The Preparation of Some Antimalarials with Quaternary Carbon Side Chains

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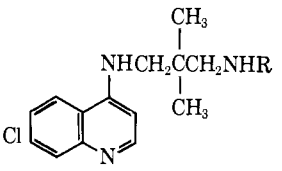
Possible nonbiodegradability of quaternary carbon side chains prompted us to insert such a chain in a typical antimalarial drug. Antimalarials of the following structure were synthesized.



1, R = H
2, R = $CONH_2$
3, R = $CO_2C_2H_5$

It is of interest that **1** and **3** were active in testing against *Plasmodium berghei*, **1** having a curative rating, while **2** was inactive. A similar relationship of the amine and corresponding ureide has been noted previously: 6-methoxy-8-(3-aminopropylamino)quinoline was 50 times more effective as an antimalarial than 6-methoxy-8-(3-ureidopropylamino)quinoline.[1]

Antimalarial compounds with quaternary side chains have been made previously but for the most part are based on the parent structure: 6-methoxy-8-(2,2-dimethyl-3-diethylaminopropylamino)quinoline.[2,3] This compound apparently is about equivalent to pamaquine in antimalarial activity[4] and in addition has some anesthetic action.

Nonbiodegradable side chains have been incorporated in antimalarial compounds previously, but they have been based on a tertiary carbon rather than quaternary carbon structure such as, for example, 7-chloro-4-(4-diethylamino-4-methylbutylamino)quinoline.[5]

Experimental Section

7-Chloro-4-(3-amino-2,2-dimethylpropylamino)quinoline (1).—To 30 g (0.3 mole) of 3-amino-2,2-dimethylpropylamine (Aldrich Chemical Co.), held at 150° with stirring, 10 g (0.05 mole) of 4,7-dichloroquinoline, dissolved in 37 g (0.36 mole) of 3-amino-2,2-dimethylpropylamine, was added dropwise over a period of 8 hr. The excess diamine was removed by distillation at water aspirator pressure, and the residue was dispersed in dilute NH_3, filtered, and washed with water. Extraction from a Soxhlet cup with hexane yielded 7.6 g (58%) of white, disklike crystals: mp 94–95°; neutr equiv, 269 (calcd 263.5). The free base tended to react with CO_2 to form a high-melting, insoluble compound which could be reconverted to the free base by reextraction in a Soxhlet. The dihydrochloride salt was made by solution in 5% HCl, evaporation to dryness, and recrystallization from isopropyl alcohol to which a few drops of water were added, mp 280–290° dec.

Anal.[6] Calcd for $C_{14}H_{20}Cl_3N_3 \cdot H_2O$: Cl, 29.97; N, 11.90. Found: Cl, 29.91; N, 11.83.

7-Chloro-4-(3-ureido-2,2-dimethylpropylamino)quinoline (2).—The diamine **1** (2.15 g, 0.0064 mole), 5 g (0.083 mole) of urea, 40 ml of water and 5 drops of concentrated HCl were refluxed for 4 hr during which time crystals deposited. The crystals were recrystallized from alcohol as 1.3 g (37%) of white needles, mp 219–219.5° gas dec.

Anal. Calcd for $C_{15}H_{19}ClN_4O$: C, 58.73; H, 6.24; Cl, 11.56; N, 18.28. Found: C, 58.52; H, 6.24; Cl, 11.56; N, 18.26.

7-Chloro-4-(3-ethylcarbamido-2,2-dimethylpropylamino)quinoline (3).—To a stirred solution of 2 g (0.0074 mole) of **1** in 10 ml of pyridine, 2.2 g (0.02 mole) of ethyl chlorocarbonate was added dropwise. The contents were then heated to 60° for 15 min, cooled, poured into water, and neutralized carefully with NH_3. The precipitate was filtered, washed with water, and recrystallized from 75% aqueous ethanol yielding colorless needles, 1.6 g (65%), mp 161–162°.

Anal. Calcd for $C_{17}H_{22}ClN_3O_2$: Cl, 10.57; N, 12.51. Found: Cl, 10.50; N, 12.46.

Pharmacology.—Five mice were infected with a lethal dose of *P. berghei* 3 days prior to administration of the chemical at various dose concentrations (see Table I). The chemical was introduced subcutaneously in oil. Mean survival time of infected control mice is 6.5 ± 0.5 days. Extension in survival time of chemically treated mice is interpreted as evidence of antimalarial activity. Number of mice surviving (out of five) after 30 days is suggestive of curative rating.

TABLE I

Compd	Dose level, mg/kg	Mean survival time, days	No. surviving at end of 30 days (cures)
1[a]	40	12.6	
	160	...	1
	640	...	2
2	160	6.6	
	640	9.4	
3	40	13.6	

[a] Tested as dihydrochloride hydrate.

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(2) M. D. Bovet, *Arch. Intern. Pharmacodyn.*, **41**, 103 (1931); *Chem. Abstr.*, **26**, 4865 (1932); O. Y. Magidson and A. L. Midzhoyan, *J. Gen. Chem. USSR*, **7**, 1557 (1937); *Arch. Pharm.*, **272**, 74 (1934); S. Tatsuoka, *et al.*, *J. Pharm. Soc. Japan*, **69**, 33 (1949); **65B**, 52 (1945); *Ann. Rept. Takeda Res. Lab.*, **10**, 16 (1951); *Chem. Abstr.*, **47**, 4886 (1953); S. Tateoka, *J. Pharm. Soc. Japan*, **65**, 1 (1945).

(3) The compounds, 7-chloro-4-(2,2-dimethyl-3-piperazinopropylamino)-quinoline and the reaction product of this with 4,7-dichloroquinoline have been prepared and claimed to display antimalarial activity: Rhone-Poulenc S.A., Belgian Patent 618,068 (Nov 26, 1962); *Chem. Abstr.*, **59**, 6370 (1963).

(4) S. Kuroda, *J. Pharm. Soc. Japan*, **64**, 71 (1944).

(5) SN-10451. D. S. Breslow, M. S. Bloom, J. C. Shivers, J. T. Adams, M. J. Weiss, R. S. Yost, and C. R. Hauser, *J. Am. Chem. Soc.*, **68**, 1232 (1946).

(6) All analyses are by Galbraith Laboratories, Knoxville, Tenn.

Nitrofuryl Heterocycles. VI.[1] 1-Alkyl- and 1-Aryl-5-(5-nitro-2-furyl)tetrazoles

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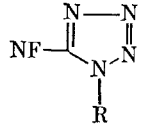
In a continuing search for new 5-nitro-2-furyl heterocycles which might possess useful antimicrobial activity, a series of 1-alkyl- and 1-aryl-5-(5-nitro-2-furyl)-tetrazoles was prepared. Syntheses and *in vitro* antibacterial data for these tetrazoles are reported.

Chemistry.—The unsubstituted 5-(5-nitro-2-furyl)-tetrazole (**1**) was prepared by the method of Finnegan,

(1) For paper V in this series see H. A. Burch, *J. Med. Chem.*, **10**, 91 (1967).

TABLE 1

5-NITRO-2-FURYLTETRAZOLES AND -AMIDES

No.	R	Yield, %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Min inhib conen, μg/ml[a] *E. coli*	*S. typhosa*	*S. pyogenes*	*S. aureus*	*Erysipelothrix insidiosa*
					 (NF = 5-nitro-2-furyl)										
1	H	29.0	128–129	$C_5H_3N_5O_3$	33.16	1.67	38.67	33.35	2.07	38.34	>50	>50	50	>50	25
2a	CH_3	20.8	153.5–154.5	$C_6H_5N_5O_3$	36.93	2.58	35.89	36.80	2.53	35.60	1.5	1.5	12.5	25	12.5
2b	$(CH_2)_3CH_3$	58.3	96.5–97	$C_9H_{11}N_5O_3$	45.57	4.67	29.53	45.42	4.88	29.30	29	>29	>29	>29	>29
2c	$CH_2C_6H_5$	60.6	134–135	$C_{12}H_9N_5O_3$	53.14	3.34	25.82	53.14	3.40	26.14	50	50	25	50	50
2d	$CH_2CH_2OCH_3$	37.6	95.5–96.5	$C_8H_9N_5O_4$	40.17	3.79	29.28	40.21	3.88	29.43	8	20	20	>120	60
2e	$CH_2CO_2C_2H_5$	23.7	118–118.5	$C_9H_9N_5O_5$	40.45	3.40	26.21	40.39	3.30	26.13	50	100	50	200	200
2f	$CH(CH_2)_5$	68.0	182.5–183	$C_{11}H_{13}N_5O_3$	50.18	4.98	26.61	50.26	5.00	26.68	>50	>50	>50	>50	>50
2g	C_6H_5	56.7	168–169	$C_{11}H_7N_5O_3$	51.36	2.74	27.23	51.47	2.81	27.51	25	6.25	6.25	12.5	12.5
2h	$C_6H_4CH_3$-*m*	45.0	147–148	$C_{12}H_9N_5O_3$	53.14	3.34	25.82	53.00	3.43	25.80	>50	50	25	25	12.5
2i	$C_6H_4CH_3$-*o*	55.5	150–151	$C_{12}H_9N_5O_3$	53.14	3.34	25.82	53.14	3.38	25.00	25	12.5	6.25	12.5	25
2j	$C_6H_4OCH_3$-*o*	63.0	132.5–133	$C_{12}H_9N_5O_4$	50.18	3.16	24.38	50.17	3.32	24.58	50	>50	12.5	12.5	50
2k	$C_6H_4OCH_3$-*p*	42.5	159.5–160	$C_{12}H_9N_5O_4$	50.18	3.16	24.38	50.26	3.15	24.55	>50	>50	25	25	>50
2l	$C_6H_4CF_3$-*m*	22.7	149–150	$C_{12}H_6F_3N_5O_3$	44.32	1.86	21.53	44.36	2.05	21.50	>50	>50	12.5	25	25
2m	2-C_5H_5N	36.7	129–130	$C_{10}H_6N_6O_3$	46.51	2.34	32.55	46.37	2.44	32.62	25	6.25	6.25	12.5	12.5
					NF–CONHR										
3a	CH_3	54.0	213–214[b]	$C_6H_5N_3O_4$	42.36	3.56	...	42.32	3.75	...	7	10	10	120	120
3b	$(CH_2)_3CH_3$	18.0	92.5–93.5[c,b]	$C_9H_{12}N_3O_4$	50.94	5.70	13.20	50.96	5.81	13.35	30	50	100	30	200
3c	$CH_2C_6H_5$	67.0	95.5–96.5[d]	$C_{12}H_{10}N_3O_4$	58.53	4.09	11.38	58.67	4.17	11.30	30	50	200	10	50
3d	$CH_2CH_2OCH_3$	28.5	73–74	$C_8H_{10}N_3O_5$	44.86	4.71	13.08	44.83	4.74	13.13	10	30	100	100	200
3e	$CH_2CO_2C_2H_5$	76.5	96–97	$C_9H_{10}N_3O_6$	44.63	4.16	11.51	44.50	4.24	11.62	30	30	100	100	200
3f	$CH(CH_2)_5$	60	153–154	$C_{11}H_{14}N_3O_4$	55.45	5.92	11.76	55.29	5.89	11.92	>80	>80	40	80	>80
3g	C_6H_5	90	187–188[e]	$C_{11}H_8N_3O_4$	...	...	...	...	...	...	1.5	1.5	25	12.5	0.75
3h	$C_6H_4CH_3$-*m*	69	149–150	$C_{12}H_{10}N_3O_4$	58.53	4.09	11.38	58.53	4.23	11.43	3.1	25	3.1	6.25	1.5
3i	$C_6H_4CH_3$-*o*	68	150–151	$C_{12}H_{10}N_3O_4$	58.53	4.09	11.38	58.77	4.35	11.34	60	>60	60	6	30
3j	$C_6H_4OCH_3$-*o*	78	151.5–152.5	$C_{12}H_{10}N_3O_5$	54.96	3.84	10.68	54.97	4.04	10.71	1.5	12.5	3.1	12.5	1.5
3k	$C_6H_4OCH_3$-*p*	58	188.5–190[f,i]	$C_{12}H_{10}N_3O_5$	54.96	3.84	10.68	54.67	3.82	10.74	3.1	6.25	6.25	6.25	3.1
3l	$C_6H_4CF_3$-*m*	64	189.5–190.5	$C_{12}H_7F_3N_3O_4$	48.01	2.35	9.33	47.89	2.40	9.39	25	>50	25	6.25	12.5
3m	2-C_5H_5N	77	197–197.5	$C_{10}H_7N_3O_4$	51.51	3.03	...	51.80	3.20	...	3.1	3.1	12.5	25	6.25
3n	$C_6H_4CO_2CH_3$-*p*	79	250.5–251.5[c]	$C_{13}H_{10}N_3O_6$	53.80	3.47	9.65	53.75	3.45	9.75	12.5	50	25	25	50
					NF–C(Cl)=NC$_6$H$_4$CO$_2$CH$_3$-*p*										
4		74.6	141–142	$C_{13}H_8ClN_3O_5$[j]	50.58	2.94	9.08	50.61	3.02	9.09	12.5	>50	12.5	12.5	1.5
Nitrofurazone[g]											3	3	6	12.5	12.5

[a] Minimum inhibitory concentration is the lowest concentration of compound that prevents visible growth after 24 hr of incubation. [b] H. Gilman and H. L. Yale, *J. Am. Chem. Soc.*, **72**, 3593 (1950), reported mp 202–203°. [c] Lit.[b] mp 89–90°. [d] H. D. Brown, A. R. Matzuk, and L. H. Sarett, U. S. Patent 2,989,530 (June 20, 1961), reported mp 90–92°. [e] C. Marquis, *Compt. Rend.*, **137**, 520 (1903), reported mp 179–180°. [f] V. Farcasan and C. Makkay, *Rev. Chim. Acad. Rep. Populaire Roumaine*, **5**, 129 (1960); *Chem. Abstr.*, **55**, 11386*i* (1961), reported mp 185°. [g] For comparison see J. G. Michels, G. Gever, and P. H. L. Wei, *J. Med. Pharm. Chem.*, **5**, 1042 (1962). [h] Solvent = C_6H_6. [i] Solvent = MeNO$_2$. [j] Showed correct analysis for Cl.

et al.[2] For the preparation of 1-alkyl- and 1-aryl-5-(5-nitro-2-furyl)tetrazoles (compounds **2a–m**) the method of Harvill, *et al.*,[3] was utilized.

The synthesis of the tetrazoles proceeded smoothly in all cases except when **3n** was used as the starting amide. In that instance, the product isolated from the reaction mixture (**4**) was not the expected tetrazole, but a compound having an imino chloride structure. This compound was unusually stable and resisted reaction with solutions of sodium azide and hydrazoic acid.

Screening Results.—The *in vitro* antibacterial testing data, given in Table I, were determined using methods described previously.[4] Data for nitrofurazone[5] are included for comparison. None of the compounds prepared possessed activity that was significantly better than that of nitrofurazone.

Experimental Section

All melting points were determined on a hot stage (Mel-Temp) melting point apparatus and are uncorrected. The infrared spectrum was obtained on a Perkin-Elmer infrared spectrophotometer Model 21.

5-(5-Nitro-2-furyl)tetrazole (1).—A mixture of 5-nitro-2-furonitrile[6] (138 g, 1.0 mole), sodium azide (72 g, 1.1 moles), and NH_4Cl (58 g, 1.1 moles) in DMF (500 ml) was stirred and heated cautiously. At first a very exothermic reaction occurred which quickly subsided. Stirring was continued for 3 hr at 100°. The solvent was removed under reduced pressure. After the residue was dissolved in water, the solution was acidified to pH 2 with concentrated HCl. A black, tarry mass formed which slowly crystallized upon cooling. The crude material was collected and recrystallized from glacial acetic acid.

N-Cyclohexyl-5-nitro-2-furamide (3f).—A solution of cyclohexylamine (182 g, 1.84 moles) in dioxane (800 ml) was placed in the flask and stirred while 5-nitro-2-furoyl chloride[7] (161 g, 0.92 mole) dissolved in dioxane (800 ml) was added. The reaction mixture was refluxed for 1 hr and poured into a large volume of water. After collecting, the product was recrystallized from 2-propanol (charcoal). Other derivatives of **3** listed in Table I except **3e** were prepared in a similar manner from the appropriate amine and were recrystallized from methanol or 2-propanol.

Ethyl N-(5-Nitro-2-furoyl)glycinate (3e).—Ethyl glycinate hydrochloride (560 g, 4 moles) was placed in the flask together with water (1000 ml) and ethylene chloride (1000 ml). Calcium carbonate (340 g) was added and the mixture was stirred vigorously for 15 min. The stirring was continued while 5-nitro-2-furoyl chloride (350 g, 2 moles) in ethylene chloride (1000 ml) was added. Stirring was continued for 3 hr, and the mixture was allowed to stand overnight at room temperature. The mixture was filtered and the two layers were separated. After the solvent was removed from the organic layer under reduced pressure, the crystallized residue was recrystallized from 2-propanol (charcoal).

1-Methyl-5-(5-nitro-2-furyl)tetrazole (2a).—Benzene (500 ml) was placed in a flask together with **3a** (44 g, 0.26 mole). The mixture was stirred while PCl_5 (54 g, 0.26 mole) was added in small portions which was accompanied by a slight endothermic reaction and the evolution of HCl. The reaction mixture was stirred at room temperature while a solution of HN_3[8] (13 g, 0.3 mole) in benzene (220 ml) was added. After stirring the mixture at room temperature for 1 hr, it was stirred at reflux for about 18 hr. After the benzene was removed under reduced pressure, the residue was poured into water and the crude product was collected and recrystallized from 2-propanol (charcoal). Other alkyl derivatives (**2b–f**) listed in Table I were prepared in a similar manner and recrystallized from methanol or 2-propanol.

The aryl derivatives (**2g-m**) were prepared in a similar manner. However, after the addition of PCl_5, it was necessary to heat the mixture to affect the formation of the imino chloride intermediate. Once a clear solution was obtained, the reaction mixture was cooled to room temperature and the procedure was continued as above.

Methyl *p*-[(α-Chloro-5-nitrofurfurylidene)amino]benzoate (4).—Compound **3n** (126 g, 0.435 mole) was placed in a flask together with PCl_5 (91 g, 0.435 mole) and toluene (1000 ml). The mixture was refluxed for 15 hr. The reaction mixture was cooled in an ice bath and filtered. The crude product was washed with water and recrystallized from 2-propanol (charcoal).

An infrared spectrum in $CHCl_3$ displayed absorption peaks at 1720 (C=O) and 1620 cm^{-1} (C=N).

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(3) E. K. Harvill, R. M. Herbst, E. C. Schreiner, and C. W. Roberts, *J. Org. Chem.*, **15**, 662 (1950).

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(5) Furacin®, 5-nitro-2-furaldehyde semicarbazone.

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(7) H. Gilman and R. V. Young, *J. Am. Chem. Soc.*, **56**, 464 (1934).

(8) H. Wolff, *Org. Reactions*, **3**, 327 (1946).

N^3-(2-Aminoethyl)-5,5-diphenylhydantoin and Derivatives[1]

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The imide hydrogen of the hydantoin ring has been found sufficiently acidic to undergo aminoethylation in an alcoholic solution. Thus, the reaction of 5,5-diphenylhydantoin with ethylenimine produced N^3-(2-aminoethyl)-5,5-diphenylhydantoin (I) in good yield. That the 2-aminoethyl group is located at N-3 and not at N-1 is suggested by the insolubility of I in aqueous alkali and from the observation that basic hydrolysis of I produced the amino acid, diphenylglycine. Infrared and nmr data also support structure I. Corral and Orazi have shown that the chemical shift of a hydantoin proton located at the N-1 position occurs at a higher field than that of a corresponding N-3 proton.[3] The N_1-H signal of I was coincident with that of the aromatic ring proton signal and was observable in the integration.

A number of examples of ethylenimine reacting with compounds containing an active hydrogen are described to form the corresponding 2-aminoethyl derivative, but apparently the only reported example with a hydantoin describes the preparation of the benzoate salt of N^3-(2-aminoethyl)-5,5-diphenylhydantoin. The free amine (I) was not isolated and characterized.[4]

We have prepared the benzoate salt of I and obtained a melting point considerably different from that reported.[4] N^3-(2-Benzamidoethyl)-5,5-diphenylhydan-

(1) Taken in part from the M.S. Thesis of J. W. S., Bucknell University, 1966.

(2) Undergraduate research participant, Bucknell University, 1965-1966.

(3) R. A. Corral and O. O. Orazi, *Spectrochim. Acta*, **21**, 2119 (1965).

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