added similarly. The reaction mixture became colorless. The crude product was precipitated by addition of water. The broad melting point of the derived HCl salt was consistent with the presence of a mixture of diastereoisomers.

N,N-**Di-*n*-butylfluorenylideneacetamide (I).** Ethyl fluorenylideneacetate[18] was hydrolyzed to the acid[19,20] and the latter converted to the title compound by a procedure described recently[21] for the direct conversion of carboxylic acids to amides. The crude product in $CHCl_3$ was washed with 5% HCl and recovered from the dry ($MgSO_4$) solution as 9.1 g (61%) of a red oil. The oil was twice distilled at 220° (0.01 mm) (bulb-to-bulb) and obtained as a viscous yellow oil. *Anal.* ($C_{23}H_{27}NO$) C, H; N: calcd, 4.20; found, 3.70.

Unsuccessful attempts were made to identify the products obtained by hydroboration with disiamylborane.[35]

2,7-Dichloro-9-hydroxy-9-(2-pyridyl)-4-fluorenecarboxylic Acid. The crude material (mp 224–232°) was obtained in 22% yield from 2,7-dichlorofluorenone-4-carboxylic acid under the conditions of the Boykin reaction.[22] A sample for analysis (CH_3CN) had mp 250–252° dec. *Anal.* ($C_{19}H_{11}Cl_2NO_3$) C, H, Cl, N.

2,7-Dichloro-9-hydroxy-9-(2-piperidyl)-4-fluorenecarboxylic Acid Hydrochloride (II). The pyridyl intermediate was hydrogenated in EtOH–HCl over Adams' PtO_2 in the usual way to give a yellow solid which, after trituration with CH_3CN, became colorless (95%, mp 244–245° dec). *Anal.* ($C_{19}H_{18}Cl_3NO_3$) C, H, Cl, N.

N-**(2-Fluorenyl)-5,5′-bis(trifluoromethyl)diphenamic Acid (IIIa).** 5,5′-Bis(trifluoromethyl)diphenic anhydride was allowed to react with 2-aminofluorene in a general procedure[13] to give the amic acid (74%), mp 240–242°. *Anal.* ($C_{29}H_{17}F_6NO_3$) H, N; C: calcd, 64.32; found, 63.72.

Compound IIIb was prepared similarly from 2-aminofluorenone and obtained in quantitative yield: mp 276–279°. *Anal.* ($C_{29}H_{15}F_6NO_4$) H, N; C: calcd, 62.71; found, 62.06.

N-**(2-Fluorenyl)-5,5′-bis(trifluoromethyl)diphenimide (IVa).** The amic acid IIIa was cyclized by Ac_2O–AcONa[13] to give the imide in 98% yield: mp 310–313°. *Anal.* ($C_{29}H_{15}F_6NO_2$) H, N; C: calcd, 66.54; found, 65.96.

Compound IVb was prepared similarly from IIIb: mp 322–325°. *Anal.* ($C_{29}H_{13}F_6NO_3$) C, H, N.

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References

(1) W. Regelson, *Annu. Rep. Med. Chem.*, 8, 163 (1973).
(2) H. E. Kaufman, Y. Centifano, E. D. Ellison, and D. C. Brown, *Proc. Soc. Exp. Biol. Med.*, **137**, 357 (1971).
(3) A. D. Sill, W. L. Albrecht, E. R. Andrews, R. W. Fleming, S. W. Horgan, E. McC. Roberts, and F. W. Sweet, *J. Med. Chem.*, 16, 240 (1973), and references cited therein.
(4) S. Ginsburg, R. J. Kitz, and J. J. Savarese, *Brit. J. Pharmacol.*, **43**, 107 (1971).
(5) F. Troxler and F. Seemann (to Sandoz), Swiss Patent 492,678 (1970).
(6) F. Troxler and F. Seemann (to Sandoz), Swiss Patent 525,858 (1972).
(7) E. T. Stiller, P. A. Diassi, D. Gerschutz, D. Meikle, J. Moetz, P. A. Principe, and S. D. Levine, *J. Med. Chem.*, 15, 1029 (1972).
(8) H. Ziegler, *Endeavour*, **29**, 112 (1970).
(9) G. Mohr, *Vortr. Gesamtgeb. Bot.*, **No. 3**, 5 (1969).
(10) G. R. Coatney, W. C. Cooper, N. B. Eddy, and J. Greenberg, Public Health Monograph No. 9, U. S. Government Printing Office, Washington, D. C., 1953, Table 92, p 183.
(11) Reference 10, p 177.
(12) F. Y. Wiselogle, "A Survey of Antimalarial Drugs 1941–1945," J. W. Edwards, Ann Arbor, Mich., 1946.
(13) C.-A. Cole, H.-L. Pan, M. J. Namkung, and T. L. Fletcher, *J. Med. Chem.*, **13**, 565 (1970); H.-L. Pan and T. L. Fletcher, *ibid.*, **13**, 567 (1970).
(14) E. A. Nodiff, *et al.*, *J. Med. Chem.*, 15, 775 (1972), and references cited therein.
(15) P.-L. Chien and C. C. Cheng, *J. Med. Chem.*, 16, 1093 (1973), and references to earlier papers cited.
(16) E. R. Atkinson and A. J. Puttick, *J. Med. Chem.*, 11, 1223 (1968).
(17) E. Pratt and J. Van de Castle, *J. Org. Chem.*, **26**, 2973 (1961).
(18) D. W. Anderson and N. Campbell, *J. Chem. Soc.*, 781 (1960).
(19) C. R. Hauser and D. Lednicer, *J. Org. Chem.*, **22**, 1245 (1957).
(20) A. Sieglitz and H. Jassoy, *Chem. Ber.*, **54**, 2133 (1921).
(21) L. E. Barstow and V. J. Hruby, *J. Org. Chem.*, **36**, 1305 (1971).
(22) D. W. Boykin, A. R. Patel, and R. E. Lutz, *J. Med. Chem.*, 11, 273 (1968).
(23) A. S. Dey and J. L. Neumeyer, *J. Med. Chem.*, in press.
(24) D. M. March and T. Henshall, *J. Phys. Chem.*, **66**, 840 (1962).
(25) L. Rane and D. S. Rane, *Proc. Helminthol. Soc. Wash.*, **39**, 283 (1972).
(26) E. K. Weisburger and J. H. Weisburger, *J. Org. Chem.*, **20**, 1396 (1955).
(27) E. H. Huntress, I. S. Cliff, and E. R. Atkinson, *J. Amer. Chem. Soc.*, **55**, 4262 (1933).
(28) E. R. Atkinson and H. J. Lawler, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 222.
(29) W. Schidlo and A. Sieglitz, *Chem. Ber.*, **96**, 2595 (1963).
(30) H. W. Underwood and E. L. Kochman, *J. Amer. Chem. Soc.*, **46**, 2069 (1924).
(31) E. K. Weisburger and H. H. Weisburger, *J. Org. Chem.*, 18, 864 (1953).
(32) W. E. Bachmann and C. E. Brockway, *J. Org. Chem.*, 13, 384 (1948).
(33) C. Graebe and Ch. Aubin, *Justus Liebigs Ann. Chem.*, **247**, 279 (1888).
(34) R. E. Lutz, *et al.*, *J. Amer. Chem. Soc.*, 68, 1813 (1946).
(35) H. C. Brown, "Hydroboration," W. A. Benjamin, New York, N. Y., 1962.

Antimalarials. 4. Tetrahydroquinolinemethanols†

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The undesirable phototoxicity of potent antimalarials in the substituted 2-phenyl-4-quinolinemethanol series has been discussed by us[1] and by others.[2] Our unsuccessful efforts to decrease phototoxicity (without at the same time decreasing antimalarial activity) involved four structural modifications.[1] More recently some success was achieved with compounds in which the 2-phenyl substituent was separated from the quinoline nucleus by CH_2, CO, and CF_2 groups.[2] When the 2-phenyl groups were replaced by aryloxy or arylamino groups there was a little to a moderate effect on both phototoxicity and antimalarial activity.[3] When the 2-phenyl groups were replaced by thienyl groups phototoxicity remained; when they were replaced by methyl or *tert*-butyl groups phototoxicity decreased but antimalarial activity did also.[4]

Our earlier[1] reduction of the well-known 6,8-dichloro-2-phenyl-α-(2-piperidyl)-4-quinolinemethanol (I) gave the 1,2,3,4-tetrahydro derivative II which was less phototoxic than I, but whose evaluation was complicated by the fact that II was toxic to mice at 50 mg/kg ip.

In order to subject our hypothesis to a more satisfactory evaluation we have now prepared IV–VI from III (variously known as SN15068 or WR 30090) by the route shown.

At the time the work began III was known to have about half the antimalarial activity of I but was much less toxic because it did not cause depletion of catecholamines with related effects.[5] It was thought that the unacceptably high phototoxicity of III in mice would prevent its clinical use, although the reported[6] minimum effective phototoxic dose in swine was just 25 mg/kg po, identical with that of qui-

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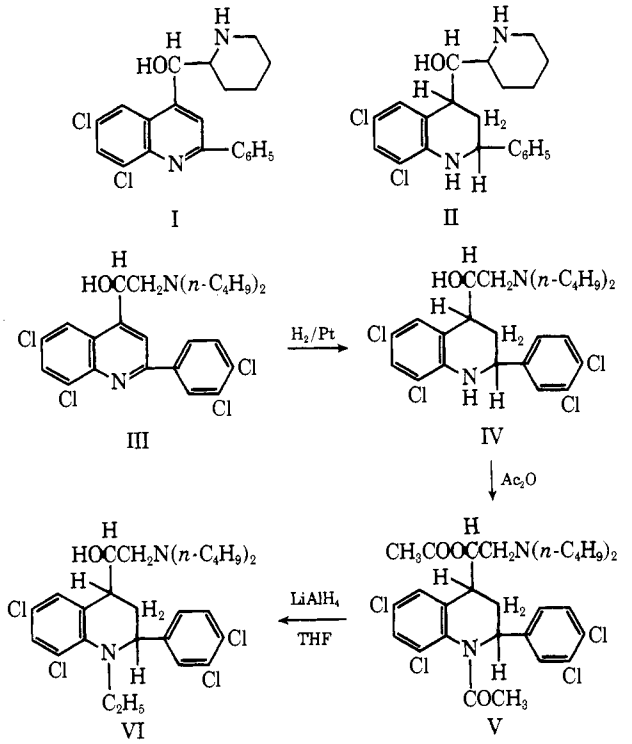

nine sulfate. Subsequent clinical studies have shown III to have an acceptably low phototoxicity in man.[7]

In the standard antimalarial test used previously[1] IV was "active" at 40 mg/kg, gave one cure at 80 mg/kg, three cures at 160 mg/kg, and five cures at 320 mg/kg. Compound VI was "active" at 80 mg/kg and gave three cures at 320 mg/kg and five cures at 640 mg/kg. Compound V was inactive even at 640 mg/kg.

The minimum effective phototoxic dose[8] of IV was found to be 400 mg/kg, while that of III was just 50 mg/kg. The phototoxic index (PI) is defined as the ratio of the minimum effective phototoxic dose (ip) to the dose required to produce an increase of 6–8 days in the mean survival time of mice inoculated with *Plasmodium berghei* (5.0 mg/kg for III, 40 mg/kg for IV). For both III and IV the PI = 10. Thus, we record another unsuccessful attempt to prepare potent quinolinemethanol drugs with acceptably low phototoxicity. The search was abandoned when nonphototoxic antimalarials became available in the Army program.

No attempt was made to separate the diastereoisomeric mixtures in which IV–VI occurred. The significant decrease in phototoxicity in these compounds was accompanied by negligible absorption above 310 nm. Unreduced phototoxic 2-phenylquinolinemethanols(such as III) all have strong absorption in the 320–360-nm region.

Experimental Section

Melting points were obtained in capillaries and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., and by the late Dr. S. M. Nagy (Belmont, Mass.). Satisfactory uv and ir spectra were recorded for IV–VI.

α-(Di-*n*-butylaminomethyl)-2-phenyl-3′,4′,6,8-tetrachloro-1,2,3,4-tetrahydro-4-quinolinemethanol Hydrochloride (IV·HCl). Compound III·HCl (kindly provided by the Division of Medicinal Chemistry, Walter Reed Army Institute of Research) was converted to its free base,‡ mp 130–132°. The latter was reduced by the procedure described[1] for the reduction of I to II and IV·HCl was isolated (80–90%) as a cream-colored flocculent solid, mp 100–160° dec. *Anal.* ($C_{25}H_{32}Cl_4N_2O$·HCl) H, N; C: calcd, 54.12; found, 54.06; Cl: calcd, 31.95; found, 30.41.

Tlc (SiO_2, MeOH–2% NH_3) showed that no unreduced material was present. The chlorine content of the products of other runs varied from 29 to 31% showing that some loss of chlorine occurred during the catalytic reduction.

1-Acetyl-α-(di-*n*-butylaminomethyl)-2-phenyl-3′,4′,6,8-tetrachloro-1,2,3,4-tetrahydro-4-quinolinemethanol Acetate Hydrochloride Monohydrate (V·HCl·H_2O). A solution of 4.6 g (0.0083 mol) of IV·HCl in 25 ml of Ac_2O was heated at reflux for 2 hr. After dilution with water and hydrolysis of excess Ac_2O the solution was acidified with excess 6 *N* HCl to precipitate V·HCl, which was washed on the filter with 2 *N* HCl and dried at 25° (1 mm) to give 4.1 g (75%), mp 90–200° slow dec. Unlike IV·HCl and VI·HCl, V·HCl was significantly soluble in H_2O; it was much less soluble in dilute HCl. *Anal.* ($C_{29}H_{36}Cl_4N_2O_3$·HCl·H_2O) C, H, Cl, N.

α-(Di-*n*-butylaminomethyl)-1-ethyl-2-phenyl-3′,4′,6,8-tetrachloro-1,2,3,4-tetrahydro-4-quinolinemethanol Hydrochloride (VI·HCl). A solution of 2 g (0.00313 mol) of V·HCl in 20 ml of dry THF was added dropwise to a stirred suspension of 2.5 g (0.0066 mol) of $LiAlH_4$ in 70 ml of THF. The free base VI was isolated in the usual way and converted to its HCl salt in dry ether solution. After drying at 35° (1 mm) VI·HCl was obtained as a tan powder (77%), mp 75–110° slow dec. The uv spectrum was qualitatively identical with that of IV and the ir spectrum showed no carbonyl absorption. *Anal.* ($C_{27}H_{36}Cl_4N_2O$·HCl) N; C: calcd, 55.64; found, 56.40; h; calcd, 6.30; found, 6.94; Cl: calcd, 30.41; found, 28.12.

It was apparent that some loss of Cl occurred during the reduction reaction. When the reaction was prolonged, Cl values fell as low as 25%; after shorter reaction times Cl values were higher, but the product contained residual carbonyl, detected by ir. Direct alkylation of IV to VI by a variety of standard procedures failed.

‡ Lutz, *et al.*,[9] record mp 128–129°.

References

(1) E. R. Atkinson and A. J. Puttick, *J. Med. Chem.*, **13**, 537 (1970), and references cited therein.
(2) A. J. Saggiomo, S. Kano, T. Kikuchi, K. Okubo, and M. Shinbo, *J. Med. Chem.*, **15**, 989 (1972).
(3) C. R. Wetzel, J. R. Shanklin, Jr., and R. E. Lutz, *J. Med. Chem.*, **16**, 528 (1973).
(4) J. P. Schaefer, K. S. Kulkarni, R. Coston, J. Higgins, and L. M. Honig, *J. Heterocycl. Chem.*, **7**, 607 (1970).
(5) D. M. Aviado and M. Belej, *Pharmacology*, **3**, 257 (1970).
(6) W. W. Bay, C. A. Gleiser, R. G. Feldman, K. R. Pierce, and K. M. Charlton, *U. S. Clearinghouse Fed. Sci. Tech. Inform. AD*, No. 701055 (1969); *Chem. Abstr.*, **73**, 75504 (1970).
(7) D. C. Martin, J. D. Arnold, D. F. Clyde, M. Al Ibrahim, P. E. Carson, K. H. Rieckman, and D. Willerson, Jr., *Antimicrob. Ag. Chemother.*, **3**, 214 (1973).
(8) W. E. Rothe and D. P. Jacobus, *J. Med. Chem.*, 11, 366 (1968).
(9) R. E. Lutz, *et al.*, *J. Amer. Chem. Soc.*, **68**, 1813 (1946).

Antineoplastic Agents. 34. *Helenium autumnale* L.[1,2]

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One of the common sneezeweeds, *Helenium autumnale* L. var. *montanum* (Nutt.) Fern. (Compositae family), displays several to many heads of bright yellow flowers and is found widely distributed throughout the western United States. The animal toxicity associated with this plant and other *Helenium* species is well known.[2,3a] In addition, severe nasal and eye irritation is generally encountered with *H. autumnale.*

During the process of evaluating Oregon plants for antineoplastic agents, we found that extracts of *Helenium autumnale* L. var. *montanum* (Nutt.) Fern. showed significant inhibitory activity in both *in vitro* (9 KB cell culture) and *in vivo* (P-388 lymphocytic leukemia) studies[4] performed under auspices of the National Cancer Institute. Encouraged by these initial biological results, sepa-