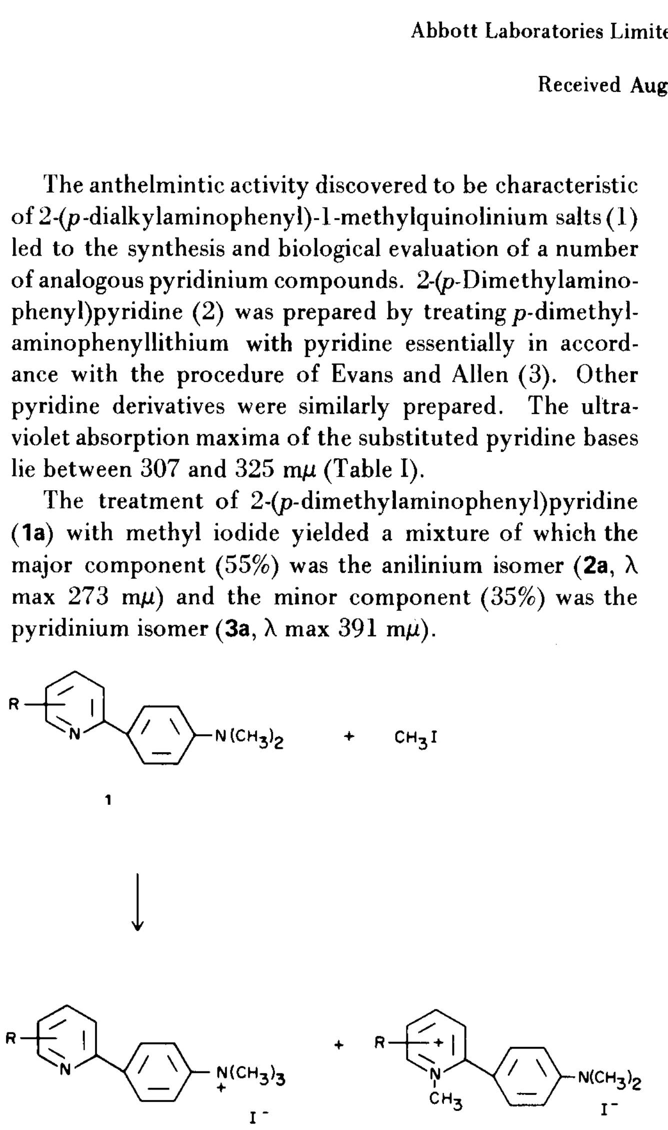
The anthelmintic activity discovered to be characteristic of 2-(*p*-dialkylaminophenyl)-1-methylquinolinium salts (1) led to the synthesis and biological evaluation of a number of analogous pyridinium compounds. 2-(*p*-Dimethylaminophenyl)pyridine (2) was prepared by treating *p*-dimethylaminophenyllithium with pyridine essentially in accordance with the procedure of Evans and Allen (3). Other pyridine derivatives were similarly prepared. The ultraviolet absorption maxima of the substituted pyridine bases lie between 307 and 325 mμ (Table I).

The treatment of 2-(*p*-dimethylaminophenyl)pyridine (**1a**) with methyl iodide yielded a mixture of which the major component (55%) was the anilinium isomer (**2a**, λ max 273 mμ) and the minor component (35%) was the pyridinium isomer (**3a**, λ max 391 mμ).

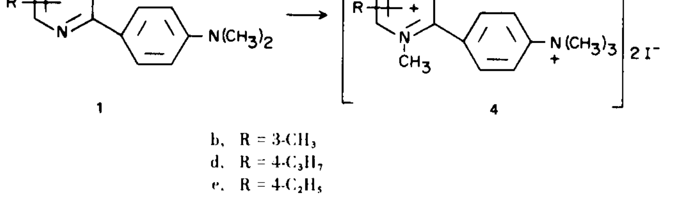


a, R = H
b, R = 3-CH_3
c, R = 4-CH_3
d, R = 4-C_3H_7
e. R = 6-CH_3O

The isomeric products were separated on the basis of the relative insolubility of **2a** in chloroform or acetone. The nmr spectrum of **2a** gave a singlet at δ 3.6 corresponding to the nine hydrogens of the trimethylammonium group. The nmr spectrum of **3a** showed singlets at δ 3.0 (6 hydrogens) and δ 4.5 (3 hydrogens) which were assigned respectively to the dimethylamino group and the *N*-methyl group. The effect of quaternization on the UV spectra of heterocyclic bases containing a dimethylamino group in conjugation with a heterocyclic nitrogen has been discussed (4). The reaction of 2-(*p*-dimethylaminophenyl)-3-methylpyridine (**1b**) with methyl iodide yielded a nearly 50:50 mixture of the two monomethiodide isomers (**2b** and **3b**).

2-(*p*-Dimethylaminophenyl)-4-methylpyridine (**1c**) reacted with methyl iodide to yield the pyridinium isomer (**3c**) as the only product, while 2-(*p*-dimethylaminophenyl)-4-propylpyridine (**1d**) reacted with the same alkylating agent to give a low yield of product, from which only the anilinium isomer (**2d**) could be isolated.

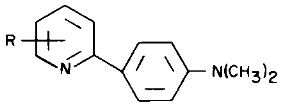
The reaction of 2-(*p*-dimethylaminophenyl)-6-methoxypyridine (**1e**) with methyl iodide at room temperature gave a quantitative yield of **2e** (λ max 292 mμ). On heating, the anilinium isomer rearranged to give the more stable pyridinium isomer (**3e**) (λ max 393 mμ). This constitutes additional support for the general observation (4) that in the alkylation of basic heterocycles the initial point of attachment is the exocyclic nitrogen, but that raising the temperature or increasing the time of the reaction results in the formation of the isomer in which the ring nitrogen is quaternized. In some cases, the reaction conditions must be particularly mild if it is desired to isolate the intermediate anilinium isomer; otherwise, as in the reaction of **1c** with methyl iodide, only the pyridinium isomer can be detected. Three of the alkyl substituted *p*-dimethylaminophenylpyridines (**1b**, **1d** and **1f**) yielded bisquaternary salts (**4b**, **4d** and **4f**) on treatment with excess methyl iodide. The ultraviolet absorption maxima of the base (**1b**, 307 mμ) was shifted to 272 mμ in the bisquaternary salt **4b** with no absorption band in the visible region. The quaternary and bisquaternary salts are listed in Table II, and the spectral data are given in Table III.



b, R = 3-CH_3
d, R = 4-C_3H_7
e. R = 4-C_2H_5

TABLE I

2-(*p*-Dimethylaminophenyl)pyridines



Compound No.	R	Formula	Boiling point (°C)	(mm)	M.p. (°C)	Yield (%)	λ max (a) mμ	C (%) Calcd.	C (%) Found	H (%) Calcd.	H (%) Found	N (%) Calcd.	N (%) Found
1a	H	$C_{13}H_{14}N_2$			98-99 (b)	79	320						
1b	3-CH_3-	$C_{14}H_{16}N_2$	150-155	0.3		60	307	79.20	79.19	7.60	7.68	13.20	13.10
1c	4-CH_3-	$C_{14}H_{16}N_2$			96-98 (c)	40	319	79.20	79.05	7.60	7.71	13.20	13.10
1d	4-C_3H_7	$C_{16}H_{20}N_2$	169-170	0.3		58	319	79.95	80.04	8.39	8.48	11.66	11.52
1e	6-CH_3O	$C_{14}H_{16}N_2O$			132-133 (c)	38	325	73.65	73.49	7.07	7.05	12.27	12.37
1f	4-C_2H_5	$C_{15}H_{18}N_2$	170-173	0.2		84	319	79.60	79.62	8.02	8.26	12.38	12.21

(a) In methanolic solution. (b) Lit. m.p. 98-98.5° (2). (c) Recrystallized from ligroin (b.p. 90-120°).

TABLE II

Mono and Bisquaternary Iodide Salts from the Quaternization of 2-(*p*-Dimethylaminophenyl)pyridines

Compound No.	R	Formula	Reaction time (a) hr.	M.p. °C	Yield %	C (%) Calcd.	C (%) Found	H (%) Calcd.	H (%) Found	N (%) Calcd.	N (%) Found	I (%) Calcd.	I (%) Found
2a (b)	H	$C_{14}H_{17}IN_2$	4	195-197 (c)	55	49.42	49.04	5.04	4.72	8.24	8.25	37.30	36.93
2b (b)	3-CH_3	$C_{15}H_{19}IN_2$	24 (d)	171-172 (e)	57	50.86	50.81	5.40	5.49	7.91	8.10	35.83	36.03
2d	4-C_3H_7	$C_{17}H_{23}IN_2$	168 (d)	166-167 (e)	20	53.41	53.30	6.06	6.03	7.33	7.13	33.20	33.57
2e	6-CH_3O	$C_{15}H_{19}IN_2O$	24	148-149 dec. (c)	99	48.66	48.32	5.17	4.98	7.57	7.55	34.28	34.08
3a (b)	H	$C_{14}H_{17}IN_2$	4	186-187 dec. (c)	35	49.42	49.19	5.04	5.33	8.24	8.29	37.30	37.58
3b (b)	3-CH_3	$C_{15}H_{19}IN_2$	24 (d)	157-158 (e)	42	50.86	51.04	5.40	5.69	7.91	8.03	35.83	36.03
3c	4-CH_3	$C_{15}H_{19}IN_2 \cdot \frac{1}{2}H_2O$	2	225-226 (e)	82	49.59	49.86	5.55	5.56	7.71	8.04		
3e	6-CH_3O	$C_{15}H_{19}IN_2O$	2 (f)	141-142 dec. (c)	46	48.66	48.19	5.17	5.75	7.57	7.73		
4b	3-CH_3	$C_{16}H_{22}I_2N_2$	4	228-230 dec. (c)	77	38.73	38.51	4.47	4.51	5.64	5.84	51.56	51.26
4d	4-C_3H_7	$C_{18}H_{22}I_2N_2$	17	156-157 dec. (e)	70	41.24	41.06	5.00	5.37	5.34	5.24		
4f	4-C_2H_5	$C_{17}H_{24}I_2N_2$	1 (g)	184-185 dec. (e)	99	40.02	40.14	4.74	4.75	5.49	5.23	49.75	49.58

(a) Each reaction was carried out at 25° using an excess of methyl iodide except where noted. (b) A mixture of the two possible monomethiodide isomers was obtained. (c) Recrystallized from alcohol. (d) An equimolar amount of methyl iodide was used in a methanolic solution. (e) Recrystallized from methanol-ether. (f) Obtained by rearrangement of 2e in refluxing hexanol. (g) Carried out at 100° in a pressure bottle.

TABLE III

UV and NMR Spectral Data of the Quaternary and Bisquaternary Salts

Compound No.	λ max mμ	$N(CH_3)_3$ δ	$N(CH_3)_2$ δ	$>N\text{-}CH_3$ δ
2a	273	3.6		
3a	391		3.0	4.5
2b	272	3.7		
3b	377		3.0	4.2
3c	378		3.0	4.4
2d	272	3.7		
2e	292	4.0		
3e	393			
4b	272	3.7		3.9
4d	272	3.7		4.1
4f	269	3.7		4.0

In contrast to the analogous quinolinium compounds, the compounds described in this paper were found to be without effect on *Ascaris suum* in mice and swine.

EXPERIMENTAL

A Beckman DB spectrophotometer was used to determine ultraviolet absorption. The nmr spectra were determined in deuterated DMSO with a Varian A-60 spectrometer, using tetramethylsilane as an internal reference. Microanalyses were performed by Dr. C. Daessle, Montreal, Quebec, and by the Microanalytical Department, Abbott Laboratories, North Chicago, Illinois. Mono and bisquaternary iodide salts obtained from the quaternization of 2-(*p*-dimethylaminophenyl)pyridines are listed in Table II, and their preparation is illustrated by the following examples.

p-(2-Pyridyl)phenyltrimethylammonium Iodide (**2a**) and 2-(*p*-Dimethylaminophenyl)-1-methylpyridinium Iodide (**3a**).

A solution of 2-(*p*-dimethylaminophenyl)pyridine (2) (19.8 g., 0.1 mole) in methyl iodide (40 ml.) was allowed to stand at room temperature for 4 hours. Addition of ether precipitated 31 g. of material. On treatment with chloroform (400 ml.) there was obtained 19.6 g. (55%) of **2a**, m.p. 195-197°. One crystallization from methanol raised the m.p. to 198-199°. Evaporation of the chloroform yielded 11.8 g. (35%) of **3a**. Three crystallizations from ethanol led to a pure sample melting at 186-187° dec.

2-(*p*-Dimethylaminophenyl)-1-methyl-6-methoxypyridinium Iodide (**3e**).

p-(6-Methoxy-2-pyridyl)phenyltrimethylammonium iodide (**2e**) (2.7 g., 0.01 mole) was heated in refluxing hexanol (10 ml.) for 2 hours. On addition of ether, a solid precipitated; yield 2.5 g. This solid was dissolved in chloroform and the insoluble anilinium isomer was filtered. Upon addition of ether, there separated 1.7 g. of solid (46%) which, after one crystallization from ethanol, melted at 141-142° dec.

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