Anthelmintic Quaternary Salts. V. 2-(*p*-Dialkylaminophenyl)-1-methylquinolinium Salts

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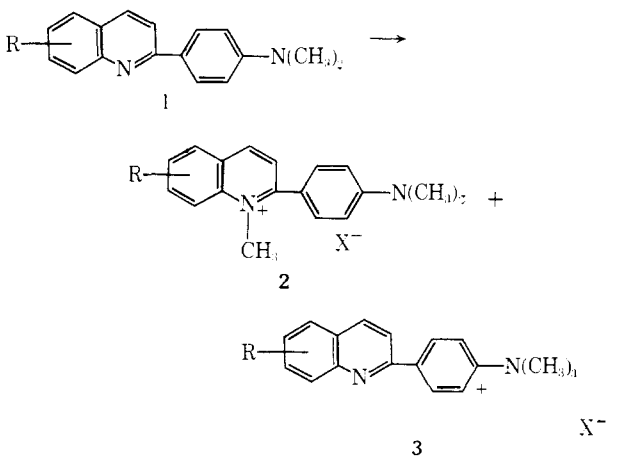
A group of 2-(*p*-dialkylaminophenyl)-1-methylquinolinium salts was prepared for evaluation as anthelmintics. The compounds showed weak activity against gastrointestinal nematodes of sheep but were potent prophylactically in protecting pigs from infections of *Ascaris suum*. The 6-methyl substituent was essential for activity against *Ascaris suum*.

The migration of the larvae of the roundworm *Ascaris suum* causes extensive damage to lung and liver tissue and loss of weight in swine. The larvae of *A. suum* are much more resistant than the adult stages to the action of anthelmintics. In recent years, however, a number of agents have been reported[1,2] to have prophylactic value in protecting swine (maintained in concrete pens) from the effects of the larval migration.

These agents, which also show activity against other parasitic nematodes, all have the conjugated amidinium structure characteristic of cyanine dyes. 2-(*p*-Dialkylaminophenyl)-1-methylquinolinium salts constitute an additional class of cyanine dyes effective against *A. suum* larvae, and their synthesis and evaluation are described in this paper.

Chemistry.—Treatment of 2-(*p*-dimethylaminophenyl)quinolines (**1**) with MeI at 100° yielded mixtures of 2-(*p*-dimethylaminophenyl)-1-methylquinolinium iodides **2** (X = I) and the isomeric *p*-(2-quinolinyl)phenyltrimethylammonium iodides **3** (X = I).



a, R = H; **b**, R = 6-Cl; **c**, R = 6-CH_3; **d**, R = 7-CH_3; **e**, R = 8-CH_3; **f**, R = 6-OC_2H_5; **g**, R = 4,6-$(CH_3)_2$

The anilinium isomers **3** were the major compounds of the mixtures; for example, when R = 6-CH_3 (**1c**), **2c** and **3c** were obtained in 12 and 86% yields, respectively.

The isomeric products were separated on the basis of the relative insolubility of **3c** in $CHCl_3$ and were characterized by their uv spectra. The unquaternized quinoline **1c** had λ_{max} 360 mμ (free base); **2c** was a reddish solid with λ_{max} 450 mμ, characteristic of cyanine dyes of this class, while **3c** was colorless with λ_{max} 256 mμ. The effect of quaternization on the uv spectra of compounds containing a dimethylamino group in conjugation with a heterocyclic N has been discussed.[3] The uv absorption maxima are given in Table I. Brief treatment of **3c** (X = I) in refluxing 1-hexanol resulted in conversion to **2c** (X = I) in 76% yield.

TABLE I

UV ABSORPTION MAXIMA

	λ_{max}, mμ					
	1	**1** sulfate	**2** (X = I)	**2** (X = OTs)	**3** (X = I)	**3** (X = OTs)
a	360	448	454	448		
b	371	460	462	460		
c	360	446	450	448	256	
d	358	446	450	448		
e	359	450	456	452		
f	360	450		454		267
g	360		436			

The ratio of isomers was dependent on the nature of the substituent on the anilino nitrogen: in case of the *p*-diethylaminophenyl analog (**4**) of **1c** (R = CH_3), only the quinolinium isomer (**5**) was obtained.

The nature of the methylating agent also had considerable effect on the ratio of isomers formed. Treating the quinolines **1** with methyl *p*-toluenesulfonate gave, with **1a–1e**, the quinolinium isomers **2a–e** (X = OTs) exclusively. An exception was **1f** (R = 6-OC_2H_5) which gave **2f** (X = OTs) and **3f** (X = OTs) in 35 and 33% yields, respectively.

The tosylate salts were not convenient for evaluation purposes, but they were readily converted to the iodide salts by the use of Amberlite IRA-400 (I^- form). Preparation of the tosylate salts followed by conversion to the iodides constituted the preferred route to the test compounds. The quinolinium salts are described in Table II.

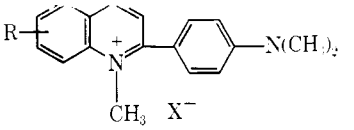
The active compound **2c** was also prepared as the

(1) (a) G. Brody and E. C. Wiest, *Am. J. Vet. Res.*, **24**, 460 (1963); (b) I. B. Wood, H. Berger, J. A. Pankavich, and E. Waletzky, *J. Parasitol.*, **50** (3) (Sect 2), 60 (1964); (c) American Cyanamid Co., U. S. Patent 3,152,042 (Oct 6, 1964).

(2) (a) D. L. Garmaise, G. Y. Paris, J. Komlossy, C. H. Chambers, and R. C. McCrae, *J. Med. Chem.*, **12**, 30 (1969); (b) D. L. Garmaise, C. H. Chambers, and R. C. McCrae, *ibid.*, **11**, 1205 (1968).

(3) D. L. Garmaise and G. Y. Paris, *Chem. Ind.* (London), 1645 (1967).

TABLE II: 2-(*p*-DIMETHYLAMINOPHENYL)-1-METHYLQUINOLINIUM SALTS



No.	R	X	Mp, °C	Yield, %	Formula	Analyses
2a	H	I	234–235[a]	89	$C_{18}H_{19}IN_2$	C, H, N
		OTs	245–247[b]	51	$C_{25}H_{26}N_2O_3S$	N
2b	6-Cl	I	264–265 dec[a]	68	$C_{18}H_{18}ClIN_2 \cdot 0.5H_2O$	N
		OTs	255–256 dec[b]	83	$C_{25}H_{25}ClN_2O_3S \cdot H_2O$	C, H, N
2c	6-CH_3	Br	165–170[b]	87[c]	$C_{19}H_{21}BrN_2 \cdot H_2O$	N
		Cl	175–180 dec[a]	100	$C_{19}H_{21}ClN_2 \cdot H_2O$	N
		I	255–257 dec[b]	76[d]	$C_{19}H_{21}IN_2 \cdot 2H_2O$	C, H, N
		OTs	221–222 dec[a]	35	$C_{26}H_{28}N_2O_3S$	C, H, N
		Pamoate	219–220 dec[b]	79[e]	$C_{61}H_{56}N_4O_6 \cdot 3H_2O$	C, H, N
2d	7-CH_3	I	240–241 dec[a]	89	$C_{19}H_{21}IN_2 \cdot 0.5H_2O$	C, H
		OTs	239–240[b]	56	$C_{26}H_{28}N_2O_3S \cdot 0.5H_2O$	C, H, N
2e	8-CH_3	I	221–222 dec[a]	94	$C_{19}H_{21}IN_2 \cdot 0.5H_2O$	C, H
		OTs	233–234[b]	50	$C_{26}H_{28}N_2O_3S$	C, H, N
2f	6-OC_2H_5	OTs	78–80[a]	35	$C_{27}H_{30}N_2O_4S \cdot H_2O$	C, H
2g	4,6-$(CH_3)_2$	I	280–281[a]	44	$C_{20}H_{23}IN_2$	C, H, N

[a] Recrystallized from EtOH. [b] Recrystallized from MeOH–Et_2O. [c] Yield calculated from the iodide. [d] Yield calculated from the isomerization of the anilinium isomer. [e] Yield calculated from the chloride.

chloride, bromide, and pamoate salts for evaluation purposes. The anthelmintic activities are given in Table III.

Biological Results.—The compounds were tested first against *Nematospiroides dubius* in mice and six species of gastrointestinal nematodes in lambs. Weak to moderate activity was shown by the various salts of the 6-methyl analog **2c**. Replacing the anilino Me by Et (**5**) gave good activity in sheep. The 6-Cl analog **2b** was weakly active, while the removal of the 6-Me, its displacement to the 7 or 8 positions, or the introduction of an additional Me in the 4 position caused reduction in activity.

A much higher level of activity was shown by the compounds in the series when tested as prophylactic agents against *Ascaris suum* in mice and swine. Compound **2c** was outstandingly effective as a prophylactic agent in both mice and swine, protecting the mammalian hosts from both liver and lung damage. Removal of the 6-Me, displacement to the 7 or 8 positions, or replacement by 6-Cl resulted in elimination of activity. Activity was retained in **2g**, containing an additional 4-Me, and **5** in which Me_2N was replaced by Et_2N.

The pamoate salt of **2b** was as active against *Ascaris suum* as the halide salts, but apparently due to its decreased solubility it was considerably less toxic by both oral and intraperitoneal administration. The unquaternized bases (**1a–g**) and the anilinium salts (**3c** and **3f**) were totally inactive.

These compounds were tested under experimental conditions in which the pigs were maintained in concrete pens. In the field, or when field conditions were simulated by granting the pigs access to soil, the effectiveness of the active compounds was markedly reduced.

Experimental Section[4]

2-(*p*-Dimethylaminophenyl)quinolines.—2-(*p*-Dimethylaminophenyl)quinoline (**1a**) was prepared by reaction of quinoline with BzCl and $PhNMe_2$ and subsequent oxidation of the intermediate dihydroquinoline.[5]

Known substituted analogs of 2-(*p*-dimethylaminophenyl)-quinoline (**1b–e**) were prepared by condensing *p*-dimethylaminophenyllithium with the appropriate quinolines followed by oxidation of the dihydroquinolines with $PhNO_2$ according to the general method of Gilman, *et al.*[6]

2-(*p*-Diethylaminophenyl)-6-methylquinoline (4) was prepared by a similar procedure in 55% yield from *p*-diethylaminophenyllithium and 6-methylquinoline, mp 142–143° (from EtOH). *Anal.* ($C_{20}H_{22}N_2$) C, H, N.

2-(*p*-Dimethylaminophenyl)-6-ethoxyquinoline (1f) was obtained in 39% yield by reaction of 6-ethoxyquinoline with *p*-dimethylaminophenyllithium, mp 122–123° (from EtOH). *Anal.* ($C_{19}H_{20}N_2O$) C, H, N.

2-(*p*-Dimethylaminophenyl)-4,6-dimethylquinoline (1g) was prepared in 66% yield from 4,6-dimethylquinoline[7] and *p*-dimethylaminophenyllithium, mp 156–158°, after one crystallization from EtOH. *Anal.* ($C_{19}H_{20}N_2$) C, H, N.

2-(*p*-Dimethylaminophenyl)-1-methylquinolinium Salts.—The following specific examples represent the methods used for making the quinolinium salts described in Table II.

2-(*p*-Dimethylaminophenyl)-1,8-dimethylquinolinium Tosylate (2e, X = OTs).—A solution of 2-(*p*-dimethylaminophenyl)-8-methylquinoline (12.4 g, 0.047 mole) and methyl *p*-toluenesulfonate (29.8 g, 0.16 mole) in 150 ml of MeOH was refluxed for 2.5 hr. The solvent was evaporated, the residue was triturated with 100 ml of $CHCl_3$, and the insoluble material was filtered. Addition of Et_2O to the filtrate precipitated 10.5 g of material (50%), mp 230–231°. Recrystallization from MeOH–Et_2O raised the melting point to 233–234°.

2-(*p*-Dimethylaminophenyl)-1,8-dimethylquinolinium Iodide (2e, X = I).—2-(*p*-Dimethylaminophenyl)-1,8-dimethylquinolinium tosylate (4.6 g, 0.01 mole) dissolved in 100 ml of MeOH was passed through 140 ml of Amberlite IRA-400 resin in the iodide form. The solvent was evaporated to yield 3.9 g, mp 218–220° (94%). Recrystallization from EtOH raised the melting point to 221–222°.

The Amberlite IRA-400 resin in the bromide or chloride form was used in a similar manner to prepare **2c** (X = Br) and **2c** (X = Cl).

Bis[2-(*p*-dimethylaminophenyl)-1,6-dimethylquinolinium] 4,4′-Methylenebis(3-hydroxy-2-naphthoate) (X = pamoate).—A solution of disodium pamoate (2.8 g, 0.0065 mole) was added slowly to 2-(*p*-dimethylaminophenyl)-1,6-dimethylquinolinium chloride (4.1 g, 0.013 mole) dissolved in 400 ml of H_2O.

(4) Uv spectra were determined in MeOH using a Beckman DB spectrophotometer. Microanalyses were performed by Dr. C. Daessle, Montreal, Quebec, and by the Microanalytical Department, Abbott Laboratories, North Chicago, Ill.

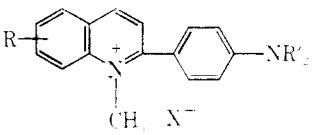
(5) W. E. McEwen, R. H. Terss, and I. W. Elliott, *J. Amer. Chem. Soc.*, **74**, 3605 (1952).

(6) (a) H. Gilman, J. L. Towle, and S. M. Spatz, *ibid.*, **68**, 2017 (1946); (b) H. Gilman and D. A. Shirley, *ibid.*, **72**, 2181 (1950).

(7) B. I. Ardashev and E. Sh. Kagan, *Zh. Obshch. Khim.*, **34**, 2228 (1964); *Chem. Abstr.*, **61**, 9462 (1964).

TABLE III

ANTHELMINTIC ACTIVITY AND ACUTE TOXICITY OF 2-(*p*-DIALKYLAMINOPHENYL)-1-METHYLQUINOLINIUM SALTS



No.	X	R	R′	Acute toxicity in mice[a] LD_{50}, mg/kg Ip	Acute toxicity in mice[a] LD_{50}, mg/kg Oral	*N. dubius* in mice[b] % redn of no. of worms (dosage, mg/kg)	GI nematodes in sheep[c] % redn of eggs/g of feces (dosage, mg/kg)	*A. suum* in mice[d] % redn of lung lesions	*A. suum* in mice[d] % redn of worms in lungs	*A. suum* in swine[e] % redn of liver lesions	*A. suum* in swine[e] % redn of larvae in lungs
2a	I	H	CH_3	>1000	>1000	0 (500)		20			
2b	I	6-Cl	CH_3	>1000	>1000	35 (750)	38 (150)	0			
2c	Br	6-CH_3	CH_3	50	50	13 (15)	90 (150)			98	100
2c	Cl	6-CH_3	CH_3	10	50	30 (10)	63 (100)			99	100
2c	I	6-CH_3	CH_3	50	200	0 (25)	0 (50)	100	100	98	100
2c	0.5 pamoate	6-CH_3	CH_3	>1000	>1000	30 (500)	54 (150)	80	100		
2d	I	7-CH_3	CH_3	>1000	>1000	6 (250)		0			
2e	I	8-CH_3	CH_3	>1000	>1000			20			
2g	I	4,6-$(CH_3)_2$	CH_3	10	<100	0 (25)		90	95		
5	I	6-CH_3	C_2H_5	>1000	>1000	0 (15)	75 (150)	100	100	97	100

[a] The LD_{50} values recorded in the table are estimates based on acute toxicity studies in which three mice were used per dose level with an average of eight dose levels for each mode of administration. [b] Each of three mice which had been infected with 50 *N. dubius* larvae several weeks earlier was administered a dose of 15–50 mg/kg orally. A similar dose was administered on the following day. On the seventh day the mice were sacrificed and a count was made of the number of worms remaining in the intestine. The unmedicated mice had 35–40 worms; the table records the percentage reduction caused by the action of the test compound. [c] The compounds were tested on sheep which had been experimentally infected with six species of gastrointestinal nematodes: *Haemonchus contortus, Cooperia curticei, Trichostrongylus colubriformis, Trichostrongylus axei, Ostertagia circumcincta,* and *Nematodirus spathiger.* The compounds were administered in two equal doses on consecutive days, and the number of eggs per gram of feces was determined during a 7-day period. The table lists the percentage reduction in the egg count at the end of this period. No particular species specificity in anthelmintic action was observed with this series of compounds. [d] A dose of 10 mg/kg was administered orally to each of three mice, followed by the administration of an infection of 100,000 embryonated *A. suum* eggs. A second dose of 10 mg/kg was administered 4 hr later. After 8 days the mice were sacrificed and the extent of lung lesions was determined by gross examination of the lungs for the number and size of hemorrhagic areas due to the migration of the *Ascaris* larvae. The table lists the percentage reduction in lung lesions of the treated animals as compared with the unmedicated controls. [e] The test compounds were administered at a level of 0.01% in feed for a period of 10 days to two pigs in concrete-floored pens. An infection of 100,000 embryonated *A. suum* eggs was administered 3 days after the start of the inclusion of the test compound in the feed. The animals were sacrificed after 10 days. The percentage reduction in liver lesions due to migrating *Ascaris* larvae in treated animals as compared with controls was determined by counting the small white scars ("milk spots") found on the surface of the liver. The number of lesions was 500 or greater in unmedicated controls (57 animals); beyond 500 the lesions tended to coalesce and could not be counted separately. The procedure used to determine the number of larvae in the lungs of the pigs was based on the method described for mice by D. K. Hass (Ph.D. Thesis, University of Wisconsin, 1962). In 57 control animals, the number of larvae found after sacrifice varied from a low of 10,000 to a high of 49,000, for an average value of 25,000.

The "pamoate" formed was filtered and dried to yield 5.1 g (79%), mp 217–218° dec. Recrystallization from MeOH–Et_2O raised the melting point to 219–220° dec.

2-(*p*-Dimethylaminophenyl)-1-methyl-6-ethoxyquinolinium Tosylate (2f, X = OTs) and *p*-(6-Ethoxy-2-quinolinyl)phenyltrimethylammonium Tosylate (3f, X = OTs).—2-(*p*-Dimethylaminophenyl)-6-ethoxyquinoline (14.62 g, 0.05 mole) and methyl *p*-toluenesulfonate (37.2 g, 0.20 mole) were heated in refluxing MeOH (150 ml) for 5 hr. The solution was reduced to a small volume and Et_2O was added, giving a semisolid which was treated with 250 ml of Me_2CO. The insoluble **3f** (X = OTs) was recovered by filtration, yield 8.1 g (33%), mp 207–208° (from EtOH). *Anal.* ($C_{27}H_{30}N_2O_4S \cdot 0.5H_2O$) C, H, O, S.

The Me_2CO filtrate was concentrated to about 100 ml. On cooling, **2f** (X = OTs) precipitated as the monohydrated salt, mp 78–80°, with solidification and remelting at 149–150°, yield 8.8 g, 35%. The analytical sample was obtained by crystallization from EtOH.

***p*-(6-Methyl-2-quinolinyl)phenyltrimethylammonium Iodide (3c, X = I) and 2-(*p*-Dimethylaminophenyl)-1,6-dimethylquinolinium Iodide (2c, X = I).**—2-(*p*-Dimethylaminophenyl)-6-methylquinoline (40 g, 0.15 mole) and MeI (100 ml) were heated in a pressure bottle at 100° for 5 hr. The reaction mixture was treated with 100 ml of boiling $CHCl_3$. The insoluble material was removed by filtration, ground in a mortar, and treated again with 100 ml of boiling $CHCl_3$. The residual (**3c** X = I) melted at 195–196° dec, yield 53.0 g (86%). *Anal.* ($C_{19}H_{21}IN_2$) C, H, I, N.

By concentrating the $CHCl_3$ extracts and adding Et_2O, 2-(*p*-dimethylaminophenyl)-1,6-dimethylquinolinium iodide dihydrate (**2c**) was obtained in 12% yield (8.0 g), mp 255–257°, with previous softening at 212–216°.

Compound **3c** (X = I) (24.4 g, 0.05 mole) was heated for 1 hr in 100 ml of refluxing 1-hexanol. The solid which separated on cooling was filtered and extracted with 200 ml of hot $CHCl_3$. By adding Et_2O to the filtrate, 18.5 g (76% yield) of **2c** (X = I) dihydrate was precipitated, mp 255–257° dec, with previous softening at 212–216°.

2-(*p*-Dimethylaminophenyl)-1,6-dimethylquinolinium Iodide (5).—2-(*p*-Diethylaminophenyl)-6-methylquinoline (10 g, 0.034 mole) and MeI (15 ml) were heated in a pressure bottle for 2 hr at 100°. The reaction mixture was triturated with Et_2O, giving the product as the dihydrate, mp 202–206° dec, in quantitative yield. Recrystallization from MeOH raised the melting point to 210–211°. *Anal.* ($C_{21}H_{25}IN_2 \cdot 2H_2O$) C, H, N.

2-(*p*-Dimethylaminophenyl)-1,4,6-trimethylquinolinium Iodide (2g, X = I).—2-(*p*-Dimethylaminophenyl)-4,6-dimethylquinoline (3.7 g, 0.013 mole) and MeI (6 ml) were heated in a pressure bottle at 100° for 1 hr. Treatment with Et_2O gave the crude product, mp 233–240° dec, in quantitative yield. The product was heated in refluxing 1-hexanol for 10 min, and the solution was cooled and filtered, giving the pure quinolinium iodide, 2.4 g (44%), mp 280–281° (after melting and resolidifying at 250–255°).

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