and concentrated to 250 mL. Solid material appeared and was filtered, washed with ethanol, dried, and recrystallized from absolute ethanol: yield 0.4 g; mp 384–385 °C dec.

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Synthesis of 2,4-Disubstituted 6-Methoxy-8-aminoquinoline Analogues as Potential Antiparasitics

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A series of 2,4-disubstituted 8-aminoquinoline analogues were synthesized and evaluated against *Plasmodium berghei* in mice and *Leishmania donovani* in hamsters. 8-[[6-(Diethylamino)hexyl]amino]-2-ethyl-6-methoxy-4-methylquinoline (**8a**) possessed significant activity against *L. donovani*. 2-Ethyl-4-methylprimaquine (**7a**) was evaluated against *Plasmodium cynomolgi* in rhesus monkey and found to have activity equal to that of primaquine.

Both 2- and 4-substituted 6-methoxy-8-aminoquinoline analogues have been reported to possess antimalarial activity comparable to that of primaquine.[1,2] In addition, some of the compounds have shown activity against *Leishmania donovani* in hamsters.[3] In this paper we describe the syntheses of some 2,4-disubstituted 6-methoxy-8-aminoquinoline analogues which possess CH_3, C_2H_5, and $CH_2{=}CH-$ substituents in the 2 and 4 positions and report antiparasitic test data for these compounds.

Chemistry. Scheme I outlines the procedures used to prepare target compounds **7a,b** and **8a,b**. Condensation of 4-methoxy-2-nitroaniline (**1**) with 3-penten-2-one under Skraup conditions gave 2,4-dimethyl-6-methoxy-8-nitroquinoline (**2**). Subjection of **2** to Mannich condensation followed by quaternization gave **3**. Treatment of **3** with base yielded the 4-methyl-2-vinylquinoline (**4**). Catalytic reduction of **4** gave 8-amino-2-ethyl-6-methoxy-4-methylquinoline (**5**), whereas reduction with stannous chloride gave 8-amino-6-methoxy-4-methyl-2-vinylquinoline (**6**). Attachment of the 4-amino-1-methylbutyl side chain to **5** and **6** followed standard procedure to give **7a** and **7b**, respectively.[2] Alkylation of **5** with 6-(diethylamino)hexyl bromide gave the expected product **8a**; however, alkylation of **6** with this reagent gave the hydrogen bromide addition product **8b**.

The synthesis of target compounds **7c** and **8c** is shown in Scheme II. Condensation of **1** with the 2-chloropropyl ethyl ketone (**9**)[4] under Skraup conditions gave 4-ethyl-6-methoxy-2-methyl-8-nitroquinoline (**10**). Stannous chloride reduction of **10** yielded the aminoquinoline (**11**). Attachments of the 4-amino-1-methylbutyl and 6-(diethylamino)hexyl side chains to **11** followed standard procedure to **7c** and **8c**.

Biological Testing. Compound **7a** was tested for radical curative activity against *P. cynomolgi* in rhesus monkeys. The test was carried out at the SEATO Medical Research Laboratory, Bangkok.[5,6] Primaquine diphosphate, which cures 90% of monkeys in this test system when administered at a dose of 1.3 mg/kg (1.0 mg/kg of free base) per day for 7 days, in combination with chloroquine serves as the standard for this test. Compound **7a** showed 3/4 cures at 1.0 mg/kg (free base).

Compounds **8a–c** and **7b–c** were tested for blood schizonticidal activity against *P. berghei* in mice[7] (Table I). Testing was carried out at the Rane Laboratory, University of Miami, Miami, Fla. Compound **7c** was active at 320 and 40 mg/kg; all other compounds were inactive at the highest dose level tested (640 mg/kg). Compound **8b** was toxic at 160 and 640 mg/kg; none of the other compounds were toxic as judged by the Rane screen.

The compounds **8a–c** and **7a** were also evaluated for antileishmanial activity against *Leishmania donovani* in hamsters by the well-established 8-day testing method (Table I).[8–10] Compound **8a** which showed a *G* index of 130, was the most active of the compounds tested.

Examination of the data in Table I shows that the 2,4-disubstituted 8-aminoquinoline analogues are, with the

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(10) Tests were carried out by Dr. W. L. Hanson, University of Georgia, Athens, Ga. The percent suppression [seven animals per drug level, 208, 52, and 13 (mg/kg)/day] when compared to infected, untreated controls (seven to ten animals) is calculated and a Glucantime index (*G*) computed [$G = (SD_{90}$ for Glucantime)/(SD_{90} for the new drug)], where SD_{90} = 90% suppression of parasites. The intramuscular route is routinely used in the initial test. Drug is administered twice a day for 4 consecutive days. (c) Glucantime is the proprietary name for meglumine antimoniate.

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Scheme I

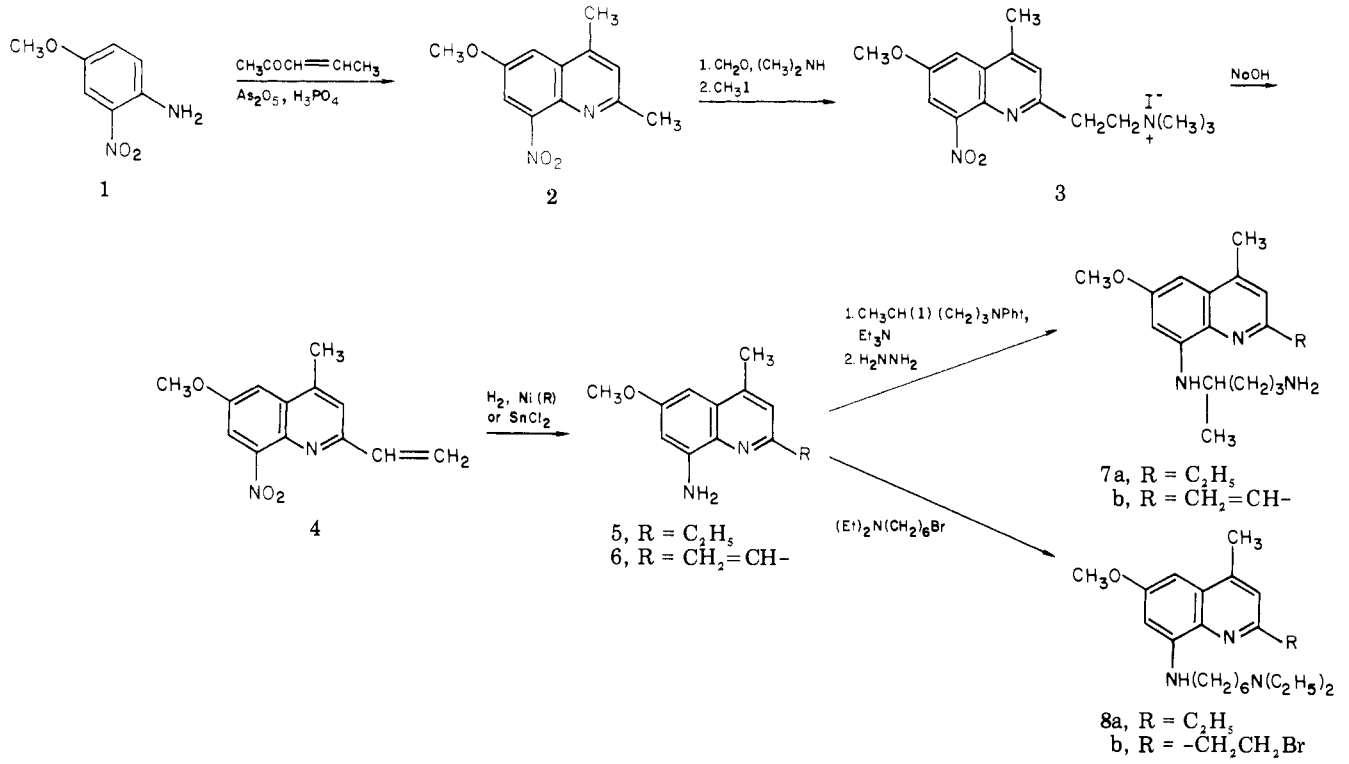
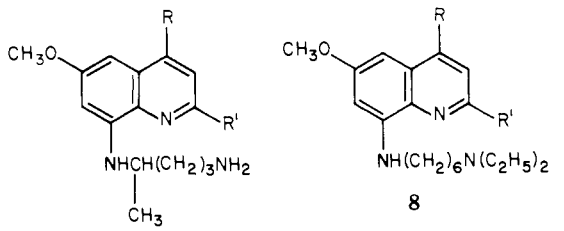


Table I. Antimalarial Activity against *P. Berghei* in Rodents and against *Leishmania Donovani* Infections of Hamsters



compd	R	R'	Δ MST (*C* or *T*) dose, mg/kg[a,b] 20	40	80	160	320	640	*G* index[c]
7a	CH_3	C_2H_5							8.99
7b	CH_3	$CH=CH_2$	0.0	0.0	0.6	0.4	2.2	6.2	
7c	C_2H_5	CH_3	1.7	2.3	3.7	5.1	7.7	10.3	
8a	CH_3	C_2H_5		0.3		0.3		0.7	130[d]
8b	CH_3	CH_2CH_2Br		0.3		0 (5T)		5T	2.6[d]
8c	C_2H_5	CH_3		1.3		2.7		4.9	29.2[d]
primaquine			4.0	5.0	9.4	2T	5T	5T	2.1[d]

[a] Tests were carried out by the Rane Laboratory, University of Miami, Miami, Fla., using blood-induced *P. berghei* infected mice (five animals per group) by the method described by Osdene et al.[7] Test data were supplied by Drs. E. A. Steck and R. E. Strube of Walter Reed Army Institute of Research. [b] Δ MST, mean survival time over controls (6.2 ± 0.5 days). A compound is considered active if MST of the treated group is more than twice that of the control group: *C*, number of cures (mice surviving 60 days); *T*, number of toxic deaths occurring on days 2–5 after infection. [c] *G* index is the relative activity of the test compound to that of Glucantime (*R*).[10] [d] Taken from ref 3.

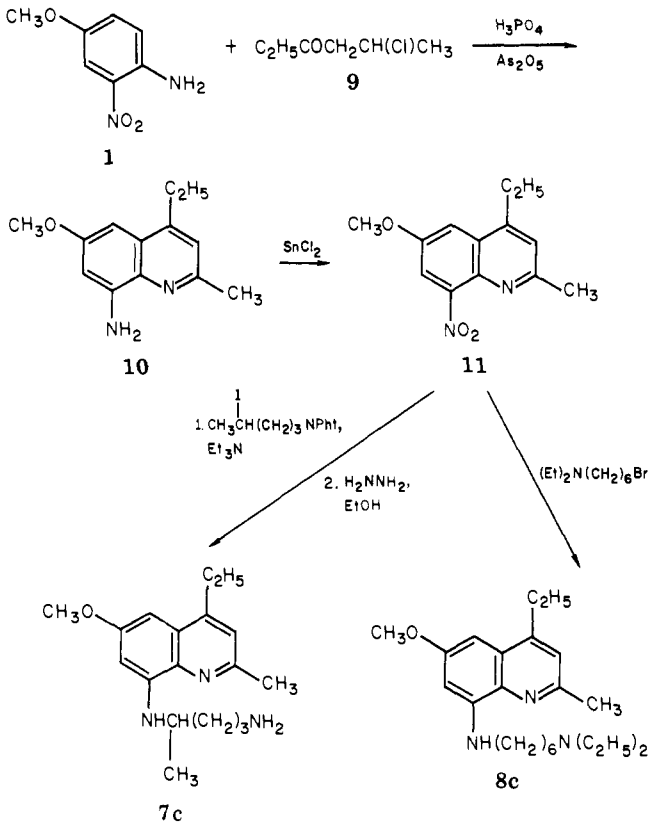
exception of **8b**, less active as a blood schizonticidal agent and less toxic than primaquine. Compound **7a**, which is a 2-ethyl-4-methylprimaquine analogue, was the only compound tested for radical curative activity. The data show that the addition of the 2-ethyl and 4-methyl to the primaquine nucleus did not increase activity in this screen. Compound **8a** is much more active than primaquine in the *Leishmania donovani* screen; however, it is not as active as other 8-aminoquinolines.[3]

Experimental Section

Melting points were determined on a Kofler hot stage microscope using a calibrated thermometer. IR spectra were measured with a Perkin-Elmer Model 267 or 467 grating infrared spectrophotometer. NMR spectra were recorded on a Varian Model HA-100 spectrometer using tetramethylsilane as an internal standard. MS were determined on an AEI-MS 902 spectrometer. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Ill., or Integral Microanalytical Laboratories, Inc., Raleigh, N.C. Where analyses are indicated by the symbols of the elements, the analytical results were within ±0.4% of the theoretical values.

2,4-Dimethyl-6-methoxy-8-nitroquinoline (2). A solution of 25 g (0.15 mol) of 4-methoxy-2-nitroaniline (1, practical grade) in 20 g (0.4 mol) of 3-penten-2-one and 50 mL of 85% phosphoric acid was heated at 85 °C until gas evolution set in, as evidenced by foaming of the mixture. In one portion, 25 g of anhydrous arsenic pentoxide was added to the solution, which raised the

Scheme II

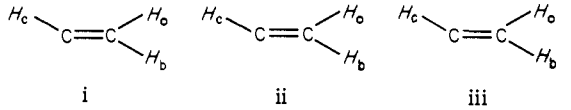


temperature to 110 °C. Stirring and heating of the mixture to 105 °C was continued for 2 h. At the end of this period, the contents of the flask had noticeably thickened. The cooled mixture was diluted with 350 mL of water, filtered, and basified with ammonia. A crude brown precipitate was collected and washed with methanol. The product remained as a light brown powder, which weighed 17 g (49%): mp 188–191 °C; NMR ($CDCl_3$) δ 2.61 (s, CH_3), 2.63 (s, CH_3), 3.94 (s, OCH_3), 7.16 (s, H_3), 7.3 (d, H_5), and 7.52 (d, H_7). Anal. ($C_{12}H_{12}N_2O_3$) C, H, N.

6-Methoxy-4-methyl-8-nitro-2-[β-(trimethylamino)-ethyl]quinolinium Iodide (3). A suspension solution of 10 g (0.043 mol) of **2**, 3.5 g (0.043 mol) of dimethylamine hydrochloride, and 1.8 g (0.06 mol) of paraformaldehyde in 50 mL of ethanol was refluxed with stirring for 48 h. The cooled mixture was filtered and the solid product dried at 100 °C. The product had mp 199–201 °C (dec) and weighed 10 g (72%). Anal. ($C_{15}H_{20}ClN_3O_3 \cdot 0.5H_2O$) C, H, N.

The free amine was prepared by stirring the product with a methylene chloride–1 N sodium hydroxide mixture. The methylene chloride phase after several hours contained the base, which crystallized after removal of the solvent. The Mannich base weighed 7.5 g (0.027 mol) and had mp 110–115 °C. This base was dissolved in 35 mL of THF, 4 g (0.027 mol) of methyl iodide was added rapidly with stirring, and the resulting slurry was heated at 100 °C in a bomb for 1 h. The product **3** was separated by filtration and washed carefully with ether–hexane, 1:1. The tan product weighed 11.0 g (96%) and had mp 189–191 °C. Anal. ($C_{16}H_{22}IN_3O_3$) C, H.

6-Methoxy-4-methyl-8-nitro-2-vinylquinoline (4). The quaternary product **3** (11 g, 0.026 mol) was stirred with 500 mL of chloroform and 300 mL of 1 N sodium hydroxide until all the solid had dissolved. Evaporation of the chloroform phase gave a yellow product, which was washed with methanol. The remaining yellow crystals (5.5 g, 87%) had mp 169–171 °C: NMR (acetone-d_6) δ 2.83 (s, CH_3), 4.04 (s, OCH_3), 5.64 (i, $J_{a,c}$ = 11 Hz,



i ii iii

$J_{a,b}$ = 1.5 Hz), 6.35 (q, ii, $J_{b,c}$ = 17.5 Hz), 6.83 and 6.99 (q, iii), 7.58 (d, H_5), 7.67 (s, H_3), 7.74 (d, H_7). Anal. ($C_{13}H_{12}N_2O_3$) C, H, N.

8-Amino-2-ethyl-6-methoxy-4-methylquinoline (5). A methanol suspension of 5.5 g (0.023 mol) of **4** was heated at 60 °C with 2 g of activated Raney nickel under 40 psi of hydrogen pressure. After 15 h, the catalyst was separated by filtration, the solvent was evaporated, and the residue was freeze-dried. The brown amine (**5**; 4.6 g, 94%) was obtained as a brown sticky syrup: NMR ($CDCl_3$) δ 1.35 (t, CH_3CH_2), 2.54 (s, CH_3), 2.9 (q, CH_2CH_3), 3.84 (s, OCH_3), 6.51 (s, H_5, H_7), 7.04 (s, H_3).

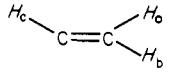
A portion of the amine was converted to the hydrobromide salt. Recrystallization from a 2-propanol and THF mixture gave the analytical sample, mp 262 °C dec. Anal. ($C_{13}H_{17}BrN_2O \cdot 0.5H_2O$).

8-[(4′-Amino-1′-methylbutyl)amino]-2-ethyl-6-methoxy-4-methylquinoline (7a) Diphosphate. The crude amino compound **5** (3.5 g, 0.016 mol) was heated in an oil bath at 110 °C while a solution of 8 g (0.024 mol) of 4-iodo-1-phthalimidopentane in 3 g (0.03 mol) of triethylamine was added dropwise with stirring over a period of 20 h. The cooled product was treated with hot benzene, filtered, evaporated, and chromatographed on silica gel 60 using chloroform as the eluent. The alkylated amine weighed 4.8 g (69%). This material was refluxed with an excess of hydrazine in 50 mL of ethanol for 2 h. The solution was filtered and the filtrate concentrated to give 2.6 g (0.01 mol) of free base **7a** as a yellow-brown syrup. An ethanolic solution (20 mL) of the amine was combined with 20 mL of ethanol, which contained 2 g (0.017 mol) of 85% phosphoric acid. The resulting precipitate was redissolved by addition of water, and the solution was heated with Norit A for 10 min on a water bath. After filtration and concentration of the solution, 3.6 g (61%) of yellow crystals of the diphosphate separated. Two recrystallizations from ethanol–water gave 2.1 g of salt: mp 152–155 °C; NMR (D_2O) δ 1.81 (m, CH_3CH_2, CH_3CH), 3.06 (s, CH_3), 3.82 (s, OCH_3). Anal. ($C_{18}H_{27}N_3O \cdot 2H_3PO_4 \cdot 0.5H_2O$) C, H, N, P.

8-[[6′-(Diethylamino)hexyl]amino]-2-ethyl-6-methoxy-4-methylquinoline (8a) Dihydrobromide. Five grams (0.023 mol) of **5** was heated at 125 °C under argon while 7 g (0.022 mol) of 6-(diethylamino)hexyl bromide hydrobromide in 25 mL of DMF was added dropwise with stirring over a period of 12 h. The cooled reaction mixture was dissolved in methylene chloride and extracted with sodium hydroxide. After removal of the organic phase and evaporation of the methylene chloride, the crude product was chromatographed on a silica gel 60 column using ethyl acetate–ethanol as the eluent. The product was combined in ethanol solution (40 mL) with 2.5 mL of 48% hydrobromic acid, and the resulting mixture was concentrated. A hydrobromide crystallized spontaneously. After washing with THF–ethanol, it was recrystallized from ethanol. This gave 3.6 g (29%) of yellow-orange crystals: mp 200–202 °C; NMR (D_2O) δ 1.42 (t, CH_3CH_2N), 2.89 (q, CH_3CH_2N), 3.92 (s, OCH_3). Anal. ($C_{23}H_{39}N_3OBr_2$) C, H, N, Br.

8-Amino-4-methyl-6-methoxy-2-vinylquinoline (6). The 8-nitroquinoline **4** (4.5 g, 0.018 mol) was reduced to the 8-amino compound by a standard procedure[2] using stannous chloride in ethanolic hydrochloric acid. The amine **6** (3 g, 79%) crystallized upon standing at room temperature. This product was unstable and was used without further purification.

8-[(4′-Amino-1′-methylbutyl)amino]-6-methoxy-4-methyl-2-vinylquinoline (7b) Phosphate. The amine **6** was alkylated with 4-iodo-1-phthalimidopentane using a procedure similar to that described for the alkylation of **5**. The usual workup gave 21% of the alkylated amine: NMR ($CDCl_3$) δ 1.28 (d, CH_3-CH), 2.51 (s, CH_3-Ar), 3.84 (s, OCH_3), 5.35 (2 d, iv, $J_{a,b}$ =

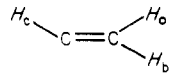


iv

2 Hz, $J_{a,c}$ = 10 Hz), 6.8 (2 d, iii, $J_{c,a}$ = 10 Hz, $J_{c,b}$ = 18 Hz), 7.65 (m, C_6H_4).

The hydrazinolysis of the product was performed in the usual way by heating an alcoholic solution of the amine with 1.5 equiv of hydrazine. This gave the primaquine analogue **7b** as a yellow oil, which was immediately treated with 1.1 equiv of phosphoric acid in 100 mL of ethanol–water. Upon careful concentration and cooling of the solution, a sticky material separated which solidified

in several days at −5 °C. The collected product weighed 500 mg: mp >170 °C dec; NMR (Me_2SO-d_6) δ 1.18 (d, CH_3CH), 3.77 (s, OCH_3), 5.38 (2 d, i), 6.78 (2 d, v, $J_{c,a}$ = 10 Hz, $J_{c,b}$ = 18 Hz). Anal.



v

($C_{18}H_{25}N_3O$·0.9H_3PO_4) C, H, N. A sample of this salt was converted back to the free base **7b**; high resolution mass spectrum *m/e* required for $C_{18}H_{25}N_3O$, 299.1997; observed, 299.1995.

2-(β-Bromoethyl)-8-[[6′-(Diethylamino)hexyl]amino]-6-methoxy-4-methylquinoline (8b) Hydrobromide. The 8-aminoquinoline **6** (3 g, 0.014 mol) was mixed with a few drops of DMF and heated at 75 °C while a solution of 7 g (0.022 mol) of 6-(diethylamino)hexyl bromide hydrobromide in 4 mL of DMF and 0.20 mL of water was added with stirring in 6 h. The pasty mixture was cooled overnight and diluted with some ethanol and THF, and the solid was separated by filtration to yield 1.3 g of yellow powder, which turned brown upon storage at room temperature. The melting point, 200–205 °C, did not change upon one precipitation of the product from ethanol–THF: yield of yellow-brown material 1 g (13%); NMR (Me_2SO-d_6) showed no signals which could be assigned to vinyl protons; UV (CH_3OH) λ_{max} 270 nm, 290 (shoulder), 351. For comparison, compound **8a**: UV (CH_3OH) λ_{max} 270 nm, 290, 352; 8-amino-6-methoxy-4-methyl-2-vinylquinoline hydrobromide: UV (CH_3OH) λ_{max} 278 nm, 382. Anal. ($C_{23}H_{37}N_3OBr_2$·1.5H_2O) C, H, N; Br: calcd, 28.55; found, 29.31.

4-Ethyl-6-methoxy-2-methyl-8-nitroquinoline (10). A mixture of 3 g (0.018 mol) of 4-methoxy-2-nitroaniline (**1**) and 3 g (0.023 mol) of 2-chloropropyl ethyl ketone (**9**)[4] was heated at 80 °C for 50 min in 7 mL of 85% phosphoric acid. Arsenic pentoxide (3 g) was added to the homogeneous mixture and heating with stirring at 85–90 °C continued for 2.5 h. The product was cooled to room temperature, diluted with 50 mL of water, and basified (pH 7.5) with ammonia. The precipitate was collected and thoroughly washed with water and then methanol. The quinoline **10** was obtained as a light orange-brown material: mp 145–147 °C; yield 1.9 g (44%); NMR ($CDCl_3$) δ 1.3 (t, CH_3CH_2), 2.55 (s, CH_3), 2.9 (q, CH_3CH_2), 3.85 (s, OCH_3), 7.03 (s, H_3), 7.25 (d, H_5), 7.37 (d, H_7). Anal. ($C_{13}H_{14}N_2O_3$) C, H, N.

8-Amino-4-ethyl-2-methyl-6-methoxyquinoline (11). Due to the low solubility of **10** in ethanolic HCl, the stannous chloride reduction was carried out in a mixture of equal volumes of THF and ethanol and 3 volumes of hydrochloric acid. The yield was 7.9 g (90%) of **11** from 10 g (0.41 mol) of **10**: NMR ($CDCl_3$) δ 1.25 (t, CH_3CH_2), 2.5 (s, CH_3), 2.82 (q, CH_3CH_2), 3.72 (s, OCH_3), 4.75 (br s, NH_2), 6.35 (s, H_5, H_7), 6.85 (s, H_3).

A portion of this amine was converted to the hydrobromide salt. Recrystallization from a 2-propanol and THF mixture gave the analytical sample, mp 266 °C dec. Anal. ($C_{13}H_{17}BrN_2O$·0.5H_2O).

8-[(4′-Amino-1′-methylbutyl)amino]-4-ethyl-6-methoxy-2-methylquinoline (7c) Diphosphate. Under argon, 3 g (0.014 mol) of **11** was heated at 95 °C bath temperature while a solution of 11 g (0.03 mol) of 4-iodo-1-phthalimidopentane in 3.5 g (0.035 mol) of triethylamine was added over a 6-h period with stirring. The cooled product was extracted with 30 mL of benzene, filtered, and evaporated. The residue was chromatographed on 230 g of silica gel using chloroform as eluent. The yield was 4.1 g of product. This product was refluxed with an excess of hydrazine in ethanol for 1.5 h. After filtering the cooled solution, the ethanol was evaporated and the residue dissolved in methylene chloride. The filtered solution was evaporated in vacuo, leaving **7c** as a yellow syrup (2.2 g, 78%). This was treated with 2.4 g (0.02 mol) of 85% phosphoric acid in ethanol–water. The yellow diphosphate of **7c** (3.6 g, 69%) was collected and recrystallized once from ethanol–water. The salt was obtained as bright yellow crystals, mp 113–115 °C. Anal. ($C_{18}H_{27}N_3O$·2H_3PO_4) C, H, N, P.

8-[[6′-(Diethylamino)hexyl]amino]-4-ethyl-6-methoxy-2-methylquinoline (8c) Dihydrobromide. To 3.4 g (0.016 mol) of **11** heated under argon at 85–90 °C was added slowly a warm solution of 7.5 g (0.024 mol) of 6-(diethylamino)hexyl bromide hydrobromide in 5 mL of DMF over a 4-h period with stirring. Upon cooling to room temperature, the mixture crystallized in part. The product was separated by filtration, washed with ethanol and THF, and air-dried (4.1 g). The filtrate, after evaporation and washing with THF–ethanol, gave some more dihydrobromide (1.6 g). The crude product melted at 210–215 °C, total yield 5.7 g (67%). Two recrystallizations raised the melting point to 220–222 °C dec. Anal. ($C_{23}H_{37}N_3O$·2HBr) C, H, N, Br.

Acknowledgment. The authors express their gratitude to Drs. E. A. Steck and R. E. Strube for many helpful suggestions and discussions during the course of this work. This work was supported by the U.S. Army Medical Research and Development Command under Research Contract DADA-17-74-C-4107. This paper has been designated as Contribution No. 1564 to the Army Research Program on Antiparasitic Drugs.

Role of Iodine in Thyroid Hormones: Molecular Conformation of a Halogen-Free Hormone Analogue

Vivian Cody

Medical Foundation of Buffalo, Inc., Buffalo, New York 14203. *Received November 26, 1979*

The molecular conformation of the halogen-free thyroid hormone analogue, *N*-acetyl-4′-methoxy-3,5,3′-trimethyl-L-thyronine ethyl ester, has been determined by X-ray diffraction techniques. The observed molecular conformation is similar to that found for the natural hormone 3,5,3′-triiodo-L-thyronine (T_3). In this structure, the 3′-methyl group is distal, the overall conformation is cisoid, and the diphenyl ether conformation is twist-skewed. These structural similarities with T_3 show that the conformational features required by the active hormone can still be maintained with methyl substitution. The observation that the halogen-free analogues have relatively high activity but extremely low protein binding affinity implies that the role of iodine in hormone transport and biological activity can be differentiated. These data suggest that the iodines enhance hormone–protein binding by virtue of their electronic, as well as steric, properties.

Many hypotheses of thyroid hormone action have assumed iodine to be an integral part of the requirements for physiological function. This was due in part to the reported inactivity of halogen-free analogues, particularly that of tetramethylthyronine.[1-5] However, recent studies have demonstrated the original synthesis of tetramethylthyronine to be in error.[6] Subsequent testing of

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