# Synthesis and Identification of the Major Metabolites of Prazosin Formed in Dog and Rat

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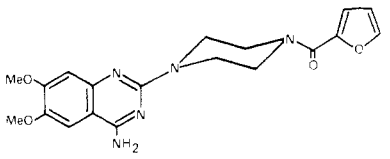
The 6-*O*-demethyl and 7-*O*-demethyl analogues of the new antihypertensive drug prazosin [2-[4-(2-furoyl)-piperazin-1-yl]-4-amino-6,7-dimethoxyquinazoline hydrochloride] have been unequivocally synthesized via separate ten-step reaction sequences starting from isovanillin and vanillin, respectively. The 6-*O*-demethyl derivative was found to be identical with the major prazosin metabolite formed in dog and rat, while the 7-*O*-demethyl derivative was identical with another, less prevalent but significant metabolite. Two minor metabolites of prazosin, 2-(1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline and 2,4-diamino-6,7-dimethoxyquinazoline, are also described. All four metabolites are less potent blood pressure lowering agents in dogs than prazosin but may contribute to its antihypertensive effect, since they account for a major portion of the administered dose.

Prazosin (1) is a new antihypertensive drug structurally

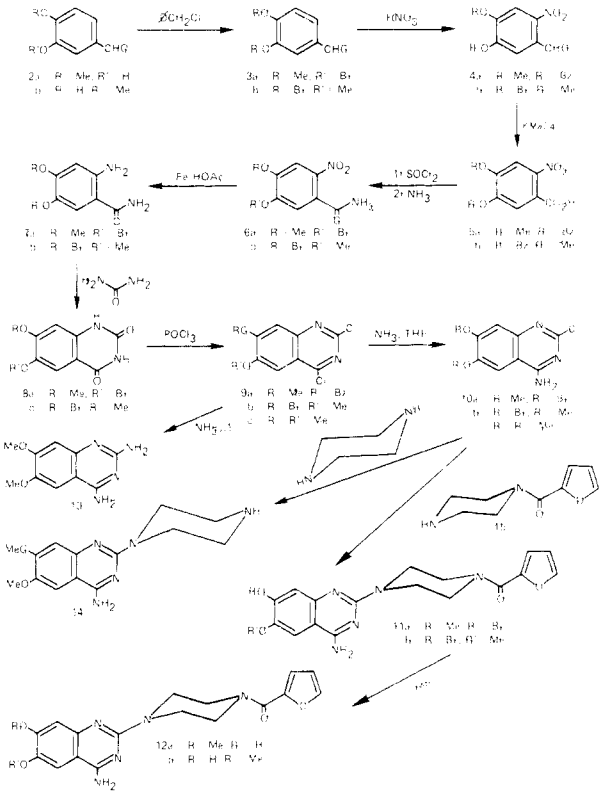


unrelated to other agents currently in use for the treatment of hypertension.[1,2] Analysis of its pharmacological mechanism of action suggests that the effect on blood pressure is a result of vasodilation which may be mediated by increased intracellular levels of cAMP. Prazosin is excreted principally in metabolized form with two isomeric *O*-demethylated metabolites accounting for approximately 75–85% of drug-related material found in urine and bile of rats and dogs.[3] In addition, two minor metabolites, 2-(1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline and 2,4-diamino-6,7-dimethoxyquinazoline, each account for 2–10% of drug-related material in urine and bile of these two species.[3] We have synthesized these four metabolites in an effort to enable unequivocal structural assignments and allow evaluation of their effects on blood pressure.

**Chemistry.** Quinazolines containing hydroxy substituents in the benzene portion of the ring system are relatively rare.[4] Such compounds have generally been synthesized by cleavage of the related methoxy compounds using aluminum chloride or hydrobromic acid[4b] or by ring closure of the respective hydroxyanthranilic acids with potassium cyanate.[4a,5] Because of a lack of desired selectivity, or potential problems in carrying a free hydroxy group through several steps of the synthesis, these methods appeared unsuitable for the unequivocal synthesis of the hydroxy metabolites of prazosin. We therefore decided to protect the hydroxy function by benzylation of suitable well-characterized starting materials which could be carried through the synthetic sequence developed for prazosin[6] and to remove the benzyl-protecting group under mild conditions in the final step of the synthesis.

Syntheses of 6-*O*-demethylprazosin (**12a**) and 7-*O*-demethylprazosin (**12b**) were accomplished in approximately 1% overall yield starting from isovanillin (**2a**) and vanillin (**2b**), respectively, using two separate ten-step reaction sequences (Scheme I). The phenolic groups of the two isomeric starting materials were protected by benzylation[7] and the resulting benzylvanillins **3a** and **3b** were nitrated to yield the nitrobenzaldehydes **4a** and **4b**. Subsequent oxidation, using potassium permanganate, afforded the nitrobenzoic acids **5a** and **5b**. These nitro acids were converted to their respective anthranilic acids, but attempts at cyclization with potassium cyanate[8] to the desired quinazoline-2,4-diones (**8a** and **8b**) were unsuccessful. Consequently, the synthesis of these key intermediates was accomplished by an alternate route. The nitro acids **5a** and **5b** were converted to their respective nitrobenzamides **6a** and **6b**, which after reduction with iron and acetic acid to **7a** and **7b** and heating with urea in pyridine and a catalytic amount of hydrochloric acid produced the quinazoline-2,4-diones **8a** and **8b** in moderate yield. Phosphorus oxychloride treatment, followed by reaction of the resulting 2,4-dichloroquinazolines (**9a** and **9b**) with ammonia, yielded the 4-amino-2-chloroquinazolines (**10a** and **10b**). The 6-*O*-benzyl and 7-*O*-benzyl analogues of prazosin (**11a** and **11b**) were obtained by reacting **10a** and **10b** with 1-(2-furoyl)piperazine (**15**). Whereas debenzylation of **11a** to 6-*O*-demethylprazosin (**12a**) was accomplished smoothly in warm trifluoroacetic acid,[9] more forcing conditions, concentrated sulfuric acid, were required for the debenzylation of **11b** to 7-*O*-demethylprazosin (**12b**). Alkylation of **12a** and **12b** with dimethyl sulfate gave prazosin (1).

Scheme I. Synthesis of Prazosin Metabolites



The two minor metabolites of prazosin, 2,4-diamino-6,7-dimethoxyquinazoline (**13**) and 2-(1-piperazinyl)-4-

Table I. Relative Abundance and Hypotensive Activity of Prazosin Metabolites

| Compound | Drug-related material excreted in urine and bile of rats and dogs,[e] % | Max decrease in blood pressure (mm) obsd with increasing doses (iv) administered at 30-min intervals[a] | | |
|---|---|---|---|---|
| | | 0.1 mg/kg | 0.4 mg/kg | 1.0 mg/kg |
| Prazosin (1) hydrochloride | 6 | 20[b] | 45[b] | 55[b] |
| 6-*O*-Demethylprazosin[c] (**12a**) sulfate | 61-66 | NT[d] | 10-17 | 15-27 |
| 7-*O*-Demethylprazosin (**12b**) sulfate | 13-21 | NT[d] | 12-15 | 18-24 |
| 2,4-Diamino-6,7-dimethoxyquinazoline (**13**) | 2 | 0 | 3-10 | 23-33 |
| 2-(1-Piperazinyl)-4-amino-6,7-dimethoxyquinazoline (**14**) hydrochloride | 2-10 | 0 | 0 | 10-16 |

[a] Values given are for the amine salts indicated and are uncorrected; **13** was tested as the free base; the average control value was 130 mmHg. [b] Mean values for six dogs; other values are ranges obtained with the dogs tested. [c] Hypotensive evaluation of the trifluoroacetate salt gave comparable results. [d] Not tested at this dose. [e] See ref 3.

amino-6,7-dimethoxyquinazoline (**14**), were prepared from the known[10] 2,4-dichloro-6,7-dimethoxyquinazoline (**9c**). Reaction of **9c** with ammonia under pressure at elevated temperature gave **13** directly, whereas reaction of **9c** with ammonia at ambient temperatures gave the 2-chloro-4-amino derivative **10c**. Reaction of **10c** with piperazine at elevated temperatures afforded **14**.

The mass spectra of compounds **12a,b**, **13**, and **14** were identical with those of the prazosin-related components isolated from urine and bile of rats and dogs. Not unexpectedly, the spectra of the isomeric hydroxy analogues **12a** and **12b** were identical, but the two compounds were differentiated by thin-layer chromatography. Comparison of the above physical constants with those of the components isolated from metabolism studies[3] unequivocally confirms the structural assignments of these metabolites and shows 6-*O*-demethylprazosin (**12a**) to be the major metabolite in rat and dog (Table I).

**Hypotensive Evaluation and Discussion.** Compounds **12a,b**, **13**, and **14** were compared with prazosin for hypotensive activity in anesthetized normotensive mongrel dogs using methods previously described.[1] Increasing doses of 0.1, 0.4, and 1.0 mg/kg body weight were administered to each dog at 30-min intervals, after which time the maximum decrease in blood pressure was measured vs. control (Table I). At least two dogs were used for each compound tested.

The results presented in Table I suggest that the four metabolites synthesized possess approximately 10–25% of the hypotensive activity of prazosin. Since these metabolites account for a major portion of the administered dose and their relative abundance is not highly species dependent, it seems conceivable that they contribute to the antihypertensive effect of prazosin.

## Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were performed by the Analytical Department of Pfizer, Inc. Where analyses are indicated by symbols of the elements, results were within 0.4% of theoretical values. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6E or a LKB-9000A spectrometer.

**3-Benzyloxy-4-methoxybenzaldehyde (3a).** A mixture of 90 g (0.59 mol) of isovanillin (**2a**), 400 ml of absolute EtOH, 81 g of anhydrous $K_2CO_3$, and 114 g (0.90 mol) of freshly distilled benzyl chloride was refluxed for 2.5 days. The reaction mixture was filtered and the solvent removed in vacuo. After cooling, the solidified oil was recrystallized from EtOH, yielding 116 g (81%) of **3a**: mp 59–64 °C (lit.[7] mp 63.5 °C).

**4-Benzyloxy-3-methoxybenzaldehyde (3b)** was prepared in analogous manner except that vanillin (**2b**) was used in place of isovanillin (**2a**). Recrystallization yielded 76.5% of **3b**: mp 61–62 °C (lit.[7] mp 64.5 °C).

**5-Benzyloxy-4-methoxy-2-nitrobenzaldehyde (4a).** Over a period of 30 min, 48 g (0.198 mol) of **3a** was slowly added to 200 ml of concentrated $HNO_3$ at 0 °C. After 30 min at 15 °C the mixture was added to ice water and the yellow precipitate collected by filtration and dried to yield 52.8 g (94%) of **4a**: mp 131 °C. Anal. ($C_{15}H_{13}NO_5$) C, H, N.

**4-Benzyloxy-5-methoxy-2-nitrobenzaldehyde (4b)** was prepared from **3b** in a manner similar to that described for **4a**: yield 89%; mp 123 °C (lit.[11] mp 133 °C). This material was used without further purification in the next step.

**5-Benzyloxy-4-methoxy-2-nitrobenzoic Acid (5a).** A hot solution of 400 ml of 10% $KMnO_4$ was gradually added to a solution of 43 g (0.15 mol) of **4a** in 600 ml of acetone. After 40 min the insoluble materials were filtered and the filter cake was washed with hot water. The acetone was removed in vacuo and the resulting aqueous solution acidified with concentrated HCl to yield a precipitate which was collected and dried to give 47.5 g of crude acid. Recrystallization from PhH–EtOH yielded 45.4 g (69%) of **5a**: mp 195.5 °C. Anal. ($C_{15}H_{13}NO_6$) H, N; C: calcd, 59.41; found, 58.95.

**4-Benzyloxy-5-methoxy-2-nitrobenzoic acid (5b)** was obtained from 4b in 69% yield using the procedure described for **5a**: mp 163–165 °C. Anal. ($C_{15}H_{13}NO_6$) C, H, N.

**5-Benzyloxy-4-methoxy-2-nitrobenzamide (6a).** A mixture of 24.0 g (0.0793 mol) of **5a** was refluxed in 180 ml of $SOCl_2$ for 22 h. Upon removal of the $SOCl_2$ under vacuum, 150 ml of dioxane was added and $NH_3$ was slowly bubbled into the solution. After 2 h, the precipitate was filtered, and the filter cake washed successively with water and *i*-PrOH and then dried to yield 16.0 g (67%) of **6a**: mp 221–222 °C. Anal. ($C_{15}H_{14}N_2O_5$) C, H, N.

**4-Benzyloxy-5-methoxy-2-nitrobenzamide (6b)** was obtained from **5b** in 66% yield using the procedure described for **6a**: mp 188–190 °C. Anal. ($C_{15}H_{14}N_2O_5$) C, H, N.

**5-Benzyloxy-4-methoxy-2-aminobenzamide (7a).** A mixture of 16.0 g (0.053 mol) of **6a** and 320 ml of glacial HOAc was heated to 90 °C and 14.8 g (0.265 mol) of iron powder was added over a period of 20 min. After another 45 min, the reaction mixture was filtered, the insolubles were washed with hot HOAc, and the filtrate was poured into 560 ml of 10% HCl. The precipitate was filtered, slurried in hot water, and made basic with 15% NaOH. Upon cooling, light tan crystals were isolated, washed with *i*-PrOH, and dried to yield 9.7 g (70%) of **7a**: mp 166–167 °C. Anal. ($C_{15}H_{16}N_2O_3$) C, H, N.

**4-Benzyloxy-5-methoxy-2-aminobenzamide (7b)** was obtained in 69% yield by reduction of **6b** in a manner analogous to that described for **7a**: mp 157–158 °C. This material was used directly in the next step without further purification.

**6-Benzyloxy-7-methoxyquinazoline-2,4-dione (8a).** A mixture of 9.70 g (35.7 mmol) of **7a** and 4.28 g (71.4 mmol) of urea was placed in 150 ml of pyridine containing 10 drops of 10% HCl and refluxed for 24 h. After cooling, the resulting tan crystals were filtered and washed with $Et_2O$ to yield 7.55 g (71%) of **8a**: mp 254–256 °C. Anal. ($C_{16}H_{14}N_2O_4 \cdot H_2O$) C, H; N: calcd, 8.86; found, 8.45.

**7-Benzyloxy-6-methoxyquinazoline-2,4-dione (8b)** was prepared from **7b** in 64% yield using the procedure described for **8a**: mp 285–286 °C dec. Anal. ($C_{16}H_{14}N_2O_4 \cdot 0.5H_2O$) C, H, N.

**2,4-Dichloro-6-benzyloxy-7-methoxyquinazoline (9a).** A mixture of 7.10 g (23.8 mmol) of **8a**, 20 ml of $POCl_3$, and 1.9 ml of *N,N*-dimethylaniline was refluxed under nitrogen for 4.5 h, cooled, and allowed to stir overnight at room temperature. The

Table II. Representative $R_f$ Values for Prazosin (1) and 12a,b, 13, and 14 on Silica-Gel Thin-Layer Chromatography Plates

| Solvent system | $R_f$ | | | | |
|---|---|---|---|---|---|
| | 1 | 12a | 12b | 13 | 14 |
| EtOAc-MeOH (2:1) | 0.48 | 0.34 | 0.15 | 0.09 | 0.00 |
| EtOAc-MeOH-HOAc (85:15:5) | 0.10 | 0.08 | 0.16 | 0.24 | 0.00 |
| EtOAc-MeOH-$Et_2NH$ (70:20:5) | 0.70 | 0.47 | 0.43 | 0.41 | 0.24 |

mixture was then added to 150 ml of ice water, and the resulting tan precipitate was filtered, washed with water, dried, and slurried with petroleum ether to yield 3.89 g (49%) of **9a**: mp 180 °C dec.

**2,4-Dichloro-7-benzyloxy-6-methoxyquinazoline (9b)** was prepared from **8b** similar to the synthesis of **9a**, except that after addition to ice water the solution was extracted several times with $CHCl_3$. The organic phase was dried over anhydrous $Na_2SO_4$, decolorized, filtered through Celite, and concentrated to yield 31% of **9b**: mp 162–163 °C. Anal. ($C_{16}H_{12}O_2N_2Cl_2$) C, H, N.

**4-Amino-6-benzyloxy-2-chloro-7-methoxyquinazoline (10a).** Over a period of 3–4 days dry $NH_3$ was bubbled intermittently into a mixture of 3.89 g (11.6 mmol) of **9a** and 80 ml of THF at ambient temperature, each day filtering off the insoluble materials which had formed. The THF solution was then concentrated and filtered to yield an additional crop of crude **10a**: total yield 1.37 g (38%); mp 225–231 °C dec. This material was used without further purification in the next step.

**4-Amino-7-benzyloxy-2-chloro-6-methoxyquinazoline (10b)** was prepared from **9b** in 88% yield using the procedure described for **10a**: mp 199–205 °C. An analytical sample was obtained by recrystallization from DMF–$Et_2O$. Anal. ($C_{16}H_{14}N_3O_2Cl$) H, N; C: calcd, 60.86; found, 59.50.

**2-Chloro-4-amino-6,7-dimethoxyquinazoline (10c).** A solution of 30 g (0.116 mol) of **9c**[10] in 800 ml of THF was saturated with anhydrous $NH_3$ and stirred at room temperature for 44 h. The precipitate that formed was collected and recrystallized from MeOH to afford 19 g (68%) of **10c**: mp 302 °C dec. Anal. ($C_{10}H_{10}ClN_3O_2$) C, H, N.

**2-[4-(2-Furoyl)piperazin-1-yl]-4-amino-6-benzyloxy-7-methoxyquinazoline Hydrochloride Monohydrate (11a).** A mixture of 1.37 g (4.34 mmol) of **10a** and 858 mg (4.77 mmol) of 1-(2-furoyl)piperazine (**15**) was heated in 20 ml of isoamyl alcohol for 2.5 h and then cooled and the resulting white precipitate collected by filtration and washed successively with isoamyl alcohol and acetone. Recrystallization from MeOH yielded 1.30 g (59%) of **11a** as the hydrochloride monohydrate: mp 259–261 °C dec; mass spectrum (70 eV) *m/e* (rel intensity) 459 (19, $M^+$), 368 (100), 309 (5), 95 (20), 91 (18). Anal. ($C_{25}H_{25}N_5O_4$·HCl·$H_2O$) H, N; C: calcd, 58.48; found, 57.56.

**2-[4-(2-Furoyl)piperazin-1-yl]-4-amino-7-benzyloxy-6-methoxyquinazoline hydrochloride monohydrate (11b)** was prepared from **10b** in 37% yield using the procedure described for **11a**: mp 269–270 °C dec; mass spectrum (70 eV) *m/e* (rel intensity) 459 (46, $M^+$), 368 (35), 309 (69), 206 (100), 92 (44), 91 (74). Anal. ($C_{25}H_{25}N_5O_4$·HCl·$H_2O$) C, H, N.

**2-[4-(2-Furoyl)piperazin-1-yl]-4-amino-6-hydroxy-7-methoxyquinazoline (12a).** A mixture of 200 mg (0.436 mmol) of **11a** and 4 ml of $CF_3CO_2H$ was refluxed for 2.5 h. The reaction mixture was then cooled to room temperature and poured into 40 ml of $Et_2O$. Filtration of the precipitate, washing with ether, and drying yielded 122 mg (58%) of the trifluoroacetate hydrate of 6-*O*-demethylprazosin (**12a**): mp 241 °C dec. Anal. ($C_{18}H_{19}N_5O_4$·$CF_3COOH$·$H_2O$) C, H, N. The hydrosulfate salt of **12a** was prepared as described below for **12b**: mp 220 °C dec; mass spectrum (70 eV) *m/e* (rel intensity) 369 (42, $M^+$), 245 (37), 231 (28), 219 (100), 191 (17), 95 (23); $R_f$, see Table II.

**2-[4-(2-Furoyl)piperazin-1-yl]-4-amino-7-hydroxy-6-methoxyquinazoline (12b).** A solution of 300 mg (0.653 mmol) of **11b** dissolved in 2.5 ml of concentrated $H_2SO_4$ was stirred at room temperature for 0.5 h. Trace amounts of insolubles were removed by filtration and the $H_2SO_4$ solution was added to about 30 ml of ice water to precipitate the product. The solids were removed by filtration and washed with $H_2O$ and *i*-PrOH to yield 188 mg (59%) of the desired 7-*O*-demethylprazosin (**12b**) as the hydrosulfate monohydrate: mp 220 °C dec; mass spectrum (70 eV) *m/e* (rel intensity) 369 (49, $M^+$), 245 (42), 231 (34), 219 (100), 191 (19), 95 (38); $R_f$, see Table II. A sample for analysis was recrystallized from $CF_3CO_2H$–$Et_2O$: mp 230 °C dec. Anal. ($C_{18}H_{19}N_5O_4$·$CF_3CO_2H$·$2H_2O$) C, H; N: calcd, 13.48; found, 12.50.

**Prazosin (1).** In two separate reactions a small amount (<1 mg) of 50% NaH in mineral oil was added to 2 mg of **12a** and **12b** in a few drops of THF. A drop of dimethyl sulfate was added to each reaction, which was then stirred for 10–20 min at room temperature. TLC on silica gel using EtOAc–MeOH–$Et_2NH$ (17:2:1) as the solvent system indicated most of the starting materials (**12a** and **12b**) were consumed and a spot corresponding to prazosin ($R_f$ 0.62) had formed.

**2,4-Diamino-6,7-dimethoxyquinazoline (13).** A solution of 7.77 g (30 mmol) of **9c**[10] in 100 ml of EtOH saturated with $NH_3$ was heated at 160 °C in a pressure bomb for 65 h, then cooled, and filtered. The solid was dissolved in 500 ml of hot $H_2O$ and the solution made basic with $NaHCO_3$, chilled, and filtered. Recrystallization from $H_2O$ yielded 5.09 g (77%) of the desired 2,4-diamino-6,7-dimethoxyquinazoline (**13**): mp 244–246 °C; $R_f$, see Table II. Anal. ($C_{10}H_{12}N_4O_2$) C, H, N.

**2-(1-Piperazinyl)-4-amino-6,7-dimethoxyquinazoline (14).** A mixture of 1.72 g (20 mmol) of anhydrous piperazine, 20 ml of EtOH, and 1.5 ml of $H_2O$ was stirred at room temperature under an atmosphere of $N_2$ as 3.38 ml (1.62 g, 20 mmol) of 48% aqueous HBr was added over a 30-min period. The temperature rose during the addition to approximately 40 °C. The mixture was then warmed to 60 °C and 2.39 g (0.01 mol) of **10c** was added portionwise over a 1-h period. The resulting mixture was heated at reflux for 4 h and cooled, and the precipitate that formed was filtered, washed with EtOH, and dried to give 4.0 g of material melting at 275–279 °C. This was dissolved in 75 ml of hot 1.0 N HCl. The resulting solution was chilled and the precipitate was washed with EtOH to give 2.87 g (75%) of the desired 2-(1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline dihydrochloride (**14**): mp 285–287 °C; $R_f$, see Table II. Anal. ($C_{14}H_{19}N_5O_2$·2HCl) C, H, N.

**1-(2-Furoyl)piperazine (15).** To a solution of 9.95 g (0.16 mol) of anhydrous piperazine in 114 ml of EtOH and 13.0 ml of $H_2O$ was added dropwise 19.3 g (0.114 mol) of 48% aqueous HBr solution maintaining a temperature of 40–45 °C. The resulting solution was then stirred at 43 °C under $N_2$ as 7.50 g (0.0574 mol) of furoyl chloride was added over a 10-min period. The slurry was stirred at 80 °C for 1.5 h, chilled to 5 °C, and filtered. The clear filtrate was concentrated in vacuo to an oil and diluted with 15.0 ml of $H_2O$, the pH adjusted to 10.2 with dilute NaOH, and the aqueous mixture then extracted with $CHCl_3$. The $CHCl_3$ extracts were dried over anhydrous $MgSO_4$ and then concentrated in vacuo to an oil that crystallized on cooling. The crude product was taken up in 10.0 ml of EtOAc and the solution stirred at room temperature as hexane (5.0 ml) was added to the cloud point. An additional 20.0 ml of hexane was slowly added as the product crystallized. The product was filtered and washed with hexane to yield 7.30 g (70%) of **15**: mp 67–68 °C.

An analytical sample was prepared by dissolving a portion of this product in EtOH and adding ethanolic HCl: mp 202–204 °C. Anal. ($C_9H_{12}O_2N_2$·HCl) C, H, N.

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# Synthesis and Biological Activity of Some New Furan Quaternary Salts

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A series of new *N*-(5-substituted 2-furfuryl)-*N*,*N*-dimethyl-*N*-aryloxyalkyl quaternary ammonium salts relating to general structure IV has been synthesized by reacting 5-substituted 2-(*N*,*N*-dimethylaminomethyl)furans IIa–d with appropriate aryloxyalkyl bromides III. The resulting compounds are tested for in vitro antimicrobial activity. A simpler synthesis of 5-nitro-2-(*N*,*N*-dimethylaminomethyl)furan (IId) involving the reduction of *N*,*N*-dimethyl-5-nitro-2-furamide (Ib) with diborane is described. A new compound, 5-bromo-2-(*N*,*N*-dimethylaminomethyl)furan (IIc), is prepared in a similar way. Many of these compounds (**22**, **28**, **34**, **37–42**, 44, and **45**) indicate high activity against *Staphylococcus aureus*, *Streptococcus faecalis*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* and are more active than nitrofurantoin. Compounds **22**, **34**, and 41 exhibit the highest in vitro antibacterial activity in the series. Some of these quaternary salts (**22**, **25**, **37**, **39–41**, and **60**) possess appreciable activity against *Mycobacterium tuberculosis* $H_{37}Rv$. None of these compounds show significant antifungal activity. Eight compounds (**18**, **21**, **22**, **26–28**, **32**, and **34**) having high in vitro antibacterial activity were inactive when tested for anthelmintic activity in rats against *Nippostrongylus brasiliensis* and *Hymenolepis nana*.

The chemotherapeutic applications of quaternary ammonium salts have gained importance since World War II. Many members of this class are known to possess antibacterial[1] and antifungal[2] activities and have found general utility in skin disinfectants as well as in the formulation of creams, ointments, lotions, powders, etc. Quaternary ammonium salts such as biphenium 3-hydroxy-2-naphthoate and thenium 4-chlorobenzenesulfonate containing a substituted phenolic ether moiety are claimed to possess anthelmintic properties.[3] 5-Nitrofuran derivatives are well known to possess antibacterial activity. In our previous paper,[4] we described the synthesis and antimicrobial activity of a series of aryl- and aryloxyalkyl-*N*-(5-nitro-2-furyl)carbamates. Aryloxyalkyl esters derived from different hydroxybenzoic acids also exhibited significant antimicrobial activity.[5] It was considered of interest to synthesize and study the antimicrobial action of several new furan quaternary salts which contain the features of appropriately substituted furan and phenolic ethers. Hence, a series of new *N*-(5-substituted 2-furfuryl)-*N*,*N*-dimethyl-*N*-aryloxyalkyl quaternary ammonium bromides IV has been prepared. In certin cases where the quaternary ammonium bromides could not be isolated owing to their hygroscopic nature, corresponding tosylates V have been prepared and tested for antimicrobial activity.

During the course of our work it came to our notice that analogous 5-substituted furan quaternary compounds find a mention in a British patent[6] and are claimed to possess anthelmintic activity. However, none of the claimed furan quaternary salts have been described in the complete specification of this patent.

**Chemistry.** Various new furan quaternary ammonium bromides IV were made by reacting 5-substituted 2-(*N*,*N*-dimethylaminomethyl)furans IIa–d with appropriate aryloxyalkyl bromides III in acetone at reflux temperature or by leaving at room temperature without any solvent. The various steps leading to the synthesis of these new furan quaternary salts are represented in Scheme I.

2-(*N*,*N*-Dimethylaminomethyl)furan[7] (IIa) and 5-methyl-2-(*N*,*N*-dimethylaminomethyl)furan[8] (IIb) were prepared by the known methods. 5-Nitro-2-(*N*,*N*-dimethylaminomethyl)furan[9] (IId) was previously prepared from 5-nitro-2-furfuryl chloride by reacting with dimethylamine in an autoclave at 40 °C. We have now prepared this amine by a more convenient method by reducing the corresponding amide Ib with diborane in situ according to the method of Brown.[10] 5-Bromo-2-(*N*,*N*-dimethylaminomethyl)furan (IIc) which has not been reported so far was also prepared in a similar way. The intermediate aryloxyalkyl bromides III were prepared following the method of Marvel[11] by heating the corresponding phenols with an excess of appropriate dibromoalkane in the presence of aqueous sodium hydroxide.

The 5-substituted furan quaternary ammonium tosylates V (compounds **35**, **43**, **45**, **49**, and **51–54**) were prepared by treating the aqueous solution of the corresponding crude quaternary ammonium bromides with sodium *p*-toluenesulfonate solution in water. However, compound **5** was prepared differently by treating 5-nitro-2-(*N*,*N*-dimethylaminomethyl)furan (IId) with 4-chlorothymyloxyethyl tosylate (VI). All the compounds were characterized by elemental analyses and are listed in Table I.

**Biological Results and Discussion.** Many of the new furan quaternary salts reported in this paper possess broad spectrum in vitro antibacterial activity against representative bacteria as shown in Table II. The highest activity is shown against gram-negative bacteria, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, with MIC values as low as 1.5 μg/ml. Only a few compounds show activity against *Escherichia coli* and *Salmonella typhi* but of a low order (50–100 μg/ml). In the case of gram-positive bacteria, some of these compounds show fairly high activity (2–10 μg/ml) against *Staphylococcus aureus* and *Streptococcus faecalis*. Many of these compounds possess appreciable activity against *Mycobacterium tuberculosis*