TABLE II

Compd no.[a]	Activity[b] D	C	TD	MST	Remarks
3	40	0	0	7.4	
	160	0	0	9.2	
	640	0	0	12.6	Active
7	40	0	0	6.2	
	160	0	0	6.4	
	640	3	0	...	Curative
19	40	0	0	6.2	
	160	0	0	11.2	
	320	0	0	15.4	Active
	640	0	0	17.0	
21	40	0	0	8.8	
	160	1	0	...	Curative
	640	2	0	...	
24	40	0	0	6.8	
	160	0	0	7.2	
	320	0	0	12.4	
	640	2	0	...	Curative

[a] Numbers refer to the serial numbers in Table I. [b] D, dose in milligrams per kilogram; C, cures; TD, toxic deaths when the mice die within 5 days postinfection which is attributed to the drug toxicity; MST, mean survival time of the treated mice; mean survival time of the control mice varies from 6.0–6.3 days. A compound is active if the mean survival time of the treated mice exceeds two times the mean survival time of the control mice (*i.e.*, 6.3 days). A compound is curative if one or more of the animals live for 60 or more days postinfection.

Acknowledgment.—This work was supported by U. S Army Medical Research and Development Command under Research Contract No. 49-193-MD-2869. This is Contribution No. 485 from the Army Research Program on Malaria.

2-(ω-Aminoalkyl)-4-*t*-butyl-6-phenylphenols as Antimalarial Agents[1]

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Received January 13, 1969

The phenolic Mannich bases (*e.g.*, **1**) were one of the most intensively studied groups of antimalarial compounds during the World War II program. Burckhalter, *et al.*,[2,3] Coatney, *et al.*,[4] and Wiselogle[5] reported extensive animal testing data for compounds of this class, and several were evaluated in preliminary clinical studies.[6] Compound **1**, for example, showed a low order of therapeutic activity in man (*ca.* one-fifth the potency of quinine) but also elicited several undesirable side effects.[6]

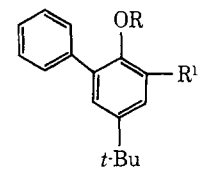
Because of the structural novelty of this class of compounds, we are reexamining it with regard to parameters not previously investigated. Thus, this paper reports the synthesis and biological evaluation of analogs of **1** and **2** having basic side chains longer than one carbon atom (*i.e.*, **3**–**5**). These compounds are no longer Mannich bases, of course, and more circuitous synthetic routes than the Mannich reaction had to be devised. The Experimental Section provides preparative details, and only a few salient features of the syntheses need be mentioned.

A Claisen rearrangement was the key step, and *o*-allylphenol derivative **7** was ultimately converted to all of the final products. The phenolic OH was protected by a benzyl group during most of the side-chain manipulations. Thus hydroboration followed by oxidation gave alcohol **8**, which provided **4** in several additional routine steps. Alcohol **8** similarly gave **5** through application of a standard cyanide chain-extension sequence. Isomerization of **7** in the presence of NaH gave the propenyl isomer (**9**), which was ozonized to aldehyde **10**. Reaction of **10** with nitromethane provided a suitably functionalized intermediate (**11**) for conversion to the Mannich base analog bearing the two-carbon side chain (**3**).

As can be seen in Table I, only the analog with the two-carbon side chain (**3**) possessed significant antimalarial activity,[7] and it was less potent and more toxic than the corresponding one-carbon Mannich base (**2**). Compound **6**, a demethyl precursor to **3**, was completely inactive, as were the three- and four-carbon side-chain members of the series (**4** and **5**). The one-carbon basic side chain is clearly preferred in this class of antimalarial agents. For comparison

TABLE I

2-PHENYL-4-*t*-BUTYLPHENOL DERIVATIVES



No.	R	R¹	Antimalarial act.[a] (toxicity deaths)
1	H	CH_2NEt_2[b]	7.5 (1/5)[c]
2	H	CH_2NMe_2[b]	9.4 (1/5)
3	H	$(CH_2)_2NMe_2$	5.9 (3/5)
4	H	$(CH_2)_3NEt_2$	1.6
5	H	$(CH_2)_4NEt_2$	1.6
6	H	$CH_2CH_2NH_2$	0.3
7	CH_2Ph	$CH_2CH{=}CH_2$	1.3[c]
8	CH_2Ph	$CH_2CH_2CH_2OH$	
9	CH_2Ph	$CH{=}CHCH_3$	
10	CH_2Ph	CHO	0.5
11	CH_2Ph	$CH{=}CHNO_2$	0.7
Quinine			6.5

[a] Results are expressed as increase in survival time (days) of treated mice (single subcutaneous dosages of 640 or 320 mg/kg) beyond that of treated controls. See F. S. Osdene, P. B. Russell, and L. Rane [*J. Med. Chem.*, **10**, 431 (1967)] for a complete description of the test. [b] Reported in ref 2 as the HCl salt. All compounds in this study were assayed as free bases. [c] Dosages of 320 mg/kg.

(1) This work was supported by the U. S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-2750. This is Contribution No. 529 from the Army Research Program on Malaria.

(2) J. Burckhalter, F. Tendick, E. Jones, W. Holcomb, and A. Rawlins, *J. Am. Chem. Soc.*, **68**, 1894 (1946).

(3) J. Burckhalter, F. Tendick, E. Jones, P. Jones, W. Holcomb, and A. Rawlins, *ibid.*, **70**, 1363 (1948).

(4) G. R. Coatney, W. C. Cooper, N. B. Eddy, and J. Greenberg, "Survey of Antimalarial Agents," Public Health Monograph No. 9, Washington, D. C., 1953, p 129.

(5) F. Y. Wiselogle, Ed., "Survey of Antimalarial Drugs, 1941–1945," Vol. II, Edwards Bros., Ann Arbor, Mich., 1946, p 375 ff.

(6) Reference 5, Vol. I, p 300.

(7) Bioassays were performed by Dr. Leo Rane of the University of Miami and the testing data were provided by Dr. David P. Jacobus of the Walter Reed Army Institute of Research.

purposes, quinine is included in Table I. No synthetic intermediates from this work displayed any antimalarial effects.

Experimental Section[8]

2-Allyloxy-5-*t*-butylbiphenyl.—4-*t*-Butyl-2-phenylphenol[9] (22.6 g, 0.10 mole) in 200 ml of DMF was converted to the Na salt by slow addition (with cooling) of 4.5 g (0.12 mole) of 53% NaH in oil. After dropwise addition of 14.4 g (0.12 mole) of allyl bromide, the mixture was heated for 3 hr at 90°, cooled, and extracted with pentane to remove mineral oil. Dilution with H_2O and extraction with Et_2O gave 24.8 g (93%) of essentially pure oil. A sample collected by glpc was analyzed. *Anal.* ($C_{19}H_{22}O$) C, H.

2-Allyl-4-*t*-butyl-6-phenylphenol.—Crude 2-allyloxy-5-*t*-butylbiphenyl (24.8 g, 0.083 mole) was heated under N_2 for 3 hr at 206–220°. Distillation of the dark mixture (104°, 0.03 mm) gave 15.7 g (59%). *Anal.* ($C_{19}H_{22}O$) C, H.

3-Allyl-2-benzyloxy-5-*t*-butylbiphenyl (7).—Alkylation as above, using benzyl chloride instead of allyl bromide, gave an 89% yield (bp 181°, 0.05 mm). *Anal.* ($C_{26}H_{28}O$) C, H.

2-Benzyloxy-5-*t*-butyl-3-(3-hydroxypropyl)biphenyl (8).—Using the general procedure of Brown and Subba Rao,[10] 71.3 g (0.2 mole) of **7** was hydroborated with 1 *M* borane in THF (Metal Hydrides, Inc.) and oxidized to give 73.4 g of crude **8**. A sample (viscous oil) was distilled and then chromatographed over silica gel for analysis. *Anal.* ($C_{26}H_{30}O_2$) C, H.

2-Benzyloxy-5-*t*-butyl-3-(3-tosyloxypropyl)biphenyl.—Crude **8** (71.2 g, 0.19 mole), dissolved in 700 ml of pyridine, was treated with 109 g (0.57 mole) of *p*-tolnenesulfonyl chloride in small portions while stirred at 0°. Slow addition of ice–H_2O to the mixture, adjustment of the solution pH to 3–5 with HCl, and extraction with $CHCl_3$ gave 96 g of crude product. Recrystallized (39 g, 37%) from MeOH it melted at 122–124°. *Anal.* ($C_{33}H_{36}SO_4$) C, H.

2-Benzyloxy-5-*t*-butyl-3-(3-diethylaminopropyl)biphenyl.—After refluxing for 2 hr, a solution of the above tosylate (10.6 g, 20 mmoles) in 100 ml of Et_2NH was diluted with H_2O and extracted with Et_2O to give a quantitative yield of oily product; oxalate salt mp 147–149°. *Anal.* ($C_{30}H_{39}NO \cdot H_2C_2O_4$) C, H, N.

4-*t*-Butyl-2-(3-diethylaminopropyl)-6-phenylphenol (4).—Hydrogenation of 8.5 g (19.8 mmoles) of 2-benzyloxy-5-*t*-butyl-3-(3-diethylaminopropyl)biphenyl in EtOH with 1.7 g of 10% Pd–C resulted in the theoretical uptake of H_2. The reaction mixture was filtered hot and diluted with H_2O to give 4.6 g of crude crystalline product. Recrystallized (EtOH–H_2O), it melted at 69–71° (3.4 g, 50%). *Anal.* ($C_{23}H_{33}NO$) C, H, N.

2-Benzyloxy-5-*t*-butyl-3-[3-(N,N-diethylcarbamyl)propyl]-biphenyl.—A solution of 21.2 g (40 mmoles) of 2-benzyloxy-5-*t*-butyl-3-(3-tosyloxypropyl)biphenyl in 250 ml of boiling EtOH was treated with 5.2 g (80 mmoles) of KCN in 15 ml of H_2O. After refluxing for 3 hr, H_2O was added and the crude, oily nitrile (15 g) was isolated by $CHCl_3$ extraction. This was hydrolyzed to the carboxylic acid with alcoholic NaOH. The crude acid (15.3 g) was converted to the acid chloride with $SOCl_2$ and treated with excess Et_2NH in Et_2O to give the crude amide product (17.7 g). Purification by chromatography over silica gel gave 14.3 g (82%) of oily product. *Anal.* ($C_{31}H_{39}NO_2$) C, H, N.

4-*t*-Butyl-2-(4-diethylaminobutyl)-6-phenylphenol (5).—2-Benzyloxy-5-*t*-butyl-3-[3-(N,N-diethylcarbamyl)propyl]biphenyl (13.7 g, 30 mmoles) was reduced to 2-benzyloxy-5-*t*-butyl-3-(4-diethylaminobutyl)biphenyl with excess borane–THF by the method of Brown and Heim.[11] Catalytic debenzylation as with **4** gave crude **5**. It was isolated by Et_2O extraction and recrystallized from Me_2CO–H_2O (mp 93–96°). *Anal.* ($C_{24}H_{35}NO$) C, H, N.

2-Benzyloxy-5-*t*-butyl-3-(1-propenyl)biphenyl (9) was formed from 2-allyl-4-*t*-butyl-6-phenylphenol and benzyl chloride when a 50–60% excess of NaH was used under the reaction conditions employed for preparing **7**. The excess NaH served to isomerize the allyl side chain to propenyl; yield 58% (bp 199°, 0.16 mm). Glpc and pmr served to distinguish it from **7**.

2-Benzyloxy-5-*t*-butyl-3-biphenylcarboxaldehyde (10).—A solution of 16.1 g (45.0 mmoles) of **9** in 80 ml of CH_2Cl_2 was ozonized (Welsbach generator) until a 50% excess of ozone had been passed in. The ozonolysis solution was added *carefully* to a suspension of 3 g of Zn dust in 75 ml of 50% aqueous AcOH. The CH_2Cl_2 was boiled off and the aqueous residue was heated on the steam bath for 1 hr. It was cooled and diluted (H_2O), and the crude, oily product was isolated by $CHCl_3$ extraction. Addition of petroleum ether (bp 30–60°) effected crystallization: yield 7.8 g (50%, mp 86–90°), mp 90–92° after recrystallization from EtOH. *Anal.* ($C_{24}H_{24}O_2$) C, H.

2-Benzyloxy-5-*t*-butyl-3-(2-nitrovinyl)biphenyl (11).—A solution of 1.2 g of NaOH in 36 ml of 95% EtOH was added slowly to a stirred solution of 4.13 g (12 mmoles) of **10** in 138 ml of 95% EtOH, 1.5 ml of THF, and 1.464 g (24 mmoles) of $MeNO_2$. The reaction temperature was held below 10° throughout the addition by ice cooling. The cold, cloudy solution was poured into a stirred solution of 18 ml of concentrated HCl and 27 ml of H_2O. The yellow precipitate of product was collected and washed with EtOH; yield 3.6 g (78%), mp 110.5–113°. *Anal.* ($C_{25}H_{25}NO_3$) C, H, N.

3-(2-Aminoethyl)-2-benzyloxy-5-*t*-butylbiphenyl.—To a stirred suspension of 12.3 g (0.322 mole) of powdered LAH in 170 ml of THF was added (dropwise) a solution of 17.8 g (46 mmoles) of **11** in 170 ml of THF. After refluxing for 18 hr, H_2O (*ca.* 50–75 ml) was added carefully until the gray color of the solids changed to white. After filtering, the filtrate and several washings of the solids (Et_2O) gave 14.5 g of crude, oily product. It was purified *via* the oxalate salt (15.4 g, 74%, mp 195–196°). *Anal.* ($C_{29}H_{29}NO \cdot H_2C_2O_4$) C, H, N.

2-(2-Aminoethyl)-4-*t*-butyl-6-phenylphenol (6).—Hydrogenolysis of 3-(2-aminoethyl)-2-benzyloxy-5-*t*-butylbiphenyl (1.0 g, 2.8 mmoles, obtained by extraction from the neutralized oxalate salt) in the manner used for **4** gave this compound. It was isolated by removal of solvent from the filtered reaction mixture and crystallized from heptane; yield 0.5 g (67%, mp 89–93°). *Anal.* ($C_{18}H_{23}NO$) C, H, N.

2-Benzyloxy-5-*t*-butyl-3-(2-dimethylaminoethyl)biphenyl.—A mixture of 8.5 g (2.4 mmoles) of 3-(2-aminoethyl)-2-benzyloxy-5-*t*-butylbiphenyl, 25 ml of 90% formic acid, and 25 ml of 37% HCHO was refluxed for 18 hr. The reaction mixture was cooled, diluted (H_2O), made basic with 20% NaOH, and extracted with Et_2O to give 8.4 g (92%) of pure oily product; oxalate salt mp 164–167°. *Anal.* ($C_{27}H_{33}NO \cdot H_2C_2O_4$) C, H, N.

4-*t*-Butyl-2-(2-dimethylaminoethyl)-6-phenylphenol (3).—Debenzylation of 2-benzyloxy-5-*t*-butyl-3-(2-dimethylaminoethyl)biphenyl, using Pd black catalyst, gave **3**. The work-up was the same as that used to obtain **4** from its O-benzyl precursor; yield 72% (mp 132–133°). *Anal.* ($C_{20}H_{27}NO$) C, H, N.

(8) Melting points were taken on a Mel-Temp apparatus and are corrected. Microanalyses were performed in the Stanford Research Institute Analytical Laboratory by Miss Betty McCarthy. Pmr spectra, used to confirm the structures of most of the compounds reported herein, were obtained on a Varian A60 instrument. Where analyses are indicated only by the symbols of the elements, analytical results for those elements were within ±0.4% of the theoretical values.

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(11) H. C. Brown and P. Heim, *ibid.*, **86**, 3566 (1964).

Synthesis and Antiviral Properties of 1-Adamantylguanidine. A Modified Method for Preparing *t*-Alkylguanidines

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Received December 12, 1968

The influenza virus inhibiting properties of 1-adamantanamine (I)[1] (Scheme I) prompted us to synthesize some of its derivatives. It seemed worthwhile, for instance, to enhance its basicity by replacing the amino group by the guanidino group. This substitution was the more interesting since guanidine itself has note-

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