compound after mixing was 5×10^{-5} M and the concentration of DNA-P for calf thymus DNA was 1.7×10^{-3} M. All reactions were carried out at 24 °C.

Thermal Transition Temperature. Thermal transition temperature was determined on a Gilford 2400-S, equipped with a variable-temperature bath. Compound **2** was dissolved in 2 drops of 0.1 M NaOH solution and then diluted with H_2O to appropriate concentration, pH being adjusted to 7.8. Studies on calf thymus DNA and the poly(deoxyribonucleotides) were made in a phosphate–EDTA buffer (pH 7.8): final concentrations were PO_4^{3-} = 0.001 M; Na^+ = 0.002 M; EDTA = 10^{-4} M; **2** = 2.5×10^{-5} M. Concentrations of DNA-P for calf thymus DNA, poly(dA)·poly(dT), poly(dA-dT), poly(dG)·poly(dC), and poly(dG-dC) were 4.0×10^{-5}, 5.4×10^{-5}, 5.1×10^{-5}, 5.6×10^{-5}, and 5.7×10^{-5} M, respectively.

Fluorescence Spectra. Fluorescence spectra were determined on an Aminco Bowman spectrofluorometer, American Instruments Co., Silver Springs, Md. Spectra of **2** were taken at a concentration of 1×10^{-6} M in phosphate buffer, pH 7.80 ± 0.01 (PO_4^{3-} = 0.001 M; NaCl = 0.002 M). Compound **2** showed an emission band at 408 nm corresponding to excitation at 300 nm. No change in the fluorescence spectra of **2** was seen in the presence of calf thymus DNA; concentration of DNA-P was 1.6×10^{-3} M.

Growth Inhibition Assay. L1210 cells and CCRF–CEM cells were grown in Roswell Park Memorial Institute (RPMI) 1640 medium supplemented with 10% dialyzed fetal calf serum (DFCS) with a doubling time of 10–12 and 18–24 h, respectively. Compound **2** was dissolved in 2 drops of 0.1 M NaOH solution, and compound **1** was dissolved in a few drops of Me_2SO. The solutions were diluted to a stock solution of 10^{-3} M with phosphate-buffered saline, sterilely filtered, and aseptically diluted by half log increments. Each concentration (0.7 mL) was added to duplicate 13 × 75 mm test tubes. Cells from logarithmically growing stock culture were suspended in prewarmed RPMI 1640 medium supplemented with 10% dialyzed fetal calf serum, 10 mM Mops (morpholinepropanesulfonic acid), and 20 mM Hepes [*N*-(2-hydroxyethyl)piperazine-*N*′-2-ethanesulfonic acid]. Cell suspension (1.8 mL) was added to each tube. The tubes were incubated upright at 37 °C in a warm room or dry incubator. Under these conditions, L1210 cells grew exponentially 15- to 25-fold from an initial density of $2\text{–}2.5 \times 10^4/cm^3$; CCRF–CEM cells grew exponentially 8- to 10-fold. After 48 h (for L1210 cells), or 72 h (for CCRF–CEM cells), the incubation was terminated and the cell densities were determined using a Coulter Counter. The degree of proliferation of each 2-mL culture was expressed as the ratio of the final cell density to the initial cell density; this index was plotted against the drug concentration employed. The concentration of drug which depresses the ratio to 50% of control (the IC_{50}) is graphically determined. Compound **1** inhibited by 25% the growth of L1210 and CCRF–CEM cells at concentrations of 1.0×10^{-4} and 8.0×10^{-5} M, respectively. For the clinically effective drug, adriamycin, $IC_{50} = 1.9 \times 10^{-9}$ and 2.0×10^{-8} M were found for L1210 and CCRF–CEM cells in culture, respectively. IC_{50} for compounds **2** and **1** could not be determined due to solubility problem; at higher concentrations, the compounds crystallized out from the medium.

Acknowledgment. We thank Steve Mickle for chemical assistance, Dr. Zoltan Tökes and Mila Suva for the cell culture studies, and Dr. H. Boettger of the Jet Propulsion Laboratory, Pasadena, Calif., for the mass spectral data. We are grateful to Professor Charles Heidelberger for critical discussions of the research and this manuscript. This investigation was supported by Contract NO1-CM-67084, from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare.

4-[(Aminoalkyl)amino]-1,2-dimethoxynaphthalenes as Antimalarial Agents

Sydney Archer,* Peter Osei-Gyimah, and Stephen Silbering

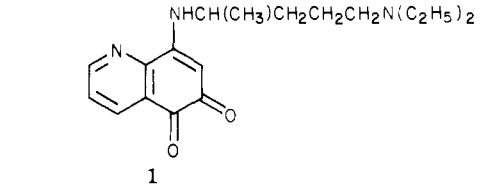
Chemistry Department, Rensselaer Polytechnic Institute, Troy, New York 12181. *Received September 5, 1979*

A series of 4-[*N*-(aminoalkyl)amino]-1,2-dimethoxynaphthalenes was prepared and tested for radical curative activity in rhesus monkeys infected with *P. cynomolgi*. Some radical curative activity was observed.

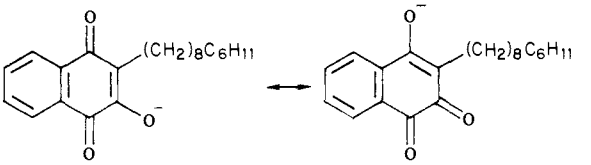
Antimalarial agents possessing suppressive activity are represented by many different structural types.[1] On the other hand, "the only drugs that accomplish radical cure in *vivax malaria* are the 8-aminoquinolines of which only *primaquine* is used now".[2] Primaquine and its congeners are toxic to some groups of individuals;[3] thus, it would be desirable to have available a less toxic radical curative agent, preferably one of a different structural type.

It is generally believed that the 8-amino-6-methoxyquinolines are biotransformed to active metabolites in the host and that the active form of pamaquine is the quinone **1**.[1] The hydroxynaphthoquinone, menoctone, was shown to have causal prophylactic activity in mice infected with *P. berghei*.[4]

Beaudoin and his colleagues devised a tissue culture system wherein they were able to study the action of drugs on the exoerythrocytic forms of the avian malaria parasite *P. fallax*.[5] Morphologically they were able to distinguish between the effects of drugs which were suppressive from the effects of drugs which were radically curative. In this system, menoctone resembled primaquine more than it did pyrimethamine, a causal prophylactic drug.



1



2 3

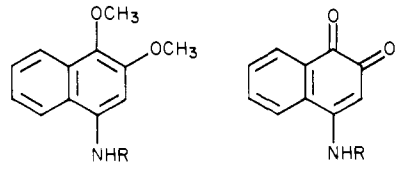
In aqueous solution menoctone exists as the ion **2**, a resonance form of which is **3**. The *o*-quinonoid form **3** resembles **1** in the sense that both are *o*-quinones which have electron-donating groups in the "para" position directly opposite one of the quinone carbonyl groups. Since

(1) R. N. Pinder, "Medicinal Chemistry", 2nd ed, A. E. Burger, Ed., Wiley-Interscience, New York, 1970, p 492.
(2) I. M. Rollo, "The Pharmacological Basis of Therapeutics", 5th ed, L. S. Goodman and A. Gilman, Eds., MacMillan, London and Toronto, 1975, p 1047.
(3) I. M. Rollo, ref 2, pp 1060-1061.
(4) D. A. Berberian, R. G. Slighter, and H. W. Freele, *J. Parasitol.*, 54, 1181 (1968).
(5) R. L. Beaudoin, C. P. A. Strome, and W. E. Clutter, *Mil. Med.*, 134, 979 (1969).

0022-2623/80/1823-0516$01.00/0

none of the *o*-quinones in the quinoline series are active orally, it was thought that any new naphthalene derivatives should be prepared as prodrugs which would be capable of being absorbed from the gut and then biotransformed in vivo to *o*-quinones.

On the basis of these considerations, it was decided to prepare compounds of the general structure **4** which could

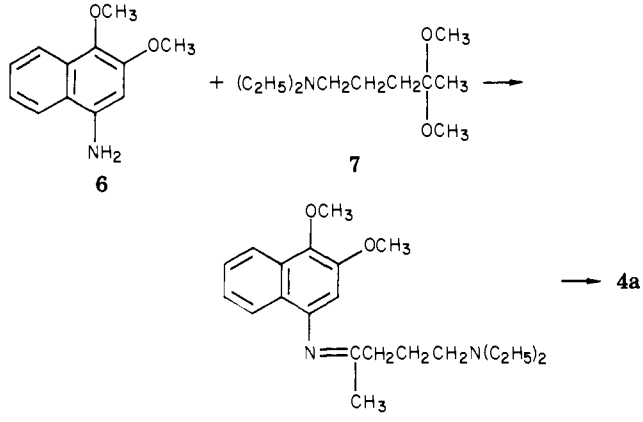


4 **5**

4a, **5a**, R = $CH(CH_3)CH_2CH_2CH_2N(C_2H_5)_2$
4b, **5b**, R = $CH(CH_3)CH_2CH_2CH_2NH_2$
4c, **5c**, R = $CH_2CH_2CH_2CH(CH_3)NH_2$
4d, **5d**, R = $CH(C_2H_5)CH_2CH_2CH_2NH_2$

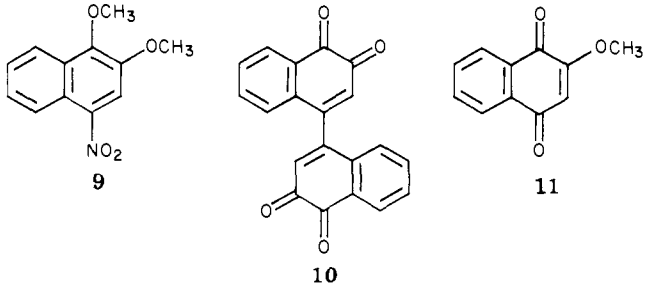
act as prodrugs for **5**, which has the requisite chemical features for being an antimalarial agent with radical curative activity. The compounds would be candidates for testing as radical curative agents in *P. cynomolgi* infected rhesus monkeys.

Chemistry. The first member of the series, **4a**, was prepared by condensing **6** with **7**[6] to give the Schiff base **8** which was reduced with $NaBH_4$ to give **4a**.



6 **7** **8** **4a**

Attempts were made to prepare **6** by direct reduction of the nitro compound **9** with $SnCl_2$. Treatment of 1,2-dimethoxynaphthalene[7] with cold 70% HNO_3 gave **9** in very poor yield. The major product was the bisquinone **10**[14] accompanied by small amounts of 2-methoxy-1,4-naphthoquinone **11**.

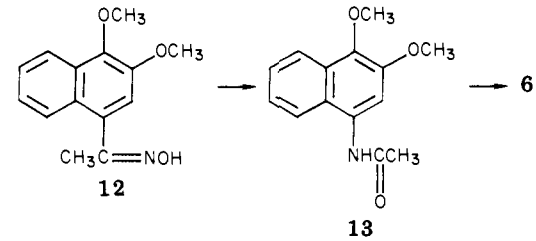


9 **10** **11**

(6) This ketal was prepared from 1-(diethylamino)-4-pentanone and methyl orthoformate according to a procedure developed by C. C. Cheng and furnished through the courtesy of T. R. Sweeney. We thank these individuals for permission to use this procedure.

(7) A. Bezdzik and P. Friedlander, *Monatsh. Chem.*, **30**, 271 (1909).

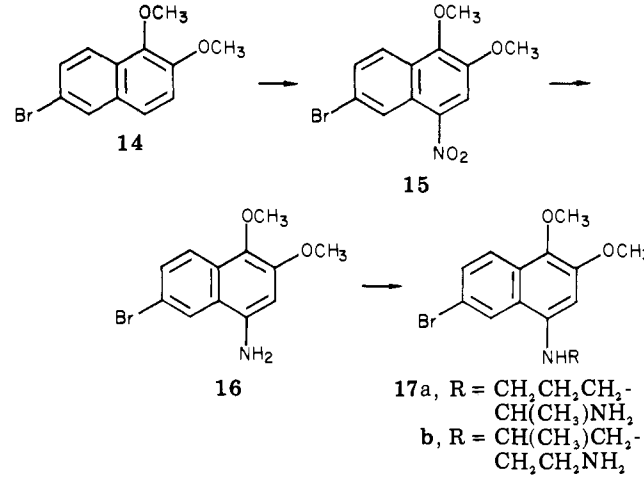
The required 4-amino-1,2-dimethoxynaphthalene was prepared by Beckmann rearrangement of the known oxime, **12**,[8] to furnish the amide **13**, hydrolysis of which gave **6**.



12 **13** **6**

The primary amine **4b** was prepared by condensing *N*-(4-bromopentyl)phthalimide[9] with **6** according to a slight modification of the procedure of Carroll et al.,[10] followed by hydrazinolysis to the primary amine. A similar sequence was used to prepare **4c** from *N*-(4-iodo-2-methylbutyl)phthalimide[9] and **4d** from *N*-(4-bromohexyl)-phthalimide.[9] The primary amines **4b–d** were isolated and purified as their fumarate salts.

In addition to the series represented by **4**, two 6-bromo analogues, **17a** and **17b**, were prepared as shown in the following scheme. 6-Bromo-1,2-naphthoquinone[11] was



14 **15** **16**

17a, R = $CH_2CH_2CH_2CH(CH_3)NH_2$
b, R = $CH(CH_3)CH_2CH_2CH_2NH_2$

reductively methylated to give **14**, which was nitrated with $Cu(NO_3)_2 \cdot 3H_2O$ in acetic anhydride to give **15**. No *ipso* nitration products were observed under these conditions. Reduction with Fe in HOAc gave **16**. Alkylation with the appropriate *N*-(haloalkyl)phthalimides, followed by hydrazinolysis, gave **17a** and **17b** purified as their fumarate salts.

Biological Results. The target molecules were tested for radical curative activity in monkeys infected with *P. cynomolgi*.[12] The tertiary amine **4a** and an isoquinoline and cinnoline analogue[13] were also tested. These tertiary amines were inactive.

Four primary amines in the naphthalene series were evaluated using a protocol which required oral dosing of the corresponding salts once a day for 7 days. In this test, primaquine diphosphate at a dose of 1.3 (mg/kg)/day for

(8) T. Bisanz, *Rocz. Chem.*, **30**, 111 (1956); *Chem. Abstr.*, **31**, 323*i* (1937).

(9) We thank Drs. Bing T. Poon and Richard E. Strube and the Walter Reed Army Institute of Research for supplying us with these intermediates.

(10) F. I. Carroll, J. T. Blackwell, and A. Philip, *J. Med. Chem.*, **19**, 111 (1976).

(11) K. Fries and K. Schimmelschmidt, *Justus Liebigs Ann. Chem.*, **484**, 245 (1930).

(12) We thank Dr. R. O. Pick of the Walter Reed Army Institute of Research for supplying the biological data.

(13) Unpublished work from this laboratory.

7 days cures 90% of the infected monkeys. Compounds **4b** and **4c** were inactive at 1.0 (mg/kg)/day and toxic at 10.0 (mg/kg)/day. In the first test, **4d** was curative at 1.0 (mg/kg)/day. In a confirmatory test, **4d** was inactive at 0.316 and 1.0 (mg/kg)/day and toxic at 10.0 (mg/kg)/day. At 3.16 (mg/kg)/day, it cured one of two monkeys. The bromonaphthalene, **17a**, was inactive at 1.0 (mg/kg)/day but was curative at 10.0 (mg/kg)/day without toxicity. Thus, 17a seems less toxic than its analogue **4c**, indicating that the introduction of a bromine atom at C-6 decreases toxicity while radical curative activity is maintained.

Experimental Section

All melting points were determined on a Mel-Temp apparatus and are corrected. Analyses were performed by Instranal Laboratories, Rensselaer, N.Y., and were within ±0.4% of the calculated values.

Nitration of Dimethoxynaphthalene. One gram of 1,2-dimethoxynaphthalene[7] was slowly added to 10 mL of stirred 70% HNO_3 while the temperature was maintained between 0 and 5 °C by means of an ice bath. After all of the compound had been added, the mixture was stirred for 1 h at the same temperature and then poured onto 60 g of ice. The orange crystals were collected by filtration and washed thoroughly with water. The crystals of the bisquinone **10** were dried, mp 320–330 °C dec.[14] The combined filtrates were extracted with ether. The ethereal extract was washed with 0.1 M $NaHCO_3$ and then with H_2O. The dried ether solution was concentrated to dryness, and the residue was chromatographed on ChromAR silica sheets using 75% $CHCl_3$/25% cyclohexane as the developing solvent. The band with an R_f of approximately 0.75 was cut out and extracted to give 4-nitro-1,2-dimethoxynaphthalene (**9**), mp 93–95.5 °C, after recrystallization from ethanol. Anal. ($C_{12}H_{11}NO_4$) C, H, N. The band with an R_f of 0.30 was extracted with $CHCl_3$. Evaporation left a crystalline solid, mp 178–182 °C, after recrystallization from ethanol. It did not depress the melting point of an authentic sample of 2-methoxy-1,4-naphthoquinone (11). Anal. ($C_{11}H_8O_3$) C, H.

4-Acetamido-1,2-dimethoxynaphthalene (13). A solution of 13.5 g (0.055 mol) of the oxime (**12**)[8] in 150 mL of 92% HCOOH was refluxed for 5 h. The excess HCOOH was removed in vacuo, and the residue was dissolved in $CHCl_3$. The solution was washed with H_2O, dried, and evaporated to leave a brown oil which crystallized. After crystallization from benzene there was obtained 11.4 g (84.5%) of the desired amide, mp 133–135 °C. Anal. ($C_{14}H_{15}NO_3$) C, H, N.

4-Amino-1,2-dimethoxynaphthalene (6). A solution of 9.6 g (0.04 mol) of the above amide was dissolved in 120 mL of C_2H_5OH. Then, 0.5 g of $SnCl_2$ and 20 mL of concentrated HCl were added and the mixture was refluxed for 3 h under nitrogen. The chilled mixture was filtered and the crystalline hydrochloride washed with ether: yield 8.9 g (90%); mp 215–220 °C. Anal. ($C_{12}H_{13}NO_2$·HCl) C, H, N. The free base was liberated with the aid of 3 N NaOH. After recrystallization from benzene–hexane it melted at 140–142 °C. From 6.3 g of the salt there was obtained 5.0 g of **6** (94%). Anal. ($C_{12}H_{13}NO_2$) C, H, N.

4-[[4′-(Diethylamino)-1′-methylbutyl]amino]-1,2-dimethoxynaphthalene (4a). A mixture of 5.46 g (0.027 mol) of 4-amino-1,2-dimethoxynaphthalene, 5.46 g (0.027 mol) of the ketal **7**, and 50 mg of *p*-toluenesulfonic acid·H_2O was heated to 155 °C in a distillation flask. Methanol started to distill almost immediately, and in the course of 2 h the bath temperature was raised to 190 °C. The cooled reaction mixture was dissolved in ether and washed with 1 N K_2CO_3. The dried ether solution was concentrated and the residue was dissolved in 60 mL of C_2H_5OH. A suspension of 2.5 g (0.060 mol) of $NaBH_4$ in 125 mL of C_2H_5OH was added and the suspension stirred overnight. The C_2H_5OH was removed and the residue was taken up in ether. The organic phase was extracted with dilute HOAc. The acid extract was neutralized with NaOH, and the liberated amine was dissolved in ether, dried, and concentrated. The oil was distilled and the fraction, bp 180–182 °C (0.4 mm), was collected, yield 6.18 g (67%). Anal. ($C_{21}H_{22}N_2O_2$) C, H, N.

4-[(4′-Amino-1′-methylbutyl)amino]-1,2-dimethoxynaphthalene Fumarate (4b). A mixture of 2.0 g (9.95 mmol) of 4-amino-1,2-dimethoxynaphthalene, 3.2 g (9.8 mmol) of *N*-(4-bromopentyl)phthalimide,[9] and 2 mL of triethylamine was heated at 160 °C for 10 h under reflux. The cooled reaction mixture was taken up in CH_2Cl_2 and filtered to remove the triethylamine hydrobromide. The filtrate was concentrated, and the resulting oil was triturated with ether and filtered. The filtrate was concentrated and chromatographed on silica gel using benzene–ether (3:7) as the eluant. An oil was obtained which crystallized from ether to give 1.5 g (36.6%) of the condensation product, mp 113–115 °C. Anal. ($C_{25}H_{26}N_2O_4$) C, H, N.

A solution of 1.5 g (3.6 mmol) of the above phthalimide and 3.5 mL of 85% $H_2NNH_2·H_2O$ in 60 mL of C_2H_5OH was stirred under reflux for 1.5 h. The cooled reaction mixture was filtered and the filtrate concentrated in vacuo. The residue was dissolved in CH_2Cl_2, filtered, and concentrated to leave a brown oil, yield 0.85 g (84%). The amine was converted to the fumarate in C_2H_5OH and crystallized from C_2H_5OH–ether, mp 178–181 °C. Anal. ($C_{17}H_{24}N_2O_2·C_4H_4O_4$) C, H, N.

4-[(4′-Amino-1′-pentyl)amino]-1,2-dimethoxynaphthalene Fumarate (4c). A mixture of 4.0 g (0.0197 mol) of **6**, 6.8 g (0.0197 mol) of *N*-(4-iodo-1-methylbutyl)phthalimide,[9] and 2.4 g of triethylamine was heated at 150 °C under reflux for 8 h. The mixture was worked up as above to obtain 3.3 g (54.5%) of the desired phthalimide as a light brown oil.

A solution of 2.7 g (0.0065 mol) of the above phthalimide and 5 mL of 85% $H_2NNH_2·H_2O$ in 100 mL of C_2H_5OH was refluxed for 2 h. The free base was obtained as an oil (0.65 g, 88%), which was converted to a crystalline fumarate in C_2H_5OH. Recrystallization from C_2H_5OH–ether gave grayish crystals, mp 181–183.5 °C. Anal. ($C_{17}H_{24}N_2O_2·C_4H_4O_4$) C, H, N.

4-[(4′-Amino-1′-ethylbutyl)amino]-1,2-dimethoxynaphthalene Fumarate (4d). A solution of 4.0 g (0.0197 mol) of **6**, 6.0 g (0.019 mol) of *N*-(4-bromohexyl)phthalimide,[9] and 2 mL of triethylamine was heated at 140 °C for 4 h. The mixture was worked up as above to give, after chromatography, 2.5 g (28.3%) of the desired product, mp 126–128 °C, after recrystallization from ether. Anal. ($C_{26}H_{28}N_2O_4$) C, H, N.

A solution of 3.4 g (0.0079 mol) of the above phthalimide, 4.0 mL of 85% $H_2NNH_2·H_2O$, and 100 mL of C_2H_5OH was refluxed under N_2 for 2 h and worked up as above to give 2.3 g (96.5%) of the free base **4d**. The fumarate salt was prepared in C_2H_5OH and recrystallized from C_2H_5OH–ether, mp 172–174 °C. Anal. ($C_{18}H_{26}N_2O_2·C_4H_4O_4·0.25H_2O$) C, H, N.

1,2-Dimethoxy-6-bromonaphthalene (14). To a stirred solution of 10.0 g (0.06 mol) of $Na_2S_2O_4$ in 60 mL of H_2O, 10.0 g (0.042 mol) of 6-bromo-1,2-naphthoquinone[11] was added portionwise. The crude diol was filtered and washed with water. It was dissolved in 100 mL of C_2H_5OH, and the solution was stirred mechanically under N_2 while 22.0 mL of $(CH_3)_2SO_4$ and 15.0 mL of 50% NaOH were added dropwise simultaneously. After 24 h under reflux, the solution was cooled and the product worked up in the usual way to give 5.9 g (56%) of an oil, bp 125–130 °C (0.2 mm), which was used directly in the next step.

1,2-Dimethoxy-4-nitro-6-bromonaphthalene (15). Finely ground $Cu(NO_3)_2·3H_2O$ (9.42 g, 0.1039 mol) was added in portions to a stirred solution of 10.0 g (0.037 mol) of **14** in 60 mL of acetic anhydride at 0 °C. The temperature was allowed to rise to 15 °C. The resulting solid mass was added to ice-cold water and the mixture was extracted with $CHCl_3$. The extract was thoroughly washed with H_2O, dried, and concentrated in vacuo to leave a brown residue, which was purified by elution with benzene through a column of silica gel. The eluates were combined and concentrated to dryness to leave yellow crystals, which after crystallization from methanol melted at 116–117 °C, yield 5.9 g (49%). Anal. ($C_{12}H_{10}BrNO_4$) C, H, N.

1,2-Dimethoxy-4-amino-6-bromonaphthalene (16). A suspension of 5.3 g (0.096 mol) of Fe dust, 25 mL of HOAc, and 25 mL of H_2O was stirred under reflux while a solution of 6.0 g (0.019

(14) Various melting points are reported in the literature for this highly insoluble quinone. For example, H. Cassebaum, *Chem. Ber.*, **90**, 2876 (1957), reports mp 289 °C; F. Wessely, J. Kotlan, and W. Metlesics, *Monatsh. Chem.*, **85**, 69 (1954), reports mp 310–315 °C. We believe that **10** and **11** resulted from *ipso* nitration [S. R. Hartshorn, *Q. Rev., Chem. Soc.*, 3, 167 (1974)] of 1,2-dimethoxynaphthalene.

mol) of 15 in 10 mL of hot HOAc was added over a period of 15 min. After an additional hour at reflux, the hot mixture was filtered. The cooled filtrate was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with saturated $NaHCO_3$ solution and then with H_2O and dried. The solution was concentrated, and the residue was suspended in ether, filtered, and recrystallized from ethanol to give microcrystals: mp 157–160 °C; yield 2.5 g (46%). Anal. ($C_{12}H_{12}BrNO_2$) C, H, N.

4-[(4′-Amino-1′-pentyl)amino]-1,2-dimethoxy-6-bromonaphthalene Fumarate (17a). A mixture of 2.5 g (0.009 mol) of 16, 3.04 g (0.009 mol) of *N*-(4-iodo-1-methylbutyl)phthalimide,[9] and 2.5 mL of triethylamine was heated at 140 °C for 4 h. The mixture was worked up as usual and chromatographed on silica gel with benzene/ether (4:3) as the eluant. An oil was obtained, which crystallized under ether. After recrystallization from C_2H_5OH the yellow crystals melted at 138–140 °C, yield 1.8 g (54%). Anal. ($C_{25}H_{25}BrN_2O_4$) C, H, N.

A solution of 1.7 g (0.0034 mol) of the above and 3.2 mL of 85% $H_2NNH_2 \cdot H_2O$ in 50 mL of C_2H_5OH was refluxed under N_2 for 2 h and worked up as usual to furnish the desired amine as a brown oil, yield 1.1 g (88%). The fumarate was prepared in C_2H_5OH and was obtained as gray microcrystals, mp 209–210 °C. Anal. ($C_{17}H_{23}BrN_2O_2 \cdot 0.5C_4H_4O_4$) C, H, N.

4-[(4′-Amino-1′-methylbutyl)amino]-1,2-dimethoxy-6-bromonaphthalene Fumarate (17b). A mixture of 2.2 g of 16, 2.3 g (0.0079 mL) of *N*-(4-bromopentyl)phthalimide,[9] and 2 mL of triethylamine was heated at 150 °C for 4 h. After the usual workup, the crude material was chromatographed on a silica gel column using benzene/ether (3:7) as the eluant. The combined fractions were concentrated to leave an oil, which crystallized under ether at 0 °C. Recrystallization from C_2H_5OH–ether gave 0.39 g (10%) of a crystalline solid, mp 144–146 °C. Anal. ($C_{25}H_{25}BrNO_4$) C, H, N.

A solution of 1.7 g (0.0034 mol) of the above phthalimide and 3.2 mL of 85% $H_2NNH_2 \cdot H_2O$ in 50 mL of C_2H_5OH was refluxed for 2 h and then worked up as usual to give 1.2 g (89%) of the free base as a brown oil. The fumarate salt, prepared in C_2H_5OH, crystallized after standing overnight in the cold, mp 174–177 °C. Anal. ($C_{17}H_{23}BrN_2O_2 \cdot C_4H_4O_4$) C, H, N.

Acknowledgment. This work was supported by the Walter Reed Army Institute of Research by Contract DAMD 17-74-C-4099. We thank Drs. B. T. Poon, R. E. Strube, and T. R. Sweeney of WRAIR for their cooperation and assistance. This is contribution no. 1566 to the Army Research Program on Malaria.

Prostaglandin Analogues Possessing Antinidatory Effects. 1. Modification of the ω Chain

Masaki Hayashi,* Hajimu Miyake, Seiji Kori, Tadao Tanouchi, Hirohisa Wakatsuka, Yoshinobu Arai, Takashi Yamato, Ikuo Kajiwara, Yoshitaka Konishi, Takeshi Tsuda, and Kimiichiro Matsumoto

Ono Pharmaceutical Co., Ltd., Research Institute, Shimamoto, Osaka 618, Japan. *Received September 14, 1979*

Novel prostaglandin analogues modified in the ω chain were prepared by the reaction of the vinyl aldehydes **1a–e** with a variety of organometallic reagents as a key step of the syntheses. Compared with the natural prostaglandin $F_{2\alpha}$ in antinidatory effect, the analogues **4**, **7**, and **10** were 40 times more potent and the analogue **11** was 50–100 times more potent in the rat.

Prostaglandin $F_{2\alpha}$ has a high luteolytic effect and is of interest because it is effective in controlling the reproduction of animals by synchronization of the sex cycle.[1] In order to develop new prostaglandin analogues which have more potent antinidatory effects than that of prostaglandin $F_{2\alpha}$, we synthesized novel analogues modified in the ω chain (the lower chain) by the reaction of the vinyl aldehydes[2] with a variety of organometallic reagents as a key step of these syntheses. Some analogues were found to show considerably higher antinidatory effects in the rat. We report herein the syntheses of these novel prostaglandin analogues and their antinidatory effects.

In this report the antinidatory effect induced by prostaglandins was examined as an indication of the luteolytic effect.[3] The antinidatory effect means a loss of pregnancy in the implantation process. Animals were sacrificed on day 11 (day 0 = sperm confirmation) in order to examine the number of implantation sites. The test group was compared with the control group.

Chemistry. As shown in Scheme I, treatment of the versatile vinyl aldehyde **1** previously reported by us[2] with a variety of organometallic reagents easily afforded the intermediates **3**, in some of which the hydroxy function at C_9 or C_{11} was protected with an acetyl or a tetrahydropyranyl (THP) group. Since the vinyl aldehyde **1** contains not only an aldehyde unit but also an ester function in the same molecule, the reaction conditions must be carefully controlled in order to avoid side reactions. The selective reaction of the aldehyde unit in **1** with organometallic reagents was realized under the following conditions. Using tetrahydrofuran (THF) as solvent, the vinyl aldehyde **1** was treated with Grignard reagents at 0 °C or alkyllithium reagents at −78 to −40 °C. When the reaction temperature was raised to higher than that required for optimum results, a byproduct was produced in which the methyl ester group was alkylated.

Because the vinyl aldehydes **1a,c,d** possess free hydroxy functions, an excess of organometallic reagent corresponding to the equivalent of the hydroxy functions was required. Therefore, it was better to protect these hydroxy functions with the acetyl or the THP group. When the intermediates **3** were converted to the final products, the THP group in **3d,e** and the acetyl group in **3b,c,e** were removed by acidic treatment (65% aqueous AcOH, 40 °C, 1 h) and basic treatment (K_2CO_3 in MeOH, 50 °C, 30 min), respectively. The stability of the ω chain under these conditions was considered in the selection of suitable vinyl aldehydes, **1a–e**. Summarized in Table I are the combination of various vinyl aldehydes and organometallic reagents, the yields of the intermediates **3** (as the mixture

(1) B. B. Pharris and L. J. Wyngarden, *Proc. Soc. Exp. Biol. Med.*, 130, 92 (1969).

(2) (a) H. Wakatsuka, Y. Konishi, S. Kori, and M. Hayashi, *Chem. Lett.*, 141 (1978); (b) H. Miyake, T. Tanouchi, Y. Yamato, T. Okada, Y. Konishi, H. Wakatsuka, S. Kori, and M. Hayashi, *ibid.*, 145 (1978).

(3) Labhsetwar observed the luteolytic effect from the antinidatory effect of prostaglandin E_1; see A. P. Labhsetwar, *Biol. Reprod.*, **8**, 103 (1973).

0022-2623/80/1823-0519$01.00/0