flukes. After the administration of therapeutic doses, IV could not be detected in the milk.[6]

### Experimental Section

**4,4',6,6'-Tetrabromo-2,2'-biphenyldiol Mono(dihydrogen phosphate) (IV).**—A mixture of 502 g (1 mole) of the biphenyldiol (I), 1.5 l. of PhMe, 2 ml of pyridine, and 110 ml (1.2 moles) of $POCl_3$ was refluxed for 6 hr. The solution was evaporated *in vacuo* to dryness to remove excess $POCl_3$, preferably repeating the distillation with an additional amount of PhMe to prevent formation in the next step of difficultly hydrolyzable pyrophosphates which would largely prevent the crystallization of the end product IV and diminish the yield. The very hard crystalline cyclic phosphorochloridate (II) was dissolved in 1.5 l. of warm PhMe and this solution was added cautiously with stirring to a solution of 232 g (5.8 moles) of NaOH in 860 ml of $H_2O$ and 300 ml of EtOH. The mixture was boiled for 2 hr and cooled. The aqueous layer was acidified with 0.5 l. of concentrated HCl and extracted (EtOAc). The extract was evaporated *in vacuo* at low temperature to a total weight of 680 g. The syrupy residue was dissolved as rapidly as possible by shaking with $C_6H_6$ (1.5 l.). Crystallization started in a few minutes. After keeping the mixture at room temperature for at least one night 436 g of crystalline phosphate (IV) was collected. The mother liquor was evaporated to dryness at low temperature, and the residue was dissolved in a small amount of EtOAc and extracted with a solution of 21 g of $NaHCO_3$. From this slightly alkaline solution an additional 64 g of IV could be obtained in an analogous way; yield 500 g (86%). Recrystallization of IV in the usual way is not possible as heating in a solvent is accompanied with gradual cyclization to the more difficultly soluble III.

Compound IV has no melting point; cyclization to III and gradual decomposition occurs on heating up to above 350°. Thorough drying is accompanied by partial dehydration. For analytical purposes the more stable cyclic phosphate (III) was prepared by refluxing for some hours a concentrated solution of IV in EtOAc and isolating the precipitated III.

*Anal.* Calcd for $C_{12}H_5Br_4O_4P$: C, 25.54; H, 0.89; Br, 56.72; P, 5.50. Found: C, 25.37; H, 0.91; Br, 56.90; P, 5.48.

By potentiometric titration one OH group could be detected in III, whereas IV revealed three OH. Additional support for the given structure of IV is obtained from its ready solubility both in EtOAc and in cold aqueous $NaHCO_3$; III is only very sparingly soluble in these media. The starting material I is readily soluble in EtOAc, not in aqueous $NaHCO_3$.

(6) H. B. de Boer and J. F. Kleinepier, *Neth. Milk Dairy J.*, in press

## Nitrofuryl Heterocycles. VIII.[1] 2-(5-Nitro-2-furyl)cinchoninic Acid Derivatives

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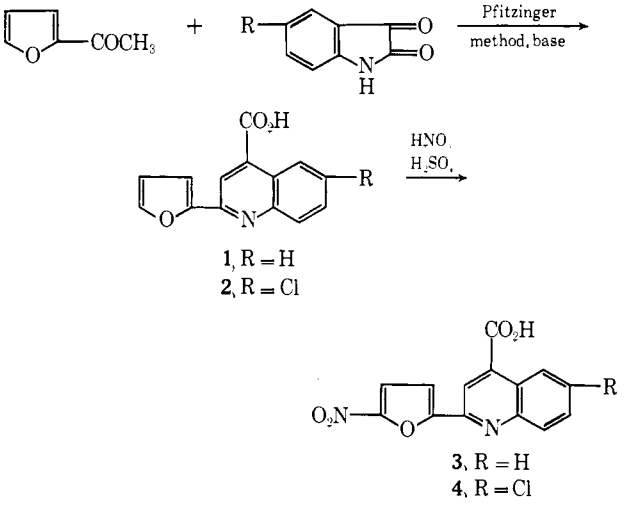
A continuing search for new nitrofuryl heterocycles possessing antimicrobial activity prompted an investigation of 2-(5-nitro-2-furyl)cinchoninic acid derivatives. 2-(2-Furyl)cinchoninic acid (**1**) reportedly has been prepared by the Doebner quinoline synthesis from furfural, pyruvic acid, and aniline.[2] Attempts to duplicate that procedure in this laboratory have failed. However, a 74% yield of **1** was obtained by the Pfitzinger quinoline synthesis from 2-acetylfuran and isatin. Mixed acid nitration of **1** and **2** gave the respective 5-nitro-2-furyl derivatives **3** and **4**. The position of nitration was confirmed by nmr analyses. Acid **3** was characterized further by the formation of its ethyl ester **5** and amide **6**.




The compounds in Table I were screened for antibacterial activity by methods reported previously.[3] Compounds **3**–**6** showed some activity *in vitro* against both gram-positive and gram-negative organisms. Amide **6** was inactive orally in mice against a *Staphylococcus aureus* infection but gave an $ED_{50}$ value of 5 mg/kg when administered intraperitoneally. Acid **4** effectively controlled a *Salmonella gallinarum* infection in chickens at a drug level of 0.011% by weight in feed.

### Experimental Section

All melting points were determined on a hot stage (Fisher-Johns) melting point apparatus and are uncorrected. The nmr spectra were determined on a Varian Model A-60 spectrometer in DMSO-$d_6$ using $Me_4Si$ as an internal standard. The ir spectra were determined as Nujol mulls on a Perkin-Elmer Model 137 spectrophotometer.

**2-(2-Furyl)cinchoninic Acid (1).**—A solution of 454 g (11.3 moles) of NaOH pellets and 355 g (2.42 moles) of isatin in 3 l. of $H_2O$ was heated for 0.5 hr at 80–90°. With vigorous stirring, 266 g (2.42 moles) of melted 2-acetylfuran was added cautiously in small portions during 0.5 hr. The reaction was very exothermic. Refluxing was continued for 2 hr following the addition after which the mixture was chilled to 0° and filtered through sintered glass. The residual Na salt was dissolved in 2.5 l. of $H_2O$ and the resulting solution was acidified with AcOH. The crude **1** separated as yellow needles decomposing at 228–230°, yield 450 g (77.6%). A decomposition point of 227° has been reported.[2]

Compound **2** was prepared similarly in 45% yield from 2-acetylfuran and 5-chloroisatin; mp 285–287° (AcOH). *Anal.* ($C_{14}H_8ClNO_3$) C, H, Cl.

**2-(5-Nitro-2-furyl)cinchoninic Acid (3).**—Powdered **1** (50.0 g, 0.21 mole) was added in small portions with stirring to 300 ml of concentrated $H_2SO_4$ at 0°. When solution was complete, a cold solution of 25 ml of concentrated $HNO_3$ in 25 ml of concentrated $H_2SO_4$ was added dropwise during 0.5 hr. Stirring was continued in the cold for 1 hr following the addition. The mixture was then poured cautiously with vigorous stirring into 4 l. of ice–$H_2O$. The crude **3** was filtered, washed ($H_2O$), and recrystallized (AcOH, charcoal). The product separated as yellow microneedles decomposing at 281.5–282.5°, yield 32.2 g (54%). *Anal.* ($C_{14}H_8N_2O_5$) C, H, N.

Compound **4** was prepared similarly from **2** in 62% yield; mp 293–295° dec (AcOH). *Anal.* ($C_{14}H_7ClN_2O_5$) C, H, N.

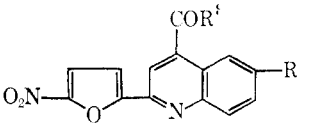
**Ethyl 2-(5-Nitro-2-furyl)cinchoninate (5).**—Anhydrous HCl was bubbled through a solution of 30 g (0.11 mole) of **3** in 1 l. of EtOH. When solution was complete, the HCl inlet tube was replaced by a stopper and the solution was refluxed for 4 hr.

(1) For the previous paper in this series see H. A. Burch, *J. Med. Chem.*, 11, 79 (1968).

(2) R. Civsa and F. Bellino, *Gazz. Chim. Ital.*, 66, 452 (1936).

(3) F. F. Ebetino, W. F. Carey, and B. F. Stevenson, *J. Med. Chem.*, 6, 633 (1963).

TABLE I



| | | | Minimum inhib. concn, μg/ml[a] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No. | R | R' | Es-2[b] | SaD-13 | Ps-10 | Pr-12 | Ae-6 | Er-4 | Mi-12 | StA-1 | StB-12 |
| 3 | H | OH | 25 | >50 | >50 | >50 | >50 | ≤0.75 | 25 | 1.5 | 6.25 |
| 4 | Cl | OH | 12.5 | >50 | >50 | >50 | >50 | 0.75 | 1.25 | 0.38 | 1.5 |
| 5 | H | $OC_2H_5$ | 0.75 | >50 | >50 | >50 | >50 | ≤0.19 | 0.38 | >50 | >50 |
| 6 | H | $CONH_2$ | ≤0.19 | 0.75 | >50 | >50 | >50 | 1.5 | 1.5 | 1.5 | 1.5 |
| Nitrofurazone | | | 3 | 3 | >100 | 100 | 100 | 12.5 | 12.5 | 6 | 12.5 |

[a] Minimum inhibitory concentration is the lowest concentration of compound that prevents visible growth of bacteria after 24 hr of incubation. Es-2 = *Escherichia coli*, SaD-13 = *Salmonella typhosa*, Ps-10 = *Pseudomonas aeruginosa*, Pr-12 = *Proteus vulgaris*, Ae-6 = *Aerobacter aerogenes*, Er-4 = *Erysipelothrix insidiosa*, Mi-12 = *Staphylococcus aureus*, StA-1 = *Streptococcus pyogenes*, and StB-12 = *Streptococcus agalactiae*. [b] The Norwich Pharmacal Co. strain number.

It was chilled, diluted with $Et_2O$, and filtered. Recrystallization of the product from aqueous DMF (charcoal) gave **5** as yellow needles, mp 174–175°, yield 8 g (23.5%). *Anal.* ($C_{16}H_{12}N_2O_5$) C, H, N. Ir showed a C=O stretching band at 1700 $cm^{-1}$ ($CO_2Et$).

**2-(5-Nitro-2-furyl)cinchoninamide (6).**—A solution of 59 g (0.21 mole) of **3** in 455 ml of $SOCl_2$ was refluxed for 5 hr. Excess $SOCl_2$ was removed under reduced pressure and the residue was poured cautiously into ice–$NH_4OH$. The resulting mixture was neutralized with HCl and filtered. Recrystallization of the residue from aqueous DMF (charcoal) gave **6** as yellow microneedles decomposing at 288–289°, yield 22 g (38%). *Anal.* ($C_{14}H_9N_3O_4$) C, H, N. Ir showed a C=O stretching band at 1670 $cm^{-1}$ ($CONH_2$).

**Acknowledgments.**—The author is grateful to Mr. Grant Gustin and Mr. Marvin Tefft for the elemental analyses, Mrs. Patricia Curtis for the nmr spectra, Mr. Warren Smith for assistance in the preparation of these compounds, and to members of the Medical and Veterinary Microbiology Sections for the testing data.

## Potential Antimalarials. Some Novel α-(Disubstituted Aminomethyl)-9-phenanthrenemethanols[1]

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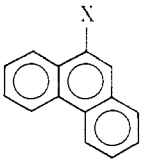
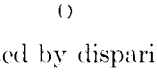
As part of the current Army Research Program on Malaria, we undertook the synthesis of some new 9-phenanthrenemethanols as potential curative agents against the drug-resistant strain of *Plasmodium falciparum*. The basis for this investigation is given by the fact that, during the search for effective antimalarials during World War II, a number of simple α-(dialkylaminomethyl)-9-phenanthrenemethanols showed significant therapeutic effect against blood-induced *Plasmodium gallinaceum* malaria;[2] particularly outstanding in this class is 6-bromo-α-(diheptylaminomethyl)-9-phenanthrenemethanol.[3] The work here described is concerned with the preparation of some simple (unsubstituted) 9-phenanthrenemethanols with novel side chains, most of which contain certain functional groups, as shown in Table II.

**Chemistry.**—The route[4] I → II → III was successfully applied for the preparation of the target compounds **7**, **8**, and **10**, in which the intermediate ketones (**2** and **4**) were isolable, in good yield, as stable, crystalline compounds (Table I). With other secondary amines, the route was unsatisfactory, resulting in failure to obtain the corresponding amino ketones[5] (II), either as the free bases, or as their HCl salts. The conversion of I into



I, X = $COCH_2Br$
II, X = $COCH_2NRR'$
III, X = $CHOHCH_2NRR'$
IV, X = $CHOHCH_2Br$
V, X = 

II was also complicated by disparities in the basicities of the various amines employed. Whereas, for example, diallylamine ($pK_a$ = 9.3) and N-(2-hydroxyethyl)-cyclohexylamine ($pK_a$ = 10.1) reacted rapidly with I, the reaction with N-(2-cyanoethyl)cyclohexylamine ($pK_a$ = 8.2) was sluggish and incomplete. As an alternative procedure,[6] the latter amine was treated with the bromohydrin IV to give the desired methanol; however, it was discovered that the epoxide[7] V, formed during the conversion, was the reacting species. When treated directly with the oxide V, the secondary amine reacted only when a proportion of its HBr salt was present. For preparative purposes, it was more convenient to prepare **12** from IV, in which the HBr salt was generated *in situ*. In contrast, N-(2-hydroxyethyl)cyclohexylamine reacted readily with V, *without*

(1) This work was supported by U. S. Army Medical Research and Development Command, Contract DADA17-67-C-7144. Contribution No. 515 to the Army Research Program on Malaria.

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(7) W. G. Duncan, W. T. Colwell, C. R. Scott, and D. W. Henry, *J. Med. Chem.*, 11, 122 (1968).