Tetrahedron, 1965, Vol. 21, pp. 3605 to 3631. Pergamon Press Ltd. Printed in Northern Ireland

TOTAL SYNTHESIS OF COLCHICINE MODELLED ON A BIOGENETIC THEORY[1,2]

A. I. SCOTT,* F. MCCAPRA, R. L. BUCHANAN, A. C. DAY[3] and D. W. YOUNG[4]
Department of Organic Chemistry, University of British Columbia, Vancouver, B.C.

(*Received* 15 *January* 1965)

Abstract—A five step synthesis of desacetamidocolchiceine (XLVI) is described in which rings A and C are joined by oxidative coupling of the tropolone system. This completes a biogenetic-type total synthesis of colchicine (I).

THE study of Colchicine has for many years provided an impressive record of innate complexity, apparently out of all proportion in a molecule containing only three rings, and one readily controlled centre of asymmetry. Thus, structural investigations have spanned the last one hundred and forty years[5] and were only effectively terminated by Dewar's far-reaching postulate[6] which invoked a tropolonoid ring to rationalize the unusual reactions of ring C of the alkaloid. The final solution of the structural[7] and stereochemical[8] details are embodied in I.

Perhaps more surprising are the several failures reported since 1950 of attempted *synthetic* routes to colchicine. Clearly the challenge to the synthetic organic chemist offered by the alkaloid was not only worthy[9] but perhaps unique.[10] In 1959, a series of elegant experiments were described in which two distinct methods were evolved for the addition of a seven-membered ring to the 6–7 system (II). This was followed by transformation of ring C to full tropolone level in a complex and often hostile environment and marked the first successful arrival at the synthetic relay desacetamidocolchiceine (VI; R = CH_3, R′ = H). Conversion of the latter to colchicine by almost identical methods involving nitrogen insertion at the activated position (II; arrow)

* New address, The Chemical Laboratory, University of Sussex, Brighton.

[1] Phenol Oxidation VII. Part VI, A. J. Baker, A. C. Day, M. B. Meyers and A. I. Scott, *Proc. Symposium on Naturally Occurring Phenols* p. 11. Delhi (1964).

[2] Part of this work was described in preliminary communications: [a] A. I. Scott, Frank McCapra, J. Nabney, D. W. Young, A. C. Day, A. J. Baker and T. A. Davidson, *J. Amer. Chem. Soc.* **83**, 3040 (1963); [b] *Idem* Pre-Symposium Meeting *Naturally Occurring Phenols* Tokyo (1964).

[3] Present address, Dyson Perrins Laboratory, Oxford.

[4] Present address, Converse Memorial Laboratory, Harvard.

[5] Cf. P. J. Pelletier and J. B. Caventou, *Ann. Chim. Phys.* (2) **14**, 82 (1820).

[6] M. J. S. Dewar, *Nature, Lond.* **155**, 141 (1945). For survey of earlier work see J. W. Cook and J. D. Loudon in R. H. F. Manske and H. C. Holmes, *The Alkaloids* Vol. II, pp. 261–329 (1952); For early reports on medicinal and physiological effects of *Colchicum*, see e.g. Theophrastus *Enquiry into Plants* IX, **16**, 5 (300 B.C.) and Dioscorides, *De materia medica* A.D. 78. More recent results are summarised by O. J. Eigsti and P. Dustin Jr., *Colchicine*, Iowa State College Press, Ames, Iowa (1955).

[7] M. V. King, J. L. de Vries and R. Pepinsky, *Acta Cryst.* **5**, 437 (1952).

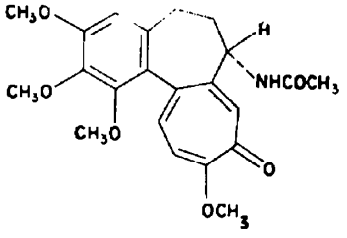
[8] H. Corrodi and E. Hardegger, *Helv. Chim. Acta* **38**, 2030 (1955).

[9] R. B. Woodward in *Perspectives in Organic Chemistry* (Edited by Lord Todd) Interscience, New York (1956).

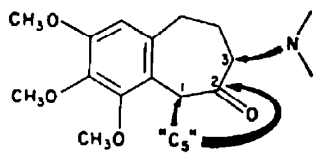
[10] E. E. van Tamelen, T. R. Spencer Jr., D. S. Allen and R. L. Orvis, *Tetrahedron* **14**, 8 (1961); Preliminary Communication, *Idem. J. Amer. Chem. Soc.* **81**, 6341 (1959).

constituted total syntheses of the alkaloid by the groups of van Tamelen[10] and of Eschenmoser.[11]

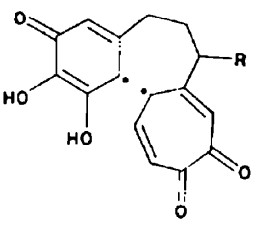
The third aspect of colchicine chemistry which appears to promise yet another challenge is the unravelling of the detailed pathway of biosynthesis leading via phenylalanine to the tricyclic system and including the formation of the tropolonoid ring C. For not only have the first reports of the incorporation of variously labelled C_6–C_3 units into the alkaloid (e.g. phenylalanine, tyrosine) shown that a straightforward rationale is difficult,[12] but further, the mechanism of formation of tropolone rings in simpler natural products is still a matter of considerable mystery.[13]



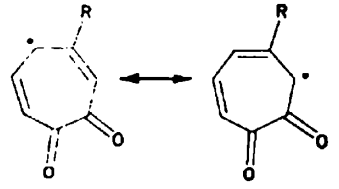
I



II



III



IV

We considered that some insight into the mechanism of possible modes of colchicine biosynthesis could be gained by the construction of an appropriate substrate whose subsequent chemical behavior could be utilized in planning further biosynthetic experiments.[14] Thus with two elegant solutions[10,11] to the synthetic problem

[11] J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel, T. Threlfall and A. Eschenmoser, *Helv. Chim. Acta* **44**, 540 (1961). Preliminary Communication: J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel and A. Eschenmoser, *Angew. Chem.* **71**, 637 (1959).

[12] E. Leete, *J. Amer. Chem. Soc.* **85**, 3666 (1963); E. Leete and P. E. Nemeth, *Ibid.* **82**, 6055 (1960); A. R. Battersby and J. J. Reynolds, *Proc. Chem. Soc.* 346 (1960); A. R. Battersby, *Quart. Rev.* **15**, 259 (1961).

[13] See for example R. Bentley, *Biochem. Biophys. Research Comm.* **2**, 107 (1960); *Idem. Fed. Proc.* **20**, 80 (1961); *Idem. Ann. Rev. Biochem.* **31**, 589 (1962).

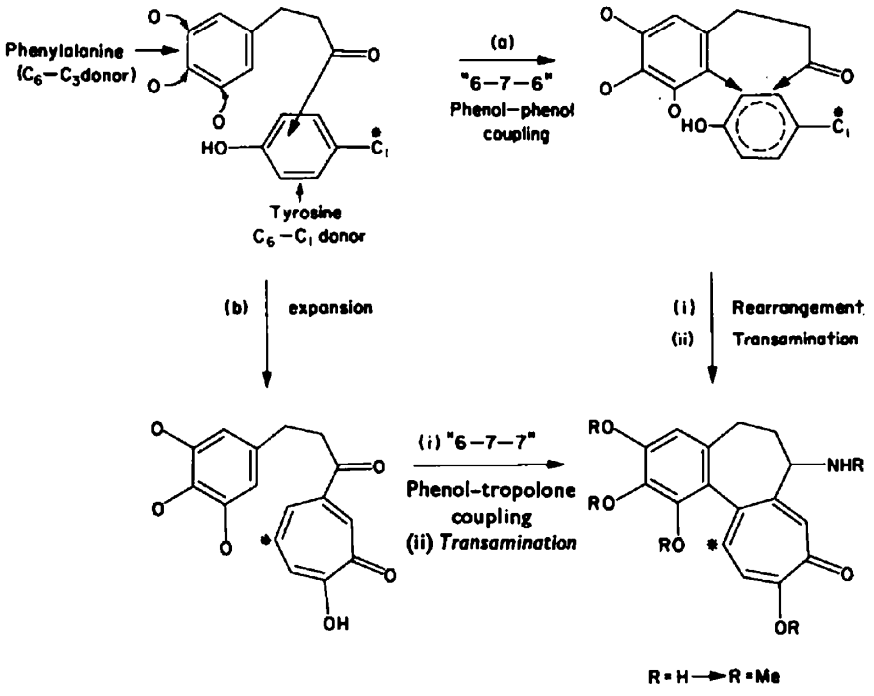
[14] Recent revision[15] of previously reported[12] incorporation experiments now render valid almost all of the published speculations[16] concerning colchicine biosynthesis. Although warnings against speculation on courses of biosynthesis have, on occasion, been sounded we believe that few meaningful tracer experiments would have been undertaken in the absence of stimulation provided by hypothetical schemes of biosynthesis. We should in turn wish to add a plea for equal reticence in the reporting of incorporation experiments which are later shown to have little or no basis in fact.

[15] E. Leete, I.U.P.A.C. Symposium, London 1963. Handbook, p. 213; A. R. Battersby, *Private communication*. We thank Professor Battersby for kindly informing us of his recent results prior to publication; see A. R. Battersby and R. B. Herbert, *Proc. Chem. Soc.* 260 (1964).

[16] For a comprehensive survey see K. Mothes, *Angew. Chem.* (International Ed.) **2**, 441 (1963).

already before us, we began the preparation of compounds which might formally arise in Nature as intermediates on the way to colchicine, our hope being that laboratory reagents could be found which would transform such substrates into the alkaloid.[17] Such syntheses would further afford stimulus in preparing similar substrates in radioactive form for incorporation work.[21]

Consideration of possible modes of biosynthesis based on preliminary incorporation data led us to formulate a proposal[23] for a radical coupling reaction (III) of tropolone (IV) and phenol rings in an intermediate derivable formally from the



[17] Such laboratory conversions cannot of course be claimed as exact counterparts of natural processes. We feel however that their value lies in indicating possible mechanisms related to *in vivo* processes as well as providing valuable intermediates, not only for incorporation but also for comparison with plant extracts. These principles have been illustrated with several classes of natural product recently.[18–20]

[18] *Griseofulvin:* A. C. Day, J. Nabney and A. I. Scott, *J. Chem. Soc.* 4067 (1961).

[19] *Tetracyclines:* A. I. Scott and C. T. Bedford, *J. Amer. Chem. Soc.* **84**, 3197 (1962).

[20] *Calycanthaceous Alkaloids:* A. I. Scott, F. McCapra and E. S. Hall, *J. Amer. Chem. Soc.* **86**, 302 (1964).

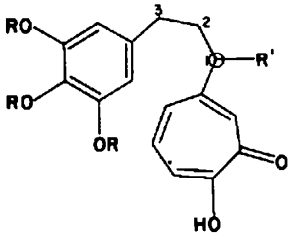
[21] The advisability of commencing synthetic work even when excellent solutions[10,11] have been offered might be questioned at a time when physical methods render structural proof by synthetic means of doubtful utility. Justification in this and other cases may be claimed where implications are raised for subsequent biochemical work and/or new reactions discovered. Indeed, during the course of our work, two further syntheses of colchicine have been completed [R. B. Woodward in *The Harvey Lectures* 1965; S. Sunagawa, J. Nakamura and K. Nakazawa, *Chem. Pharm. Bull.* **8**, 843 (1960); **9**, 81 (1961); **10**, 281 (1962)]. For another viewpoint of this philosophical dilemma see footnote p. 248 in Ref. 22.

[22] R. B. Woodward, M. P. Cava, W. J. Ollis, A. Hunger, H. V. Daeniker, *Tetrahedron* **19**, 247 (1963).

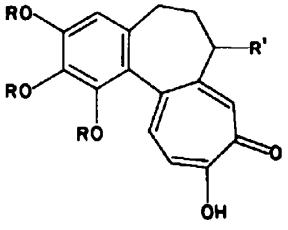
[23] A. I. Scott, *Nature, Lond.* **186**, 556 (1960).

building blocks of phenylalanine and/or tyrosine. More recent labelling experiments[15] are summarized without mechanistic implication in Chart I.

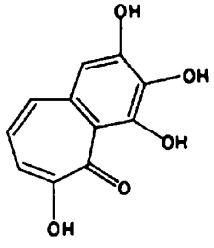
Our objective in this model of biosynthesis was the preparation of a β-phenylpropyl tropolone (as V) and a study of its behavior under a variety of oxidative conditions. Successful entry into the tricyclic series (as VI) would then constitute a new synthetic route to colchicine.[24]



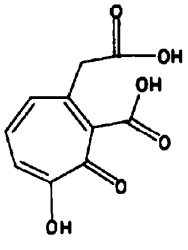
V



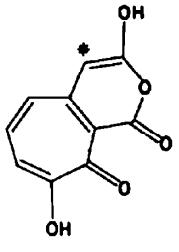
VI



VII



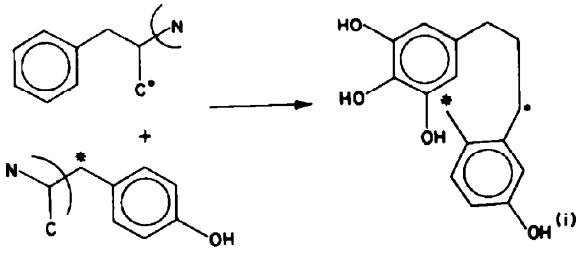
VII a



VIII

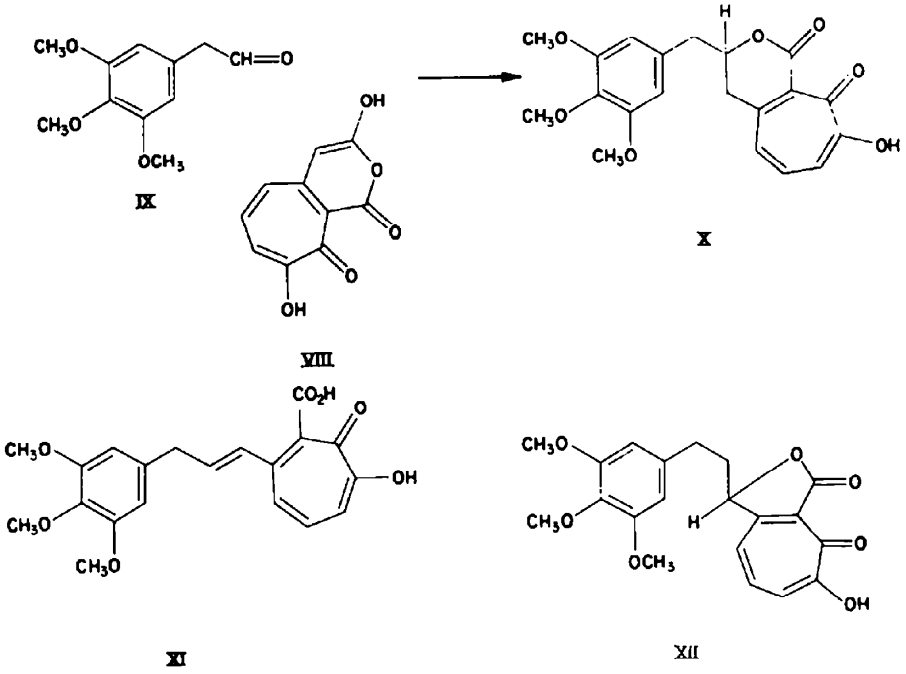
Our starting material for the construction of V was the versatile purpurogallin (VII), both rings of which were retained in the annelation approach,[10,11] but which was used in our studies as a source of an appropriately substituted *intact tropolone* unit. With some modifications of the original methods[25] purpurogallin could be converted by preferential oxidation of the pyrogallol ring to the anhydride (VIII) of the dicarboxylic acid (VIIa). The reactivity of the methylene position (marked with

[24] As in other preparations[10,11] of the alkaloid, the nitrogenous function is added in the very late stages. Experiments in progress are designed to test the effect of the presence of nitrogen on cyclizations (V → VI; N at C-1). It is perhaps noteworthy that work on biosynthesis indicates that the nitrogen function of phenylalanine and tyrosine are not used directly in the genesis of precursors of type (i):



[25] R. D. Haworth and J. D. Hobson, *J. Chem. Soc.* 561 (1951), W. D. Crow, R. D. Haworth and P. R. Jeffries, *Ibid.* 3705 (1952).

an asterisk in VIII) as a nucleophilic centre had already been noted.[25,26] The obvious choice for such condensation with VIII is 3,4,5-trimethoxyphenylacetaldehyde (IX). However, although successful Knoevenagel-type reactions of benzaldehyde,[25,26] and

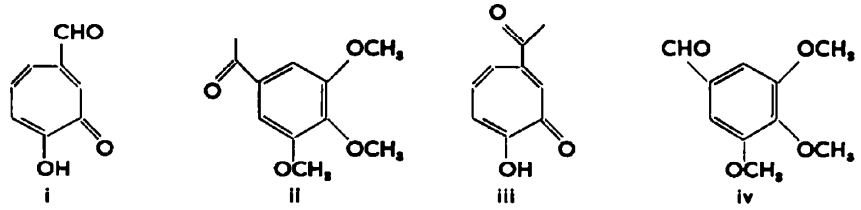


phenylacetaldehyde[26] with VIII have been reported, it had been shown[26] that oxygenated phenylacetaldehydes failed to condense with the anhydride. In spite of this observation, we felt that such a convenient method of assembling in one step all of the essential carbon atoms for our oxidative experiments should be examined in some detail.[27]

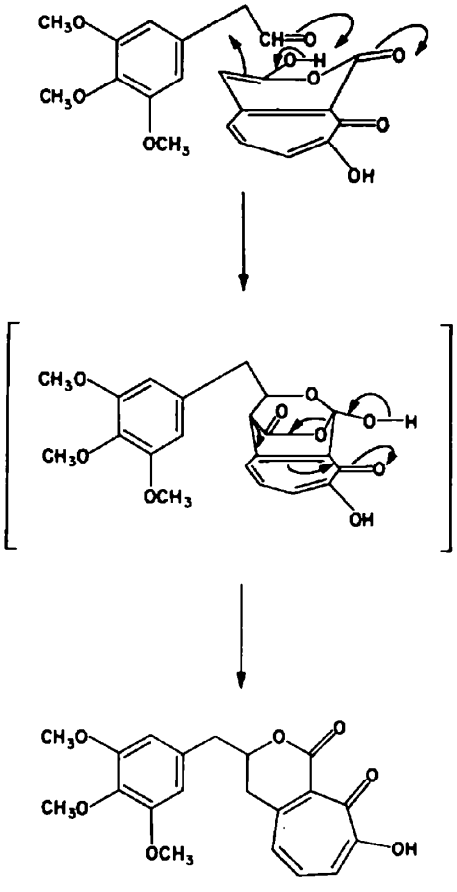
In fact we were able to confirm the reported failure[26] of the base-catalysed condensation of VIII and IX under a wide variety of conditions. However in

[26] T. Nozoe, Y. Kitahara, and K. Doi, *Proc. Japan Academy* **29**, 203 (1953); T. Nozoe, Y. Kitahara, K. Doi, and S. Masamune, *Ibid.* **28**, 291 (1952). T. Nozoe in Ginsburg (Fd.) *Non-Benzenoid Aromatic Compounds*. Interscience, New York (1956).

[27] Numerous other methods for the construction of C_6–C_3–C_7 systems were examined. We may mention two of these which were set aside for a variety of reasons. Thus, condensation of β-formyltropolone (i) with 3,4,5-trimethoxyacetophenone (ii) proceeded with difficulty and the attractive method of Nozoe[28] using β-acetyltropolone (iii) and 3,4,5-trimethoxybenzaldehyde (iv) has not, until recently, been evaluated due to the difficulty of obtaining (iii). This situation has now been relieved through the generosity of Professor T. Nozoe. The results of these experiments will be published elsewhere, as will certain supplemental experiments germane to the first approach.



the course of the many trial experiments it was found that a smooth reaction between VIII and IX accompanied by loss of carbon dioxide could be effected simply by heating their mixture at 100° for 20 min. The resultant highly crystalline condensate (m.p. 170°) exhibited analytical and spectroscopic properties consistent only with structure X. Thus, the absence of olefinic protons in the NMR spectrum and lack of carboxylic acidity rendered the unsaturated acid formulation (XI) untenable. Secondly, X is preferred to its isomer (XII) on the basis of the following evidence. The presence of a dilactone fused to an aromatic ring is suggested by carbonyl absorption in the IR at 1720 cm^{-1}. The corresponding γ-lactone (XII) would, by analogy with phthalide carbonyl frequencies be expected[28] to absorb at ca. 1750–1760 cm^{-1}. Furthermore, in the NMR spectrum the presence of a four proton "benzylic" pattern with a broad multiplet (I H) of chemical shift characteristic of CH—O— in the lactone favors X, since XII would be expected to show benzylic (2H) methylene

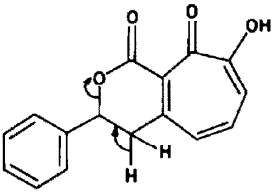


X

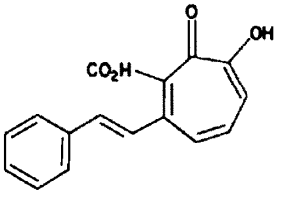
[28] W. R. Allison and G. T. Newbold, *J. Chem. Soc.* 3335 (1959); Phthalide 1761 cm^{-1}; 7-OH phthalides 1732–48 cm^{-1}.

(2H) and Ar—CH—O (low field) resonances.[29] The formation of a stable lactone under these conditions is worthy of comment since benzaldehyde forms the unsaturated acid (XV) under similar conditions.[26] A mechanism such as that depicted above serves to rationalize lactone formation as well as explaining the preference for the open acid (XV) in the case of benzaldehyde. Thus in the latter, the lactone opening (XIV) gains driving force *via* incipient carbonium ion formation as shown.

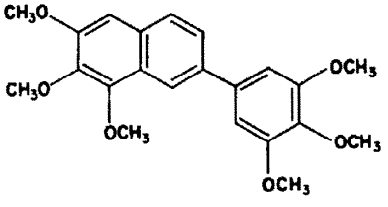
A neutral by-product of the reaction formed in larger amounts where rigorous purification of trimethoxyphenylacetaldehyde was not enforced is the neutral self condensation product (XVI) whose genesis follows well-authenticated precedent.[30]



XIV



XV



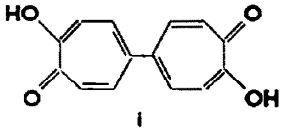
XVI

Further prosecution of this condensation reaction, which could be realized in yields up to 80%, was now temporarily suspended while we considered the details of the ultimate state of protection of ring A as required by efficient free radical reactivity, combined with reasonable defence against oxidative rupture. Of three convenient possibilities (XVII–XIX) we adjudged XVII to be most suitable for our purpose in that the corresponding radical (XVIIa) was accompanied by a superior stability specific of the catechol ether grouping compared with say that of XIX. For we had good reason[31] to believe that forcing conditions might be necessary to bring the oxidative coupling potential of the tropolone ring into play.

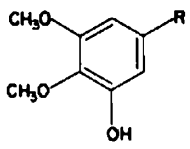
[29] G. V. D. Tiers, *Summary of NMR Data.* Minnesota Mining and Manufacturing Co., St. Paul, Minnesota.

[30] E. g. E. Zincke, *Liebigs Ann.* **240**, 137 (1887).

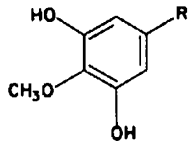
[31] Based on the rather drastic conditions required for example, to effect hydroxylation (persulphate reaction) at the γ-position of the tropolone ring (T. Nozoe, S. Serv, S. Ito, M. Sato and T. Karono, *Science Reports, Tohoku University* Series I, 37, 191 (1953). Preliminary experiments (Dr. T. Money, Glasgow University, 1959 unpublished) had indicated that the γ-position of the parent tropolone could participate in a radical coupling reaction. Thus in the presence of hot, alkaline ferricyanide (CO_3 absent) tropolone gave a small yield of its 4-carboxylic acid possibily *via* 4:4′-bitropolonyl (i)



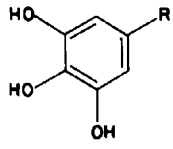
i



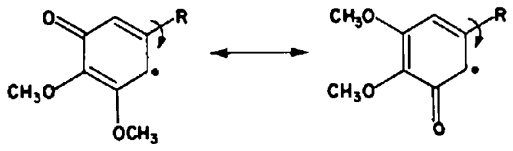
XVII



XVIII

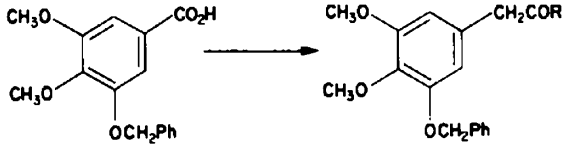


XIX



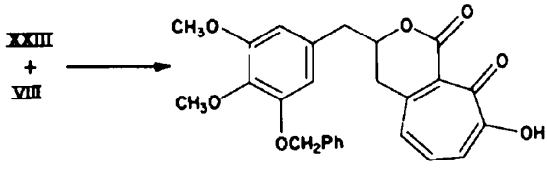
XVII a

A method for the selective functionalization of gallic acid in the required sense for the preparation of XVII was available[32] and allowed the preparation of XX on a large scale. Arndt-Eistert homologation of XX afforded 3,4-dimethoxy-5-benzyloxyphenyl acetic acid (XXI) in good yield and conditions were found for carrying out Rosenmund reduction on the acid chloride (XXII) in 90% yield. The desired aldehyde (XXIII) when heated at 100° with the anhydride (VIII) for a short period yielded the corresponding lactone (XXIV) in 71% yield. Alkaline solutions of this lactone were



XX

XXI R = OH
XXII R = Cl
XXIII R = H



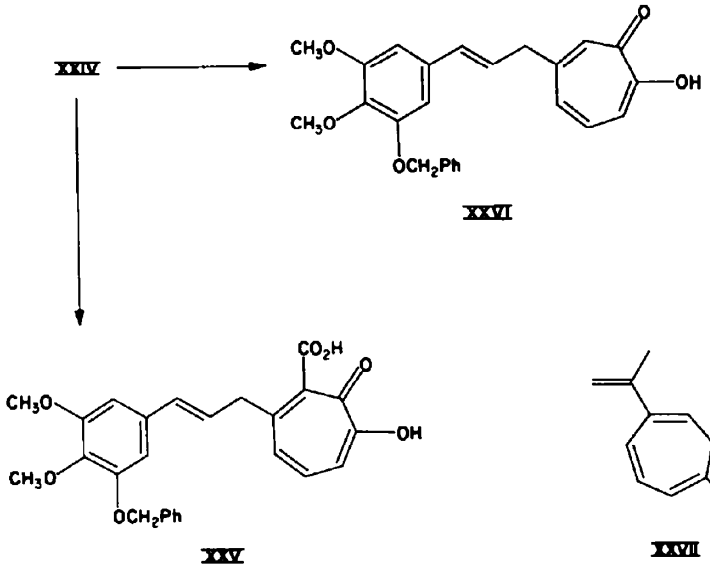
XXIV

found to be quite soluble in chloroform and in one experiment a sodium complex was isolated from the chloroform layer. In order to minimize extraction difficulties the series of the alkaline salts were examined and, as expected, a minimum effect of this

[32] L. Jurd, *J. Amer. Chem. Soc.* **81**, 4606 (1959).

kind was found with rubidium, while the lithium complex was most soluble in chloroform. Vigorous base treatment of the lactone (XXIV) furnished the unsaturated acid (XXV), whose decarboxylative behavior was found to be capricious. We therefore sought another method of removing the elements of carbon dioxide.

Under specific conditions the decarboxylation of the lactone could be effected in 70% yield by heating it to 270° *in vacuo* in the presence of copper bronze or quartz powder. The resultant styrene (XXVI) was isolated by distillation from the reaction vessel and characterized by its IR spectrum (954 cm^{-1}; *trans* CH=CH; 736/697 cm^{-1}, benzyl grouping; 1610 cm^{-1}, tropolone C=O) and UV absorption (λ_{max} 273 mμ). The conjugation of the double bond with the trimethoxyphenyl nucleus rather than with the tropolone ring followed from the close correspondence of its absorption to the chromophore of 3,4,5-trimethoxystyrene[33] (λ_{max} 264 mμ). On the other hand, β-dolabrin (XXVII) has λ_{max} 254 mμ.[34] The absence of tropolone and



carbonyl conjugated absorption was evident from the spectrum of the anion of XXVI which absorbed at 394 mμ compared with the lactonic anion, whose longest wavelength absorption is 428 mμ. The styrene (XXVI) could be characterized by conversion to a beautifully crystalline benzylamine *salt*.

The removal of the *trans* geometry of XXVI to allow the required approach of the 4-position of the tropolone ring to the aromatic nucleus was achieved by controlled catalytic reduction to the β-phenylpropyl-tropolone (XXVIII). Continued reduction, rather than promoting the desired hydrogenolysis of the benzyl group, led to disproportionate reduction of the tropolone ring under many conditions. Chemical and spectroscopic evidence showed that a mixture of cycloheptanone and cycloheptenone compounds was produced in this way.

[33] Isoelemicin (I) has λ_{max} 266 mμ (log ε 4·4).

[34] T. Nozoe, Y. Kitahara and K. Doi, *Chem. & Ind.* 1070 (1957).

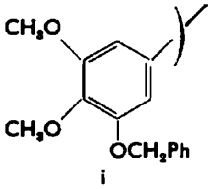
The dihydro compound (XXVIII) was therefore isolated and characterized by mass spectrometry and by the absence of styrene UV and IR characteristics.[35]

Selective removal of the benzyl grouping of XXVIII could in fact be promoted using hydrochloric acid. In this way the 2,3-dimethoxyphenol (XXIX) was isolable as a liquid, whose spectroscopic (UV, IR mass) and analytical constants revealed that only the desired debenzylation had occurred.[37]

We were now ready to attempt the closure of the seven-membered ring B of the colchicine framework by a series of oxidative experiments in which the intermediate di-radical (XXIXa) could serve as the reactive species. The required outcome of one such oxidation would have concluded the problem at once but as each successive reagent returned the starting phenol (XXVIII) unscathed (e.g. potassium ferricyanide) or as metal complex (e.g. ferric chloride, manganese dioxide) from which only starting material could eventually be liberated, it became apparent that access to the tricyclic series (as XXX) was not to be gained easily from the present intermediate.

We, therefore, now examined not only possible causes of such failure but, more importantly, an appropriate remedy for the task in hand. The inability of the 2,3-dimethoxyphenol (XXIX) to form a radical (XXIXa) sufficiently long-lived to be effective in coupling with the tropolone ring seemed a distinct possibility, although other cases of successful coupling of monohydric phenolic compounds bearing two methoxyl groups in the same ring are well-known.[38] A return to the consideration of the patterns (XVII–XIX) and their derived radicals left a clear choice between electing to preserve ring stability (XVIII) or perhaps arriving at the closest possible biological

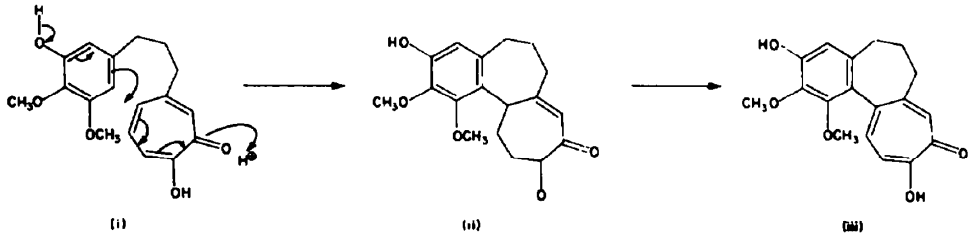
[35] The partial chromophore (i) might be expected to appear in the UV spectrum. However steric hindrance to coplanarity of the three oxygenated function with the ring is known to lower intensity to ca. ε 600[36] in pyrogallols, compared with, for example, resorcinols[36] ε_{max} ~3000).



i

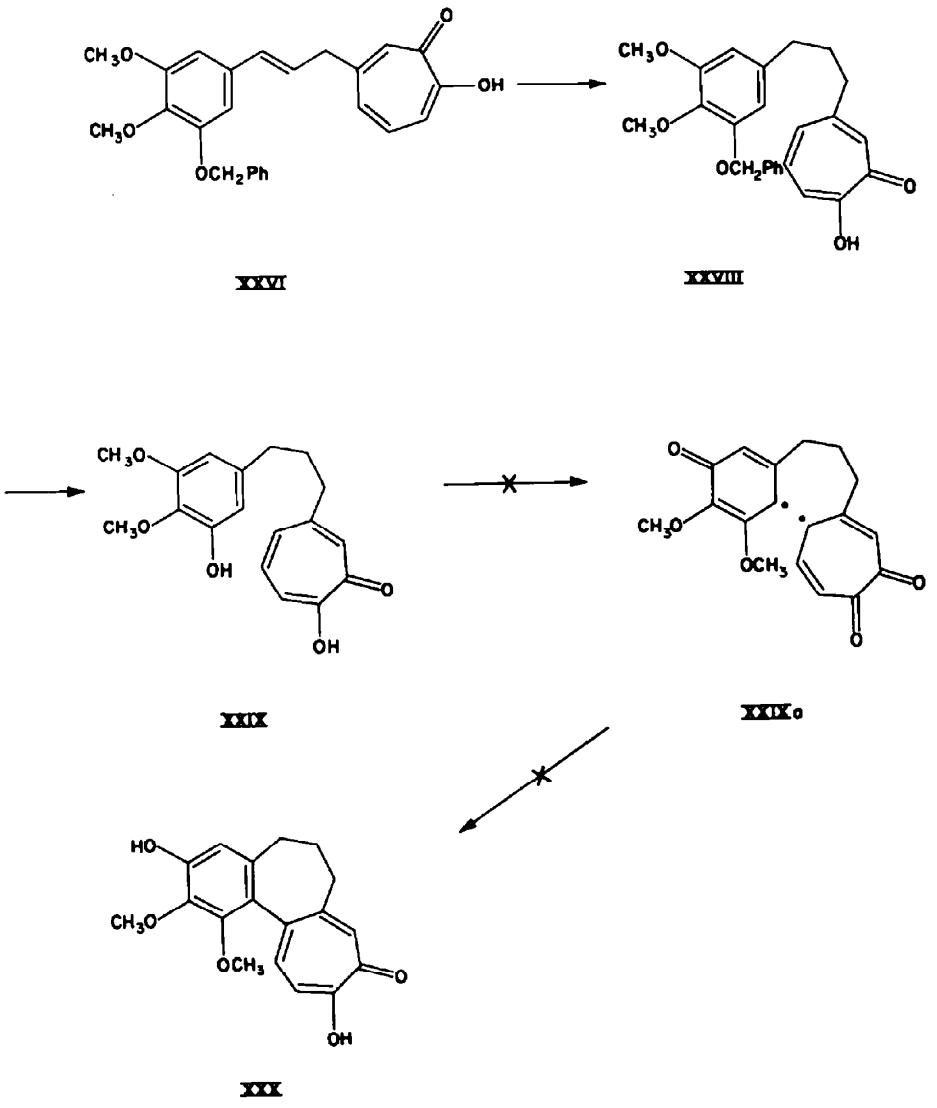
[36] A. I. Scott, *Interpretation of the Ultraviolet Spectra of Natural Products* Chap. 3. Pergamon, Oxford (1964) and Refs. cited.

[37] It was our hope that even at this stage under acidic conditions the feasibility of interaction of rings A and C (i, arrows) could be demonstrated by analogy with the reported "tropylation" of phenols.[38] However despite a close search no tricyclic material corresponding to (ii) or its further oxidation product (iii) could be detected in these and other debenzylation or demethylation reactions of (i) and its close relatives.



(i) (ii) (iii)

[38] A. F. Bickel, A. P. ter Botg and R. van Helden, *Rec. Trav. Chim.* **81**, 599 (1962).

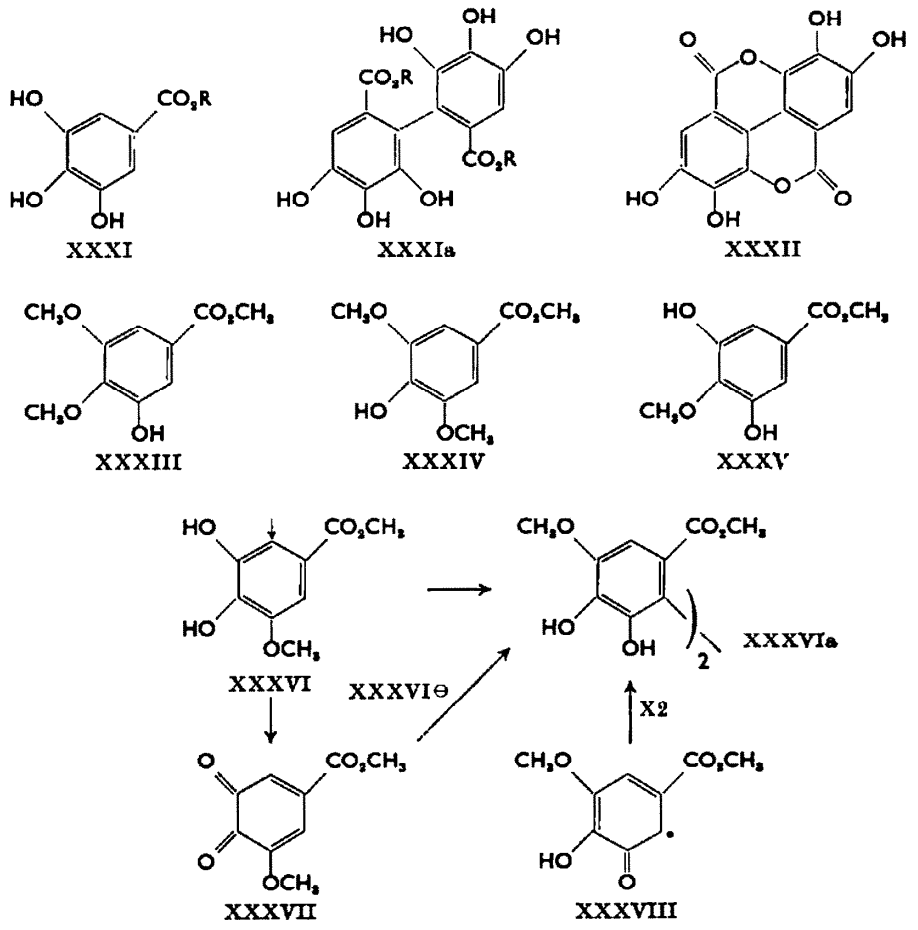


model in choosing the free pyrogallol (XIX) whose intervention in other coupling reactions reported.[38a]

We were further encouraged in this direction by the observation[39] that while gallic acid and its esters (as XXXI) are readily converted in 90% yield by aeration in ammoniacal solution to ellagic acid (XXXII) *via* isolable intermediates exemplified by (XXXIa), the two dimethyl ethers (XXXIII, XXXIV) and the monomethyl ether (XXXV) were unaffected by these conditions. However the monomethyl ether (XXXVI) could be induced to undergo carbon–carbon coupling in small yield XXXVI (arrow) in the expected way. It is not possible to distinguish between the O-quinone (XXXVII) and

[38a] For several pertinent references see D. H. R. Barton and T. Cohen *Festschrift A. Stoll* p. 117. Birkhauser, Basle (1957).

[39] D. E. Hathway, *J. Chem. Soc.* 519 (1957).

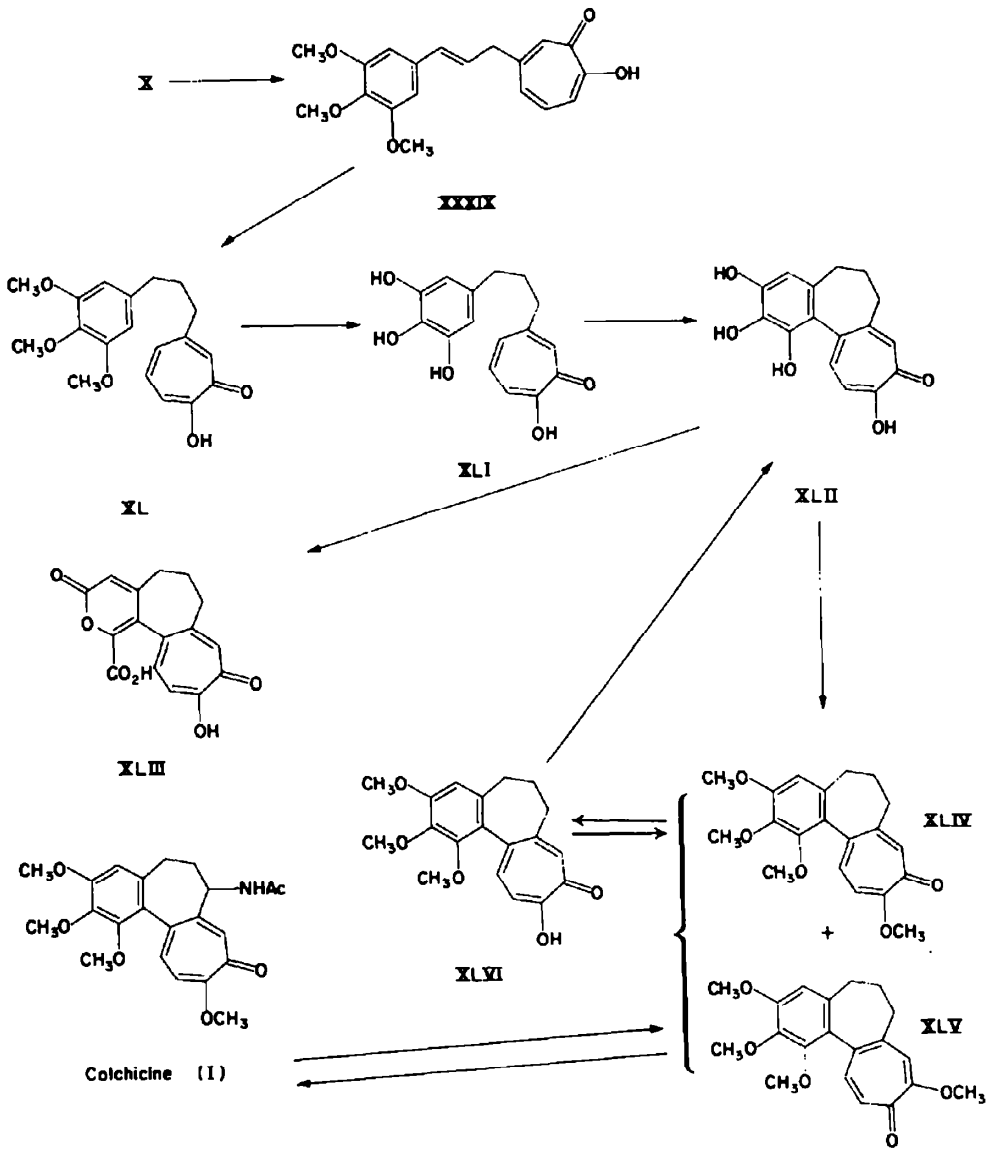


free radical (XXXVIII) mechanisms for these and other reactions of catechols and pyrogallols simply on the basis of product analysis. However, as a result of electron–spin resonance experiments, radical species in oxidized pyrogallols have been identified.[40] Pending more exact definition of these species we must reserve judgment, but for our immediate purpose the above analogy was felt to be sufficiently striking to employ the pyrogallol XLI for the next set of oxidations.

The preparation of XLI followed the course already set by the dimethyl ether approach described above, with certain crucial modifications in experimentation. Thus pyrolysis of the lactone (X) could be carried out under comparatively mild conditions. The resultant styrene (XXXIX) obtained in 78% yield was smoothly reduced to β-(3,4,5-trimethoxyphenyl)-propyltropolone (XL) in quantitative yield.

Removal of the methyl ether groupings with hydrobromic acid was effected in yields of 60–65% after some practice and by working rapidly during the extraction of the bicyclic precursor (XLI) whose splendid crystallinity allowed complete characterization. In particular the NMR spectrum of this compound showed that complete

[40] *Free Radicals in Biological Systems* (Edited by H. Blois) Academic Press, New York (1962); H. Musso, *Angew. Chem.* (International Edn.) **2**, 723 (1963).



demethylation had occurred and that no side reactions had modified the C_3-bridge (4-benzylic; 2 methylene protons) of the tropolone ring. The UV absorption spectrum was that of a mono-alkylated tropolone (Fig. 1) and was to prove of the greatest value in following the course of later transformations. Moreover, a suitable paper chromatographic technique was evolved to provide rapid and certain identification of the bicyclic pyrogallol (XLI) in reaction mixtures. At the same time we were able to confirm by a combination of these analytical techniques that our fears for the stability of XLI in even mildly basic media were well founded. Furthermore, the extreme water solubility of this polyhydroxy intermediate required salt saturation for its effective recovery from aqueous solution.

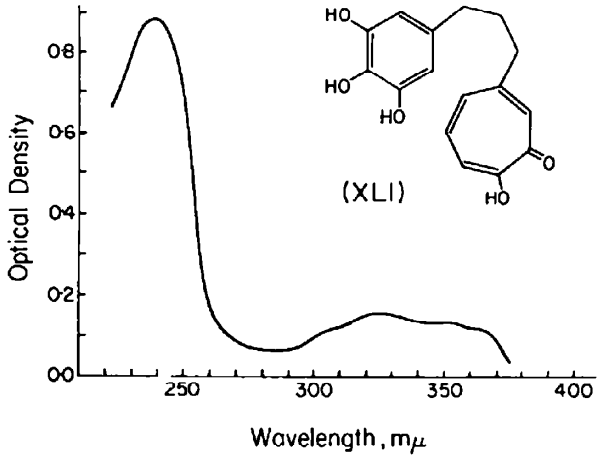


Fig. 1

It was now necessary to have in hand the ultimate relay material in our synthetic route—demethyldesacetamindocolchiceine (XLII). This new degradation product of colchicine was prepared by controlled demethylation of desacetamidocolchiceine XLVI using hydrobromic acid. Although eventually obtained as a nicely crystalline

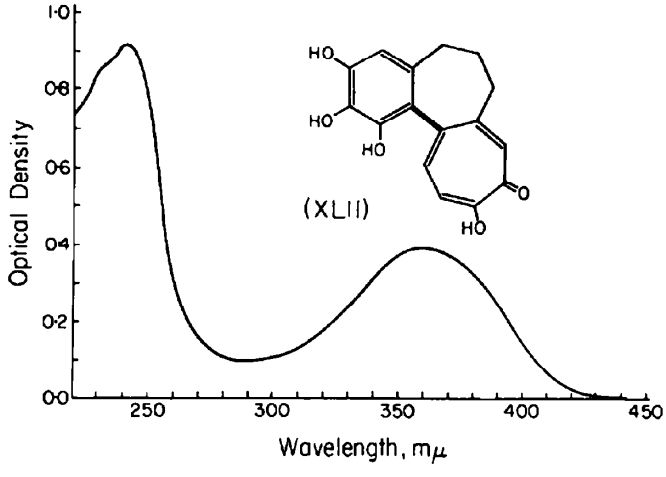


Fig. 2

compound m.p. 230–240° of required analytical and spectral characteristics (Fig. 2) the most useful assay for this compound was found in its paper chromatographic behavior. Full confirmation of the structure of XLII was first made by remethylation with methyl iodide and potassium carbonate in acetone solution, chromatography of the mixture of methyl ethers (XLIV, XLV) and finally hydrolysis of these ethers by a previously described method to desacetamidocolchiceine (XLVI) identical with the degradation product of colchicine. With the well-authenticated conversion[10,11] of (XLVI) to colchicine (C_1 activation: N-insertion) before us, our biogenetic-type

total synthesis lacked only one-step—the crucial and unprecedented oxidative coupling-for completion.

Whereas we had expected a degree of instability in the tricyclic relay (XLII) comparable to that of the bicyclic precursor (XLI), the former was found to have a half-life of less than 3 hr in sodium hydrogen carbonate solution.† It was thus evident that careful monitoring of spectral and chromatographic behavior of both XLI and XLII in presence of suitable oxidants would be necessary before any preparative experiments were contemplated. In fact, with the exception of two reagents, all of the oxidation conditions tried (Experimental) caused either profound and undesired spectral changes and/or complex formation whose reversal effectively destroyed the spectra of XLI and XLII. The details of these experiments need not concern us except to mention that manganese and lead dioxides, ceric sulphate and oxygen in presence of barium hydroxide, sodium hydroxide, sodium (bi)carbonate or ammonia solutions resulted in the ultimate destruction of chromophores and identities of both XLI and XLII.

In dramatic contrast the action of potassium ferricyanide in decinormal sodium bicarbonate solution under nitrogen left the UV spectrum of both the bicyclic precursor (XLI) and the tricyclic relay (XLII) qualitatively unchanged. Again, in preliminary test runs it was found that alcoholic ferric chloride solution, although resulting in ferric salt formation with the tropolone ring, constituted another "stable" medium in that regeneration of starting materials (XLI) and XLII could be achieved by liberation of these polyhydroxy compounds from their salts with mineral acid.

The quantitative aspects of the oxidizing action of these two reagents were now examined. It was at once apparent that solutions of XLII in alkaline ferricyanide solution underwent only slight changes in UV absorption (cf Fig. 3) showing that the principal electron transfer band indicative of continued operation of conjugation between rings A and C, remained intact. However, within one minute the paper chromatograms of such oxidations revealed the presence of new yellow fluorescent material of R_f substantially greater than that of either XLI or XLII. Our first evidence of successful formation of the required bond from the bicyclic series was obtained when after a delay of 39–40 min an identical fluorescent zone became apparent in the chromatograms of ferricyanide solutions of the bicyclic pyrogallol (XLI). At the same time the required change in UV spectrum (Fig. 4) from isolated tropolone absorption (320, 340 mμ) to the intense conjugated absorption (361 mμ) could be followed in the spectra of aliquots of the reaction of the bicyclic intermediate. These changes were at once indicative of quite considerable reaction in the desired sense.

In preparative experiments the same new yellow crystalline compound could be isolated from both tricyclic (XLI) and bicyclic (XLI) tropolones after 2 min and 60 min respectively. This left little doubt that the concept of oxidative coupling of the tropolone ring had been proved, but as part of a synthetic operation the new oxidation product (XLIII) proved to be singularly unhelpful in that its formation was found to involve an irreversible step into a new but undesired series.

Thus, analytical data established a formula $C_{16}H_{12}O_6$, its generation from XLII

† The determination of the UV spectrum and paper chromatographic behavior (Experimental) of XLII in *base* could not be defined in terms of product analysis. However, both the pyrogallol and tropolone rings seemed to suffer profound degradation. This effect was evident even in aqueous solutions of XLII at pH 7.

($C_{17}H_{14}O_5$) requiring loss of CH_2 and addition of one oxygen. The chemical and spectroscopic behavior of XLIII indicated carboxylic acid, lactonic and tropolone functions. The intactness of the —$(CH_2)_3$— unit was shown by NMR spectroscopy which also revealed that the one aromatic proton in XLII (τ 3·75) had been replaced

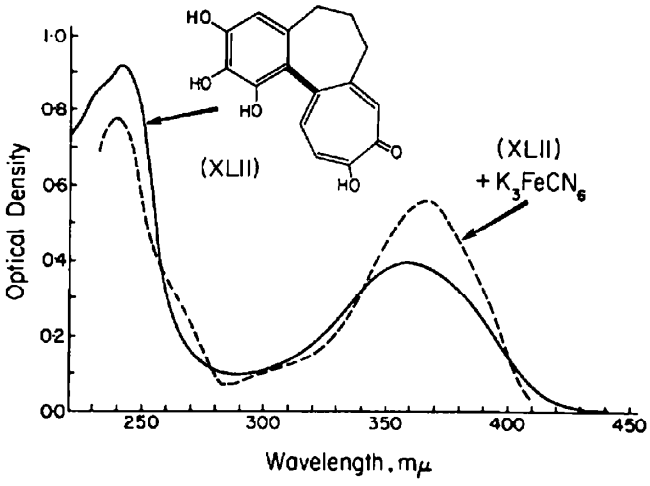


FIG. 3

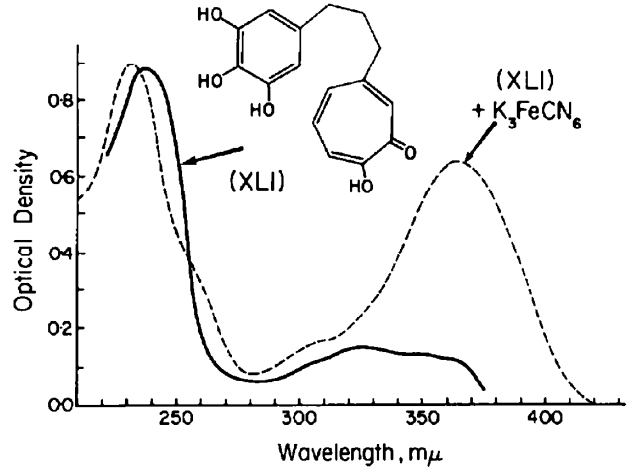
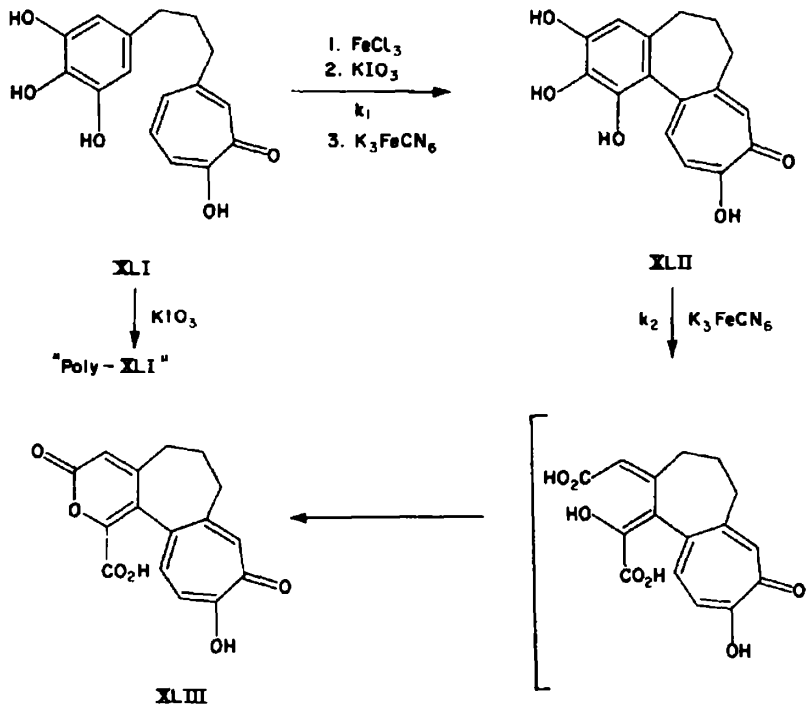


FIG. 4

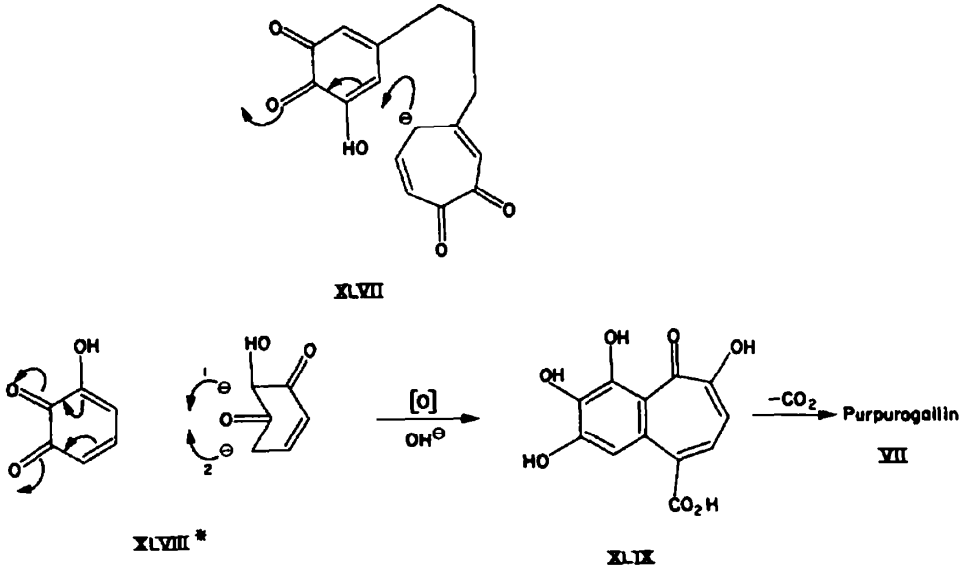
by a new ethylenic proton at 2·72τ. Thus, rupture of the pyrogallol ring had indeed occurred and by analogy with related oxidation of pyrogallols,[41,42] we were confident in assigning the pyrone-acid structure (XLIII) to this oxidation product.

Inasmuch as the yield of crystalline pyrone acid (XLIII) from the *bicyclic* precursor (XLI) could be raised to 20%, the conversion XLI → XLII must proceed to the extent of 25–30% since control experiments revealed that exposure of XLIII to these

[41] T. W. Campbell, *J. Amer. Chem. Soc.* 73, 4190 (1951).
[42] J. Grimshaw, R. D. Haworth and K. Pindred, *J. Chem. Soc.* 833 (1955).



oxidative conditions caused destruction of up to 40% of the pyrone acid during the time required for the oxidation XLI → XLII. The comparative rates of oxidation of the two substrates indicated that the conversion of XLI → XLII takes place one thousand times more slowly than the step XLII → XLIII. This demonstration of the feasibility of the coupling reaction was now followed by a more intensive search for a



reagent with similar potential for radical production combined with a less disruptive influence on the pyrogallol system.

The use of reagents promoting the intervention of semiquinone and orthoquinone forms of the pyrogallol ring was now considered. Such an intermediate could, by addition of the 4-anion of ring C (XLVII), lead to the required end by a process reminiscent of the first reaction of our study: namely the oxidation of pyrogallol. Thus Horner[43] has provided circumstantial evidence that a condensation such as depicted in XLVIII → XLIX provides a rationalization of purpurogallin formation. The effect of potassium iodate solution (10^{-3} M) on a very dilute solution (10^{-4} M) of XLI was to precipitate in 95% yield a polymeric substance whose spectral properties showed that the desired carbon–carbon bond had not been formed. However, the polymer free portion of the reaction mixture revealed by chromatography the presence of minute amount of the required tricyclic phenol (XLII). In effect the problem was now solved in principle but the practical difficulties of isolation required us to cast around for yet another oxidant.

As will be recalled from the preliminary experiments on the choice of oxidizing agent, only ferric chloride had apparently wrought no change on either starting material or product, as judged by complex formation and regeneration. In the hope of providing eventual unique sequestration techniques for both XLI and XLII we re-examined the hydrolytic behavior of such complexes and in the course of this study uncovered the requirements for the successful and much-sought coupling reaction.

Thus whilst regeneration of the free tropolone (XLI) could be accomplished smoothly from its ferric chloride solution by extracting rapidly with mineral acid solution after periods extending up to 2 hr, it was found that one such aliquot when left in presence of sulfuric acid for 48 hr showed that the tricyclic compound (XLII) was present to the extent of 4–5% by spectral and paper chromatographic control. For preparative purposes a two-phase system of chloroform containing XLI (0·005%) and acidic ethanolic ferric chloride was allowed to remain without stirring under nitrogen for 48 hr. Isolation by extraction and separation of XLII from XLI was achieved by inert-atmosphere preparative paper chromatography[44] of several runs followed by spectroscopic comparison of synthetic XLII with the authentic material prepared by demethylation of desacetamidocolchiceine. Complete correspondence of solution spectra (UV, IR) confirmed their identity. Additional confirmation was obtained by remethylation of XLII to desacetamidocolchiceine (XLVI) and spectral and mixed m.p. comparison with authentic XLVI. The formal total synthesis of colchicine patterned on a biogenetic theory was thus complete at this juncture. Experiments are in progress to evaluate the role of such intermediates as XLI in colchicine biosynthesis.

EXPERIMENTAL

For general directions see Part I.[45] M.ps were recorded on the Kofler block. IR spectra were determined in $CHCl_3$ solution (unless stated otherwise) on Perkin–Elmer 21 and INFRACORD instruments, UV spectra (in EtOH) on the CARY 14 spectrophotometer, NMR (in $CDCl_3$) on the VARIAN A-60 instrument (T.M.S. internal standard). Microanalysis are by J. M. L. Cameron.

[43] L. Horner and W. Dunkheimer, *Z. Naturforschung* **14b**, 744 (1959).

[44] Deterioration of both XLI and XLII on paper in the acidic system necessary for their separation was considerable in the presence of air.

[45] A. C. Day, J. Nabney and A. I. Scott, *J. Chem. Soc.* 4067 (1961).

B. Sc., (Glasgow), Mrs. C. Aldrich (Vancouver) and A. Bernhardt (Mulheim) and their respective staffs.

Paper chromatography. This was carried out on phosphate-impregnated Whatman No. 3. paper unless specified otherwise using butanol:acetic acid:water (60:40:35), (System 1) or acetic acid:water:HCl (20:10:1) (System 2).

Mass spectra were determined (unless stated to the contrary) on the M.S. 2 instrument by Dr. J. M. Wilson to whom we extend our best thanks.

The anhydride (VIII)

Purpurogallin (VII) was prepared by the method[46] of Evans and Dehn. α-Carboxy-β-carboxymethyltropolone (VIIa) was obtained from purpurogallin by oxidation with alkaline hydrogen peroxide consistently in 30–35% yield using Haworth and Hobson's technique[26] with the following modifications found, in our hands, to be critical. (i) The H_2O_2 is added at such a rate that the temp is maintained at 90–95°. (ii) Continuous ether extraction of the product requires at least 48 hr. (iii) Addition of water to the filtrate after removal of K_2SO_4 eliminates mechanical difficulties (crystallization) during the continuous extraction. *The anhydride* (VIII) was obtained in yields of 55–60% from this acid by Haworth's[26] method and was used without further purification.

The 2,3-*Dimethoxyphenol Series*

3-*Benzyloxy*-4,5-*dimethoxyphenylacetic acid* (XXI)

Compound XX[22] (20·1 g) was stirred with dry benzene (150 ml) oxalyl chloride (25 ml) and dimethylformamide (0·05 ml) for 5 hr. The evaporated solution gave the crude acid chloride as a semi-solid (ν 1760 cm^{-1}) which was at once placed in dry ether (500 ml) and added dropwise (30 min) to ethereal diazomethane (3 moles/400 ml) containing dry triethylamine[47] (12 ml) at −5 to −10° with stirring. The mixture was than stirred overnight at room temp, the triethylamine hydrochloride filtered off and the solution evaporated ($t \gtrsim 30°$) to give the diazoketone as a bright yellow oil, ν 3455, 3050, 2927, 2080, 1673, 1612 and 1577 cm^{-1}, used in the next step.

This diazoketone dissolved in dry MeOH (200 ml) was heated at 60° with a slurry of Ag_2O (13·6 g) in MeOH (70 ml) and a few drops of triethylamine. After 15 min, the mixture was heated under reflux for 90 min, treated with charcoal (0·5 g) filtered, and the solution evaporated. The neutral fraction after filtration through alumina (Grade III) in benzene afforded the crude *ester* (15·3 g). Hydrolysis to the *acid* was effected in refluxing for 3 hr MeOH–KOH (40%) solution (1:1; 300 ml). The resultant *phenylacetic acid* (XXI) had m.p. 108–109° (from benzene-light petroleum) (Found: C, 67·6; H, 6·0; $C_{17}H_{18}O_6$ requires: C, 67·5; H, 6·0%.)

3-*Benzyloxy*-4,5-*dimethoxyphenylacetaldehyde* (XXIII)

The preceding acid (13·5 g) in dry benzene (150 ml) was treated with oxalyl chloride (50 ml) and 2 drops of dimethylamine. After 18 hr at 25°, solvent and excess reagent were removed *in vacuo* to leave the crude XXII (ν 1760 cm^{-1}) used at once in the Rosenmund reduction. Dissolution of this chloride (from 13·5 g acid) in dry xylene (75 ml) and hydrogenation over Pd–$BaSO_4$ (5%; 2·8 g) and Quinoline-S solution (0·28 ml) at 120° gave, after 8 hr and working up in the usual way, the required aldehyde (11·52 g; 90%) ν 2820, 2720, 1720, 740, 700 cm^{-1}. The semicarbazone formed plates from MeOH m.p. 156°. (Found: C, 62·7; H, 6·1; N, 12·3; $C_{18}H_{21}N_3O_4$ requires: C, 63·0; H, 6·2; N, 12·2%.)

The lactone (XXIV)

The anhydride (VIII; 1·92 g) was heated on a steam bath with XXIII (11·02 g) for 45 min. The melt was dissolved in benzene (70 ml) and filtered hot, and the solution was concentrated (to 45 ml) and treated with petrol (15 ml). After standing overnight, the yellow solid (2·71 g; 65%) m.p. 139–143°, was filtered off. No more solid could be obtained by evaporation of the mother liquors, treatment with petrol and seeding. (For investigation of these mother liquors, see below.) Recrystallized twice

[46] T. W. Evans and W. M. Dehn, *J. Amer. Chem. Soc.* **52**, 3647 (1930).
[47] Cf. M. S. Newman and P. F. Beal, *J. Amer. Chem. Soc.* **71**, 1506 (1949).

from acetone, XXIV was obtained as pale yellow plates, m.p. 145–146°. (Found: C, 69·49; H, 5·65. $C_{26}H_{24}O_7$ requires: C, 69·63; H, 5·39%.)

UV spectrum. λ_{max} 257, 329, 377·5 mμ (log ε 4·20, 3·71, 3·86), inflexion at 320 mμ (log 3·66); λ_{max} 0·01 NaOH: 270, 348, 428 mμ (log ε 4·10, 3·93, 4·19), shoulder at 278 mμ (log ε 4·06). The IR spectrum (nujol) resembled that of the trimethoxy analogue (X),—ν 1735 (lactone C=O) 1610 (tropolone C=O) cm^{-1}.

When shaken in $CHCl_3$ with 2 N NaOH, the lactone gave a sodium salt soluble in the chloroform layer and not in the alkali. Dissolved in benzene and reprecipitated with light petroleum, this had m.p. 135–137° (decarboxylation above 170°) and was an intensely yellow solid, ν 1700 cm^{-1}, λ_{max} 268, 354, 429 mμ (log ε 3·90, 3·74, 4·02), shoulder at 277 mμ. The solid gave a persistent yellow flame test, leaving a trace of white residue, and gave back XXIV when suspended in EtOH and treated with HCl aq.

Chloroform solutions of the lactone were shaken with aqueous solutions of Cs_2CO_3, Rb_2CO_3, K_2CO_3, Na_2CO_3, and LiOH. In all cases, the aqueous phase was only faintly yellow, whereas the $CHCl_3$-solution became deep yellow. The strengths of the colors of the aqueous phases increased from LiOH (colorless) to Cs_2CO_3 (pale yellow, but still very faint). These observations are in agreement with the normally observed trends in complexing ability of the alkali metals. The presence of a 1700 cm^{-1} band in the case of the sodium derivative shows that the lactone ring is unopened: the derivatives are complex tropolone–alkali metal salts.

The dark mother liquors of the reaction mixture from which the lactone crystallized out were evaporated and dissolved in a little $CHCl_3$, diluted with ether, and shaken with 4 N NaOH. The bulky brown precipitate was filtered off, dissolved in $CHCl_3$, shaken with acid, washed, dried and evaporated to give a gum (1·16 g) which gave more of the lactone (260 mg) m.p. 142–144° on crystallization from acetone–petrol, bringing the yield to 71%. The ethereal solution obtained in this filtration was distilled to give a fraction of b.p. 160–172°/0·15 mm shown by its IR spectrum to be predominantly the arylacetaldehyde (1·78 g 17% recovery). This was used without further purification for another condensation with the anhydride (63% yield of lactone obtained from this recovered aldehyde).

The first time the above condensation was carried out, the lactone crystallized from benzene–light petroleum as a solvate m.p. 75–79°. (Found: C, 72·90, 73·69; H, 6·56, 6·37%.) In its reactions this behaved like the unsolvated form, and its mass spectrum had peaks at m/e 448 (M: lactone), 404 (M—CO_2) and 78 (benzene). This solvate was not encountered again.

Pyrolysis of the lactone XXIV

The styrene XXVI. The lactone (100 mg) was mixed with Cu bronze (20 mg), placed in a sublimation tube ($\frac{5}{16}$" diameter), and evacuated to less than 0·05 mm. The tube was then placed vertically in a sublimation block (which had been preheated to 265–270°) until vigorous frothing abated (2–3 min). Then the tube was set horizontally and after 10 min it was cooled. The clear, yellow distillate was washed out with ether (leaving some ether insoluble residue), yields of 60–65 mg (68–72%) being obtained in this way. It is important to have no hold up in the tube such as a glass wool plug. The use of powdered quartz (4 parts to 1 part lactone) gave inferior yields. A slower rate of distillation likewise lowered the yield.

The XXV had ν (CS_2) 954 (*trans*-CH=CH) and 736 and 697 cm^{-1} (phenyl) and no band in the C=O region above 1610 cm^{-1}.

UV spectrum. λ_{max} 271 (log ε 4·36) and 366 mμ (log ε 3·52), 265 (Sh) mμ (log ε 4·27); in 0·01 N NaOH λ_{max} 269, 335, 394 mμ (log ε 4·27, 4·15, 4·11).

Treated in ethereal solution with 3 drops benzylamine, the styrene (79 mg) gave the *benzylamine salt* (80 mg, 80%) as a gum which crystallized when scratched, m.p. 106–108°. Recrystallized from ethyl acetate, this had m.p. 110–112°. (Found: C, 75·2; H, 6·5; N. 2·5. $C_{33}H_{33}O_6N$ requires: C, 75·1; H, 6·5; N, 2·75%.)

UV spectrum. λ_{max} 272, 368, 390 mμ (log ε 4·41, 3·87, 3·70).

The β-phenyltropolone (XXVIII)

The styrene (XXVI; 400 mg), when shaken under H_2 in ethyl acetate (40 ml) with 5% Pd–C (100 mg) absorbed 1 mole H_2 in ca. 7 hr. The product was chromatographed on silica gel (20 g). Elution with ether (200 ml) gave XXVIII (336 mg) as a pale yellow viscous oil which gave a deep red

precipitate with ferric chloride solution. After distilling twice at 254°/0·07 mm, the IR spectrum (in CS_2) showed the presence of benzyl (734 and 696 cm^{-1}) and absence of any ethylenic group at 954 cm^{-1}. (Found: C, 73·59; H, 6·42. $C_{28}H_{30}O_6$ requires: C, 73·86; H, 6·45%.)

UV spectrum. λ_{max} 326 mμ (log ε 3·89): inflexions at 230 and 348 mμ (log ε 4·56, 3·85). In EtOH containing a trace of alkali: λ_{max} 335, 392 mμ (log ε 4·19, 4·19): inflexion at 241 mμ (log ε 4·60).

If hydrogenation were continued, the compound slowly absorbed several moles more H_2 to give products which still contained the benzyl grouping (IR spectrum), but which had a carbonyl band band at 1700 cm^{-1}, gave a precipitate with 2,4-dinitrophenylhydrazine, and no colouration with ferric chloride. A similar result was obtained when acetic acid was used as solvent, 2 moles H_2 being absorbed in 2 hr.

Action of base on the lactone (XXIV)

The lactone (XXIV; 50 mg) was heated under reflux with a solution of Na (1 g) in dry MeOH (10 ml) for 2 hr. The alkali soluble fraction (45 mg), which was isolated in the usual way, was a yellow gum which solidified on trituration with ether; m.p. above 100° over a range of temp (vigorous effervescence above 150°); the IR spectrum showed the presence of carboxyl. After pyrolysis at 265°/0·06 mm for 10 min, the resultant acid XXV (27·3 mg) gave XXVI (5·1 mg), identified by its IR spectrum (in CS_2), which was identical with the material obtained by direct pyrolysis.

A similar result was obtained with potassium t-butoxide in t-butanol at reflux for 20 min.

Catalytic hydrogenation of the lactone (XXIV)

The lactone (42 mg) in ethyl acetate (4 ml) with 10% Pd–C (20 mg) absorbed 1 mole H_2 in 3 hr. (Absorption appeared to be still continuing.) The product (40 mg), an uncrystallizable yellow glass was shown by its IR spectrum to contain a carbonyl at 1730 cm^{-1} and a benzyl function (790 cm^{-1}).

The lactone did not absorb H_2 in a solution of potassium t-butoxide in t-butanol over 10% Pd–C.

The dimethoxyphenol (XXIX)

A solution of XXVIII (268 mg) in acetic acid (10 ml) and conc. HCl aq (10 ml) was set aside overnight at room temp. After dilution with water, the product was isolated with $CHCl_3$. A few ml benzene were distilled off the material to remove the last traces of benzyl chloride and the dark gum was chromatographed on silica gel (10 g). Elution with benzene–ether (9:1; 50 ml) gave a trace of yellow gum which crystallized on addition of a drop of MeOH, and had a carbonyl band at 1700 cm^{-1}. Elution with 1:1 benzene–ether (150 ml) gave a brownish gum (131 mg) which, when distilled at 270°/0·02 mm, was obtained as a pale yellow, viscous oil.

IR showed no peaks due to the benzyl grouping and ν 1615 (tropolone C=O) cm^{-1}.

UV spectrum. λ_{max} 322, 349 mμ (log ε 3·70, 3·68); in OH^- λ_{max} 335, 391 mμ (log ε 3·99, 3·99): Ferric chloride colouration. Red. (Found: C, 68·55; H, 6·78. $C_{19}H_{20}O_6$ requires: C, 68·34; H, 6·37%.) Mass spectrum. M/e 316 (Parent).

Attempted oxidative coupling of the hydroxy-compound (XXIX)

A. *With manganese dioxide.* The phenol (XXIX; 4·9 mg) was heated under reflux with MnO_2 (20 mg) in $CHCl_3$ (15 ml). At intervals over 2 days, aliquots were taken, washed with 6 N H_2SO_4 (to remove Mn) and then with brine, dried, evaporated, and the UV spectrum taken on the residue dissolved in EtOH. The spectrum was virtually unchanged throughout (aliquots taken after 2½, 5, 16 and 37 hr).

In other experiments, either at reflux or in the cold, aliquots were worked up simply by filtration from suspended MnO_2 and evaporation. A peak appeared at 334 mμ* in the UV of greater intensity than the tropolone bands. However, such samples were shown to contain Mn by the following test:

The material (0·3–0·5 mg) was treated with 1 drop conc HNO_3 and heated 2 or 3 min on the

* It appears that a manganese–tropolone complex is responsible for the 334 mμ peak: the tropolone anion has a strong band at 335 mμ, and one of approximately equal intensity at 390 mμ. The longer wavelength band of the anion was not observed in these manganese-containing products.

steambath. After the addition of 2 drops water, the mixture was cooled and sodium bismuthate (2 mg) added with shaking. A distinct permanganate color developed rapidly.

B. *With ferricyanide.* The compound XXIX (42 mg) dissolved in a solution of AnalaR anhydrous Na_2CO_3 (3·2 mg) in de-aerated, distilled water (25 ml) on warming. The solution was cooled to room temp and stirred under N_2 during the dropwise addition of 1% solution of potassium ferricyanide (15·6 ml) in de-aerated, distilled water. After a further 1½ hr with stirring under N_2, the solution was acidified (6 N H_2SO_4), and extracted with $CHCl_3$. (The aqueous solution gave a positive test for ferrocyanide with $FeCl_3$; a blank test for ferrocyanide on the original solution of the oxidant was negative.) The $CHCl_3$ solution gave a gum (26 mg), the UV spectrum of which resembled starting material (polymer?).

Treated in CH_2Cl_2–MeOH with excess of ethereal diazomethane, this gave a neutral fraction (19·7 mg) which was heated on a steambath with 4 N NaOH (5 ml) and a few drops of MeOH. The gummy, alkali-soluble material so obtained appeared to contain little tropolone, as shown by its UV spectrum and $FeCl_3$ colouration.

C. *Palladized-charcoal.* Heated at 360° for 30 min with 10% Pd–C, XXIX gave a product, the UV spectrum of which was very similar to that of starting material, except that the 323 mμ peak was slightly more intense (Pd–tropolone complex?).

D. *Lead dioxide.* The phenol (XXIX; 10 mg) was heated under reflux with lead dioxide (100mg in $CHCl_3$ (30 ml) for 3 hr. Evaporation of the filtered solution gave a gum with λ_{max} 335 mμ which was not further investigated.

The Pyrogallol Series

3,4,5-*Trimethoxyphenylacetaldehyde* (IX)

3,4,5-Trimethoxyphenylacetic acid[48] (7·92g) was dissolved in oxalyl chloride (20 ml). After 18 hr at room temp evaporation of solvent *in vacuo* left the *acid chloride* (8·2 g) as a pale brown oil ν1800 cm^{-1} which was used directly in the Rosenmund reduction. This chloride in dry redistilled xylene (75 ml) containing Quinoline-S solution (0·16 ml) was hydrogenated over Pd–$BaSO_4$ (5%; 1·6 g) at 118–120° with vigorous stirring. After an initial induction period (20 min) HCl evolution proceeded smoothly. and after 5 hr 95% of the theoretical amount of HCl had been evolved. The filtered solution was diluted with ether, and worked up in the usual way. The yield of aldehyde (ν 2850, 2750, 1730 cm^{-1}) was 6·8 g (90%) although this was frequently surpassed in later runs (≮95%). The semicarbazone formed prisms m.p. 186·5–188°. (Found: C, 53·9; H, 6·2; N, 15·4. Calc. for $C_{12}H_{17}N_3O_4$. C, 53·9; H, 6·4; N, 15·7%.) Hahn and Wassmuth[49] give m.p. 191°.

Condensation of Trimethoxyphenylacetaldehyde (IX) *with the Anhydride* (VIII)

The anhydride (VIII; 1 g) was heated on a steambath with IX (4·8 g) until effervescence ceased (ca. 30 min). The dark homogeneous oil was dissolved in benzene, and filtered, and the solution was evaporated to 25 ml. A portion of the solution diluted with either ether or petrol gave solid, which was used to seed the bulk of the solution. The resultant khaki solid (1·59 g) was recrystallized from benzene (charcoal) to give yellow needles, m.p. 160–168°. A second recrystallization from benzene gave X (1·44 g 78%) as pale yellow prisms m.p. 170–171°: deep green $FeCl_3$ color, ν ($CHCl_3$) 1720 cm^{-1}; (Nujol) 1730 cm^{-1}. (Found: C, 64·33; H, 5·63; OMe, 24·62. M 372, $C_{20}H_{28}O_7$ requires: C, 64·51; H, 5·41; OMe, 25·0%, M 372).

UV spectrum. λ_{max} 255, 332, 377, 387 mμ (log ε 4·20, 3·72, 3·83, 3·83).

The dark mother liquors from which the first crop of crystals were obtained gave on evaporation a white solid (0·88 g) m.p. 163–165°, in two crops. This gave no $FeCl_3$ colouration. Recrystallized twice from benzene–light petroleum (60–80°) with charcoal decolourization, the *arylnaphthalene* (XVI) was obtained as very pale cream crystals (562 mg), m.p. 165·5–166°. (Found: C, 68·71; H, 6·47; OMe, 48·25. $C_{33}H_{34}O_6$ requires; C, 68·73; H, 6·29; OMe, 48·43%.) M(mass spectrometric) 384 (Calc. 384).

[48] V. de Laire and R. Tiemann, *Chem. Ber.* **26**, 2018 (1893); K. Mauthner, *Ibid.* **41**, 3665 (1908). In our hands, the Arndt-Eistert synthesis from trimethyl galloyl chloride proved most convenient. The material could also be purchased from Fluka AG.

[49] G. Hahn and H. Wassmuth, *Chem. Ber.* **67**, 696 (1934).

UV spectrum. λ_{max} 230, 261, and 299 mμ (log ε 4·59, 4·66, 4·18). The compound gave a *picrate*, m.p. 128–130°, but this decomposed on attempted recrystallization from EtOH to give back the naphthalene.

Attempts to bring about this condensation by the use of a variety of basic catalysts (e.g. pyridine, piperidine, triethylamine) failed. The use of the dicarboxylic acid (VIIa) in place of the anhydride (VIII) was also unsuccessful.

Pyrolysis of the lactone (X)

The stryene (XXXIX). The lactone (50 mg) was heated at 190–200° with a trace of Cu–bronze until effervescence ceased (ca. 10 min), then for a further 5 min. The dark melt was filtered in benzene solution through silica gel (1 g). Elution with 15% ether in benzene (25 ml) followed by charcoal treatment gave styrene (28 mg) 70% m.p. 105–180°. Recrystallized twice from aqueous MeOH, the *styrene* (XXXIX) was obtained as a granular yellow solid, m.p. 115–116°. (Found: C, 69·30; H, 5·99. $C_{19}H_{21}O_5$ requires: C, 69·50; H, 6·14%.) M(mass spectrometric) 328 ($C_{19}H_{20}O_5$ requires M, 328), (Nujol) 968 cm^{-1} (*trans*-CH=CH).

NMR spectrum. Tropolone (3H) 2·5/3·0τ—Aromatic (2H) 3·59τ (s),—olefinic (2H) 3·5τ (m)—OCH_3 (9H) 6·15τ (s)—$C\underline{H}_2$—CH=CH 6·48τ (d) J = 5 c/s.

UV spectrum. λ_{max} 273, 374 mμ (log ε 4·35, 3·76).

The Phenylpropyl tropolone (XL)

The styrene (XXXIX; 25 mg) was added to a reduced catalyst Pd–C 10%; 20 mg) in ethyl acetate (5 ml) and shaken under H_2 until uptake (1 mole; 1·98 ml) was complete. Filtration through celite and recovery gave XL (24 mg; 96%) as plates (from EtOH) m.p. 113–115°. (Found: C, 68·98; H, 6·52. $C_{19}H_{20}O_5$ requires: C, 69·07; H, 6·71%.) R_f 0·95 (system 1).

Infra-red spectrum. ν 3200 (OH), 1590 (tropolone > C=O and aromatics) 1150 (OMe) cm^{-1}.

UV spectrum. λ_{max} 250, 334 mμ (log ε 4·4, 3·7).

Mass spectrum. m/e 330 (Parent).

The pyrogallol (XLI)

The phenylpropyltropolone (XL; 300 mg) was treated with refluxing HBr (48%; 30 ml) for 30 min. Removal of HBr and water *in vacuo* (10^{-2} mm; T > 40°) left a gum which after digestion in hot water formed brown prisms 160 mg (60%) (solvated) m.p. 100° ($H_2O\uparrow$) and 127–128°. For analysis a sample was sublimed at 120°/10^{-2} mm. to form white needles m.p. 128–130°. (Found: C, 66·51; H 5·78. $C_{16}H_{16}O_5$ requires: C, 66·66; H, 5·59%.)

UV spectrum. λ_{max} 238, 325, 350 mμ (log ε 4·4, 3·6, 3·7).

NMR spectrum. $-C\underline{H}_2C\underline{H}_2C\underline{H}_2$—(6H) 7·5τ (m); Aromatic $-H_1$ (2H) 3·83τ (s); Tropolone $-H$ (4H) 2·7/3·0τ (m).

Mass spectrum. m/e 288 (Parent M).

Remethylation of (XLI)

The pyrogallol (XLI; 10 mg) was dissolved in MeOH (0·3 ml) and ethereal diazomethane (excess) added. After 18 hr solvents were removed and the resultant gum treated with 0·1 N H_2SO_4 (7 ml) on the steam bath for 1 hr. Worked up in the usual way gave a gum (5·5 mg) which was shown to be largely XL by paper chromatography in (R_f 0·95; system 1). Sublimation of 140°/10^{-1} mm gave XL m.p. and mixed 108–113° after recrystallization from EtOH.

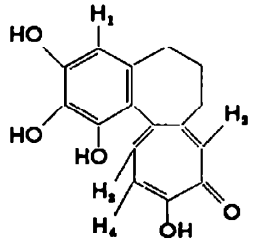
The tricyclic pyrogallol (XLII) *from colchicine*

Desacetamidocolchiceine (XLVI;[10] 200 mg) was treated with HBr (48%; 20 ml) under reflux for 4 hr and the dark solution taken to dryness *in vacuo* (10^{-2} mm). The resultant black gum was digested with an ether–water mixture, the aquous phase further extracted with $CHCl_3$ and the organic layer washed with brine. Removal of solvent gave a semi-solid (101 mg; 58%) which, after one week, crystallized from EtOH as yellow green micro-prisms m.p. 238–240°. (Found: C, 67·31; H, 5·20; $C_{16}H_{14}O_5$ requires: C, 67·12; H, 4·93%.)

UV spectrum. λ_{max} 242, 363 mμ (log ε 4·4, 4·2)

$\lambda_{max}^{OH^-}$ 260, 402 mμ (log ε 4·5, 4·3).

NMR spectrum. Ar–$\underline{H}_1$ (1H) 3·75τ (s)



Tropolone–H_3 (1H) 2·67τ (s)

Tropolone–H_2;H_4 [(1H) 2·53τ (d); (1H) 2·86τ (d)] J_{AB} 12 c/s.

$C\underline{H}_3$–(6H) 7·5/8·0τ (m)

Remethylation of authentic tricyclic pyrogallol (XLII) *to desacetylamidocolchiceine* (XLVI)

The tricyclic compound (XLII; 10 mg), MeI (0·5 ml) and dry K_2CO_3 (AR; 500 mg) and acetone (10 ml) were heated on the steam bath for 18 hr. The product was worked up and hydrolysed with H_2SO_4 as in the bicyclic series preparation of XL above, to furnish desacetyamidocolchiceine (6 mg) m.p. and mixed m.p. 162–166°. Authentic desacetylamidocolchiceine had m.p. 162–166° (sublimed at 158–160°) in our hands (lit. m.p. 168–169°[11]; 165–167°[10]). The IR spectra of the two samples were identical in every respect.

Oxidation of the pyrogallols XLI *and* XLII

A. *Air–Sodium Carbonate.* XLI (25 mg) was dissolved in Na_2CO_3 aq (80 mg) in water (10 ml). Air was passed through the solution and aliquots worked up in the usual way. The UV spectra of these were identical with that of the starting material over 48 hr. In system 1 the R_f of starting material was 0·75. This changed slowly to an indefinite trail R_f 0·4–0·9 on the final (48 hr) aliquot.

Compound XLII (10 mg) treated similarly showed changes in UV spectrum but the only identifiable spot on chromatograms at 3, 24 and 48 hr was that of XLII (R_f 0·81).

B. *Air–barium and ammonium hydroxide.* Treatment of XLI (10 mg) as above using $Ba(OH)_2$ (700 mg) in water (10 ml) or 3 N NH_4OH (30 ml) left the bicyclic pyrogallol unchanged (UV–paper chromatogram), the Ba-salt being very insoluble.

C. *Lead dioxide.* Solutions of XLI and XLII (10 mg in each) in dry acetone (10 ml) were stirred vigorously at 25° with lead dioxide (100 mg). The solutions became transparent in the region 250–400 mμ after 1 min. After 150 min, paper chromatography of an acid extract of the residual lead salts showed only unchanged starting material in each case.

D. *Manganese dioxide** (Run 19). The bicyclic pyrogallol (LXI; 40 mg) was shaken in acetone (40 ml) solution with "activated" MnO_2 (40 mg) for 30 min. At this time a yellow spot R_f 0·81 was apparent (*vide* ferricyanide experiment (ii) *infra*) as well as a great diminution in the amount of free tropolone present (UV spectrum → Mn complex). Recovery gave a crude product (10 mg) from which only starting material (2 mg) m.p. and mixed m.p. 184–191° could be recovered.

Compound LXII (15 mg) treated similarly rapidly developed a yellow spot R_f 0·50 (15 min) in the chromatograms. The starting material could not be recovered from this experiment.

E. *Potassium ferricyanide.* (i) Tricyclic pyrogallol (XLII; 100 mg) was dissolved in Na_2CO_3 aq (800 mg) in distilled water (60 ml) and a solution of potassium ferricyanide (1%; 38 ml) added under N_2. After stirring for 40 min at 25° (UV/paper chromatogram control) dil. H_2SO_4 was added and the salt-saturated solution extracted with ether (3 × 20 ml) and $CHCl_3$ (3 × 20 ml). Isolated in the usual way XLIII crystallized in yellow needles (36 mg) as the solvate from EtOH m.p. 284–288°. (Found: C, 62·42; H, 5·6. $C_{16}H_{12}O_6$. C_2H_6O requires: C, 62·42; H, 5·24%.) The unsolvated material was obtained as yellow needles m.p. 286–288° by sublimation at 220°/0·3 mm. (Found: C, 64·07; H, 4·13. $C_{16}H_{12}O_6$ requires: C, 64·00; H, 4·03%.)

* Of many runs with this reagent only one (typical) set of conditions is reported here.

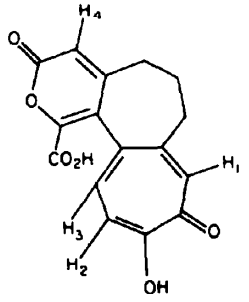
Infra-red spectrum. ν 3500 (OH) 3250 (OH bonded) 1750 (CO_2H) 1700 (pyrone C=O) and 1610 (tropolone C=O) cm^{-1}.

Ultra-violet spectrum. λ_{max} 233 and 365 mμ (ε 9740, 7,000); $\lambda_{max}^{OH^-}$ 239 and 404 mμ (ε 18,000 13,300)

NMR spectrum. H_1–(1H) 2·68τ (s)

H_3 (2H) 2·48τ
H_2 2·82τ } AB quartet—
H_3 2·82τ J = 12 c/s.

H_2 2·7τ (s)



Mass spectrum.[51] (Found: m/e 300 (M); 272 (M—28) (CO); 256 (M—44) (CO_2); $C_{16}H_{12}O_6$ requires: M = 300) R_f (system 1) 0·56 (yellow fluorescent)

(ii) Bicyclic pyrogallol XLI (100 mg) was treated as above for 1 hr after which time chromatographic control indicated a maximal content of XLIII, as well as considerable starting material (XLI). At no time was XLII detected. Worked up as in (i) gave XLVI (10 mg) m.p. and mixed m.p. with XLII 286–270° and having an IR spectrum identical with that of the acid prepared from XLII.

(iii) *With two moles of ferricyanide.* Bicyclic pyrogallol XLI; (20 mh) in $NaHCO_3$ aq (160 mg in 12 ml water) was treated with a solution potassium ferricyanide (1%; 4·6 ml; 2 equiv). Starting material (R_f 0·75) was found to be present at all times up to 60 min at which time the pyrone acid (R_f 0·57) made its appearance.

(iv) *With 0·5 mole ferricyanide.* Compound XLI (700 mg) in Na_2CO_3 aq (800 mg in 120 ml water) was treated with potassium ferricyanide (0·8 mole; 0·5% solution; 12 ml). After 15 min the reaction was worked up to give a gum (59 mg) which finally crystallized from EtOH m.p. 74–103°. This material was shown to be largely starting pyrogallol (R_f 0·75). The mother liquors contained a further amount together with the pyrone (R_f 0·57).

(v) *Ferricyanide at* pH 7. The results recorded in (iv) could be duplicated by working at pH 7.

F. *Sodium iodate.* A solution of the bicyclic pyrogallol (10 mg) in water (250 ml) was treated with $NaIO_3$ (10 mg) in water (20 ml) over 1 hr with stirring at 5°. Working up in the usual way gave a polymer (9·3 mg). The ethanolic washings of this material were bulked and placed on Whatman #3 MM paper which had been prewashed with the system HOAc: H_2O:HCl:60:30:3. Development in this solvent system (System 2) revealed a sharp distinction between bicyclic pyrogallol XLI (Brown R_f 0·75) and XLII (Green; R_f 0·82). Preparative separation on this scale was not attempted.

G. *With ferric chloride. Totally synthetic desmethyldesacetamidocolchiceine* (XLII). The bicyclic precursor XLI (10 mg) and ferric chlorides hexahydrate (10 mg) were dissolved in 10 ml absolute EtOH. Without delay, 125 ml 6 N H_2SO_4, followed by 125 ml $CHCl_3$ were added to the reaction mixture. The two-phase system was then allowed to stand for 72 hr at room temp.* Starting material

* The above conditions are optimal. A series of separate experiments revealed that significant variation such as in concentration of reactants, the time of reaction or the amount of acid or chloroform, resulted in either negligible reaction or extensive decomposition of reactant and products.

[50] Cf. L. R. Morgan, *J. Org. Chem.* **27**, 343 (1962).

[51] We thank Dr. H. Budzikiewicz (Stanford) for this determination.

and products were isolated by extraction with $CHCl_3$ then ether, washing the organic extracts with NaCl aq and evaporation of solvent. In this way 6·1 mg of a crude orange-red gum was obtained. The UV spectrum of the crude mixture revealed it to be mainly the bicyclic precursor (λ_{max} 238, 323, 350, mμ (s)) but broadening of the absorption in the 360–370 mμ region indicated that the mixture contained 4–5% of the tricyclic compound by comparison of the spectrum with those of authentic mixtures of the bicyclic and tricyclic compounds.

The crude mixture from the oxidation was dissolved in acetone and applied as a series of spots to Whatman No. 3 mm paper which had been prewashed with an acid mixture (System 2), water and EtOH. Ascending paper chromatography was carried out for 20 hr, using the solvent system 2, in a tank that was constantly purged with N_2 saturated with the acid eluting mixture. Without delay the yellow-green spots of tricyclic material, were cross-cut in wedges, using stainless steel scissors. While still wet the wedges were placed in a N_2 atmosphere and the tricyclic compound was eluted by descending chromatography, using ethyl acetate as the solvent. The ethyl acetate and acid eluting mixture were removed by evaporation under a stream of N_2. The residue consisted of partially purified tricyclic compound (λ_{max} 238, 357 mμ) as well as residue from the paper. The remaining XLI was now removed by a similar chromatographic procedure using purified paper* and running the ascending chromatogram for 3 hr. The material obtained in this way† (0·20 mg) displayed spectral and paper chromatographic properties (Systems 1 and 2) identical in every respect with desmethyldesacetamidocolchiceine.

UV spectrum. λ_{max} 242, 363 mμ (log ε 4·39, 4·15) $\lambda_{max}^{OH^-}$ 260, 402 mμ (log ε 4·5, 4·3).

IR ν_{max} 3280, 2900, 1600, 1530, 1450, 1270, 1120, 1030, 975, 850 cm^{-1}. Authentic XLII has ν_{max} 3280, 2900, 1600, 1530, 1450, 1270, 1120, 1030, 975, 850 cm^{-1}.

Previous work with authentic material had shown that the tricyclic compound could not be conveniently crystallized on the milligram scale. The combined synthetic material from 10 runs was therefore converted to the highly crystalline *methylated* series (below) for mixed m.p. comparison.

Methylation of synthetic desmethyldesacetylaminocolchiceine

The synthetic XLII (2·0 mg) was refluxed for 10 hr in acetone with excess MeI and anhydrous K_2CO_3. The reaction mixture was evaporated to small volume, excess water was added and the solution was extracted 3 times with ether. The ether extracts were washed with dil. NaOH aq, then with water and dried over anhydrous $MgSO_4$. Removal of solvent gave a yellow gum which had a UV spectrum (λ_{max} 244, 350 mμ) corresponding to the expected mixture of desacetylaminocolchiceine and desacetylaminoisocolchiceine. The crude mixture of isomers was purified by chromatography through a column of Woelm #2 grade alumina, (see above) but separation of the isomers was not attempted at this stage.

The isomeric tetramethylethers (2·1 mg) were heated on a steam bath for 1 hr in 2 ml water containing 2 drops conc. H_2SO_4. The mixture was then extracted with $CHCl_3$ and ether and the organic extracts were washed with salt NaCl aq. After drying over anhydrous $MgSO_4$ and removal of solvent a yellow gum was obtained, which had a UV spectrum (λ_{max} 245 (s), 349 mμ) corresponding exactly to that of desacetamidocolchiceine.

The gum was washed with $CHCl_3$ to remove some of the colorless oil in which the yellow material was embedded. The gum was then dissolved in MeOH and spotted onto a small glass plate. The solvent was evaporated under a stream of N_2. After 24 hr crystalline nuclei were apparent over the entire surface of the film and after 4 days crystallization had proceeded to a maximum.

The semi-crystalline mass was sublimed at 154–165° (atm. press.). The m.p. of the sublimed material (0·7 mg) was 162–165°. Authentic sublimed desacetylaminocolchiceine prepared in the same way had m.p. 162–166° alone and mixed with synthetic material. The UV and IR (micro disc) spectra of authentic and synthetic samples were identical in every respect.

* S & S orange ribbon.

† *Note.* The tricyclic compound is stable in air *only in the absence of acid.* Prolonged exposure of the wet "acid" chromatographic papers to air resulted in oxidation and irreversible absorption of the tricyclic compound on the paper. Traces of metallic ions also had to be avoided. The use of ordinary scissors, subject to corrosion by the acid eluting mixture, caused complexing of the tropolone system with the metallic ions, resulting in loss of material.

Acknowledgements—We wish to thank Drs. J. Nabney, A. J. Baker and T. A. Davidson for help in the early stages, Miss P. Mackenzie and P. Tremaine for excellent technical assistance and Dr. R. L Reed and Professor C. Djerassi and their associates for mass spectroscopic services.

We record with pleasure our thanks to the following agencies for generous financial support: Glaxo Laboratories Ltd., Eli Lilly & Co., National Research Council of Canada. We also thank Drs. A. Brossi (Hoffmann LaRoche Inc.) and W. Parker and G. L. Buchanan (Glasgow University) for generous gifts of colchicine.