precipitation of the DBED salt was carried out as in the preparation of IIa. In this case, the product was eluted from the column with 5% acetic acid and amounted to 1.23 g after freeze drying. The yield of the DBED salt was 0.93 g. This material was dissolved in a mixture of 18 ml of DMF and 6 ml of the potassium 2-ethylhexanoate reagent. The addition of 75 ml of 2-propanol caused the precipitation of 0.595 g (7% over-all) of the potassium salt of the product. This material could be recrystallized by dissolving in 1:1 water–2-propanol and adding excess of 2-propanol. The air-equilibrated material had mp 176–177° dec; infrared assay, 99%; electrophoretic mobility, 0.27.

*Anal.* Calcd for $C_{17}H_{18}KN_3O_6S \cdot H_2O$: C, 45.63; H, 4.05; N, 9.39. Found: C, 45.79; H, 4.10; N, 9.58.

**(1-Methyl-3-pyridyl)methylpenicillin, Dipolar Ion.**—To a solution of 2.5 g (6.54 mmoles) of the potassium salt of Ib in 25 ml each of methanol and water was added 5 ml of methyl iodide. After 24 hr at room temperature, the mixture was extracted several times with 1:1 ether–ethyl acetate and then with a 5% solution of dioctyl sodium sulfosuccinate[30] in ethyl acetate. The aqueous phase was stirred with a solution of 4.0 g of the sulfosuccinate in 30 ml of ethyl acetate and brought to pH 2 with HCl. The organic phase was separated and brought to neutrality (test paper) by adding triethylamine, and the yellow oil which deposited was washed (decantation) first with ethyl acetate, then with ether, and dried *in vacuo*. Trituration with DMF gave 0.70 g (30%) of the crystalline product. The material was recrystallized by dissolving in a small volume of methanol and adding several volumes of DMF and a large quantity of acetone. Vacuum-dried material[31] had mp 196–198° dec; iodimetric assay,[32] 97%; electrophoretic mobility, −0.02.

*Anal.* Calcd for $C_{16}H_{19}N_3O_4S \cdot 0.5H_2O$: C, 53.62; H, 5.62; N, 11.72. Found: C, 53.40; H, 5.65; N, 11.94.

**Acknowledgments.**—The authors wish to thank Dr. H. Winicov for some valuable suggestions which contributed to the synthetic procedures reported herein. They are indebted to Mr. J. J. Taggart for the infrared assays, to Mr. J. W. Hamill for the iodimetric assays, to Miss M. A. Carroll and her staff for the microanalytical data, and to Dr. W. E. Thompson and his staff for the nmr spectra. In the microbiological work, they had the skilled assistance of Mr. D. Ziv, Miss M. Davis, and Mr. J. Freeman.

(30) Aerosol® OT. This material, which in solution constitutes a liquid cation exchanger, was used by D. A. Johnson, C. A. Panetta, and D. E. Cooper, *J. Org. Chem.*, **28**, 1927 (1963), for extraction of an amphoteric penicillin derivative.

(31) Apparently the compound scavenged sufficient water from the solvents to form a hemihydrate.

(32) The material was not sufficiently soluble in DMSO for the infrared assay. In mull it showed a strong β-lactam carbonyl stretching band at 5.69 μ.

# 5-Phenyl-2,4-pentadienamides as Potential Antimalarial Agents[1]

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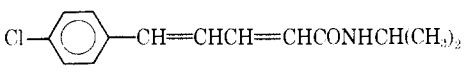
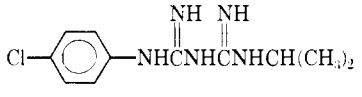
In view of the reported effectiveness of 5-(*p*-chlorophenyl)-N-isopropyl-2,4-pentadienamide against *Plasmodium gallinaceum* in the chick, various 5-phenyl-2,4-pentadienamides were prepared for evaluation against drug-resistant malarial parasites. Condensation of substituted benzaldehydes with triethyl 4-phosphonocrotonate afforded the 5-phenyl-2,4-pentadienoic acid ethyl esters. Hydrolysis with methanolic KOH gave the corresponding acids, which were converted to the acid chlorides with thionyl chloride or oxalyl chloride. Treatment of the acid chlorides with amines afforded the desired pentadienamides. None of the 5-aryl-2,4-pentadienamides was active against normal strains of *P. berghei* when administered to mice in a single subcutaneous dose of 640 mg/kg. Antimalarial studies against *P. gallinaceum* are in progress, and a satisfactory explanation is being sought for the apparent discrepancy between earlier reports and results of the current investigation.

5-(*p*-Chlorophenyl)-N-isopropyl-2,4-pentadienamide (I) is reported to be approximately four times as potent as quinine against *Plasmodium gallinaceum* in the chick and to have a therapeutic index of 12.5.[2] The structural relationships between I and chlorguanide (II) are noteworthy. The current need for an agent effective



I



II

against drug-resistant malarial parasites[3] prompted a reinvestigation of the synthesis and biological properties of I and allied substances.[1]

The preparation of I and simple homologs thereof is not described in the literature, although there are many references to the 5-aryl-2,4-pentadienoic acid and ester precursors. The most common route to such intermediates involves the condensation of a cinnamaldehyde with malonic acid followed by decarboxylation of the intermediate product.[4] However, this process requires the preparation of a variety of substituted cinnamaldehydes, which in itself was deemed unattractive, and the over-all yields are poor.

The Reformatsky reaction has also been applied to the preparation of vinylogs of haloacetic esters. Thus *p*-chlorobenzaldehyde and ethyl γ-iodocrotonate gave 5-(*p*-chlorophenyl)-2,4-pentadienoic acid *via* the ethyl ester[5] while 3,4,5-trimethoxybenzaldehyde and methyl γ-bromocrotonate afforded the corresponding methyl ester.[6] Once again, poor yields and the known possibility of abnormal reactions on the α-carbon atom in

(1) This investigation was supported by the U. S. Army Medical Research and Development Command under Contract DA-49-193-MD-2754.

(2) G. R. Coatney, W. C. Cooper, N. B. Eddy, and J. Greenberg, "Survey of Antimalarial Agents," Public Health Service Publication No. 193, Washington, D. C., 1953, pp 98, 139, 262, 276.

(3) For a recent review, see E. F. Elslager in "Annual Reports in Medicinal Chemistry, 1965," C. K. Cain, Ed., Academic Press Inc., New York, N. Y., 1966, p 136.

(4) (a) C. Liebermann, *Chem. Ber.*, **28**, 1441 (1895); (b) A. Riedel, *Ann.*, **361**, 96 (1908); (c) H. Stobbe, *Chem. Ber.*, **45**, 3396 (1912); (d) I. S. Dutt, *J. Indian Chem. Soc.*, **1**, 297 (1924–1925); (e) D. Vorlander and K. Gieseler *J. Prakt. Chem.*, [2] **121**, 247 (1929).

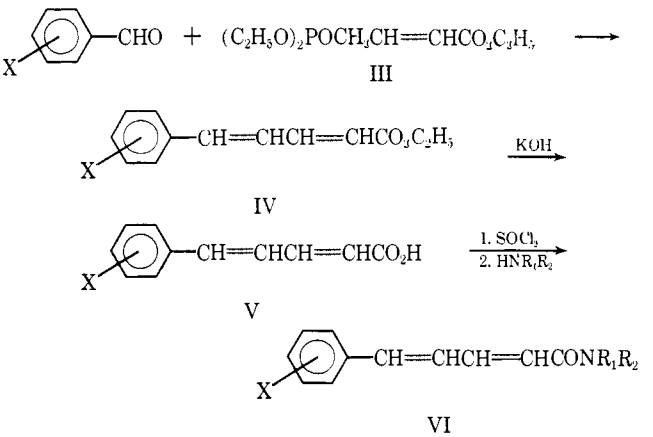
(5) R. C. Fuson, R. T. Arnold, and H. G. Cooke, Jr., *J. Am. Chem. Soc.*, **60**, 2272 (1938).

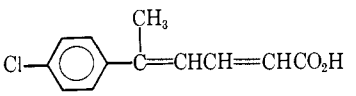
(6) A. S. Dreiding and R. J. Pratt, *ibid.*, **75**, 3717 (1953).

the Reformatsky reaction[7] discouraged further exploration of this method. Several other alternative routes were also considered but discarded, including the aluminum isopropoxide reduction of 1,1-dichloro-5-oxo-5-phenyl-1,3-pentadiene to the 5-hydroxy compound followed by acid hydrolysis to the 5-phenyl-2,4-pentadienoic acid,[8] and the condensation of a cinnamaldehyde with ethyl acetate in the presence of 2 equiv of lithium amide in liquid ammonia[9] or sodium ethoxide.[10]

Bohlmann,[7] in an extension of the reaction devised by Wittig and Haag,[11] successfully converted a series of aromatic aldehydes to the 5-phenyl-2,4-pentadienoic acid methyl esters by treatment with the triphenyl phosphonium salt of methyl $\gamma$-bromocrotonate and sodium methoxide. Modifications of this technique were quick to appear. Thus Horner, *et al.*,[12] showed that the condensation of benzaldehyde with diphenyl methyl phosphonocrotonate in toluene at 130° for 10 hr using potassium *t*-butoxide as the base afforded, after saponification, 52% of 5-phenyl-2,4-pentadienoic acid. Other workers demonstrated that either the triphenylphosphonium reagents[13,14] or the alkyl phosphonates[15,16] could be used to convert cinnamaldehydes to the 5-aryl-2,4-pentadienoic esters utilizing a variety of bases and solvent systems. This work was also extended[17] to the use of (trialkylamino)phosphonium reagents, but this approach seems to offer no particular advantage over the other available combinations.

Recently Wadsworth and Emmons[18] demonstrated that phosphonate anions possessed significant advantages over the triaryl phosphoranes or "Wittig" reagents in that they were less expensive, reacted with a wider variety of ketones and aldehydes, and worked under milder conditions. Therefore, the experimental conditions employed by these authors, *i.e.*, the reaction of triethyl phosphonoacetate in 1,2-dimethoxyethane using sodium hydride, were extended to the preparation of the desired 5-aryl-2,4-pentadienoic acids. The reaction of triethyl 4-phosphonocrotonate (III)[19] with a series of substituted benzaldehydes under these conditions led smoothly to the desired ethyl esters (IV) (Table I), generally in yields of 50–80%. The method failed with *p*-nitrobenzaldehyde, but in this case the desired product was obtained from triethyl phosphonoacetate and *p*-nitrocinnamaldehyde. The only attempt to apply the method to aromatic ketones was successful. Thus, *p*-chloroacetophenone was converted to 5-(*p*-chlorophenyl)sorbic acid (VII) *via* the ethyl ester.



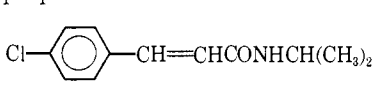




VII

The intermediate esters IV were readily hydrolyzed to the acids V (Table II) with methanolic potassium hydroxide. In those cases where the crude ester was obtained as an oil or a semisolid, it was converted directly to the acid without further purification.

The early literature[4b] indicated that 5-phenyl-2,4-pentadienoic acid could not be converted to its acid chloride by the usual procedures, although later authors[4e,20,21] reported the successful isolation of such materials. We have also found that, in general, the acids can be converted satisfactorily to the acid chlorides by heating in excess thionyl chloride for 2–5 hr. Since it was usually difficult to obtain the acid chlorides in a state of analytical purity, the isolation procedure generally involved removal of excess thionyl chloride *in vacuo* followed by a single recrystallization from heptane to separate the product from unchanged acid. If the acid chloride failed to crystallize, the heptane was removed and the crude product was used as is. 5-[*p*-(Dimethylamino)phenyl]-2,4-pentadienoic acid did not prove amenable to this technique but was successfully converted to its acid chloride with oxalyl chloride.

The acid chlorides were converted readily to the desired amides (Table III) by stirring with excess amine at room temperature using benzene or excess amine as solvent. *p*-Chloro-*N*-isopropylcinnamamide (VIII) was prepared in a similar manner. An attempt




VIII

to synthesize *N*-isopropyl-5-phenyl-2,4-pentadienamide (**29**) from 5-phenyl-2,4-pentadienoic acid and isopropylamine using *N*,*N*′-dicyclohexylcarbodiimide as the condensing agent gave only 1,3-dicyclohexyl-1-(5-phenyl-2,4-pentadienoyl)urea. Although several simple amides of 5-phenyl-2,4-pentadienoic acid have been prepared in low yield by heating the methyl ester and

(7) F. Boldmann, *Chem. Ber.*, **90**, 1519 (1957).

(8) L. I. Zakharkin and L. P. Sorokina, *Izv. Akad. Nauk SSSR, Otd. him. Nauk*, 936 (1959); *Chem. Abstr.*, **54**, 1402*f* (1960).

(9) W. R. Dunnavant and C. R. Hauser, *J. Org. Chem.*, **25**, 503 (1960).

(10) V. N. Belov and E. I. Shepelenkova, *Tr. Vses. Inst. Sintetich. i Natural Dushistykh Vishchestv.*, 24 (1955); *Chem. Abstr.*, **51**, 17818*c* (1957).

(11) G. Wittig and W. Haag, *Chem. Ber.*, **88**, 1654 (1955).

(12) L. Horner, H. Hoffmann, H. G. Wippel, and G. Klahre, *ibid.*, **92**, 2499 (1959).

(13) Badische Anilin u. Soda Fabrik Akt.-Ges., British Patent 813,539 (1959); *Chem. Abstr.*, **54**, 15320*c* (1960).

(14) V. F. Kucherov, B. G. Kovalev, I. I. Nazarova, and L. A. Yanovskaya, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk.*, 1512 (1960); *Chem. Abstr.*, **55**, 1420*b* (1960).

(15) W. Stilz and H. Pommer, German Patent 1,109,671 (1958); *Chem. Abstr.*, **56**, 8571*d* (1962).

(16) H. Takahashi, K. Fujiwara, and M. Ohta, *Bull. Chem. Soc. Japan*, **35**, 1498 (1962).

(17) (a) K. Eiter and H. Oediger, German Patent 1,170,933 (1964); *Chem. Abstr.*, **61**, 14580*h* (1964); (b) H. Oediger and K. Eiter, *Ann.*, **682**, 58 (1965).

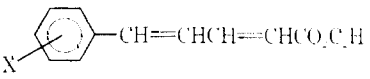
(18) W. S. Wadsworth, Jr., and W. D. Emmons, *J. Am. Chem. Soc.*, **83**, 1733 (1961).

(19) This intermediate, which was described recently by K. Sato, S. Mizuno, and M. Hirayama, *J. Org. Chem.*, **32**, 177 (1967), was prepared at our request and supplied by the Aldrich Chemical Co., Milwaukee, Wis.

(20) W. Dymek and K. Stoklosa, *Dissertationes Pharm.*, **13**, 327 (1961); *Chem. Abstr.*, **57**, 7226*c* (1962).

(21) I. Saikawa and Y. Suzuki, *J. Pharm. Soc. Japan*, **84**, 646 (1964).

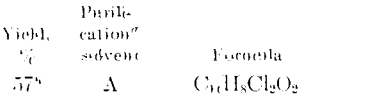
Table I
5-Phenyl-2,4-pentadienoic Acid Ethyl Esters



| No. | X | Mp, °C | Yield, % | Purification[a] solvent | Formula | Carbon, % Calcd | Carbon, % Found | Hydrogen, % Calcd | Hydrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 3,4-$Cl_2$ | 99–100 | 43–79 | A | $C_{13}H_{12}Cl_2O_2$ | 57.58 | 57.49 | 4.46 | 4.64 |
| 2 | 4-Br | 71–72 | 54 | B | $C_{13}H_{13}BrO_2$ | 55.53 | 55.40 | 4.66 | 4.86 |
| 3 | 4-$NO_2$ | 118–120 | 56 | C | $C_{13}H_{13}NO_4$[b] | 63.15 | 63.17 | 5.30 | 5.29 |
| 4 | 4-CN | 116–117 | 79 | C | $C_{14}H_{13}NO_2$[c] | 73.99 | 74.06 | 5.76 | 5.68 |
| 5 | 4-$CH_3$ | 54–55 | 72 | B | $C_{14}H_{16}O_2$ | 77.74 | 77.80 | 7.46 | 7.80 |
| 6 | 4-$OCH_3$ | 60–61 | 77 | C | $C_{14}H_{16}O_3$ | 72.39 | 72.58 | 6.94 | 7.11 |
| 7 | 4-$N(CH_3)_2$ | 123–124 | 70 | C | $C_{15}H_{19}NO_2$[d] | 73.44 | 72.98 | 7.81 | 7.64 |
| 8 | 4-$C_6H_5$ | 109–110 | 86 | D | $C_{19}H_{18}O_2$ | 81.98 | 81.97 | 6.52 | 6.45 |
| 9 | 4-$OCH_2C_6H_5$ | 104–105 | 98 | E | $C_{20}H_{20}O_3$ | 77.90 | 78.14 | 6.54 | 6.74 |

[a] A, methanol–water; B, ethanol; C, ethanol–water; D, benzene; E, dimethylformamide–water. [b] *Anal.* Calcd: N, 5.07. Found: N, 5.61. [c] *Anal.* Calcd: N, 6.16. Found: N, 6.09. [d] *Anal.* Calcd: N, 5.71. Found: N, 5.82.

Table II
5-Phenyl-2,4-pentadienoic Acids



| No. | X | Mp, °C | Yield, % | Purification[a] solvent | Formula | Carbon, % Calcd | Carbon, % Found | Hydrogen, % Calcd | Hydrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|
| 10 | 2,6-$Cl_2$ | 208–210 | 57[b] | A | $C_{11}H_8Cl_2O_2$ | 54.35 | 54.26 | 3.32 | 3.54 |
| 11 | 3,4-$Cl_2$ | 220–221 | 84 | B | $C_{11}H_8Cl_2O_2$ | 54.35 | 54.61 | 3.32 | 3.50 |
| 12 | 2-Cl | 200–202 | 39[b] | A | $C_{11}H_9ClO_2$ | 63.32 | 63.29 | 4.35 | 4.57 |
| 13 | 3-Cl | 173–174 | 91 | A | $C_{11}H_9ClO_2$ | 63.32 | 63.19 | 4.35 | 4.46 |
| 14 | 4-Cl | 250–252 | 53 | C | $C_{11}H_9ClO_2$ | 63.32 | 63.16 | 4.35 | 4.48 |
| 15 | 4-Br | 257–258 | 72 | C | $C_{11}H_9BrO_2$ | 52.20 | 52.14 | 3.59 | 3.68 |
| 16 | 4-$CH_3$ | 228–229 | 64 | C | $C_{12}H_{12}O_2$ | 76.57 | 76.60 | 6.42 | 6.65 |
| 17 | 4-$OCH_3$ | 180–182 | 80 | C | $C_{12}H_{12}O_3$ | 70.57 | 70.50 | 5.93 | 5.86 |
| 18 | 4-$N(CH_3)_2$ | 244–245 | 54–94 | D | $C_{13}H_{15}NO_2$[c] | 71.85 | 72.11 | 6.96 | 6.97 |
| 19 | 4-$C_6H_5$ | 218–220 | 84 | A | $C_{17}H_{14}O_2$ | 81.61 | 81.92 | 5.62 | 5.81 |
| 20 | 4-$OCH_2C_6H_5$ | 190–201 | 73 | C | $C_{18}H_{16}O_3$ | 77.13 | 77.21 | 5.75 | 5.85 |

[a] A, ethanol–water; B, benzene; C, ethanol; D, purified by base–acid reprecipitation. [b] Ester not purified; theoretical yield calculated on the basis of the aldehyde. [c] *Anal.* Calcd: N, 6.45. Found: N, 6.41.

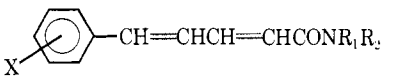
an amine in a bomb at 150°.[4b] attempts to prepare I from the ethyl ester and isopropylamine led only to the recovery of unchanged starting materials. Further, it was confirmed that heating the free acid with amines leads only to salt formation.[4b]

The stereochemistry of the pentadienamides is presumed to be the normal stable *trans,trans* form. The malonic acid–cinnamaldehyde synthesis of 5-phenyl-2,4-pentadienoic acid generally gives this stereoisomer, although the *allo* ($\gamma,\Delta$-*trans*, $\alpha,\beta$-*cis*) isomer is occasionally isolated.[4a,c,e,22,23] The *cis,trans* isomer has been prepared by another route[22] while the *cis,cis* form has apparently not been isolated. The Wittig reaction between ketones and triethyl phosphonoacetate has been shown to give a mixture of unsaturated esters.[24] One might expect therefore under the conditions we used to obtain a mixture of the *trans,trans* and *cis,trans* isomers. Gas chromatographic analysis of purified samples of the low-melting ethyl esters of 5-(*p*-methoxyphenyl)-2,4-pentadienoic acid and 5-(*p*-bromophenyl)-2,4-pentadienoic acid did in fact indicate small amounts (4–8%) of a second component. The ease with which *allo*-5-phenyl-2,4-pentadienoic acid rearranges to the stable *trans,trans* form[25,26] would suggest that the vigorous basic hydrolysis used to prepare the acids would afford only the *trans,trans* isomer which would then be carried through to the amides unchanged. A sample of 5-(*p*-chlorophenyl)-2,4-pentadienoic acid prepared from *p*-chlorocinnamaldehyde and malonic acid was shown to be identical with the material prepared from *p*-chlorobenzaldehyde and triethyl 4-phosphonocrotonate.

Soon after the introduction of chlorguanide (II) evidence was presented indicating that the drug was essentially inactive against malaria parasites *in vitro*, suggesting that a metabolite or metabolites are responsible for the antimalarial activity. A search for metabolites culminated in a report by Carrington, *et al.*,[27] that the active metabolite was 4,6-diamino-1-(*p*-chlorophenyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine (IX). In an attempt to prepare cyclic analogs (X) of the 5-phenyl-2,4-pentadienamides, we reinvestigated the work of Shamma and Rosenstock[28] who reported that the condensation of 5-phenyl-2,4-pentadienoic acid with 40% aqueous methylamine at 180° gave 1-methyl-6-phenyl-5,6-dihydro-2-pyridone (X, X = H:

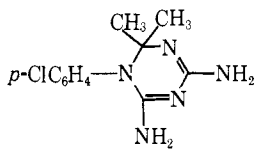
(22) H. Lebahn, *Ann.*, **513**, 219 (1934).
(23) K. Alder and M. Schumacher, *ibid.*, **571**, 108 (1951).
(24) H. Takimoto, S. Umemoto, T. Shōnizu, and A. Kagemoto, *Yakugaku Zasshi*, **85**, 975 (1965).
(25) J. C. Ghosh and S. Gupta, *Quart. J. Indian Chem. Soc.*, **2**, 241 (1925).
(26) J. C. Ghosh and M. N. Mitra, *ibid.*, **3**, 273 (1926).
(27) H. C. Carrington, A. F. Crowther, D. G. Davey, A. A. Levi, and F. L. Rose, *Nature*, **168**, 1080 (1951).
(28) M. Shamma and P. D. Rosenstock, *J. Org. Chem.*, **26**, 718 (1961).

Table III
5-Phenyl-2,4-pentadienamides

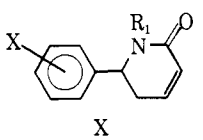


| No. | X | $NR_1R_2$ | Mp, °C | Over-all yield,[a] % | Purification[b] solvent | Formula | Carbon, % Calcd | Carbon, % Found | Hydrogen, % Calcd | Hydrogen, % Found | Nitrogen, % Calcd | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 21 | 3,4-$Cl_2$ | $NHCH_3$ | 179–181 | 14 | B | $C_{12}H_{11}Cl_2NO$ | 56.27 | 56.13 | 4.33 | 4.43 | 5.47 | 5.21 |
| 22 | 3,4-$Cl_2$ | $NHCH(CH_3)_2$ | 164–165 | 15 | A | $C_{14}H_{15}Cl_2NO$ | 59.16 | 59.00 | 5.32 | 5.38 | 4.93 | 4.83 |
| 23 | 2,6-$Cl_2$ | $NHCH(CH_3)_2$ | 172–173 | 40 | A | $C_{14}H_{15}Cl_2NO$ | 59.16 | 59.02 | 5.32 | 5.34 | 4.93 | 4.64 |
| 24 | 2-Cl | $NHCH(CH_3)_2$ | 135–137 | 26 | A | $C_{14}H_{16}ClNO$ | 67.33 | 67.17 | 6.46 | 6.50 | 5.61 | 5.77 |
| 25 | 3-Cl | $NHCH(CH_3)_2$ | 128–129 | 41 | A | $C_{14}H_{16}ClNO$ | 67.33 | 67.43 | 6.46 | 6.43 | 5.61 | 5.85 |
| 26 | 4-Cl | $NHCH(CH_3)_2$ | 202.5–204 | 54 | A | $C_{14}H_{16}ClNO$ | 67.33 | 67.45 | 6.46 | 6.41 | 5.61 | 5.32 |
| 27 | 4-Br | $NHCH(CH_3)_2$ | 196–197 | 43 | A | $C_{14}H_{16}BrNO$ | 57.15 | 57.03 | 5.49 | 5.62 | 4.76 | 4.66 |
| 28 | 4-$NO_2$ | $NHCH(CH_3)_2$ | 213–214 dec | 52 | B | $C_{14}H_{16}N_2O_3$ | 64.57 | 64.23 | 6.19 | 6.15 | 10.79 | 10.65 |
| 29 | H | $NHCH(CH_3)_2$ | 174–176 | 70 | A | $C_{14}H_{17}NO$ | 78.10 | 78.27 | 7.96 | 8.10 | 6.51 | 6.36 |
| 30 | 4-CN | $NHCH(CH_3)_2$ | 184–185 | 8 | B | $C_{15}H_{16}N_2O$ | 74.97 | 74.68 | 6.71 | 6.67 | 11.66 | 11.97 |
| 31 | 3,4-$Cl_2$ | $N(CH_3)CH(CH_3)_2$ | 90–91 | 21[c] | D | $C_{15}H_{17}Cl_2NO$ | 60.41 | 60.48 | 5.74 | 5.46 | 4.70 | 4.69 |
| 32 | 4-$CH_3$ | $NHCH(CH_3)_2$ | 195–196 | 51 | A | $C_{15}H_{17}NO$ | 78.56 | 78.46 | 8.35 | 8.37 | 6.11 | 5.96 |
| 33 | 4-$OCH_3$ | $NHCH(CH_3)_2$ | 193–195 | 41[c] | B | $C_{15}H_{17}NO_2$ | 73.43 | 73.49 | 7.81 | 7.91 | 5.71 | 5.42 |
| 34 | 3,4-$Cl_2$ | $N[(CH_2)_2]_2NCH_3$ | 129–130 | 8 | D | $C_{16}H_{18}Cl_2N_2O$ | 59.08 | 58.86 | 5.58 | 5.55 | 8.61 | 8.43 |
| 35 | 4-$N(CH_3)_2$ | $NHCH(CH_3)_2$ | 185–186 | 13[c] | B | $C_{16}H_{20}N_2O$ | 74.39 | 74.24 | 8.58 | 8.39 | 10.84 | 10.64 |
| 36 | 3,4-$Cl_2$ | $NHC_6H_4$-*p*-Cl | 230–231 | 7 | E | $C_{17}H_{12}Cl_3NO$ | 57.90 | 57.68 | 3.43 | 3.40 | 3.97 | 3.84 |
| 37 | 3,4-$Cl_2$ | $NH(CH_2)_3N(CH_2)_5$ | 115–117 | 8 | F | $C_{19}H_{23}Cl_2N_2O$ | 62.12 | 61.98 | 6.59 | 6.55 | 7.62 | 7.62 |
| 38 | 4-$C_6H_5$ | $NHCH(CH_3)_2$ | 229–230 | 34 | B | $C_{20}H_{21}NO$ | 82.43 | 82.18 | 7.26 | 7.45 | 4.81 | 4.75 |
| 39 | 4-$OCH_2C_6H_5$ | $NHCH(CH_3)_2$ | 197–198 | 10 | C | $C_{21}H_{23}NO_2$ | 78.47 | 78.32 | 7.21 | 6.97 | 4.36 | 4.31 |

[a] Over-all yield from the pentadienoic acid. [b] A, product was purified by rapidly pouring an ethanol solution of the crude material into a large amount of water to precipitate the amide; B, ethanol–water; C, ethyl acetate; D, isooctane; E, dimethyl sulfoxide–water; F, crude product was dissolved in water and treated with dilute sodium hydroxide to precipitate the free base of the amide; this was further purified by recrystallization from ethanol–water. [c] Method II.



IX



X

$R_1$ = $CH_3$) in 52% yield. We obtained a viscous oil which on the basis of vapor phase chromatography and tlc appeared to be a 60:40 mixture which was not amenable to separation by distillation. An attempt to prepare 1-isopropyl-6-phenyl-5,6-dihydro-2-pyridone [X, X = H; $R_1$ = $CH(CH_3)_2$] under similar conditions gave a solid product which contained at least three components. Efforts to separate the mixture using a variety of chromatography and differential solubility techniques led only to the isolation of the unchanged pentadienoic acid and a material which, on the basis of infrared analysis, appeared to be the isopropylamine salt of 5-phenyl-2,4-pentadienoic acid.

The 5-aryl-2,4-pentadienoic acid derivatives were screened against *Plasmodium berghei* in mice by Dr. Leo Rane at the University of Miami.[29] In the primary test, mice are infected with a lethal dose of *P. berghei* 3 days prior to drug administration. Routinely, the drugs are administered subcutaneously in oil at each of three dose levels, namely at 40, 160, and 640 mg/kg. The mean survival time of infected control mice is 7.0 ± 0.5 days. Extension in survival time of treated mice is interpreted as evidence of antimalarial activity. Compounds are arbitrarily considered to be "active" when the mean survival time of the treated group is more than twice the mean survival time of the control group. None of the compounds tested was "active" when judged by this criterion. The pentadienoic acid derivatives are currently undergoing evaluation against *P. gallinaceum* in chicks and a satisfactory explanation is being sought for the apparent discrepancy between earlier reports[2] and results of the current investigation.

Representative compounds described in the present communication were also tested against certain bacteria *in vitro* including *Staphylococcus aureus* (UC-76), *Pseudomonas aeruginosa* (28), *Mycobacterium tuberculosis* ($H_{37}Rv$), and *Escherichia coli* (Vogel). However, none was active at a concentration of 20 μg/ml. 5-(4-Biphenylyl)-2,4-pentadienoic acid (**19**) exhibited anti-inflammatory activity in the ultraviolet erythema test in guinea pigs[30] at a dose of 50 mg/kg.

## Experimental Section[31]

**5-Phenyl-2,4-pentadienoic Acid Ethyl Esters (Table I).**—To a mixture of 9.6 g (0.2 mole of a 50% dispersion in mineral oil) of NaH in 350 ml of 1,2-dimethoxyethane cooled to 10–20° was added dropwise 50.0 g (0.2 mole) of triethyl 4-phosphonocrotonate[19] and the mixture was stirred 1 hr at room temperature. To this was added a solution of 0.2 mole of the substituted benzaldehyde in 150 ml of 1,2-dimethoxyethane while the temperature was maintained below 25°. The mixture was then stirred 1 hr at room temperature, heated under reflux for 1 hr, allowed to stand overnight at room temperature, and poured into 3 l. of water. If a solid formed it was collected and dried; if an oil formed it was extracted with $CHCl_3$, dried, and concentrated *in vacuo*. In those cases where the requisite esters are omitted from the tables the crude ester was converted to the acid without purification.

**5-Phenyl-2,4-pentadienoic Acids (Table II).**—The crude ester was dissolved or suspended in methanol and to the mixture was added a warm solution of 4 equiv of KOH in methanol. The

(29) Antimalarial test results were supplied through the courtesy of Dr. David P. Jacobus of the Walter Reed Army Institute of Research.

(30) C. V. Winder, J. Wax, V. Burr, M. Been, and C. E. Rosiere, *Arch. Intern. Pharmacodyn. Therap.*, **116**, 261 (1958).

(31) Melting points (corrected) were taken in open capillary tubes in a Thomas-Hoover capillary melting point apparatus.

mixture was heated under reflux for 6 hr and allowed to stand overnight at room temperature. If a solid formed it was collected, dried, and dissolved or suspended in water. If no solid formed, the mixture was evaporated *in vacuo* and the residue was dissolved or suspended in water. The mixture was acidified with concentrated HCl and the solid formed was filtered and dried *in vacuo* to give the crude acid.

**5-Phenyl-2,4-pentadienoic Acid Chlorides. Method I. 5-*p*-Tolyl-2,4-pentadienoic Acid Chloride.**—A mixture of 9.2 g (0.049 mole) of 5-*p*-tolyl-2,4-pentadienoic acid (**16**) and $SOCl_2$ (15 ml) was heated under reflux for 5 hr. The dark mixture was cooled and excess $SOCl_2$ was removed *in vacuo*. The residue was recrystallized from hexane[32] to give 6.6 g of the chloride, mp 60–63° (66%).

**Method II. 5-[*p*-(Dimethylamino)phenyl]-2,4-pentadienoic Acid Chloride.**—To 5.0 g (0.023 mole) of 5-[*p*-(dimethylamino)-phenyl]-2,4-pentadienoic acid (**18**) in a glass dish was added dropwise with intermittent grinding 10 ml of oxalyl chloride. The reaction was exothermic and a large volume of gas was evolved. The mixture was thoroughly ground and allowed to air dry briefly. The crude acid chloride was not purified further.

**5-Phenyl-2,4-pentadienamides (Table III). Method I. N-Isopropyl-5-*p*-tolyl-2,4-pentadienamide (32).**—To a solution of 6.6 g (0.032 mole) of 5-*p*-tolyl-2,4-pentadienoic acid chloride in 150 ml of benzene was added dropwise a solution of 3.8 g (0.064 mole) of isopropylamine in 30 ml of benzene. The mixture was stirred at room temperature for several hours, and the solid which formed was filtered and dried to give 9.4 g of crude product. Purification and conversion to small particle size material was effected by dissolving the product in ethanol, and pouring it rapidly into a large volume of water. This gave 5.7 g of **32**, mp 195–196° (78%).

**Method II. N-Isopropyl-5-(*p*-methoxyphenyl)-2,4-pentadienamide (33).**—To the residue left after removal of excess $SOCl_2$ from a 0.073-mole run of 5-(*p*-methoxyphenyl)-2,4-pentadienoic acid chloride was added 100 ml of isopropylamine. The mixture was stirred until the mixture had changed from dark red to pale yellow in color. The solid formed was collected and recrystallized from ethanol–water to give **33** as a yellow solid, 7.3 g, mp 193–195° (41%).

**5-(*p*-Chlorophenyl)-2,4-pentadienoic Acid (14) *via* *p*-Chlorocinnamaldehyde.**—To a mixture of 6.6 g (0.04 mole) of *p*-chlorocinnamaldehyde[33] and 6.2 g (0.06 mole) of malonic acid was added slowly 25 drops of concentrated $H_2SO_4$. The mixture was heated 20 min in an oil bath at 80°. It was then cooled, triturated with water, filtered, and recrystallized from ethanol to give 1.3 g (16%) of **14**, mp 250–252°, identical (mixture melting point, infrared) with the material prepared from *p*-chlorobenzaldehyde and triethyl 4-phosphonocrotonate.

*Anal.* Calcd for $C_{11}H_9ClO_2$: C, 63.32; H, 4.35. Found: C, 63.64; H, 4.48.

**5-(*p*-Nitrophenyl)-2,4-pentadienoic Acid Ethyl Ester (3).**—To a mixture of 4.8 g (0.1 mole of a 50% dispersion in mineral oil) of sodium hydride in 180 ml of 1,2-dimethoxyethane was added dropwise 22.4 g (0.1 mole) of triethyl phosphonoacetate, and the mixture was stirred 1 hr at room temperature. To it was then added dropwise a solution of 17.7 g (0.1 mole) of *p*-nitrocinnamaldehyde[33] in 1,2-dimethoxyethane. The mixture was stirred 1 hr at room temperature, heated under reflux 1 hr, and allowed to stand overnight at room temperature. It was poured into 3 l. of water and the solid which formed was filtered and recrystallized from ethanol–water to give 12.8 g (52%) of **3** as a bright yellow solid, mp 118–120°.

**5-(*p*-Chlorophenyl)sorbic Acid (VII).**—To a suspension of 4.8 g of NaH (0.1 mole of 50% dispersion in oil) in 200 ml of 1,2-dimethoxyethane was added dropwise at 20°, 25.0 g (0.1 mole) of triethyl 4-phosphonocrotonate. The solution was stirred for 1 hr and to it was added dropwise a solution of 15.5 g (0.1 mole) of *p*-chloroacetophenone in 20 ml of 1,2-dimethoxyethane at 25–30°. The mixture was stirred at room temperature for 1 hr, heated under reflux for 2 hr, and poured into 2.5 l. of iced water. The oil which resulted was extracted with ether, the extracts were combined and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The residue was dissolved in methanol, 15.0 g of KOH was added, and the mixture was heated under reflux for 6 hr. The cooled mixture was filtered to give 4.2 g of solid. The filtrate was evaporated to dryness and the residue was triturated with water and acidified with concentrated HCl. The original solid was treated similarly. The combined solids which resulted were recrystallized twice from ethanol to give 2.4 g (11%) of the product, mp 213–216°.

*Anal.* Calcd for $C_{12}H_{11}ClO_2$: C, 64.72; H, 4.98. Found: C, 64.71; H, 5.23.

***p*-Chloro-*N*-isopropylcinnamamide (VIII).**—A mixture of 9.1 g (0.05 mole) of *p*-chlorocinnamic acid in 15 ml of $SOCl_2$ was heated under reflux for 5 hr. The solvent was removed *in vacuo*, and the residual foamy semisolid was recrystallized from 100 ml of heptane to give 7.0 g (63.5%) of the acid chloride as an off-white solid, mp 74–78°.

To the above acid chloride in benzene was added with intermittent cooling 4.1 g (2 equiv) of isopropylamine. A solid formed rapidly. The mixture was stirred for several hours at room temperature, poured into water, and stirred vigorously for 1 hr. The resultant mixture was filtered to give 6.7 g of a white solid. Recrystallization from ethanol–water gave 5.2 g of the desired product, mp 181–184.° This material was dissolved in warm ethanol and reprecipitated by addition from a dropping funnel below the surface of a large volume of water. The solid was filtered and dried *in vacuo* to give 4.4 g (56%) of VIII, mp 179–185.5° (sinters first and then shrinks and gradually melts) as needles.

*Anal.* Calcd for $C_{12}H_{14}ClNO$: C, 64.43; H, 6.31; N, 6.26. Found: C, 64.46; H, 6.30; N, 6.08.

The infrared spectrum (*trans* C=C, 968 $cm^{-1}$) and the nmr spectrum ($CDCl_3$, two paired doublets centered at $\delta$ 6.45 and 7.6 ($J$ = 16 cps), indicate *trans* isomer.

**1,3-Dicyclohexyl-1-(5-phenyl-2,4-pentadienoyl)urea.**—A mixture of 10.3 g (0.05 mole) of *N*,*N*′-dicyclohexylcarbodiimide and 8.7 g (0.05 mole) of 5-phenyl-2,4-pentadienoic acid in THF was stirred 30 min and a white solid formed. To this mixture was added a solution of 3.0 g of isopropylamine in THF, and the mixture was stirred 1 hr and allowed to stand overnight. The solid was collected and washed with acetonitrile. The material insoluble in acetonitrile was recrystallized twice from hot DMF, then washed with water to give 6.5 g (34.3%) of 1,3-dicyclohexyl-1-(5-phenyl-2,4-pentadienoyl)urea, mp 203–205°.

*Anal.* Calcd for $C_{24}H_{32}N_2O_2$: C, 75.75; H, 8.48; N, 7.36. Found: C, 75.87; H, 8.53; N, 7.21.

**Acknowledgments.**—The authors are indebted to Dr. Leo Rane of the University of Miami for the antimalarial studies and to Dr. M. W. Fisher and Dr. C. V. Winder of Parke, Davis and Company for the antibacterial and antiinflammatory testing. We also wish to thank Mr. C. E. Childs and associates for the microanalyses and Dr. J. M. Vandenbelt and co-workers for determination of the infrared, ultraviolet, and nmr spectra.

(32) Excepting this case, heptane was used as the solvent. Where recrystallization was unsatisfactory, the heptane extract was evaporated and the crude acid chloride used as is.

(33) G. Cignarella, E. Occelli, and E. Testa, *J. Med. Chem.*, **8**, 326 (1965).