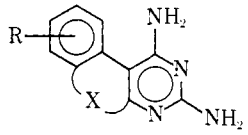
Quinazolines. 12. 1,3-Diaminobenzo[f]quinazolines Containing Long-Chain Alkyl or Chloro Substituents on the Central Ring. Synthesis and Biological Evaluation as Candidate Antifolate and Antimalarial Agents†,1

Andre Rosowsky,* Ping C. Huang, Nickolas Papathanasopoulos, and Edward J. Modest

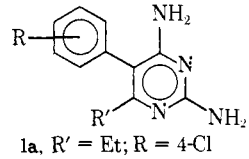
The Children's Cancer Research Foundation and the Departments of Biological Chemistry and Pathology, Harvard Medical School, Boston, Massachusetts 02115. *Received May 13, 1974*

1,3-Diaminobenzo[f]quinazoline antifolates bearing *n*-hexyl or *n*-heptyl groups at positions 5, 6, and 8 were synthesized in order to assess the effect of long-chain alkyl substitution on growth-inhibitory activity against bacterial and mammalian cells in culture. These compounds were also evaluated as antimalarial agents against *Plasmodium berghei* in mice and their activity was compared with that reported previously for pyrimethamine and related 2,4-diamino-6-alkyl-5-arylpyrimidines. A 6-chloro and a 5,6-dihydro-6-phenyl analog were also prepared. Whereas long-chain alkyl groups appeared to lead either to no increase in antibacterial and cytotoxic action or to a reduction in activity, depending on the position of substitution and the type of target cell, a favorable therapeutic effect was observed in mice infected with *P. berghei*. The 6-*n*-hexyl derivative **2c** showed the best level of activity and least toxicity in the antimalarial assay, whereas in bacterial systems the most active compound against *Streptococcus faecium* ATCC 8043 was the 6-chloro analog **2d**.

Tricyclic 2,4-diaminopyrimidine derivatives of general structure I have been investigated systematically in this laboratory for several years because of their high level of antifolate activity *in vitro*, their cytotoxic activity in bacterial and mammalian cell culture systems, and their possible chemotherapeutic interest as antimalarial and experimental antineoplastic agents.[2] They are structurally related to the 2,4-diamino-6-alkyl-5-arylpyrimidine antifolates,[3] two notable examples of which are pyrimethamine (**1a**), a widely prescribed clinical antimalarial,[4] and 2,4-diamino-5-(3,4-dichlorophenyl)-6-methylpyrimidine (DDMP, DMP, 1b), which has been shown to possess some experimental and clinical antitumor activity.[5] Both



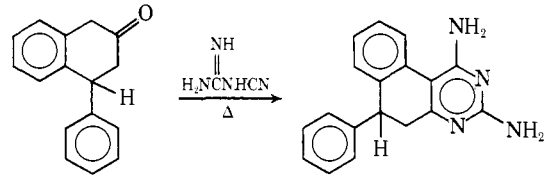
I



1a, R′ = Et; R = 4-Cl
b, R′ = Me; R = 3,4-Cl$_2$

compounds have recently been the object of renewed interest because of their ability to penetrate the central nervous system and their resultant possible value in the treatment of meningeal leukemia.[6] The tricyclic systems represented by structure I may be viewed as conformationally rigid analogs of **1a** and 1b in which the precise spatial relationship between the phenyl and pyrimidine rings can be varied by appropriate modification of the central ring.[7] Of the several variants examined for biological activity in diverse test systems,[2] the most promising as a group have proved to be the 1,3-diaminobenzo[f]quinazolines (I, X = CH=CH).[8-10] Because these molecules are fully aromatic and possess planar geometry, they may exhibit better antifolate activity than is possible with indeno[2,1-*d*]pyrimidines (I, X = CH_2),[11] 5,6-dihydrobenzo[f]quinazolines (I, X = CH_2CH_2),[12,13] 5*H*-[1]benzopyrano- (and thiopyrano-) [3,4-*d*]pyrimidines (I, X = OCH_2, SCH_2),[14] or 10,11-dihydro-9*H*-benzo[3,4]cyclohepta[1,2-*d*]pyrimidines (I, X = $CH_2CH_2CH_2$),[15] all of which contain a nonaromatic central ring and are nonplanar.

1,3-Diaminobenzo[f]quinazolines examined in our program thus far have been those in which halogen, alkyl, or methoxy substituents are present in positions 7, 8, and/or 9.[10] However, it was also of interest to prepare a selected number of compounds in this and the 5,6-dihydro series with substituents at positions 5 or 6, *i.e.*, on the central ring. Long-chain alkyl substitution was judged to be especially attractive because of the striking enhancement in antibacterial activity displayed by pyrimethamine analogs in which the 6-ethyl group has been replaced by 6-*n*-pentyl and 6-*n*-undecyl[16] and by structurally related 4,6-diamino-1-aryl-1,2-dihydro-*s*-triazines with long-chain alkyl substituents at position 2.[17] In the present paper we wish to report the synthesis of five new compounds of the 5- and 6-substituted type, namely, the 5-*n*-hexyl and 5-*n*-heptyl derivatives **2a** and 2b (Scheme I), the 6-*n*-hexyl derivative **2c** (Scheme III), the 6-chloro derivative **2d** (Scheme V), and 1,3-diamino-5,6-dihydro-6-phenylbenzo[f]quinazoline (**3**). In addition, the heretofore undescribed 8-*n*-heptyl congener **2e** is reported (Scheme IV).



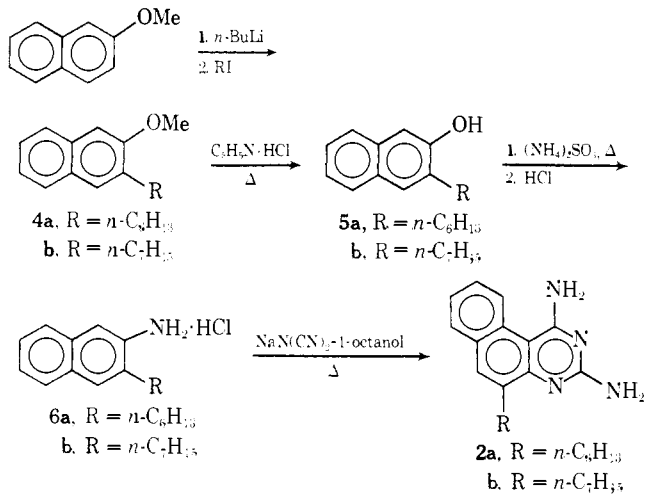
3

Chemistry. Metalation of 2-methoxynaphthalene at the 3 position by reaction with *n*-BuLi[18,19] followed by direct treatment of the lithio derivative with *n*-hexyl or *n*-heptyl iodide led to the 3-alkyl-2-methoxynaphthalenes **4a** (73%) and **4b** (83%), respectively (Scheme I). Cleavage of the methoxy groups with pyridine hydrochloride[20,21] afforded the corresponding 2-naphthols **5a** and **5b** (80–90%), and further reaction with ammonium sulfite and ammonia at elevated temperature provided the hitherto undescribed long-chain 3-alkyl-2-naphthylamines **6a** and 6b (isolated as HCl salts, 60–70% yield). Condensation of **6a**·HCl with excess sodium dicyanamide in boiling 1-octanol[10] furnished **2a** in 38% yield. Similar treatment of **6b**·HCl gave 2b (57%).

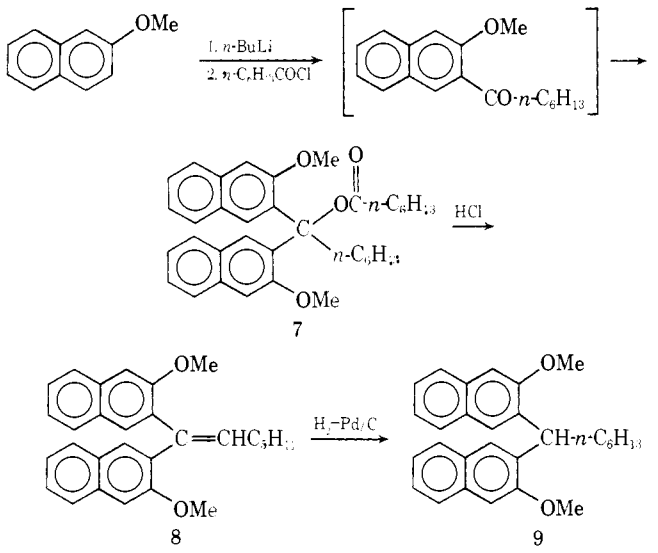
Unexpected results were obtained when the 3-lithio derivative of 2-methoxynaphthalene was allowed to react with *n*-heptanoyl chloride (Scheme II). Instead of 3-*n*-heptanoyl-2-methoxynaphthalene, a product was isolated (53%) which failed to undergo Wolff-Kishner or Clemmensen reduction and whose ir and nmr spectra and microanalyses were consistent with structure 7. The ester rather than ketonic nature of 7 was indicated especially

†This work was supported in part by Research Contract DA-49-193-3008 from the U. S. Army Research and Development Command, Office of the Surgeon General, and by Research Grant C6516 and Research Career Development Award K3-CA-22,151 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service. This is Contribution No. 1181 from the U. S. Army Program on Malaria.

Scheme I



Scheme II



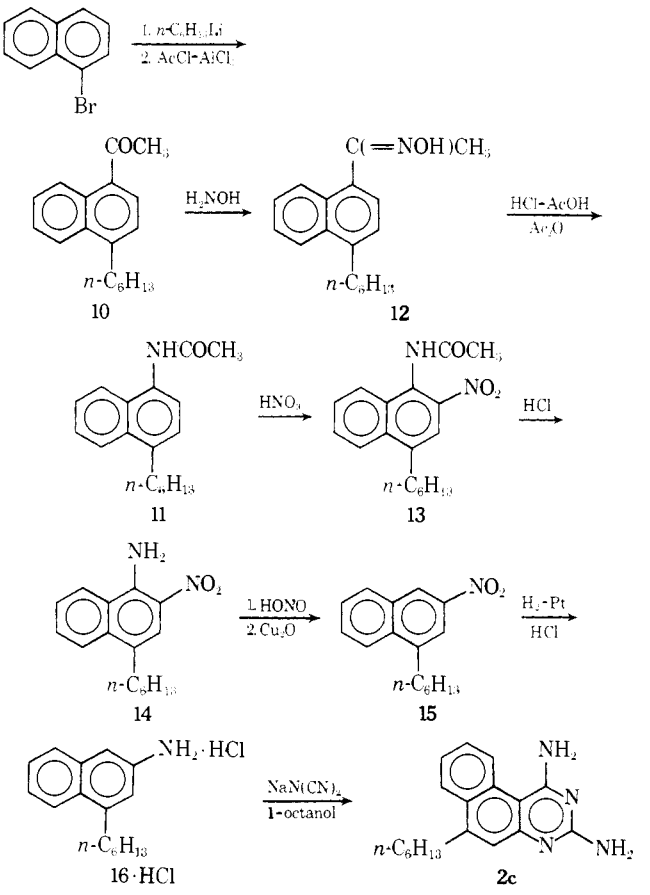
by its prominent ir absorption at 1740 cm^{-1}. Chemical support for structure **7** was also provided by acid hydrolysis and catalytic hydrogenation, which led successively to **8** (91%) and **9** (92%). The origin of **7** can be rationalized by assuming that the primary adduct, 3-*n*-heptanoyl-2-methoxynaphthalene, condenses very rapidly with 3-lithio-2-methoxynaphthalene to give an alkoxide which then reacts immediately with another molecule of *n*-heptanoyl chloride.

1-*n*-Hexylnaphthalene, derived from 1-bromonaphthalene and *n*-hexyllithium,[22] was subjected to Friedel-Crafts acylation with acetyl chloride and $AlCl_3$ in nitrobenzene. As indicated in Scheme III, the resultant acetyl derivative **10** (84%) was converted into amide **11** (76%) *via* acid-catalyzed Beckmann rearrangement of oxime **12**. Mononitration of **11** yielded the 1-acetamido-2-nitro derivative **13** (52%), which was hydrolyzed to the amine **14** (94%) with HCl in ethanol under reflux. Diazotization of **14** followed by nitrogen elimination with Cu_2O in MeOH afforded the nitro compound **15** (76%), from which 4-*n*-hexyl-2-naphthylamine hydrochloride (**16**·HCl, 70% yield) was obtained by catalytic hydrogenation in the presence of HCl. This reaction sequence has been reported previously as a route to 4-methyl-2-naphthylamine[23] but has not been extended to long-chain 4-alkyl-2-naphthylamines until now. As in the cyclization of **6a**·HCl and **6b**·HCl, condensation of **16**·HCl with excess sodium dicyanamide in boiling 1-octanol resulted in the formation of **2c** (36%).

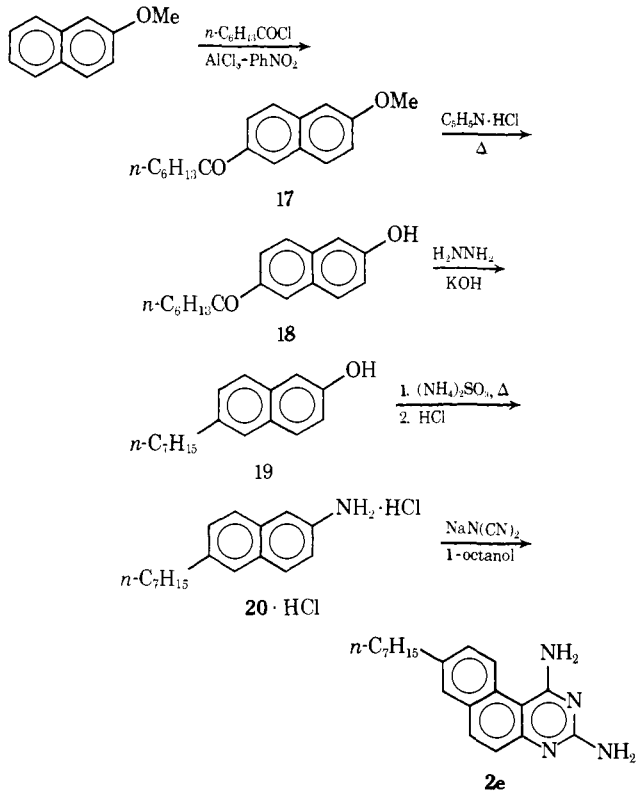
Friedel-Crafts acylation of 2-methoxynaphthalene with *n*-heptanoyl chloride and $AlCl_3$ in nitrobenzene led to the 8-*n*-heptanoyl derivative **17** (82%), which on heating with pyridine hydrochloride and Wolff-Kishner reduction gave successively 8-*n*-heptanoyl-2-naphthol (**18**, 93%) and 8-*n*-heptyl-2-naphthol (**19**, 71%).[20] The latter, on being subjected to a Bücherer reaction, gave the hitherto undescribed 8-*n*-heptyl-2-naphthylamine **20** (74%, as the HCl salt). Condensation of **20**·HCl with sodium dicyanamide then furnished the desired product **2e** (40%) (Scheme IV).

3-Nitro-1-naphthoic acid was converted into 3-nitro-1-naphthylamine (**21**) *via* a Schmidt reaction (Scheme V), using NaN_3 and H_2SO_4.[24] Conversion of **21** into 1-chloro-3-nitronaphthalene (**22**, 57%) *via* a Sandmeyer reaction and reduction of **22** with iron filings in EtOH under reflux gave 4-chloro-2-naphthylamine (**23**, 35% yield as the HCl salt). Previously reported routes to **22** and **23** have involved deamination of 4-chloro-2-nitro-1-naphthylamine[25,26] and catalytic hydrogenation.[26] The present sequence employing a more easily available commercial starting material appeared to be a convenient and more direct method of synthesis. Unfortunately, cyclization of **23**·HCl with sodium dicyanamide in boiling 1-octanol furnished **2d** only in poor yield (*ca.* 10%). The presence of an electron-withdrawing substituent on the same ring as the amino group is therefore assumed to be seriously detrimental to the reaction. In accord with this conclusion, we have not been able to effect ring closure with 3-chloro-2-naphthylamine under a variety of reaction conditions. For the synthesis of 3-chloro-2-naphthylamine, which was unknown at the time of this investigation, 2,3-dinitronaphthalene was reduced to the monoamine with Na_2S, the

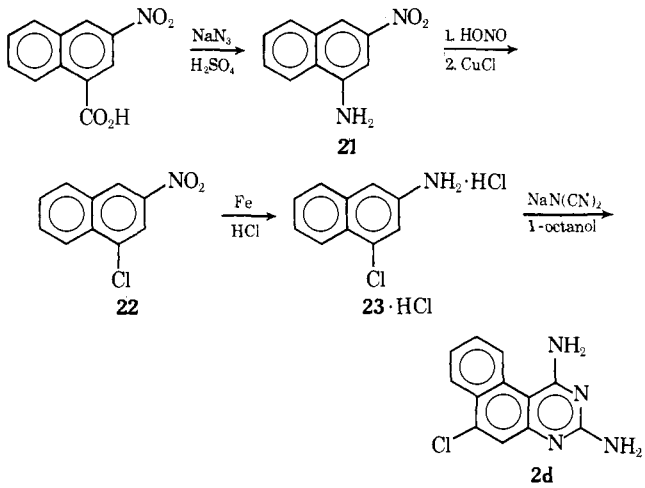
Scheme III



Scheme IV



Scheme V



amino group was replaced with chlorine *via* a Sandmeyer reaction, and the remaining nitro group was reduced with $SnCl_2$.

Lastly, for the synthesis of **3**, cyanoguanidine was condensed with 4-phenyl-2-tetralone[27] under the dry fusion conditions usually employed in this laboratory with other 2-tetralones[13] and related compounds.[28] The product was isolated most conveniently in the form of an HCl salt (55% yield).

Biological Results. Compounds **2a–e** and **3** were examined in several standard *in vitro* bioassay systems at The Children's Cancer Research Foundation.[29-31] The results are summarized in Table I. Using the parent compound 1,3-diaminobenzo[*f*]quinazoline (**2f**)[8,9] as a reference point, long-chain alkyl substitution at position 8, as in **2e**, appears to have little effect on the ID_{50} in the *Streptococcus faecium* or *Pediococcus cerevisiae* system but causes an approximately tenfold increase in activity against *Lactobacillus arabinosus*. In contrast, the *n*-hexyl group at position 5 or 6 (compounds **2a** and **2c**) has little effect in the *L. arabinosus* systems but leads to substantial loss of inhibition against *S. faecium* and *P. cerevisiae*. Extension of the 5-alkyl chain length from *n*-hexyl (**2a**) to *n*-heptyl (**2b**) results in some loss of activity against *S. faecium* as well as *L. arabinosus*. However, none of the types of long-chain alkyl substitution represented by these compounds shows any appreciable effect in the *L. fermenti* assay. Thus, in general accord with our previous conclusions in the triazine series,[17] as well as those of Hitchings and coworkers in the pyrimidine series,[16] long-chain alkyl substitution affects the antimicrobial activity of 1,3-diaminobenzo[*f*]quinazolines in some instances, but the manner in which activity is affected depends both on the position of substitution and on the target organism.

Table I. Inhibition of Microbial and Mammalian Cell Growth *in Vitro* (ID_{50}, μM)

	Assay system[a]					
Compd	1	2	3	4	5	6
2f[b]	0.1	1	2	0.1	1	2
2a	2	1	1	2	3	10
2b	5	8	9	2	0.9	3
2c	0.7	1	1	4	0.9	20
2d	0.003	na[c]	na	na	na	na
2e	0.1	0.1	0.07	0.07	0.7	8
4a·HCl	0.6	>4	>4	0.8	>4	>4

[a] System 1, *Streptococcus faecium* 8043/folate (0.001 μg/ml); system 2, *Lactobacillus arabinosus* 17-5/pantothenate (0.01 μg/ml); system 3, *L. arabinosus* 17-5/nicotinate (0.01 μg/ml); system 4, *Pediococcus cerevisiae* 8081/citrovorum factor (0.01 μg/ml); system 5, *Lactobacillus fermenti* 9338/thiamine (0.01 μg/ml); system 6, KB cells (human epithelial carcinoma) in Eagle's medium (see ref 29–31 for *in vitro* assay methods). [b] References 8 and 9. [c] na, not assayed.

Replacement of the 6-alkyl groups in **2a** and **2b** by a 6-chloro substituent (compound **2d**) resulted in a dramatic enhancement in activity against *S. faecium*, but limited supply unfortunately precluded evaluation against malarial organisms *in vivo*. The pronounced favorable effect of halogen substitution appears consistent with previous findings in the benzo[*f*]quinazoline series.[2]

With respect to substitution of a phenyl group and reduction of the 5,6 bond, as in **3**·HCl, some loss of activity was observed in all the microbial systems. However, it should be noted that the magnitude of this loss was not greater than has been witnessed in other 1,3-diamino-5,6-dihydrobenzo[*f*]quinazolines relative to the corresponding fully aromatic derivatives.[2]

In tests against malignant epidermal carcinoma of human origin (KB cells) in culture, none of the long-chain alkyl compounds was as active as the parent member of the series. Substitution by *n*-hexyl at position 5 or 6 caused the greatest loss of activity. Use of the *n*-heptyl group in place of *n*-hexyl at position 5, on the other hand, seemed to be somewhat less detrimental, as was placement of the *n*-hexyl group at position 8 instead of 5 or 6.

Antimalarial assays were performed under the auspices of the Walter Reed Army Institute of Research *via* the established procedure,[32] in which ICR/Ha mice are injected with a single subcutaneous dose of compound in oil 3 days after intravenous infection with *Plasmodium berghei* and the mean survival time of the treated animals is compared to that of controls. The results, some of which have been reported in preliminary fashion,[2] are given in Table II. At the 640 mg/kg dose it is apparent that, relative to

Table II. Antimalarial Activity against *Plasmodium berghei* in Mice

Compd	Run	Mean survival, days[a] 40 mg/kg	160 mg/kg	640 mg/kg
2f	1	7.2	6.2 (3T)	0.0 (5T)
	2	6.4	6.8	10.0 (4T)
2a	1	6.4	6.4	6.6
	2	6.2	6.2	6.2
2b	1	6.8	6.8	7.0
	2	6.2	6.2	6.2
2c	1	6.8	8.2	*18.0*
	2	7.0	8.4	*17.8*
2e	1	6.8	7.0	9.8
	2	6.4	6.8	8.8
	3	6.4	7.0	10.0
	4	6.4	6.6	9.0
4a·HCl		6.2	6.2	6.6

[a] Mean survival of untreated controls = 6.2 days; "activity" is defined as 100% or greater increase in mean survival of five test animals and is denoted in italics; numbers in parentheses refer to toxic deaths among the treated animals (see ref 32 for assay method).

the parent compound **2f**, long-chain alkyl substitution at position 5 (compounds **2a** and **2b**) is essentially ineffectual and that substitution at position 8 (compound **2e**) produces only a small increase in life span. On the other hand, substitution at position 6 (compound **2c**) results in a nearly threefold extension in survival. It is also of interest that the toxicity associated with the parent compound **2f** was not observed with any of the substituted derivatives in this group. Thus it appears that appropriate selection of a long-chain alkyl substituent can effect a favorable alteration in the *in vivo* pharmacological properties of 1,3-diaminobenzo[*f*]quinazolines.

Comparison of the results in Tables I and II suggests that bacterial and mammalian cell culture data *in vitro* and antimalarial data *in vivo* are not necessarily correlated. For example, although **2e** appeared to be the most promising antimalarial candidate among the long-chain alkyl derivatives on the basis of the *in vitro* against *S. faecium* and *P. cerevisiae*, compound **2c** actually proved to be superior to **2e** *in vivo*. This, together with the rather generalized antibacterial effect of these long-chain alkyl compounds, suggests the possibility that their mode of action in microorganisms may not be confined exclusively to folate metabolism. Possible variations among different members of the series with respect to drug absorption or detoxification, for example, may also be responsible for these discrepancies. A fuller understanding of these factors will require more detailed pharmacological investigations.

Experimental Section

Uv spectra were measured with Cary Model 11 and Model 15 spectrophotometers. Ir spectra were measured with a Perkin-Elmer Model 137B double beam recording spectrophotometer. Nmr spectra were determined by means of a Varian A-60 instrument, with $CDCl_3$ as the solvent and Me_4Si as the internal reference. Melting points were taken in Pyrex capillary tubes in a modified Wagner-Meyer apparatus[33] at a heating rate of 2°/min and are uncorrected. Unless otherwise specified, solutions were dried with anhydrous Na_2SO_4 or $MgSO_4$. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Where analyses are given by element symbols, results for those elements were within ±0.4% of theoretical values.

3-*n*-Heptyl-2-methoxynaphthalene (4b). To a solution of 2-methoxynaphthalene (38 g, 0.24 mol) in dry THF (200 ml) at 0° under N_2 was added with stirring a solution of *n*-BuLi in *n*-hexane (100 ml of 22.3% solution, 0.26 mol, Alfa Inorganics, Inc., Beverly, Mass.). The mixture was stirred at 0° for 1 hr and under reflux for 1 hr. A solution of *n*-heptyl iodide (54 g, 0.24 mol) in dry THF (20 ml) was then added dropwise and refluxing was continued for another 3 hr. The cooled mixture was poured onto Dry Ice (10 g) and extracted with water (2 × 100 ml), saturated $NaHCO_3$ (2 × 100 ml), and distilled water (2 × 100 ml), and the organic layer was dried and evaporated under reduced pressure. Distillation of the residue gave 47 g (83%) of colorless oil: bp 135–140° (0.1 mm); $n^{20}D$ 1.5617. *Anal.* ($Cl_{18}H_{24}O$) C, H.

3-*n*-Hexyl-2-methoxynaphthalene (4a). Reaction of 2-methoxynaphthalene (38 g, 0.24 mol), *n*-BuLi (100 ml of 22.3% solution in *n*-hexane, 0.26 mol), and *n*-hexyl iodide (51 g, 0.24 mol) in anhydrous THF (200 ml) as described in the preceding experiment gave 43 g (73%) of colorless oil: bp 125–130° (0.1 mm). *Anal.* ($C_{17}H_{22}O$) C, H.

3-*n*-Heptyl-2-naphthol (5b). A mixture of **4b** (7.5 g, 0.029 mol) and dry C_5H_5N·HCl (60 g) was heated with stirring at 220° (oil bath) for 2 hr. After being cooled to about 100°, the mixture was poured into ice water (150 ml) and extracted with benzene (2 × 50 ml). The combined organic layers were washed with water, dried, and evaporated. Distillation of the residue yielded a colorless oil which solidified on standing in the cold: bp 140–150° (0.1 mm). Recrystallization from *n*-heptane gave 6 g (85%) of colorless plates: mp 77–78°. *Anal.* ($C_{17}H_{22}O$) C, H.

3-*n*-Heptyl-2-naphthylamine Hydrochloride (6b·HCl). A mixture of **5b** (3.5 g, 0.014 mol), ammonium sulfite (10 g), 2-(2-ethoxyethoxy)ethanol (10 ml), and concentrated NH_4OH (50 ml) was heated to 195–200° (internal temperature) in a stainless steel autoclave. After 3 days, the mixture was filtered, the filtrate was extracted with benzene, and the organic layer was washed with water, dried, and evaporated. The crude amine **6b** was dissolved in ether (20 ml), and the solution was cooled and saturated with dry HCl gas for 15 min. The HCl salt was filtered, washed with ether, and dried: yield 2.7 g (67%); mp 192–194° dec. For microanalysis, a portion of the crude **6b**·HCl (0.2 g) was dissolved in DMSO (1 ml) and the solution was poured with stirring into saturated $NaHCO_3$ (15 ml). The oily free base was extracted into benzene (10 ml), the benzene solution was dried and evaporated, the residue was taken up in 95% EtOH (2 ml), and saturated ethanolic picric acid solution (7 ml) was added. Brief heating followed by overnight refrigeration afforded a light brown solid. Washing with absolute EtOH gave light yellow needles of the *picrate* derivative: mp 156–157° dec. *Anal.* ($C_{17}H_{23}N·C_6H_3N_3O_7$) C, H, N.

3-*n*-Hexyl-2-naphthylamine Hydrochloride (6a·HCl). Reaction of **4a** (15 g, 0.062 mol) with C_5H_5N·HCl (50 g) at 220° (oil bath) for 1.5 hr as described in the synthesis of **5b** gave 12.5 g (89%) of yellow oil. Fractional distillation yielded a colorless liquid: bp 145–150° (0.1 mm), solidifying on standing in the cold. Crystallization from ligroine (bp 65–90°) afforded colorless needles: mp 77–78°. The crude naphthol **5a** (12 g, 0.053 mol), ammonium sulfite (20 g), 2-(2-ethoxyethoxy)ethanol (5 ml), and concentrated ammonia (20 ml) were heated to 200–210° (internal temperature) in a stainless steel autoclave for 2 days and worked up as described in the preceding synthesis of **6b**·HCl: yield 8.5 g (65%), after recrystallization from a mixture of EtOH and 1 *N* HCl; mp 202–204° dec. *Anal.* ($C_{16}H_{21}N·HCl$) C, H, N.

1-(*n*-Heptanoyloxy)-1,1-bis(3-methoxy-2-naphthyl)-*n*-heptane (7). To a solution of 2-methoxynaphthalene (25 g, 0.16 mol) in anhydrous ether (300 ml) was added dropwise a solution of *n*-BuLi in *n*-hexane (66 ml, 22.3% w/w, 0.17 mol). The mixture was stirred at room temperature for 2 hr, then refluxed under nitrogen for 22 hr, and finally cooled in an ice bath while a solution of *n*-heptanoyl chloride (24 g, 0.16 mol) in ether (100 ml) was added dropwise over a period of 30 min. The reaction was exothermic, with deposition of a white precipitate. After being stirred at room temperature for 16 hr, the mixture was treated with water (150 ml) and stirred an additional 10 min. The organic layer was separated, washed with 2% NaOH (100 ml), rinsed to neutrality with distilled water, and dried. Solvent evaporation and trituration of the residue with EtOH (5 ml) afforded a white crystalline product. Recrystallization from 95% EtOH gave 22 g (53%) of colorless prisms: mp 118–120°. *Anal.* ($C_{36}H_{44}O_4$) C, H.

1,1-Bis(3-methoxy-2-naphthyl)-1-heptene (8). A mixture of **7** (3.0 g, 0.0055 mol), EtOH (30 ml), and concentrated HCl (5 ml) was refluxed with stirring for 20 hr. The solution was cooled slowly and the white solid was filtered, washed with a small volume of EtOH, and dried: yield 2.1 g (91%); mp 127–128°; positive tests with bromine water and $KMnO_4$ reagent, indicating the presence of a double bond. *Anal.* ($C_{29}H_{30}O_2$) C, H.

1,1-**Bis(3-methoxy-2-naphthyl)-*n*-heptane** (**9**). A solution of 8 (1.3 g, 0.0032 mol) in a mixture of EtOH (50 ml) and 2-ethoxyethanol (50 ml) was hydrogenated in a Parr apparatus (2–3 atm) in the presence of 100 mg of 10% Pd/C. When hydrogen uptake ceased, the mixture was filtered through Celite and the filtrate was evaporated under reduced pressure. Crystallization of the residue from EtOH afforded 1.2 g (92%) of colorless prisms: mp 124–125°. The nmr spectrum in $CDCl_3$ solution showed the absence of vinyl protons and the appearance of a new tertiary proton at τ 4.96. *Anal.* ($C_{29}H_{32}O_2$) C, H.

1-**Acetyl-4-*n*-hexylnaphthalene** (**10**). A solution of 1-*n*-hexylnaphthalene (47 g, 0.21 mol)[21] in nitrobenzene (150 ml) was stirred mechanically while anhydrous $AlCl_3$ (60 g) was added slowly. The resulting black mixture was treated dropwise with acetyl chloride (20 ml) over a 2-hr period, the internal temperature being maintained at −3°. After being warmed gradually to room temperature and stirred for 20 hr, the mixture was poured into ice water (600 ml), and the organic layer was separated, washed with water, and steam distilled. After all the nitrobenzene had been removed by steam distillation, the remaining aqueous mixture was extracted with benzene (2 × 100 ml) and the combined benzene extracts were dried and evaporated. Crystallization of the crude residue from 95% EtOH afforded 40 g (84%) of colorless prisms: mp 24–25°. *Anal.* ($C_{18}H_{22}O$) C, H.

1-**Acetamido-4-*n*-hexylnaphthalene** (**11**). To a warm solution of **10** (15 g, 0.062 mol) in 95% EtOH (100 ml) was added a solution of $HONH_2 \cdot HCl$ (6.3 g, 0.091 mol) in water (10 ml), followed by a solution of NaOH (4.4 g) in water (10 ml). The mixture was refluxed with stirring for 2 hr, cooled, and poured into ice water (200 ml). The oily oxime **12** was dissolved directly in a mixture of Ac_2O (50 ml) and glacial AcOH (50 ml), and the cooled solution was saturated with dry HCl gas. After the mixture was kept at room temperature for 5 hr and then treated with ice water (200 ml), the crystalline product was filtered, washed with 2% $NaHCO_3$ (200 ml), rinsed with water, and dried. Recrystallization from aqueous EtOH gave 13 g (76%) of colorless plates: mp 110–111°. *Anal.* ($C_{18}H_{23}NO$) C, H, N.

1-**Acetamido-4-*n*-hexyl-2-nitronaphthalene** (**13**). A mixture of **11** (13 g, 0.047 mol) and urea (0.6 g) was dissolved in Ac_2O (10 ml) by warming at 40°. The solution was cooled slowly with stirring until, at about 30°, crystals began to reappear. The mixture was then cooled in an ice bath while fuming nitric acid (90%, 2.9 ml) was added dropwise with stirring. The internal temperature was maintained below 10° throughout the addition. The yellow mixture was stirred at 10° for 1 hr and at room temperature for another hour and then stored in the refrigerator overnight. The precipitate was filtered, washed with water (100 ml) and 3% $NaHCO_3$ (200 ml), rinsed again with water (100 ml), and dried. Recrystallization from aqueous EtOH yielded 7.5 g (52%) of yellow needles: mp 269–270°. *Anal.* ($C_{18}H_{22}N_2O_3$).

1-**Amino-4-*n*-hexyl-2-nitronaphthalene** (**14**). A mixture of **13** (5.0 g, 0.016 mol), concentrated HCl (10 ml), and EtOH (50 ml) was refluxed for 12 hr. The reddish solution was cooled and the precipitate was collected, washed with 3% $NaHCO_3$, rinsed with water, and dried. Recrystallization from EtOH gave 4.1 g (94%) of orange needles: mp 93–94°. *Anal.* ($C_{16}H_{20}N_2O_2$) C, H, N.

1-*n*-**Hexyl-3-nitronaphthalene** (**15**). A slightly warm solution of **14** (5.0 g, 0.018 mol) in glacial AcOH (40 ml) was added slowly to a solution of $NaNO_2$ (3 g) in concentrated H_2SO_4 (12 ml) and glacial AcOH (20 ml). The mixture was cooled in an ice–salt bath during addition so that the internal temperature did not exceed 20°. After addition was complete (40 min), the orange mixture was stirred for 30 min, the foaming mixture was diluted with ice water (150 ml) and stored in the refrigerator overnight, and the brown precipitate was filtered, washed with water, and recrystallized from EtOH: yellow needles (3.6 g, 76%); mp 75–76°. *Anal.* ($C_{16}H_{19}NO_2$) C, H, N.

4-*n*-**Hexyl-2-naphthylamine Hydrochloride** (**16·HCl**). A solution of **15** (1.5 g, 0.0058 mol) in 2-ethoxyethanol (50 ml) and EtOH (50 ml) containing concentrated HCl (3 ml) was hydrogenated in a Parr apparatus (2–3 atm) in the presence of PtO_2 (50 mg). After 30 min the mixture was filtered through Celite, the filtrate was evaporated to dryness, and the residue was treated with Et_2O (50 ml) in the cold. The crystalline product was filtered, washed with petroleum ether (bp 30–60°), and dried: yield 1.1 g (70%); mp 178–180° dec. For microanalysis, a 100-mg portion of the HCl salt (**16·HCl**) was dissolved in DMF (1 ml), and the solution was added dropwise to 20 ml of saturated $NaHCO_3$. The oily free base was extracted into benzene (2 × 25 ml), and the benzene solution was washed with water, dried, and evaporated. The residue was treated with saturated 95% ethanolic picric acid solution (7 ml) on the steam bath. Filtration of the yellow precipitate, washing with EtOH (2 × 25 ml), and drying yielded the *picrate* salt: mp 175–178° dec. *Anal.* ($C_{16}H_{21}N \cdot C_6H_3N_3O_7$) C, H, N.

6-*n*-**Heptyl-2-naphthylamine Hydrochloride** (**20·HCl**). Anhydrous $AlCl_3$ (40 g) was added during 15 min to a mechanically stirred solution of 2-methoxynaphthalene (40 g, 0.25 mol) and *n*-heptanoyl chloride (40 g, 0.27 mol) in nitrobenzene (200 ml) at 0°. The dark green mixture was stirred at 0° for 1 hr, kept at room temperature overnight, and poured onto ice (300 g). The organic layer was separated, washed with water (2 × 100 ml), and steam distilled until all the nitrobenzene was removed. When the remaining aqueous mixture was cooled in an ice bath, a waxy solid was deposited which was filtered and dried: yield 55 g (82%). Recrystallization from MeOH afforded colorless plates: mp 71–72° (lit.[19] 72°). A mixture of this compound (17, 45 g, 0.17 mol) and $C_5H_5N \cdot HCl$ (150 g) was stirred under reflux for 1 hr, cooled, and poured into ice-cold 0.5 *N* HCl (300 ml). Stirring for 15 min and filtration gave a tan solid: yield 40 g (93%); mp 113–115°. This naphthol (18, 20 g, 0.074 mol) was added directly to a solution of KOH (20 g) in diethylene glycol (120 ml) containing 20 ml of 95% hydrazine hydrate. After 1 hr under reflux, the condenser was removed, the temperature was raised gradually to 210° over a 45-min period, and refluxing was resumed for another 3 hr. The mixture was then cooled, poured onto ice (300 g), and acidified with concentrated HCl (32 ml). The tan solid was filtered, washed with water, and dried. Recrystallization from *n*-heptane gave 13 g (72%) of colorless plates: mp 96–97°. *Anal.* ($C_{17}H_{22}O$) C, H. This compound (**19**, 10 g, 0.41 mol) was heated at 200–210° (internal temperature) for 2 days in a stainless steel autoclave containing ammonium sulfite (5 g), concentrated ammonia (30 ml), and 2-(2-ethoxyethoxy)ethanol (5 ml). On being worked up as in the synthesis of **6b·HCl**, the mixture gave 8.5 g (74%) of crude **20·HCl**. Recrystallization from a mixture of EtOH and 1 *N* HCl (decolorizing carbon) afforded colorless plates: mp 196–198° dec. *Anal.* ($C_{17}H_{23}N \cdot HCl$) C, H, N.

4-**Chloro-2-naphthylamine Hydrochloride** (**23·HCl**). A suspension of 3-nitro-1-naphthylamine sulfate (20 g, 0.42 mol)[25] in concentrated HCl (280 ml) and water (160 ml) was cooled to −10° and treated dropwise with a solution of $NaNO_2$ (12 g) in water (60 ml). The temperature was allowed to rise to 0° and the mixture was poured into an ice-cold solution of CuCl (52 g) in concentrated HCl (400 ml). After 1 hr at room temperature, the mixture was poured onto ice (1 kg) and the tan solid was filtered and dried, giving 18 g (*ca.* 100%) of 1-chloro-3-nitronaphthalene (**22**): mp 130–133° dec (lit.[27] 128–129°). This crude material was added directly to EtOH (1200 ml) containing etched iron filings (90 g). After being stirred under reflux for 4 hr, the hot mixture was filtered, the filtrate was decolorized with charcoal and evaporated under reduced pressure, and the residue was taken up in CH_2Cl_2. Treatment with dry HCl gas caused precipitation of **23·HCl** as an off-white powder (12 g, 65%): mp 250–253° dec (lit.[27] 223–228° dec).

3-**Chloro-2-naphthylamine Hydrochloride**. A well-stirred suspension of 2,3-dinitronaphthalene (30 g, 0.14 mol)[34,‡] in boiling MeOH (500 ml) was treated dropwise with a solution of Na_2S (60 g) and $NaHCO_3$ (20 g) in water (150 ml).[35] The mixture was refluxed for another 20 min, cooled, and poured into ice water (10 l.). After 1 hr, the solid was filtered and digested with boiling 10% HCl (3 l.). The filtrate was concentrated to dryness under reduced pressure in order to obtain 3-nitro-2-naphthylamine hydrochloride (29 g, 98%), which was suspended directly in concentrated HCl (660 ml) and water (340 ml). The mixture was cooled to −10° and treated dropwise with a solution of $NaNO_2$ (36 g) in water (180 ml). The temperature was allowed to rise to 0° and the diazotized mixture was poured into a solution of CuCl (156 g) in ice-cold concentrated HCl (1 l.). After being stirred at room temperature for 2 hr, the mixture was poured into ice water (10 l.) and the solid was filtered, washed thoroughly with water (2 l.), and dried. Continuous extraction with CH_2Cl_2 for 24 hr and evaporation under reduced pressure left a dark red solid (14 g, 52%). Recrystallization from EtOH yielded 3-chloro-2-nitronaphthalene in the form of red needles: mp 59–60° dec. *Anal.* ($C_{10}H_6ClNO_2$) C, H, Cl, N. The nitro compound (14 g, 0.065 mol) was added with stirring to a solution of $SnCl_2 \cdot 2H_2O$ (54 g) in concentrated HCl (500 ml) at room temperature and the mixture was stirred overnight, cooled at 0°, and filtered. The solid was washed with ice-cold concentrated HCl (50 ml) in small portions, rinsed with CH_2Cl_2 (500 ml), and dried, giving 3-chloro-2-naphthyl-

‡A generous sample of this compound was provided kindly by Dr. Julius Hyman, Fundamental Research Co., Berkeley, Calif.

amine hydrochloride as a grey solid (13 g, 99%): mp 265–270° dec. For analysis, the hydrochloride salt was dissolved in water, the solution was treated with decolorizing carbon, and the *free base* was precipitated by addition of ammonia: mp 169–171° dec (EtOH). *Anal.* ($C_{10}H_8ClN$) C, H, Cl, N.

1,3-Diamino-5-*n*-hexylbenzo[*f*]quinazoline (2a). A mixture of **6a**·HCl (4.0 g, 0.014 mol) and sodium dicyanamide (4.0 g, 0.040 mol) in 1-octanol (60 ml) was stirred under reflux for 20 hr and then steam distilled until all the 1-octanol was removed. The remaining aqueous mixture was concentrated to 50 ml under reduced pressure and the semisolid precipitate was filtered, washed with water, and dried. The crude product (3.5 g) was suspended in ether (50 ml), stirred 15 min, filtered, washed with petroleum ether (bp 30–60°, 3 × 20 ml), and dried: yield 1.7 g (38%). Recrystallization from aqueous EtOH (40 ml) gave colorless plates: mp 137–138°. *Anal.* ($C_{18}H_{22}N_4$) C, H, N.

1,3-Diamino-5-*n*-heptylbenzo[*f*]quinazoline (2b). Application of the foregoing procedure with **6b**·HCl gave a 26% yield of **2b**: mp 116–117° (aqueous EtOH). *Anal.* ($C_{19}H_{24}N_4$) C, H, N.

1,3-Diamino-6-*n*-hexylbenzo[*f*]quinazoline (2c). Application of the foregoing procedure with **16**·HCl gave a 36% yield of **2c**: mp 144–146° (aqueous EtOH). *Anal.* ($C_{18}H_{22}N_4 \cdot H_2O$) C, H, N.

1,3-Diamino-6-chlorobenzo[*f*]quinazoline (2d). A mixture of **23**·HCl (0.90 g, 0.042 mol), sodium dicyanamide (0.9 g, 0.001 mol), and 1-octanol (25 ml) was stirred under reflux (nitrogen atmosphere) for 18 hr. The hot reaction mixture was filtered, and the filtrate was cooled in ice and saturated with dry HCl gas. The resulting solid (**2d**·HCl) was filtered, washed with CH_2Cl_2, and dried. The pale yellow product (0.2 g, 17%) was dissolved in boiling water, the solution was decolorized with charcoal and basified with ammonia, and the precipitated free base **2d** (0.1 g, 10%) was filtered, washed with water, and dried: mp 257–259° dec. *Anal.* ($C_{12}H_9ClN_4$) C, H, Cl, N.

1,3-Diamino-8-*n*-heptylbenzo[*f*]quinazoline (2e). Reaction of **20**·HCl with sodium dicyanamide as described for the synthesis of **2a** afforded a 40% yield of **2e**: mp 188–190° (aqueous EtOH). *Anal.* ($C_{19}H_{24}N_4$) C, H, N.

1,3-Diamino-5,6-dihydro-6-phenylbenzo[*f*]quinazoline Hydrochloride (3·HCl). A mixture of 4-phenyl-2-tetralone (4.4 g, 0.022 mol)[26] and cyanoguanidine (1.9 g, 0.022 mol) was heated at 180° (internal temperature) for 1.5 hr in an open pear-shaped flask. The cooled melt was pulverized in a mortar and triturated thoroughly with acetone (75 ml). Addition of ether (200 ml) to the triturate, followed by addition of concentrated HCl (2 ml), caused precipitation of a solid which was filtered, washed with acetone–ether, and dried: yield 3.5 g (55%). The analytical sample was obtained by repeated crystallization from 95% EtOH: mp 300–302° dec (shrinkage at 297°). *Anal.* ($C_{18}H_{16}N_4 \cdot HCl$) C, H, N.

Acknowledgment. We are indebted to Dr. George E. Foley and Mr. Harold Riley, The Children's Cancer Research Foundation, for carrying out microbioassay studies and to Dr. Edgar A. Steck, Walter Reed Army Institute of Research, for providing us with antimalarial data. We are also indebted to Miss Janice Richman and Mrs. Rebecca G. Stephenson for assistance in some of the synthetic work and to Mr. Chester Rosansky for ir spectral determinations.

References

(1) A. Rosowsky, E. P. Burrows, P. C. Huang, and E. J. Modest, *J. Heterocycl. Chem.*, **9**, 1239 (1972) (paper XI).
(2) A. Rosowsky and E. J. Modest, *Ann. N. Y. Acad. Sci.*, **186**, 258 (1971).
(3) G. H. Hitchings and J. J. Burchall, *Advan. Enzymol. Relat. Subj. Biochem.*, **27**, 417 (1965).
(4) I. M. Rollo in "The Pharmacological Basis of Therapeutics," 4th ed, L. S. Goodman and A. Gilman, Ed., Macmillan, New York, N. Y., 1970, pp 1108–1112.
(5) J. A. Stock, *Exp. Chemother.*, **4**, 102 (1966).
(6) (a) G. F. Geils, C. W. Scott, Jr., C. M. Baugh, and C. E. Butterworth, *Blood*, **38**, 131 (1971); (b) D. R. Stickney, W. S. Simmons, R. L. DeAngelis, R. W. Rundles, and C. A. Nichol, *Proc. Amer. Ass. Cancer Res.*, **14**, 52 (1973); (c) B. T. Hill, J. H. Goldie, and L. A. Price, *Brit. J. Cancer*, **28**, 263 (1973).
(7) A. Rosowsky and E. J. Modest, Abstracts of Papers, Xth International Cancer Congress, Houston, Texas, May 28, 1970, pp 392–393.
(8) A. Rosowsky and E. J. Modest, *J. Org. Chem.*, **31**, 2607 (1966).
(9) A. Rosowsky and E. J. Modest, *J. Heterocycl. Chem.*, **3**, 387 (1966).
(10) A. Rosowsky, K. K. N. Chen, M. E. Nadel, N. Papathanasopoulos, and E. J. Modest, *J. Heterocycl. Chem.*, **9**, 275 (1972).
(11) A. Rosowsky, A. S. Dey, J. Battaglia, and E. J. Modest, *J. Heterocycl. Chem.*, **6**, 613 (1969).
(12) E. P. Burrows, A. Rosowsky, and E. J. Modest, *J. Org. Chem.*, **32**, 4090 (1967).
(13) A. Rosowsky, K. K. N. Chen, N. Papathanasopoulos, and E. J. Modest, *J. Heterocycl. Chem.*, **9**, 263 (1972).
(14) A. Rosowsky, P. C. Huang, and E. J. Modest, *J. Heterocycl. Chem.*, **7**, 197 (1970).
(15) A. Rosowsky, K. K. N. Chen, M. Lin, M. E. Nadel, R. St. Amand, and S. Yeager, *J. Heterocycl. Chem.*, **8**, 789 (1971).
(16) G. H. Hitchings, E. A. Falco, H. Vanderwerff, P. B. Russell, and G. E. Elion, *J. Biol. Chem.*, **199**, 43 (1952).
(17) E. J. Modest, G. E. Foley, W. D. Winter, Jr., and S. Farber, *Proc. Amer. Ass. Cancer Res.*, **2**, 35 (1955).
(18) S. V. Sunthankar and H. Gilman, *J. Org. Chem.*, **16**, 8 (1951).
(19) R. Huisgen and H. Rist, *Justus Liebigs Ann. Chem.*, **594**, 137 (1955).
(20) N. P. Buu-Hoi, *Recl. Trav. Chim. Pays-Bas*, **68**, 759 (1949).
(21) M. L. Khorana and S. Y. Pandit, *J. Indian Chem. Soc.*, **40**, 789 (1963); *Chem. Abstr.*, **60**, 469 (1964).
(22) H. Gilman, C. G. Brannen, and R. K. Ingham, *J. Org. Chem.*, **22**, 685 (1957).
(23) J. Sauer, R. Huisgen, and A. Hauser, *Chem. Ber.*, **91**, 1461 (1958).
(24) F. F. Blicke and J. E. Gearien, *J. Amer. Chem. Soc.*, **76**, 2429 (1954).
(25) H. H. Hodgson and H. S. Turner, *J. Chem. Soc.*, 748 (1942).
(26) D. P. Spalding, E. C. Chapin, and H. S. Mosher, *J. Org. Chem.*, **19**, 357 (1954).
(27) S. A. Fine and R. L. Stern, *J. Org. Chem.*, **32**, 4132 (1967).
(28) S. K. Sengupta, S. Chatterjee, H. K. Protopapa, and E. J. Modest, *J. Org. Chem.*, **37**, 1323 (1972).
(29) G. E. Foley, R. E. McCarthy, V. M. Binns, E. E. Snell, B. M. Guirard, G. W. Kidder, V. C. Dewey, and P. S. Thayer, *Ann. N. Y. Acad. Sci.*, **76**, 413 (1958).
(30) G. E. Foley and H. Eagle, *Cancer Res.*, **18**, 1012 (1958).
(31) H. Eagle and G. E. Foley, *Cancer Res.*, **18**, 1017 (1958).
(32) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).
(33) E. C. Wagner and J. F. Meyer, *Ind. Eng. Chem., Anal. Ed.*, **10**, 584 (1938).
(34) M. Look and H. L. Cheifetz, U. S. Patent 3,085,115 (April 9, 1963); *Chem. Abstr.*, **59**, 11380 (1963).
(35) E. R. Ward and T. M. Coulson, *J. Chem. Soc.*, 4545 (1954).