[CONTRIBUTION FROM THE SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH]

Catechol Derivatives of Estrogens[1]

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Received September 18, 1959

The preparation of 2-methoxyestriol (IIa), 2-hydroxyestriol, 3-methyl ether (IIc), 2-hydroxyestradiol, 3-methyl ether (IVc), 2-hydroxyestradiol (IVf), and 2-hydroxyestrone (Vb), with various derivatives and intermediates is described.

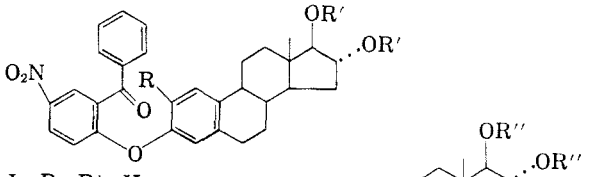
The synthesis of actual or anticipated estrogen metabolites has been a continuing concern of these laboratories and recently emphasis has been given to compounds with an additional oxygen function on ring A.[2,3] This communication deals with the preparation of some catechol derivatives of estrogens together with certain of the mono- and dimethyl ethers of these steroids. The natural occurrence of these products as female hormone metabolites is under active investigation.

Since metabolic transformation of the estrogenic hormone in man yields large amounts of estriol,[4] it was logical to anticipate, in analogy to the presence of 2-methoxyestrone,[5] that the 2-methoxy derivative of estriol would also be present as the end product of a particular biochemical pathway. This indeed proved to be the fact[6] and identification and isolation of the metabolite were enormously facilitated by the availability of that compound through an effective synthesis. Starting with estriol the procedure for introduction of a methoxyl group used for the preparation of 2-methoxyestradiol[2] was clearly applicable. An alternate route starting with 2-methoxyestrone and elaborating the ring-D glycol structure by the method of Leeds *et al.*[7] was also considered, but was abandoned in favor of the direct preparation.

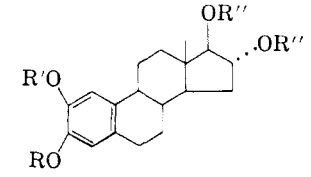
Condensation of estriol with 2-chloro-5-nitrobenzophenone gave the ether Ia, which was acetylated to the diacetate Ib. Cyclization of the latter in a sulfuric-acetic acid mixture and subsequent oxidation with 30% hydrogen peroxide gave the 2-hydroxy compound Ic which, on direct methylation with diazomethane, yielded the 2-methoxy derivative Id. Alkaline hydrolysis of Id removed both the acetate and nitrobenzophenone groups, and after purification by counter current distribution, 2-methoxyestriol (IIa), m.p. 215–218° was obtained. The new compound was, as expected, somewhat less polar than estriol, and exhibited the characteristic ultraviolet absorption maximum at 286 mμ.

Compounds like the 2-hydroxybenzophenone ether Ic readily undergo the Smiles rearrangement in the presence of alkali,[8] and brief treatment of Ic with alkali resulted in a mixture of starting material and rearrangement product. Methylation

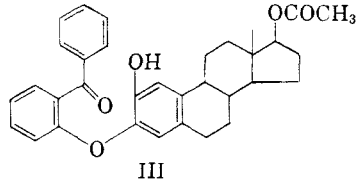
CHART I



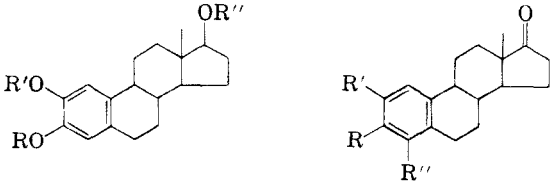
Ia. R = R′ = H
b. R = H, R′ = CH_3CO
c. R = OH, R′ = CH_3CO
d. R = CH_3O, R′ = CH_3CO



IIa. R = R″ = H, R′ = CH_3
b. R = CH_3, R′ = H, R″ = CH_3CO
c. R = CH_3, R′ = R″ = H
d. R = R′ = CH_3, R″ = H



III



IVa. R = CH_3, R′ = H, R″ = CH_3CO
b. R = H, R′ = CH_3, R″ = CH_3CO
c. R = CH_3, R′ = R″ = H
d. R = R′ = CH_3, R″ = CH_3CO
e. R = R′ = CH_3, R″ = H
f. R = R′ = R″ = H
g. R = R′ = H, R″ = CH_3CO

Va. R = R′ = CH_3O, R″ = H
b. R = R′ = OH, R″ = H
c. R = R′ = C_6H_5COO, R″ = H
d. R = CH_3O, R′ = H, R″ = OH
e. R = R″ = OH, R′ = H

(1) This investigation was supported in part by a grant from the American Cancer Society and a research grant (CY-3207) from the National Cancer Institute of the National Institutes of Health, United States Public Health Service.

(2) J. Fishman, *J. Am. Chem. Soc.*, **80**, 1213 (1958).

(3) S. Kraychy, *J. Am. Chem. Soc.*, **81**, 1702 (1959).

(4) C. T. Beer and T. F. Gallagher, *J. Biol. Chem.*, **214**, 335, 351 (1954).

(5) S. Kraychy and T. F. Gallagher, *J. Am. Chem. Soc.*, **79**, 1213 (1957); *J. Biol. Chem.*, **229**, 519 (1957).

(6) J. Fishman and T. F. Gallagher, *Arch. Biochem. and Biophys.*, **77**, 511 (1958).

(7) N. S. Leeds, D. K. Fukushima, and T. F. Gallagher, *J. Am. Chem. Soc.*, **76**, 2943 (1954).

(8) J. D. Loudon and J. A. Scott, *J. Chem. Soc.*, 265 (1953).

of the mixture with diazomethane and removal of the benzophenone group with piperidine yielded, after chromatography on alumina, two main products. The unaltered fraction, after hydrolysis yielded 2-methoxyestriol (IIa), while the rearrangement product, IIb, on similar hydrolysis, afforded 2-hydroxyestriol, 3-methyl ether (IIc), m.p. 268–271°. The structure of the latter was indicated by the analytical data, the identity of ultraviolet, and similarity of the infrared spectra with that of 2-methoxyestriol (IIa). Final proof of the structure was provided by further methylation of IIc to give IId, identical in all respects with that obtained from 2-methoxyestriol. The possibility that the high melting isomer IIc was 2-methoxyestriol, while the low melting IIa was the rearranged product can be excluded since only one product, IIa, m.p. 215–218°, was obtained when base was excluded during the handling and methylation of Ic.

The relative ease of the Smiles rearrangement in this sequence prompted its use in the preparation of another estradiol derivative. When the 2-hydroxy ether (III) derived from estradiol[2] was dissolved in Claisen alkali, acidified, and extracted, a rearrangement mixture resulted. Methylation and reacetylation followed by piperidine cleavage gave the two expected isomers, 2-methoxyestradiol, 17–acetate (IVb),[2] and 2-hydroxyestradiol, 17–acetate, 3-methyl ether (IVa). Further methylation of either compound gave the identical dimethoxy derivative, IVd. Hydrolysis of IVd afforded 2,3-dimethoxyestradiol (IVe), which on oxidation with chromic acid gave 2,3-dimethoxyestrone (Va). Alkaline hydrolysis of the monoacetate (IVa) gave 2-hydroxyestradiol, 3-methyl ether (IVc) isomeric with 2-methoxyestradiol. Pyridine hydrochloride fusion of either IVc or 2-methoxyestradiol gave in excellent yield 2-hydroxyestradiol (IVf). This compound was also prepared by an alternate route, via the piperidine cleavage of III, and acid hydrolysis of the resulting 2-hydroxyestradiol, 17–acetate (IVg).

Similar demethylation of the two isomeric methoxyestriols, IIa and IIc, proceeded with concomitant dehydration[9] to give 2-hydroxyestrone (Vb); the same product was also readily obtained by demethylation of 2-methoxyestrone. Yet another route proceeded *via* the dibenzoate Vc obtained from oxidation of the dibenzoate of 2-hydroxyestradiol. For comparison purposes 4-hydroxyestrone (Ve) was prepared by the demethylation of 4-hydroxyestrone, 3-methyl ether (Vd) prepared previously in these laboratories[3] and was found to be different from Vb.

The preparation of 2-hydroxyestrone by a different route has already been recorded in the literature[10] although there is some doubt as to the homogeneity of the nitro compound used in that preparation.[11] Some biological properties of 2-hydroxyestradiol and 2-hydroxyestrone have been described,[12,13] but no chemical details or physical constants have been recorded.

NOTE ADDED IN PROOF: After the submission of this manuscript, the preparation of 2-hydroxyestradiol by a different route has been reported. L. R. Axelrod and P. Narasimha Rao, Chemistry and Industry, 1954 (1959).

EXPERIMENTAL[14]

16α,17β-Dihydroxy-$\Delta^{1,3,5(10)}$-estratriene, 3-(2-benzoyl-4-nitro)-phenyl ether (Ia). To a solution of 8.3 g. of estriol in 250 ml. of 95% ethanol containing 1.5 g. of potassium hydroxide, was added 6.5 g. of 2-chloro-5-nitrobenzophenone. The solution was refluxed for 48 hr., acidified with dilute sulfuric acid to *p*H 3, and continuously extracted with ether for 24 hr. The ether extract, after drying and evaporation, was taken up in chloroform and passed through a 300 g. alumina column. All material eluted with chloroform was discarded. Elution with chloroform containing 5% methanol afforded 5.6 g. of product, m.p. 122–130°, while 10% methanol eluted 1.5 g. of estriol. The benzophenone ether was recrystallized from methanol to give the analytical sample of Ia, m.p. 132–144°; λ_{max}^{EtOH} 255 mμ (ε 16,000), 297 mμ (ε 11,000), λ_{min}^{EtOH} 238 mμ (ε 13,000), 282 mμ (ε 10,500). Further recrystallizations did not change the melting point.

Anal. Calcd. for $C_{31}H_{31}O_6N$: C, 72.49; H, 6.08. Found: C, 72.67; H, 6.55.

16α,17β-Diacetoxy-$\Delta^{1,3,5(10)}$-estratriene, 3-(2-benzoyl-4-nitro)-phenyl ether (Ib). Acetylation of Ia with acetic anhydride in pyridine yielded the 16α,17β-diacetate as a viscous oil; the infrared spectrum in chloroform solution showed no hydroxyl absorption at 3600 cm.$^{-1}$ An analytical sample crystallized from acetic acid, melted 74–76°.

Anal. Calcd. for $C_{35}H_{35}O_8N$: C, 70.34; H, 5.87. Found: C, 70.63; H, 6.08.

2-Hydroxy-16α,17β-diacetoxy-$\Delta^{1,3,5(10)}$-estratriene, 3-(2-benzoyl-4-nitro)phenyl ether (Ic). One g. of the diacetate Ib was dissolved in 2 cc. acetic acid and 2 cc. of ice-cold concentrated sulfuric acid was added with cooling. After standing for 0.5 hr. at room temperature the mixture was diluted with 15 cc. of glacial acetic acid and an excess of 30% hydrogen peroxide was added dropwise. The solution was allowed to stand for an additional 0.5 hr., and was then poured into water. The precipitate was filtered off and washed well with water; the dried tan solid weighed 750 mg. The infrared spectrum in chloroform solution exhibited a strong band at 1655 cm.$^{-1}$ characteristic of the conjugated ketone strongly hydrogen bonded with the new hydroxyl.[2]

2-Methoxy-16α,17β-diacetoxy-$\Delta^{1,3,5(10)}$-estratriene, 3-(2-benzoyl-4-nitro)phenyl ether (Id). Seven hundred mg. of Ic were dissolved in the minimum amount of an ethanol-ether mixture and allowed to stand for 24 hr. with an excess of distilled ethereal diazomethane. Evaporation of solvents and

(9) J. C. Sheehan, W. F. Erman, and P. A. Cruickshank, *J. Am. Chem. Soc.*, **79**, 147 (1957).

(10) J. B. Niederl and H. J. Vogel, *J. Am. Chem. Soc.*, **71**, 2566 (1949).

(11) H. Werbin and C. Holloway, *J. Biol. Chem.*, **223**, 651 (1956).

(12) G. C. Mueller, *Nature*, **176**, 127 (1955).

(13) C. Huggins and E. P. Jensen, *J. Experimental Med.*, **102**, 335 (1955).

(14) Melting points were determined on a hot-stage apparatus and are corrected. Rotations were determined in a 2-dcm. tube and chloroform was the solvent unless otherwise specified. Analyses were performed by Spang Microanalytical Laboratories.

crystallization of the residue from methanol gave the product, m.p. 151–154°. The infrared spectrum of this compound in chloroform solution showed the normal conjugated band at 1672 cm.$^{-1}$ The analytical sample melted 155–158°.

Anal. Calcd. for $C_{36}H_{37}O_9N$: C, 68.88; H, 5.94. Found: C, 69.14; H, 6.36.

2-Methoxyestriol (IIa). In a nitrogen atmosphere 600 mg. of Id was refluxed for 1 hr. with 6% ethanolic potassium hydroxide. Acidification with sulfuric acid and extraction with chloroform and ether gave the crude product which was purified by a 99 tube counter current distribution in the system 50% aqueous methanol and 1:1 cyclohexane-ethyl acetate. Crystals contained in tubes 20–35 were combined and recrystallized from dilute acetone to give 180 mg. of IIa, m.p. 211–214°.

The analytical sample was obtained from methanol-benzene and melted at 215–218°; $[\alpha]_D^{26}$ +83° (ethanol), λ_{max}^{EtOH} 286 mμ (ε 3500), λ_{min} 253 mμ (ε 350).

Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.28; H, 8.21.

2-Hydroxyestriol, 3-methyl ether, 16,17-diacetate (IIb). Five g. of the benzophenone ether (Ib) were cyclized and oxidized as described previously. The 2-hydroxy product (Ic) was dissolved in alkali, allowed to stand for 15 min., acidified and the partially rearranged product was re-extracted. The crude material was taken up in ethanol and treated with an excess of ethereal diazomethane. The product obtained, a mixture melting at 160–190°, was then reacetylated. The total material was refluxed in 60 cc. of piperidine for 1.5 hr. under nitrogen. The cooled solution was diluted with 200 cc. of benzene and washed well with cold 5% sulfuric acid. After washing with 5% sodium bicarbonate solution and water, an oily residue was obtained when the solvent was removed. This was taken up in benzene and chromatographed on 220 g. of acid washed alumina. Elution with 20% ether-benzene gave 0.6 g. of crystalline material, m.p. 176–180°. The analytical sample of 2-hydroxyestriol, 3-methyl ether, 16,17-diacetate (IIb) was obtained from benzene-petroleum ether and melted at 178–181° $[\alpha]_D^{27}$ −16.5°.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.86; H, 7.51. Found: C, 68.80; H, 7.36.

Preceding chromatographic fractions were oils which on hydrolysis with 5% ethanolic potassium hydroxide gave after purification 1 g. of 2-methyloxyestriol (IIa).

2-Hydroxyestriol, 3-methyl ether (IIc). Hydrolysis of 0.5 g. of the diacetate (IIb) in 5% ethanolic potassium hydroxide and crystallization of the product from methanol-benzene gave 230 mg. of material m.p. 260–269°. The analytical sample was obtained as needles m.p. 268–271°, $[\alpha]_D^{25}$ +64° (ethanol). The ultraviolet spectrum was identical with that of 2-methoxyestriol (IIa), the infrared spectrum in potassium bromide showed differences only in the 650–1400 cm.$^{-1}$ region.

Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.69; H, 8.24.

2-Methoxyestriol, 3-methyl ether (IId). A small amount of IIc was methylated with diazomethane in ether-ethanol. Purification of the product by alumina chromatography and elution with chloroform gave crystals which melted at 100–110°, resolidified, and then melted at 188–191°. The analytical sample was obtained from acetone–petroleum ether as needles melting at 190–192°, $[\alpha]_D^{27}$ +69°. Despite vacuum drying at 50° the sample retained water.

Anal. Calcd. for $C_{20}H_{28}O_4 \cdot H_2O$: C, 68.55; H, 8.57. Found: C, 68.31; H, 8.44.

Similar methylation of 2-methoxyestriol (IIa) gave material m.p. 189–191°, identical with the above by mixed melting point and infrared spectra comparison.

2-Hydroxyestradiol, 3-methyl ether, 17-acetate (IVa). Eight g. of III was dissolved in Claisen alkali and was allowed to stand at room temperature for 15 min. Acidification and extraction with chloroform gave a crude mixture which was methylated with diazomethane. The methylated product was reacetylated and was then refluxed in 100 ml. of piperidine for 1 hr. After the usual work-up the product was chromatographed on alumina. Elution with 30% benzene in petroleum ether gave 1 g. of 2-methoxyestradiol, 17-acetate (IVb). With 50% benzene in petroleum ether 3.1 g. of IVa, m.p. 198–208° was obtained. The analytical sample of 2-hydroxyestradiol, 3-methyl ether, 17-acetate (IVa) was recrystallized from benzene petroleum ether and melted 210–212°, with long needles forming at 188°, $[\alpha]_D^{27}$ +43.0°.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.17. Found: C, 73.25; H, 8.24.

2-Hydroxyestradiol, 3-methyl ether (IVc). One g. of the acetate IVa was hydrolyzed in the usual manner with 5% ethanolic potassium hydroxide to give 0.85 g. of product. Crystallization from acetone afforded the analytical sample of IVc, m.p. 179–181°, $[\alpha]_D^{28}$ +74°.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 74.98; H, 8.44.

2-Methoxyestradiol, 3-methyl ether, 17-acetate (IVd). Methylation of IVa with ethereal diazomethane gave after separation from unchanged material the dimethyl ether IVd, m.p. 178–180° from ethanol. The analytical sample melted at 179–182° with sublimation, $[\alpha]_D^{27}$ +53°.

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.75; H, 8.38. Found: C, 73.75; H, 8.71.

The product obtained from a similar methylation of 2-methoxyestradiol, 17-acetate (IVb) was identical with the above by mixed melting point and infrared spectral comparison.

Hydrolysis of the dimethoxy compound IVd with methanolic potassium hydroxide gave 2-methoxyestradiol, 3-methyl ether (IVe), m.p. 131–133° from methanol-ether. The material retained solvent tenaciously with melting at 100–110° and resolidification. The analytical sample showed similar behavior in melting point, $[\alpha]_D^{27}$ +85°.

Anal. Calcd. for $C_{20}H_{26}O_3 \cdot {}^1/_2CH_3OH$: C, 74.59; H, 8.92. Found: C, 74.12; H, 9.02.

2-Methoxyestrone, 3-methyl ether (Va). Oxidation of a small amount of the dimethoxyestradiol compound IVe, with chromic acid in acetone gave, on the usual work-up, the 17-keto derivative Va, m.p. 172–175° from methanol. The analytical sample of 2-methoxyestrone, 3-methyl ether (Va), was obtained as needles, m.p. 173–176°.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.43; H, 8.28. Found: C, 76.41; H, 8.21.

The same compound was also obtained by methylation of 2-methoxyestrone.

2-Hydroxyestradiol (IVf). One g. of the 3-methyl ether (IVc) was heated with 2 g. of freshly distilled pyridine hydrochloride for 15 min. at 200–220°. Dilution with water and extraction with a chloroform-ethanol mixture gave 700 mg. of product as tan colored crystals from dilute methanol. Recrystallization from the same solvent afforded the analytical sample which melted at 110–113° resolidified and melted again at 155–158°; $[\alpha]_D^{28}$ +90° (ethanol), λ_{max}^{EtOH} 289 (ε 3600), λ_{min} 251 (ε 650). The material was hydroscopic and despite drying at 65° retained a molecule of water.

Anal. Calcd. for $C_{18}H_{24}O_3 \cdot H_2O$: C, 70.56; H, 8.55. Found: C, 70.87; H, 8.56.

This same compound (IVf) was also obtained by an alternate route from III. Piperidine cleavage of III gave 2-hydroxyestradiol, 17-acetate (IVg), which crystallized from benzene-petroleum ether and melted at 100–109°, resolidified, and melted 182–185°. The analytical sample of IVg was dried at 65° for 12 hr. and melted 182–185°, $[\alpha]_D^{26}$ +59°.

Anal. Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.88; H, 7.74.

Acid hydrolysis of the above with 10% ethanolic sulfuric acid afforded 2-hydroxyestradiol (IVf).

2-Hydroxyestrone (Vb). One hundred mg. of 2-methoxyestrone was heated with pyridine hydrochloride as previously described. The reaction mixture was diluted with water

and filtered. The precipitate (63 mg.), crystallized from benzene, melted at 192–194°. The analytical sample of Vb melted at 194–196°; $[\alpha]_D^{27}$ +172° (ethanol).

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.52; H, 7.69. Found: C, 75.14; H, 7.76.

The same compound was obtained from either IIa or IIc on heating with pyridine hydrochloride for 1 hr. at 200°.

An alternative route led via the Schotten-Bauman benzoylation of 2-hydroxyestradiol (IVf) to give the dibenzoate which on oxidation with chromic acid in acetic acid gave 2-hydroxyestrone, 2,3-dibenzoate (Vc) m.p. 172–174° from ethanol.

Anal. Calcd. for $C_{32}H_{30}O_5$: C, 77.71; H, 6.11. Found: C, 77.66; H, 6.10.

Mild alkaline hydrolysis of the above under a nitrogen atmosphere gave 2-hydroxyestrone (Vb).

4-Hydroxyestrone (Ve).[15] Pyridine hydrochloride fusion of 200 mg. 4-hydroxyestrone, 3-methyl ether (Vd) gave 138 mg. of product which crystallized from benzene-methanol with a m.p. 260–265° dec. The analytical sample obtained from the same solvent melted at 266–270° dec. with sublimation; $[\alpha]_D^{27}$ +155° (ethanol).

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 74.99; H, 7.67.

Acknowledgment. The authors wish to thank Dr. T. F. Gallagher for his advice and interest in this work. They wish to thank Mrs. Beatrice S. Gallagher for the infrared spectra.

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(15) The diacetate of this compound has been prepared by oxidation with lead tetracetate, A. M. Gold and E. Schwenk, *J. Am. Chem. Soc.*, **80**, 5683 (1958).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY, GLASGOW]

Compounds Related to a Possible Precursor of Diploicin[1]

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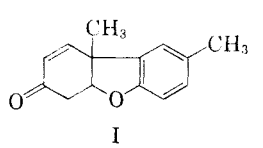
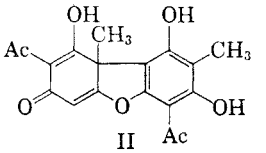
Received September 23, 1959

The synthesis of compounds related to a possible biosynthetic precursor of diploicin (IVb) a chlorine-containing lichen substance, is described. The relative ease of decarboxylation of 3,5-dichloro-*o*-orsellinic acid and two of its derivatives is discussed. 2,4-Dichloroörcinol undergoes diacylation preferentially, despite steric factors which should favor monoacylation.

Recent work on oxidative coupling of phenols, involving one-electron-transfer oxidizing agents, has elucidated the true nature of the crystalline dimer obtained by oxidizing *p*-cresol with alkaline ferricyanide (I).[3] Usnic acid (II), a lichen metabolite, has been synthesized by a similar process.[3] Scott has also utilized this coupling process in carrying out the partial synthesis of (±)-dehydrogriseofulvin and (±)-geodin methyl ether from related benzophenone derivatives.[4] Brockmann and coworkers have demonstrated related oxidations of hypericin precursors.[5] Bruice oxidized 3-methoxymesitol with alkaline ferricyanide and obtained only linear coupling and hydroxylation products,[6] in contrast to I and II, which resulted from free radical coupling followed by ionic cyclization. The concept of oxidative coupling of phenols as a biogenetic mechanism has been discussed in detail by Barton and Cohen.[7]



I



II

Diploicin (IVb), a chlorine-containing lichen metabolite,[8] was selected as a prospective further example of a natural product which could be synthesized by oxidative coupling of a phenolic precursor *in vitro*. The structure of diploicin, which is obtained from *Buellia canescens*, was elucidated by Nolan and co-workers.[9,10,11] Our initial objective was preparation of a compound such as IIIb, whose blocking groups could be readily removed. A subsequent conversion IIIa→IVa, effected by oxidative cyclization through electron pairing, was envisioned as follows:

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(1) This investigation was supported by Research Grant EF-5415 from the National Institutes of Health.

(2) National Heart Institute Research Fellow, University of Glasgow, 1955–56. Present address, Northern Regional Research Laboratory, Peoria, Illinois.

(3) D. H. R. Barton, A. M. Deflorin, and O. E. Edwards, *J. Chem. Soc.*, 1956, 530.

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(7) D. H. R. Barton and T. H. Cohen in *Festschrift Arthur Stoll*, Birkhäuser AG, Basel, 1957, p. 117.

(8) For reviews on lichen substances, *cf.* Y. Asahina and S. Shibata, *The Chemistry of Lichen Substances*, Japan Society for Promotion of Science, Tokyo, 1954; S. Shibata in *Encyclopedia of Plant Physiology*, Vol. X, ed. by W. Ruhland, Springer-Verlag, Berlin, 1958, p. 560.

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