[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF SWARTHMORE COLLEGE]

Quinoline Analogs of Podophyllotoxin. I. Preliminary Experiments. Syntheses of Some 4-Phenylquinoline Derivatives[1]

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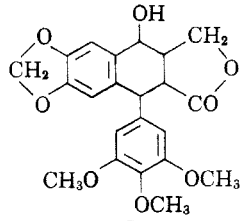
A number of 4-phenylquinoline derivatives showing structural resemblances to podophyllotoxin have been synthesized for evaluation as potential antitumor agents.

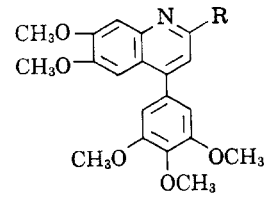
The discovery of tumor-damaging properties in podophyllotoxin (I) and some related naturally occurring lignans[2] has prompted the preparation



I

by several groups of investigators of a number of synthetic podophyllotoxin analogs for evaluation as potential antitumor agents. Most of the work which has been reported thus far has been concerned with the replication of all or part of the carbon-oxygen skeleton of the natural product and has involved the preparation of derivatives of butyrolactone,[3] 1,2,3,4-tetrahydronaphthalene,[4] 1-phenyl-1,2,3,4-tetrahydronaphthalene,[5] and 1-phenylnaphthalene.[6] More recently, Reeve and Paré have reported tumor-damaging activity in a 1-phenyldihydroisoquinoline derivative showing a close structural resemblance to podophyllotoxin.[7]

It seemed of interest to explore the possibility that certain quinoline analogs of podophyllotoxin might exhibit antitumor activity. Since the methylenedioxy moiety of podophyllotoxin may be replaced by two methoxyl groups without loss of activity[8] and since this modification simplified the synthetic procedure by permitting the use of somewhat more readily available starting materials, our initial experiments were concerned with the preparation of a series of 4-phenylquinoline derivatives of type II. The route to these products is



II

(R = H, CH_3, CHO, COOH)

outlined in the accompanying reaction diagram.

1-(3,4,5-Trimethoxyphenyl)-1,3-butanedione (III), prepared by a Claisen condensation between 3,4,5-trimethoxyacetophenone and ethyl acetate in the presence of sodium, was condensed with 3,4-dimethoxyaniline to give the anil IV or, more probably,[9] its tautomer V. Cyclodehydration of this product in cold concentrated sulfuric acid provided 6,7-dimethoxy-4-(3,4,5-trimethoxyphenyl)quinaldine (VI) in 76% over-all yield from III. Treatment of VI with selenium dioxide in dioxane gave a mixture of the aldehyde VII and the acid VIII, the latter being obtainable in excellent over-all yield either by isolating the aldehyde and oxidizing it further with hydrogen peroxide in acetone or, more simply, by subjecting the crude mixture of VII and VIII to the action of this reagent. Decarboxylation of the acid VIII occurred readily at temperatures slightly above its melting point, yielding 6,7-dimethoxy-4-(3,4,5-trimethoxyphenyl)quinoline (IX).

All attempts to reduce VI, VIII, and IX to the corresponding 1,2,3,4-tetrahydroquinoline derivatives by the usual methods (catalytic hydrogenation over platinum black or palladium-charcoal, electrolytic reduction at a lead cathode, chemical reduction with tin and hydrochloric acid) were unsuccessful and resulted only in recovery of unchanged starting material. The action of sodium on an ethanolic solution of IX yielded a reduction product having a composition corresponding to the

(1) This investigation was supported by research grant C-2726 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) See the excellent review by W. M. Hearon and W. S. MacGregor, *Chem. Revs.*, **55**, 957 (1955), which includes numerous references to articles dealing with the pharmacology of these compounds.

(3) N. L. Drake and W. B. Tuemmler, *J. Am. Chem. Soc.*, **77**, 1204 (1955).

(4) K. N. Campbell, J. A. Cella, and B. K. Campbell, *J. Am. Chem. Soc.*, **75**, 4681 (1953).

(5) G. N. Walker, *J. Am. Chem. Soc.*, **75**, 3390, 3393 (1953).

(6) W. Reeve and H. Myers, *J. Am. Chem. Soc.*, **75**, 4957 (1953).

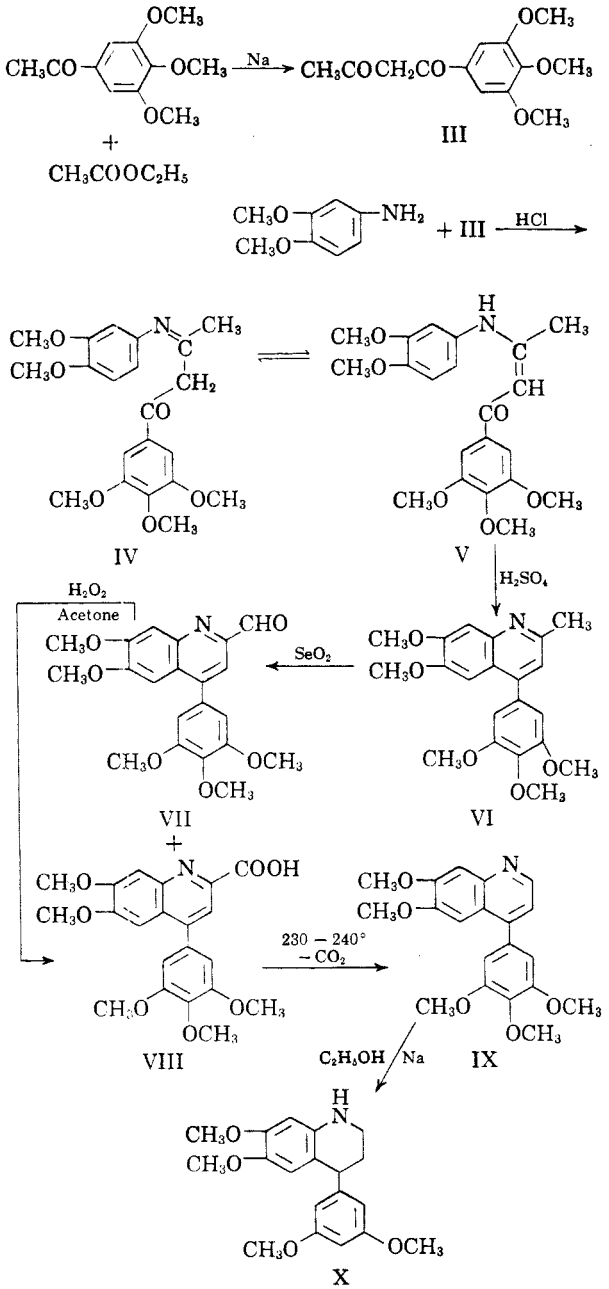
(7) W. Reeve and P. J. Paré, *J. Am. Chem. Soc.*, **79**, 675 (1957).

(8) *Cf.* sikkimotoxin, which is 1-hydroxy-2-hydroxymethyl-6,7-dimethoxy-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-3-carboxylic acid lactone; reference in footnote 2.

(9) *Cf.* F. Lions, *J. Proc. Roy. Soc., N. S. Wales*, **71**, 242 (1938); *Chem. Abstr.*, **32**, 7460 (1938).

formula $C_{19}H_{23}NO_4$ rather than to the desired $C_{20}H_{25}NO_5$. Since the central methoxyl group of the *vic*-trimethoxyphenyl moiety is known to be subject to hydrogenolysis under these conditions,[10] the product may be provisionally assigned structure X. Further study of the anomalous reduction behavior of this series of compounds is planned.

The preparation of 6,7-dimethoxy-4-phenylquinaldehyde (XI) and 6,7-dimethoxy-4-phenylquinaldic acid (XII), which were obtained during exploratory experiments with the readily accessible 6,7-dimethoxy-4-phenylquinaldine, is described in the Experimental part. Pharmacological data for compounds described in this paper will be reported elsewhere.



EXPERIMENTAL[11]

1-(3,4,5-Trimethoxyphenyl)-1,3-butanedione (III). About 20 ml. of a solution of 20.3 g. (0.097 mole) of 3,4,5-trimethoxyacetophenone[12] in 100 ml. of freshly purified[13] anhydrous ethyl acetate was added to 6.8 g. (0.30 g.-atom) of sodium sand in a nitrogen atmosphere. The mixture was stirred, and after the exothermic reaction had begun the remainder of the ketone solution was added dropwise at such a rate as to maintain refluxing (*ca.* 15 min.). Stirring and refluxing were continued for another 4 hr. After standing at room temperature overnight, the reaction mixture was diluted with 200 ml. of water, acidified with 30 ml. of acetic acid and extracted with three 150-ml. portions of chloroform. The combined chloroform extracts were washed once with 100 ml. of water and were then extracted with four 80-ml. portions of 10% aqueous sodium hydroxide. Acidification of the combined alkaline extracts with 55 ml. of acetic acid provided a yellow solid precipitate, which was collected, washed with water, dried, and recrystallized from aqueous methanol to yield 16.9 g. (69%) of pale yellow crystals, m.p. 97–99°. Further recrystallization from aqueous methanol gave colorless leaflets melting at 101–102°.

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.88; H, 6.39. Found: C, 61.82; H, 6.38.

β-(3,4-Dimethoxyanilino)-3,4,5-trimethoxycrotonophenone (V). A mixture of 16.8 g. (0.067 mole) of III and 10.2 g. (0.067 mole) of 3,4-dimethoxyaniline was heated in a boiling water bath until a clear amber melt was obtained. Four drops of 6*N* hydrochloric acid was then added and heating was continued until the mixture solidified (*ca.* 5 min.). The resultant yellow solid was pulverized and dissolved in *ca.* 300 ml. of boiling methanol. On cooling this solution, 21.1 g. (82%) of bright yellow crystals, m.p. 143–144°, were obtained. Dilution of the mother liquor with an equal volume of water and recrystallization of the resultant precipitate from fresh methanol provided an additional 2.3 g. of product of comparable purity; total yield 23.4 g. (90%). Recrystallization from methanol raised the m.p. to 145–146°.

Anal. Calcd. for $C_{21}H_{25}NO_6$: C, 65.10; H, 6.51; N, 3.62. Found: C, 65.30; H, 6.26; N, 3.61.

6,7-Dimethoxy-4-(3,4,5-trimethoxyphenyl)quinaldine (VI). Finely powdered V (17.4 g.) was added in small portions with vigorous stirring over a 20-min. period to 90 ml. of cold concentrated sulfuric acid. The resultant yellow solution was poured onto 160 g. of cracked ice, and 300 ml. of concd. ammonium hydroxide was then added cautiously while stirring and cooling in an ice bath. The gummy suspension was heated to boiling for 5 min., and the precipitate was then collected, washed with water, and recrystallized from aqueous methanol to give 15.4 g. (93%) of almost colorless needles, m.p. 152–154°. Treatment of this material with Nuchar and further recrystallization from aqueous methanol or benzene-cyclohexane provided colorless crystals which melted at 153–154°; λ_{max}^{EtOH} 236 mμ (log ε 4.63), 320 mμ (log ε 4.00), 334 mμ (log ε 4.03).

Anal. Calcd. for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.52; H, 6.47; N, 3.74.

The *methiodide* of VI was prepared by dissolving 0.70 g. of VI in 5 ml. of benzene, adding 1.60 g. of methyl iodide, and allowing the mixture to stand at room temperature for several months. The yellow precipitate was collected, washed with benzene, and dried to give 0.60 g. (62%) of

(10) See, for example, the discussion in J. Houben, *Die Methoden der Organischen Chemie*, 3rd ed., Verlag Georg Thieme, Leipzig, 1925, vol. 2, p. 235.

(11) Microanalyses are by the Clark Microanalytical Laboratory, Urbana, Ill.

(12) E. C. Horning, J. Koo, and G. N. Walker, *J. Am. Chem. Soc.*, **73**, 5826 (1951).

(13) L. F. Fieser, *Experiments in Organic Chemistry*, 3rd ed., D. C. Heath and Co., Boston, 1955, p. 287.

yellow crystals, m.p. 220–225° with decomposition beginning above 205°. Recrystallization from absolute ethanol raised the m.p. to 228–230° (dec.).[14]

Anal. Calcd. for $C_{22}H_{26}INO_5$: C, 51.67; H, 5.13. Found: C, 51.83; H, 5.21.

Selenium dioxide oxidation of VI. A mixture of 7.97 g. (0.0216 mole) of VI, 3.00 g. (0.0270 mole) of selenium dioxide,[15] 27 ml. of purified[16] dioxane, and 2.2 ml. of water was refluxed for 6 hr., after which the hot reaction mixture was filtered to remove the precipitated selenium. On cooling, the dark red solution deposited crude *6,7-dimethoxy-4-(3,4,5-trimethoxyphenyl)quinaldic acid* (VIII) in the form of orange crystals, which were collected, washed with dioxane, and dried; yield 4.46 g. (52%), m.p. 205–210° (dec.) with previous sintering. Repeated recrystallization of this material from ethanol and from dioxane provided silky yellow needles of the pure acid, m.p. 224–225° (dec.).

Anal. Calcd. for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30; neut. equiv., 399. Found: C, 62.93; H, 5.58; neut. equiv., 399.

After removal of the crude acid, the dioxane filtrate from the above oxidation reaction was diluted with *ca.* 200 ml. of water and allowed to stand overnight. The resultant yellow precipitate was collected, washed with water, and dried to give 3.30 g (40%) of *6,7-dimethoxy-4-(3,4,5-trimethoxyphenyl)quinaldehyde* (VII), m.p. 176–178°. Recrystallization from ethanol gave pale yellow crystals which melted at 179–180°.

Anal. Calcd. for $C_{21}H_{21}NO_6$: C, 65.78; H, 5.52. Found: C, 65.78; H, 5.54.

Hydrogen peroxide oxidation of VII. A mixture of 4.12 g. (0.0108 mole) of VII, 120 ml. of acetone, and 10 ml. (0.088 mole) of 30% hydrogen peroxide was refluxed for 2 hr. and allowed to stand overnight. The precipitate was then collected, washed with a little acetone, and dried to give 3.70 g. (86%) of yellow powder, m.p. 222–224° (dec.) alone and when mixed with the acid VIII obtained above.

6,7-Dimethoxy-4-(3,4,5-trimethoxyphenyl)quinoline (IX). Small (1 to 2 g.) samples of the acid VIII were heated on an oil bath at 230–240° for 10 min. and were then extracted repeatedly with 10-ml. portions of boiling cyclohexane until the extracts no longer deposited solid material on cooling. The yellow solid thus obtained was collected, washed with petroleum ether, and dried. Yields varied from 60% to 78% in three runs; the combined yield from 3.44 g. of VIII was 2.17 g. (71%) of yellow microcrystalline powder, m.p. 136–139° with previous sintering. Recrystallization from cyclohexane provided pale yellow needles melting at 140–141°.

Anal. Calcd. for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96. Found: C, 67.71; H, 5.74.

Sodium-ethanol reduction of IX. Nine grams of sodium was added in small pieces over a 90-min. period to a refluxing solution of 2.15 g. of IX in 60 ml. of absolute ethanol, and refluxing was continued for another 3 hr. About 30 ml. of water was then added cautiously to the boiling mixture, the condenser was set for distillation, and another 60 ml. of water was added gradually to the boiling mixture while *ca.* 70 ml. of distillate was collected. The residual aqueous solution was cooled, extracted several times with ether, and the combined ether extracts were washed with water and dried over anhydrous magnesium sulfate. Evaporation of the ether solution to dryness on the steam bath left a pale yellow tacky sirup, which slowly crystallized to an almost colorless waxy solid, m.p. 90–94°; yield 1.09 g. Recrystallization of this material from cyclohexane and from aqueous ethanol provided a white microcrystalline powder which melted at 101–103°; λ_{max}^{EtOH} 310 mμ (log ε 3.58).

Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04. Found: C, 69.22, 69.50; H, 7.01, 6.94.

Selenium dioxide oxidation of 6,7-dimethoxy-4-phenylquinaldine. A mixture of 5.58 g. (0.020 mole) of 6,7-dimethoxy-4-phenylquinaldine,[17] 2.22 g. (0.020 mole) of selenium dioxide,[15] 15 ml. of purified [16] dioxane, and 1.5 ml. of water was refluxed for 6 hr., after which the hot reaction mixture was filtered to remove the precipitated selenium (1.51 g., 96%). On cooling, the dark red filtrate deposited crude *6,7-dimethoxy-4-phenylquinaldic acid* (XII) as an orange solid, which was collected, washed with a little ether, and recrystallized from a relatively large volume of ethanol to give 1.14 g. (18%) of yellow needles, m.p. 180–181° (dec.). Further recrystallization from ethanol raised the m.p. to 182–183° (dec.).

Anal. Calcd. for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89. Found: C, 70.04; H, 4.91.

Concentration of the dioxane filtrate on the steam bath afforded a viscous red oil which slowly solidified. The dark colored solid was taken up in boiling ethanol, water was added to the hot solution until a slight turbidity appeared, and the solution was allowed to stand for several days. The orange waxy solid (1.5 g., 26%) thus obtained was recrystallized repeatedly from aqueous ethanol and finally from cyclohexane to give yellow crystals of 6,7-dimethoxy-4-phenylquinaldehyde, which melted at 121–123°, then resolidified and remelted at 136–137°.

Anal. Calcd. for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.16. Found: C, 73.25, 73.23; H, 5.27, 5.39.

The *p-nitrophenylhydrazone* of this product, prepared in the usual way,[18] was obtained as a red-orange microcrystalline powder, m.p. 260–261°.

Anal. Calcd. for $C_{24}H_{20}N_4O_4$: C, 67.28; H, 4.71. Found: C, 67.33; H, 4.93.

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(14) Melting point taken on Fisher-Johns apparatus preheated to 220°.

(15) H. A. Riley and A. R. Gray, *Org. Syntheses*, **Coll. Vol. II**, 510, note 2 (1943).

(16) L. F. Fieser, *Experiments in Organic Chemistry*, 3rd ed., D. C. Heath and Co., Boston, 1955, p. 285, method (a).

(17) Prepared in 77% yield from 3,4-dimethoxyaniline and 1-phenyl-1,3-butanedione according to the directions of Lions.[9] After recrystallization from aqueous methanol, the product was obtained in the form of colorless needles, m.p. 141–142°; λ_{max}^{EtOH} 238 mμ (log ε 4.64), 334 mμ (log ε 4.03).

(18) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., John Wiley and Sons, Inc., New York, 1956, p. 219.