241 nm (ε 14800); ν (KBr) 2240, 1680, and 1585 cm^{-1}; NMR (D_2O) 5.93 (C-4), 3.28 (C-7), 1.23 (C-19), 0.90 ppm (C-18). Anal. ($C_{23}H_{30}NO_4K$) K.

7α-Isocyanato-17-hydroxy-3-oxo-17α-pregn-4-ene-21-carboxylic Acid γ-Lactone (1g). To a stirred, cold (0°) solution of anhydride **1e** (5.30 g, 10.9 mmol) in anhydrous acetone (100 ml) was added a solution of NaN_3 (2.3 g, 35.4 mmol) in H_2O (15 ml). A white precipitate formed rapidly and the mixture was stirred at 0° for 30 min. The reaction was concentrated in vacuo and filtered to give 2.7 g of a white solid whose infrared spectrum showed it to consist of a mixture of the acid azide and the corresponding isocyanate. This solid was dissolved in benzene (150 ml) and the solution refluxed with stirring under nitrogen for 1 h. Concentration of the reaction solution in vacuo gave a crystalline solid which was recrystallized twice from ethyl ether to give 1.2 g (29%) of **1g**, mp 158–160°. An analytical sample was obtained by one further recrystallization from ethyl ether: mp 161–162°; ν 2280, 1779, 1680, and 1628 cm^{-1}; $[\alpha]_D$ +38° (*c* 1.000); $[\alpha]_{365}$ −115° (*c* 1.000); NMR 5.95 (C-4), 3.81–4.03 (C-7), 1.22 (C-19), 1.00 ppm (C-18). Anal. ($C_{23}H_{29}NO_4$) C, H, N.

7α-Cyano-17-hydroxy-3-oxo-17α-pregna-1,4-diene-21-carboxylic Acid γ-Lactone (4). A solution of **1b** (3.68 g, 10 mmol) and dichlorodicyanobenzoquinone (2.72 g, 12 mmol) in benzene (130 ml) was refluxed with stirring for 26 h. Solvent was removed in vacuo and the red residue was dissolved in CH_2Cl_2 (400 ml). The organic layer was extracted six times with 2% aqueous Na_2SO_3 solution and twice with saturated NaCl solution and dried (Na_2SO_4, $MgSO_4$). The solvent was removed in vacuo to give 2.3 g of a light yellow foam which was recrystallized from MeOH to give 1.37 g (37%) of analytically pure **4**: mp 258–263°; λ_{max} 241 nm (ε 17700); $[\alpha]_D$ +45° (1.000); $[\alpha]_{365}$ +129° (1.000); ν 1779, 1678, 1636, and 2245 cm^{-1}; NMR 7.09 (d, *J* = 11 Hz, C-1), 6.29 (d, *J* = 11 Hz, C-2), 6.20 (broad singlet, C-4), 3.14 (broad, C-7), 1.29 (C-19), 1.03 ppm (C-18). Anal. ($C_{23}H_{27}NO_3$) C, H, N.

17-Hydroxy-7α-(methoxycarbonyl)amino-3-oxo-17α-pregn-4-ene-21-carboxylic Acid γ-Lactone (1h). Crude azide **1f** (1.86 g, 4.52 mmol), prepared according to the procedure described above from anhydride **1e** (4.0 g, 8.2 mmol) and NaN_3 (1.17 g, 18 mmol), was dissolved in benzene (150 ml) and the solution refluxed for 3 h. The solvent was removed in vacuo and the residue dissolved in MeOH and let stand at room temperature for 3 days. The solution was concentrated in vacuo and the residue treated with ethyl ether to give a white crystalline solid. This material was recrystallized from ethyl acetate–Skellysolve B and dried at 110° (0.2 mmHg) to give 1.67 g (88.9%) of analytically pure **1h**: mp 229–231°; $[\alpha]_D$ +1.0° (*c* 0.995); ν 1772, 1730, 1675, 1622, and 3440 cm^{-1}; λ_{max} 241 nm (ε 14000); NMR 5.79 (C-4), 4.89 (C-7), 3.69 (–OCH_3), 1.25 (C-19), and 1.00 ppm (C-18). Anal. ($C_{24}H_{33}NO_5$) C, H, N.

7α-(Ethoxycarbonyl)amino-17-hydroxy-3-oxo-17α-pregn-4-ene-21-carboxylic Acid γ-Lactone (1i). Crude azide (0.51 g, 1.24 mmol), prepared in the usual manner, was dissolved in benzene (50 ml) and the solution refluxed with stirring under nitrogen for 3.5 h. The solvent was removed in vacuo, the residue dissolved in absolute EtOH, and this solution refluxed for 8 h. After standing overnight at room temperature, the solvent was removed in vacuo and the resulting white foam recrystallized from ethyl ether to give 272 mg (51.1%) of analytically pure **1i**: mp 122–125°; $[\alpha]_D$ +0.9° (*c* 1.128); λ_{max} 241 nm (ε 13300); ν 1775, 1728, 1680, and 1625 cm^{-1}. Anal. ($C_{25}H_{35}NO_5$) C, H, N.

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References and Notes

(1) R. M. Weier and L. M. Hofmann, *J. Med. Chem.*, 18, 817 (1975).
(2) J. A. Cella and R. C. Tweit, *J. Org. Chem.*, 24, 1109 (1959).
(3) R. G. Christiansen and W. S. Johnson, *Steroids*, 1, 620 (1963).
(4) H. O. House, "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 625.
(5) (a) H. H. Jaffé, *Chem. Rev.*, 53, 191 (1953); (b) H. van Bekkum, P. E. Verkade, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, 78, 821 (1959).
(6) (a) R. C. Tweit, F. B. Colton, N. L. McNevin, and W. Klyne, *J. Org. Chem.*, 27, 3325 (1962); (b) R. M. Lemieux, R. K. Kullney, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, 79, 1005 (1957).
(7) This argument is described in some detail in ref 1.
(8) (a) C. M. Kagawa, D. J. Bouska, M. L. Anderson, and W. F. Krol, *Arch. Int. Pharmacodyn. Ther.*, 149, 8 (1964); (b) L. M. Hofmann, H. A. Wagner, and R. S. Jacobs, *ibid.*, 165, 476 (1967).
(9) R. C. Tweit and C. M. Kagawa, *J. Med. Chem.*, 7, 524 (1964).

On the Use of Fibonacci Searches in Structure–Activity Studies

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The Fibonacci search is applicable only to response surfaces that increase smoothly toward the optimum from both sides; the search will fail on response surfaces on which there is superimposed noise.

Two recent papers[1,2] have advocated the use of a Fibonacci search[3,4] to locate the most biologically active compound in a series of analogues between set limits in a predetermined number of steps. It should be pointed out that the Fibonacci search is applicable only to response surfaces that increase smoothly toward the optimum from both sides; the search will fail on response surfaces on which there is superimposed noise (arising either from experimental error—e.g., in the determination of biological activity—or from anomalous behavior—e.g., of drugs). The high efficiency of the Fibonacci search is obtained by excluding certain regions of the factor domain (e.g., log *P* values) from further search; it is this same feature of the search that causes it to fail in the presence of noise.

To illustrate, consider the graphical presentation (Figure 1) of the 22 data points (numbered 0–21) in Table IV of Santora and Auyang.[2] Point numbers 8 and 13 are circled and represent the initial two experiments of the Fibonacci search. On the basis of these two results, the search proceeds to evaluate point 16 and in so doing excludes from future search points 0–7 (oversize dots). The consequences, in this case, are not serious.

Consider, however, a different data set in which the first two points of Figure 1 are not included but two additional

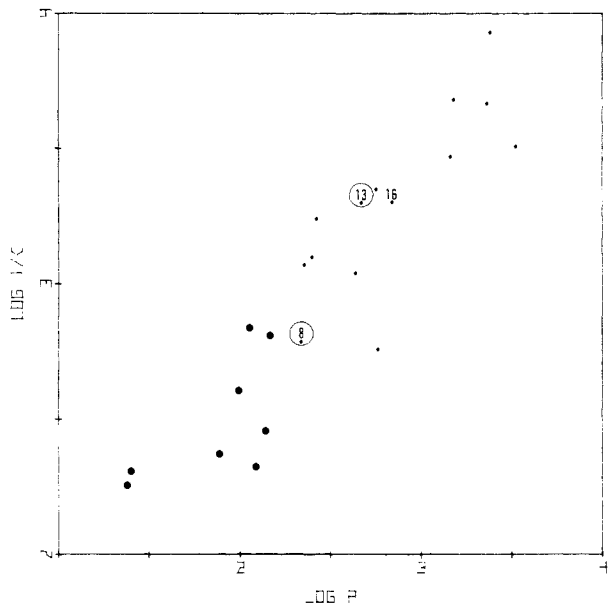

Figure 1. Plot of log $1/C$ vs. log P for data in Table IV of ref 2. Fibonacci progress is shown.

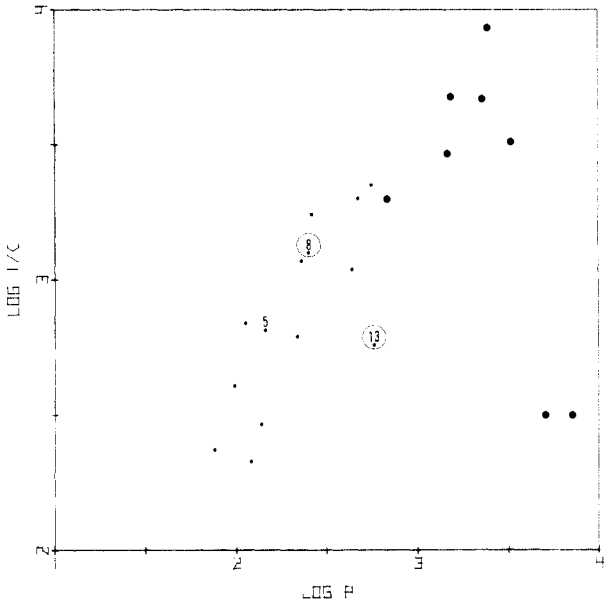

Figure 2. Plot of log $1/C$ vs. log P for data set of Figure 1 excluding first two data points. Fibonacci progress is shown.

points have been added at the right to give the desired total of 22 points. This situation is shown in Figure 2. The Fibonacci points 8 and 13 (circled) are evaluated. On the basis of these two results, the search proceeds to evaluate point 5 and in so doing *excludes from future search* points 14–21 (oversize dots). The consequences, in this case, are that the region containing the most active compounds will be overlooked entirely.

Efficient single-factor searches utilizing discrete levels of the factor and dealing with noise in the response surface are probably few if, in fact, any exist. More complete discussions of the general problem may be found in the literature.[5,6]

References and Notes

(1) T. M. Bustard, *J. Med. Chem.*, 17, 777 (1974).
(2) N. J. Santora and K. Auyang, *J. Med. Chem.*, 18, 959 (1975).
(3) S. M. Johnson, *Rand Corp. Rep. P-856*, Santa Monica, Calif., 1956.
(4) N. N. Vorob'ev, "Fibonacci Numbers", Pergamon, New York, N.Y., 1966.
(5) G. S. G. Beveridge and R. S. Schechter, "Optimization: Theory and Practice", McGraw-Hill, New York, N.Y., 1970.
(6) P. G. King and S. N. Deming, *Anal. Chem.*, 46, 1476 (1974).

Antimalarials. 9. Methylthio- and Methylsulfonyl-Substituted 9-Phenanthrenemethanols

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Nine di- and trisubstituted 9-phenanthrenemethanols bearing methylthio and methylsulfonyl substituents in the 2 and/or 6 positions of the phenanthrene nucleus were prepared and screened for antimalarial activity against *Plasmodium berghei* in mice. Six of the nine compounds were curative at or below 160 mg/kg. The most active structures contained a methylthio substituent in combination with two chlorine atoms.

The efficacy of many simple 9-phenanthrenemethanols against *Plasmodium gallinaceum* in chicks was reported by Coatney et al.[1] in their monograph. The compound with the highest chemotherapeutic index was 6-bromo-α-(di-*n*-heptylaminomethyl)-9-phenanthrenemethanol prepared by May and Mosettig.[2] More recently, the search for drugs effective against drug-resistant *falciparum* malaria resulted in the reinvestigation of the 9-phenanthrenemethanols. Cheng et al.[3] investigated the effects of modifying the amino alcohol side chain upon antimalarial activity.[4] Also, Nodiff et al.[5] prepared a number of trifluoromethyl- and halo-substituted 9-phenanthrenemethanols which possessed superior activity against *P. berghei* in mice; one compound, 2,4-bis(trifluoromethyl)-6,7-dichloro-α-(di-*n*-propylaminomethyl)-9-phenanthrenemethanol, was curative at a dosage of 5 mg/kg.

The purpose of the present work was to investigate the effects of introducing sulfur-containing substituents onto the phenanthrene nucleus upon the antimalarial activity. No potential antimalarial amino alcohols bearing these substituents on the aromatic nucleus have been reported.

Chemistry. The requisite phenanthroic acids (Table II) were prepared by the standard Perkin–Pschorr phenanthrene synthesis.[6-8] Thus, the Perkin reaction between the appropriate phenylacetic acids and benzaldehydes afforded the intermediate nitrocinnamic acids shown in Table I. In two of the four cases, a mixture of *cis*- and *trans*-cinnamic acids was obtained. However, these mixtures were converted to the desired 9-phenanthroic acids without difficulty, albeit in relatively low yields.

In the cases where the methylthiophenylacetic acids were not purchasable, the properly substituted halo-