HINDERED DIPHENYL ETHERS RELATED TO THE BISBENZYLISOQUINOLINE ALKALOIDS[1]

MARJORIE ALLEN[2] AND R. Y. MOIR
Department of Chemistry, Queen's University, Kingston, Ontario
Received in original form August 31, 1961; as revised August 28, 1962

ABSTRACT

Sixteen steps from vanillin led to syntheses of (*a*) dimethyl 3-(4′-carbomethoxyphenoxy)-4,5-dimethoxyphthalate (I*c*), a known degradation product of isochondrodendrine, and (*b*) the more hindered dimethyl 3-(4′-carbomethoxy-2′-methoxyphenoxy)-4,5-dimethoxyphthalate (I*a*), which has not been derived from any alkaloid, though the usual concepts of biosynthesis do not rule out the occurrence of alkaloids which could lead to it. Diphenyl ethers related to I*a* would be expected to show the effects of steric hindrance, but even with the most hindered member of the group, 7-(4′-carboxy-2′-iodophenoxy)metameconine (VA*e*), no evidence for an appreciable half-life of rotational isomers could be obtained. Attempts to make diphenyl ethers through the condensation of phenols with dicyclohexylcarbodiimide led to other products.

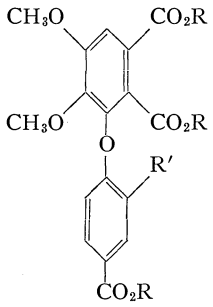
Diphenyl ethers of type I are of interest both because of their relationship to the bisbenzylisoquinoline alkaloids, and because of their place in the study of steric effects in diphenyl ethers. For example, the ester I*a* would be expected to arise from the hypothetical alkaloid II*a* in the same reactions that actually gave I*c* as the degradation product of the dimethyl ether of isochondrodendrine (II*b*) (1). Indeed, our whole study of diphenyl ethers arose from the efforts of Dr. J. A. McRae and his students to form the ester I*a*, the same biosynthetic argument[3] that had succeeded for the structure of isochondrodendrine leading them to suppose II*a* to be a probable structure for the alkaloid cularine (2, 3). The synthesis of I*a* proved unexpectedly difficult, and the challenge presented by the difficulty maintained our interest even when it became apparent many years ago that I*a* was not in fact closely related to cularine (III) (3).

The early efforts of Dr. McRae and his students to synthesize I*a* had several practical results. Prolonged attempts to use the Ullmann reaction directly led to the independent discovery of the transmethylation side reaction (5–7). Attempts to use the phthalide group as a guarded source of carboxyl groups led to two lines of attack continued in the present work: a study of the place of steric hindrance in the synthesis of diphenyl ethers (5, 9, 10, 13), and an extensive development of the chemistry of metameconine (IV*a*) (5, 8–12). Oxidation of the metameconines yielded phthalic acids. One of these (9) was related to pellotine (14) and to capaurine (15, 16), and another (11), an essential link in determining the structure of the bisbenzylisoquinoline alkaloids bebeerine and tubocurarine (17, 18), was synthesized by methods which added greatly to the security of its proof of structure.

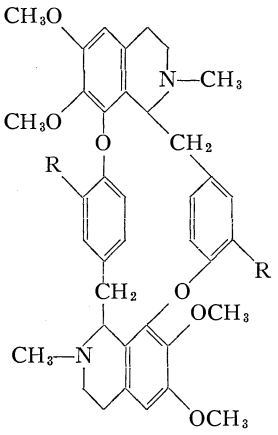
[1]*Most of the material is taken from a thesis written by Mrs. J. R. Allen as part of the requirements for the degree of Doctor of Philosophy, Queen's University, May, 1961.*

[2]*Holder of a Scholarship from the National Research Council of Canada, 1960–61.*

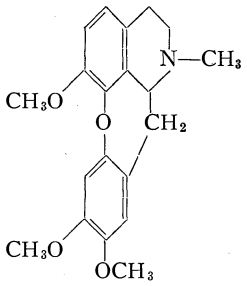
[3]*To exclude structure II*a*, the argument based on accepted biosynthetic pathways must be supplemented by the observation that with one or two exceptions no bisbenzylisoquinoline alkaloid is known which bears, on a benzyl moiety, a methoxyl or hydroxyl meta to the methylene group (4). Groups so situated are a commonplace in the benzylisoquinoline alkaloids, and it is interesting that the extra meta groups in the known exceptions are at positions involving little steric interference about the diphenyl ether linkage.*



Ia: R = Me; R′ = OMe
Ib: R = H; R′ = H
Ic: R = Me; R′ = H
Id: R = H; R′ = OMe



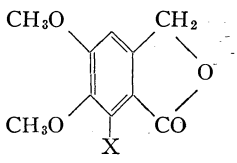
IIa: R = OMe
IIb: R = H



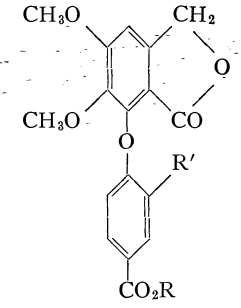
III

Synthesis of Ia

Success was made possible by the application of a method of synthesis discovered by Hems and his co-workers (19). Many years ago we took the decisive step for the preparation of I*a* in using the Hems synthesis to convert 7-hydroxymetameconine (IV*c*) into the diphenyl ether VA*a*, in which all the groups were correctly placed (9). The principal difficulty in completing the work lay in the (indirect) replacement of the nitro group of VB*a* by the methoxyl group of VA*d*. Once this was accomplished, the ester I*a* was fairly easily obtained by oxidation and methylation of the intermediate VA*d*.



IVa: X = H
IVb: X = I
IVc: X = OH



V

Substituent code

a: R′ = NO_2 A: R = H
b: R′ = NH_2 B: R = Me
c: R′ = H
d: R′ = OMe
e: R′ = I
f: R′ = OH

Replacement of the nitro group by the methoxyl group was made especially difficult by the fact that the first step of the conversion, reduction of the nitro group of VB*a* to the amino group of VB*b*, took place in low yields only. We were therefore restricted to the trial of only three methods of converting the amino acid group to methoxyl:

(*a*) The obvious treatment of the diazotized amine with methanol led to the replacement of the diazonium group with hydrogen rather than with methoxyl. The resulting product VB*c* was itself of considerable interest since on oxidation it gave the acid I*b*; this acid and the methyl ester appeared to be identical with the compounds obtained by Faltis and Frauendorfer (1) from the dimethyl ether of isochondrodendrine (II*b*). They also synthesized the acid and the ester with the use of the Ullmann reaction, which succeeded because of the presence of only two groups ortho to the diphenyl ether linkage (1, 10).

(*b*) Attempts to proceed via the diazonium fluoborate and the acetoxy compound failed. No attempt was made to proceed via the phenol by hydrolysis of the diazonium derivative because of the uniformly negative results obtained with this reaction in the metameconine series.

(*c*) The method that finally succeeded had been previously used by us in the metameconine series (5, 9), and had also been recommended by Blair and Newbold (20). Diazotization of the amino ester VB*b*, followed by the treatment with potassium iodide and iodine over chloroform (21), gave the iodo ester VB*e*. After many trials, themselves interesting in outlining the capabilities of the Ullmann reaction in this series, the iodo group of VBe was converted to the free phenolic group of VA*f*. An easy methylation then completed the conversion of VA*f* to VA*d*, the desired methoxy acid from which I*a* was made by oxidation and methylation.

The 16 steps by which vanillin was converted to the final product I*a* included 7 reactions of substitution on the benzene ring. Five of these occurred in the synthesis of VB*a*, and were shown in our previous work to take place without rearrangement (5, 8–12). Of the two remaining substitution reactions, one (in the conversion of the amino group in VB*b* to the iodo group in VB*e*) has been used so often in synthetic and structural work that there seems no point in discussing the possibility of rearrangement in it. Some attention must be given to the possibility of rearrangement in the final substitution reaction, the Ullmann reaction in which the iodo compound VB*e* was converted to the phenolic acid VA*f*, since a restricted class of Ullmann reactions is known which involves some rearrangement. Such a possibility is no light matter, since the structures given for almost all the known bisbenzylisoquinoline alkaloids rest either on the tacit assumption of the lack of rearrangement in the Ullmann reaction (22), or upon a similar assumption in the degradation of diphenyl ethers with metals and amines, a reaction that has also been called into question (23).

However, the following considerations seem to show that the possibility of rearrangement is not of concern in the present work. The expected rearrangement reaction would occur through a benzyne intermediate, and would require (in the present series) the presence of a hydrogen atom ortho to the halogen undergoing displacement (24). In related reactions, 4-bromoveratrole reacted with ethylamine without rearrangement, though ortho protons were available (25), and the iodometameconines (e.g. IV*b*) reacted easily in Ullmann reactions with hydroxide, methoxide, or ethoxide ions, though no ortho protons were available (5, 9). A still closer experimental parallel is the rather high-temperature Ullmann reaction by which Lowenthal and Pepper (26) converted 5-bromosalicylic acid without rearrangement into 2,5-dihydroxybenzoic acid. From a wider point of view, the fact that although the rearrangement as a side reaction was discovered a long time ago (27), the known examples are confined to aryl halides bearing, at most, alkyl groups as other substituents suggests that there is a limitation to the rearranging mechanism. This conclusion is supported to some extent by the fact that no inconsis-

tencies have arisen in the widespread and uncritical use of the Ullmann reaction in structural investigation of alkaloids. Perhaps most convincing is the consideration that the rearrangement reaction belongs to the class of benzyne reactions in which an ortho proton must be removed by a base (24). Ionization of the proton would be made very difficult by the presence on the ring of a negatively charged group, and in fact no example of a benzyne reaction has ever been observed with any aryl halide bearing a negatively charged group on the ring, even when bases much stronger than aqueous sodium hydroxide have been used (24). It is shown in the experimental part that the Ullmann reaction with VB*e* was preceded by saponification of the carbomethoxy group to give the negatively charged carboxyl ion. Bottini and Roberts (23) showed that the formation of cresols from hydroxide ion and halogenated toluenes gave a much lower ratio of "rearranging" to "non-rearranging" reaction at 250° than at 350°. The rearranging reaction could scarcely be predominant at the still lower temperature (175°) of our reaction in which the charge situation was less favorable to it.

*Attempted Resolution of the Triply Ortho-substituted Diphenyl Ether VA*e

Two characteristics made 7-(2′-iodo-4′-carboxyphenoxy)metameconine (VA*e*) an attractive compound for an attempt to demonstrate rotational isomerism in the series. First, it formed a well-characterized strychnine salt. Secondly, it possessed in the iodine atom a more promising blocking group than the nitro group previously used (10); as Trotter has shown in a series of papers (28), the nitro group is rather easily twisted out of coplanarity with the ring to which it is attached.

The behavior to be expected from such a salt depends on the half-life of the rotational isomers. With a half-life of the order of minutes or less, separation into diastereoisomers becomes too difficult, but a compensating factor appears. Usually one diastereoisomer is less soluble than the other, so that at equilibrium (now quickly reached because of the short half-life) the crystals deposited from the solution consist of one diastereoisomer only, and this diastereoisomer may be obtained pure in yields much greater than the maximum of 50% possible with stable isomers. The possibility of distinguishing a resolution of this type from a simple failure to resolve again depends on the half-life of the rotational isomers in solution. With half-lives of the order of several minutes, dissolution of the crystals is followed by an easily observable mutarotation; examples are known in the diphenyl series (29). However, half-lives much less than the time required for dissolution would give mutarotations observable only by the closest attention to experimental errors.

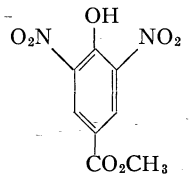
The properties of the strychnine salt of VA*e* showed it to be a single substance; the yield in which it was obtained was too large to allow it to be regarded as one of a pair of stable diastereoisomers. Failure to resolve would then have been due either to double-salt formation or to maintenance in the crystal of free rotation about the diphenyl ether linkage; with the bulky and irregular molecule of VA*e*, both possibilities seem sufficiently unlikely to make further discussion worthwhile. No mutarotation was observed on dissolution of the salt, and as shown in the experimental part, the necessary attention to the precision of the measurements ensured that the mutarotation, if it occurred, must have had a half-life much less than the 3 minutes required for dissolution and initial observation. As a check on the work, it may be noted that both a failure to resolve, or rapid racemization, should give solutions of specific rotations appropriate to the strychnine salt of an inactive acid. Such a check was obtained with the brucine salt of the previous work (10), but the strychnine salt of VA*e* had a specific rotation very different

from that expected. This anomalous result may be compared with the wide variation of rotations recorded for strychnine salts, as noted in the experimental part.

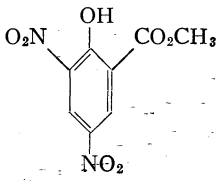
Further progress in attempts to demonstrate rotational isomerism in this series can only be made if the techniques of X-ray crystallography and nuclear magnetic resonance spectroscopy become available to us. The effects of the ortho substitution upon the infrared and ultraviolet spectra of the ethers of this series will be reported in another paper.

An Attempted New Synthesis of Diphenyl Ethers

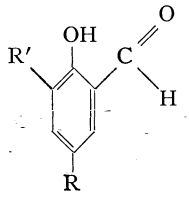
In accord with a suggestion of Dr. J. K. N. Jones, an attempt was made to condense phenols to diphenyl ethers by the action of dicyclohexylcarbodiimide. Highly activated phenols, such as VI, VII, and VIII, reacted readily with the reagent, but under the conditions used, the less acidic phenol salicylaldehyde did not react, nor could cross reaction with more reactive phenols be induced with it. Since there is general agreement (30) that the first step in such reactions is the formation of an isoureide, the proposed synthesis amounted to setting up a competition between external and internal nucleophilic attacks on the activated benzene ring of the isoureide: external attack by a phenol or phenoxide ion to give a diphenyl ether, and internal attack by a nitrogen atom of the isoureide to give an N-phenylurea. A similar competition occurs in the well-known reaction of carbodiimides with carboxylic acids; anhydrides are not formed if the intermediate acylisourea undergoes sufficiently rapid rearrangement to the acylurea (30). Busch, Blume, and Pungs (31) found that diphenylcarbodiimide and certain activated phenols (not those of the present work) gave rearranged triphenylureas. It was not surprising, then, that the highly activated phenols VI and VII with dicyclohexylcarbodiimide gave 1:1 addition products whose infrared spectra showed the bands expected for ester groups and for



VI



VII



VIII*a*: R = R′ = NO_2
VIII*b*: R = NO_2; R′ = H
VIII*c*: R = H; R′ = NO_2

amides of the type AcNHR. The absence of dicyclohexylurea in the reaction products confirmed the fact that no diphenyl ether had been formed, and when the addition product from VI was heated strongly with another mole of VI, it was recovered unchanged.

The reactions of the nitrosalicylaldehydes VIII*a*, VIII*b*, and VIII*c* were of special interest since, in our hands, the Hems synthesis has failed when applied to highly substituted salicylaldehydes. In fact, dicyclohexylurea was obtained in the reaction of dicyclohexylcarbodiimide with each of VIII*a*, VIII*b*, and VIII*c*, but the condensation so indicated was not that of diphenyl ether formation. With 3,5-dinitrosalicylaldehyde (VIII*a*), the initial crude product became warm when treated with methanol; recrystallized from methanol the product was shown by analysis to correspond to a 1:1 addition product which had undergone the loss of water and the addition of methanol.

No doubt the interpretation of these results is obvious, but since analysis and spectra showed that the reaction product from 5-nitrosalicylaldehyde (VIII*b*) was quite different in character from that with dinitrosalicylaldehyde (VIII*a*), we prefer to regard our results

as merely establishing the fact that the reaction cannot be expected to offer a route to diphenyl ethers. New observations on the nitration of salicylaldehyde are reported in the experimental part.

EXPERIMENTAL

Melting points and infrared spectra were determined as previously described (11) but the wavelength values quoted are uncorrected.

7-(4′-Carbomethoxy-2′-nitrophenoxy)metameconine (VBa)

This material was made in nine steps from vanillin as previously described (9, 10).

7-(2′-Amino-4′-carbomethoxyphenoxy)metameconine (VBb)

7-(4′-Carbomethoxy-2′-nitrophenoxy)metameconine (2.0 g) was kept at 60–70° for 30 minutes with iron powder (1.0 g) and glacial acetic acid (50 ml). A small amount of insoluble material was removed by filtration and washed with a little acetic acid; the combined filtrates were evaporated to a black sticky residue which gave a white precipitate when treated with water. The white precipitate was recovered and very thoroughly washed with water. As five recrystallizations did not give a pure product, the material was then extracted with dilute hydrochloric acid; the small amount of insoluble material was recovered as usual and identified as unchanged starting material by melting point and mixture melting point. The acid extract was carefully neutralized with sodium bicarbonate and the precipitated solid twice recrystallized from ethanol to give white fluffy needles which partially melted at 200°, resolidified, and melted again at 209–211°. Two more recrystallizations gave the analytical material with the same partial melting point at 200°, and final melting point of 210–212°. Found: C, 60.19, 60.22; H, 4.79, 4.87; N, 4.04, 3.97%. Calc. for $C_{18}H_{17}O_7N$: C, 60.17; H, 4.73; N, 3.90%.

In two similar experiments, the nitro compound (8.15 g) was reduced to give the amine having a final melting point of 210–211° in a yield of 3.03 g or 40%. In five further runs the relative amount of acetic acid was doubled and the temperature of reduction increased to 85–90°; the crude yield was 12.2 g, or 59% from 22.4 g of starting material, but purification of a portion of the amine showed that the overall yield of reasonably pure material was only 43%.

7-(2′-Amino-4′-carboxyphenoxy)metameconine (VAb)

7-(2′-Amino-4′-carbomethoxyphenoxy)metameconine (0.2 g) was heated on the steam bath for 30 minutes with aqueous sodium hydroxide (10 ml, 10%). The solution was cooled and acidified and the resulting precipitate recovered and twice recrystallized, once from aqueous methanol, and once from methanol, to give a product of m.p. 269.5–270.5°. The melting point reported previously (9) for material made in a different way was 268.4–268.8°.

7-(4′-Carbomethoxy-2′-iodophenoxy)metameconine (VBe)

(*a*) The method is that used by Chalmers, Dickson, Elks, and Hems (21) in the synthesis of a precursor of thyroxine. Sodium nitrite (0.5 g) was dissolved in concentrated sulphuric acid (10 ml) with gentle warming; the solution was then cooled to 0° and diluted with glacial acetic acid (10 ml). A second solution, prepared from 7-(2′-amino-4′-carbomethoxyphenoxy)metameconine (2.0 g, m.p. 210–211°), concentrated sulphuric acid (20 ml), and glacial acetic acid (20 ml), was cooled to 0° and then added over the course of 2 hours to the first solution while the reaction mixture was vigorously stirred and kept between −2° and 1°. Stirring was continued for 1 hour after the addition was complete, the diazonium solution was then poured, with vigorous stirring but without cooling, into a mixture of chloroform (50 ml), water (100 ml), potassium iodide (5.0 g), iodine (5.0 g), and urea (2.0 g); the temperature rose to 40°. Stirring was continued for an additional hour; the layers were then separated and the aqueous layer twice extracted with chloroform (100-ml portions). The chloroform solutions were combined, twice washed with water, and then covered with a solution of sodium sulphite (10 g) in water. Sulphur dioxide was bubbled into the mixture until the color due to the iodine had been discharged; the pale yellow chloroform layer was separated, twice washed with water, dried with magnesium sulphate, and evaporated. The dry residue was recrystallized from ethanol (150 ml) to give white needles, m.p. 208–209°, in a yield of 1.03 g or 39%. It was found (after the product had been recovered unchanged from a second attempt at diazotization) that the needles were insoluble in hydrochloric acid, contained halogen but not nitrogen, and that admixture with the starting material markedly depressed the melting point. Three more recrystallizations of the needles from ethanol gave the analytical sample of VB*e*, m.p. 206.5–207.5°. Found: C, 45.99, 46.10; H, 3.27, 3.19; I, 27.24, 27.34%. Calc. for $C_{18}H_{15}O_7I$: C, 45.97; H, 3.22; I, 26.99%.

In two other runs the crude amino compound (6.0 g, m.p. 196–200°) was converted to purified iodo compound (only one diazotization step being performed for each run!), m.p. 206–207°, in a yield of 3.96 g or 50%.

(*b*) The crude amino compound (2.0 g) was diazotized at 20° with butyl nitrite, hydrogen chloride, and acetic acid, and the mixture poured into a mixture of potassium iodide, water, iodine, and chloroform. Crude product, m.p. 201–209°, was isolated in a yield of only 0.51 g, but one recrystallization from ethanol gave the pure iodo compound VB*e*, m.p. 206–207°.

(*c*) Attempts to proceed via the isolated diazonium fluoborate failed. In the first attempt, the amine failed to dissolve in a mixture of hydrochloric acid and aqueous sodium fluoborate, and eventually most of it was recovered unchanged. In the second attempt, modelled on a different preparation of Niemann and McCasland (32), the amine was first diazotized with butyl nitrite and hydrogen chloride in acetic acid solution; sodium fluoborate solution (33) and hydrochloric acid were then added but no precipitate formed even when the solution was held 60 hours below 0°. A diazonium compound still remained at the end of this time, since the solution gave a bright red precipitate with a solution of β-naphthol. It is not unusual for this method to fail with ortho-substituted amines (34).

Reaction of 7-(4′-Carbomethoxy-2′-iodophenoxy)metameconine with Bases

In this section, the increasing severity of the conditions demonstrates the relative reactivities of the iodo and carbomethoxy groups towards alkali. Saponification occurred in all the experiments, but the Ullmann reaction only under the most severe conditions used.

(*a*) 7-(4′-Carbomethoxy-2′-iodophenoxy)metameconine (2.0 g, m.p. 204–206°) and a trace of copper catalyst were heated under reflux with the solution made from potassium (1.0) and dry methanol (50 ml) for 12 hours, the preparation being protected from atmospheric moisture. A very long isolation procedure gave crude starting material (m.p. 200–206°, undepressed by admixture) and crude 7-(4′-carboxy-2′-iodophenoxy)metameconine (0.24 g, m.p. 249–252°), easily identified since, when treated with diazomethane in ether, it gave the starting material (after one recrystallization the m.p. being 206–208°, undepressed by admixture).

(*b*) 7-(4′-Carbomethoxy-2′-iodophenoxy)metameconine (0.95 g) was heated under reflux for 2 hours with acetone (10 ml) and aqueous potassium hydroxide (20 ml of 5%); the solution was then cooled and acidified, and the oily mixture extracted with ether. Evaporation of the ethereal extract and recrystallization of the residue from ethanol gave a product (0.56 g) of m.p. 256–258°. Two more recrystallizations yielded white crystals (0.3 g) of 7-(4′-carboxy-2′-iodophenoxy)metameconine which melted sharply at 260°.

(*c*) 7-(4′-Carbomethoxy-2′-iodophenoxy)metameconine (0.3 g), aqueous sodium hydroxide (5 ml of 10%), and a trace of copper catalyst (Kahlbaum's copper bronze #02219) were heated under reflux with stirring. After 1 hour, more sodium hydroxide (5 ml) was added, and after a second hour acetone (5 ml) and water (5 ml) were added to dissolve the insoluble material; heating and stirring were continued for an hour longer. The copper was then removed by filtration, and the filtrate acidified; it deposited a sticky precipitate which solidified when strongly cooled; after recrystallization from ethanol (10 ml) the precipitate weighed 0.2 g, m.p. 256–259°. A second recrystallization yielded crystals of two types; as one type did not depress the other's melting point on admixture, the two forms were reunited and recrystallized to give the analytical sample, m.p. 260.5–261.0°, of 7-(4′-carboxy-2′-iodophenoxy)metameconine (VA*e*). Found: C, 45.45, 45.28; H, 3.05, 2.85%. Calc. for $C_{17}H_{13}O_7I$: C, 44.76; H, 2.87%.

Methylation of a portion of the analytical sample with diazomethane gave a product which after one recrystallization from ethanol had m.p. 205–207°, undepressed by admixture with authentic 7-(4′-carbomethoxy-2′-iodophenoxy)metameconine, the starting material.

(*d*) 7-(4′-Carbomethoxy-2′-iodophenoxy)metameconine (0.5 g) was heated under reflux with aqueous sodium hydroxide (15 ml of 10%) until a clear solution was obtained (2 hours). The solution was transferred to a copper test tube, and copper catalyst (0.5 g) was added. The copper test tube was then placed, upright, inside a glass tube sealed at one end; the system was cooled strongly, evacuated, sealed, heated slowly to 120° (bath temp.), held at this temperature for 1 hour, cooled, and opened. The contents of the tube was filtered, the filtrate acidified, and the precipitate recrystallized from ethanol to give 0.28 g of a product whose melting point (251–257°) was not depressed by admixture with the 7-(4′-carboxy-2′-iodophenoxy)metameconine of (*c*) part.

(*e*) Conditions were the same as those in (*d*) part, except that the reaction temperature was 170–180°. In three runs 7-(4′-carbomethoxy-2′-iodophenoxy)metameconine (2.3 g) was converted into crude 7-(4′-carboxy-2′-hydroxyphenoxy)metameconine (1.42 g or 84%), m.p. near 255°, markedly depressed on admixture with the analytical sample of the iodo acid from (*c*) part. The product was interesting in being almost insoluble in either ethanol or water, though quite soluble in a mixture of the two. Two recrystallizations of a small portion of the crude material raised the melting point of the supposed 7-(4′-carboxy-2′-hydroxyphenoxy)metameconine (VA*f*) to 282–288°, but the recovery was very small. Because of this difficulty of purification, and because of the great scarcity of material, the substance was characterized and purified as its methyl ether methyl ester, as shown in the next section.

7-(4′-Carbomethoxy-2′-methoxyphenoxy)metameconine (VBd)

Supposed 7-(4′-carboxy-2′-hydroxphenoxy)metameconine (0.6 g, crude, from (*e*) part of the previous section) was suspended in methanol while a solution of diazomethane in ether was slowly added in excess. During the addition the crystals at first slowly dissolved; later, a precipitate formed. Next morning the precipitate was recovered (m.p. 190–192°; yield 0.25 g); two recrystallizations from aqueous methanol gave the analytical sample, m.p. 189.6–190.2°. Found: C, 61.24, 61.18; H, 5.10, 5.08%. Calc. for $C_{19}H_{18}O_8$: C, 60.96; H, 4.85%. In two more runs, 0.74 g starting material was converted to crude product, m.p. 185–188°, in a yield of 0.35 g or 44%.

Dimethyl 3-(4′-Carbomethoxy-2′-methoxyphenoxy)-4,5-dimethoxyphthalate (Ia)

(a) Oxidation

7-(4′-Carbomethoxy-2′-methoxyphenoxy)metameconine (0.10 g, m.p. 185–188°) was heated on the steam bath with aqueous potassium hydroxide (5 ml of 10%) until solution was obtained (1 hour). Potassium permanganate (0.30 g) in water (5 ml) was added and the heating continued for 30 minutes. Sulphur dioxide was then passed into the cooled reaction mixture until it was colorless; a few drops of concentrated sulphuric acid were added and a trace of solid removed by filtration. The filtrate was cooled in an ice bath; the crystals which separated were recovered (m.p. 241–246°) and recrystallized from water (5 ml) to give colorless plates (0.06 g) which first melted and then resolidified as fine needles at 208–210°, and then melted again at 264–265°, when observed between cover glasses on the hot stage of the microscope. A second oxidation of 0.25 g of starting material gave two crops of acid, final m.p. 264–265°, in a combined yield of 0.17 g, or 65%, of the supposed 3-(4′-carboxy-2′-methoxyphenoxy)-4,5-dimethoxyphthalic acid (I*d*). Because of the unsatisfactory nature of the free phthalic acids as derivatives, we followed the usual policy (11, 13) of characterizing the acid through its methyl ester.

(*b*) *Esterification*

Treatment of the acid product of the oxidation (0.14 g, as just above) with an excess of diazomethane gave a vigorous reaction. Next morning the solution was evaporated and the residue recrystallized from methanol to give small, diamond-shaped plates, m.p. 156.0–157.5°. One more recrystallization gave the first analytical sample, m.p. 157.0–157.2°. Found: C, 58.80, 58.50; H, 5.29, 5.24%. In a second experiment, the acid (0.09 g) was methylated in the same way; after four recrystallizations from methanol the second analytical sample had m.p. 157–158°. Found: 57.71, 57.71; H, 4.97, 5.23%. Calc. for $C_{21}H_{22}O_{10}$: C, 58.06; H, 5.11%.

7-(4′-Carbomethoxyphenoxy)metameconine (VBc)

The method was similar to the general method of Hodgson and Walker (35). Sodium nitrite (0.25 g) was dissolved in concentrated sulphuric acid (5 ml) with gentle warming. The solution was then cooled to 0° and glacial acetic acid (5 ml) was added with stirring and cooling. 7-(2′-Amino-4′-carbomethoxyphenoxy)metameconine (VB*b*) (1.0 g, m.p. 209.0–210.5°) was stirred with acetic acid (5 ml), and sufficient sulphuric acid (2 ml) was added to give a pale yellow, viscous solution; this second solution was cooled and added over a period of 90 minutes to the first solution with vigorous stirring. Stirring was then continued for another 90 minutes, the temperature being maintained at −2 to 0°. Methanol (50 ml) was then added; the temperature rose to 10°, and some frothing occurred. The mixture was gradually warmed and finally heated under reflux for 90 minutes. Some solvent (about 30 ml) was removed by distillation; the cooled residue was poured onto ice (100 g), the resulting orange precipitate recovered and recrystallized from ethanol to give short orange needles (0.38 g or 40%), m.p. 162–172°. Four more recrystallizations from ethanol gave the pale orange analytical sample, m.p. 194–195°. Found: 62.57, 62.54; H, 4.69, 4.70%. Calc. for $C_{18}H_{16}O_7$: C, 62.79; H, 4.68%. A second run using the same quantities and conditions gave 0.5 g of once-recrystallized material as remarkable lenticular plates, m.p. 191–193°; after another recrystallization the crystals (0.36 g, m.p. 194.0–195.5°) still had slightly curved edges.

Dimethyl 3-(4′-Carbomethoxyphenoxy)-4,5-dimethoxyphthalate (Ic)

(a) Oxidation

7-(4′-Carbomethoxyphenoxy)metameconine (0.36 g, m.p. 194.0–195.5°) was heated with water (10 ml) and aqueous potassium hydroxide (2 ml of 10%) for 1 hour, a clear red solution being obtained. Potassium bicarbonate (1 g) was added, and while the mixture was heated on the water bath, solid potassium permanganate (0.35 g) was added until a permanent pale purple color remained. Heating was continued for 45 minutes in all; the mixture was then cooled and filtered, and the precipitate washed with a little water. The combined filtrates were decolorized with sulphur dioxide and acidified with hydrochloric acid. A precipitate slowly settled out; it was recovered and recrystallized from water to give a product (crystals "A") which melted at 141–146°, resolidified, and melted again over the range 171–191°, yield 0.16 g or 42%. This product was purified as its ester (see below). The aqueous mother liquors from this experiment and from another experiment (in which 0.16 g of starting material had given no crystalline precipitate) were continuously extracted with ether; the ethereal extract was evaporated; the solid residue dissolved in potassium hydroxide solution, reprecipitated with acid, recovered, and twice recrystallized from water to give fine needles which on the hot stage of the microscope melted at 138–140° with effervescence, resolidified at 151–154°, and slowly melted again at 245–259°. The acid, 3-(4′-carboxyphenoxy)-4,5-dimethoxyphthalic acid (I*b*), has previously been reported to form a dihydrate (36), first m.p. 207°, second 245°; and a monohydrate (1), first m.p. 178° or 188°, second m.p. 245° (less stable form) and 254–255°, or sinters 247°, melts 250–253° (more stable form) (in a capillary). This interesting dependence on the rate of heating adds to the unsatisfactory properties of the free phthalic acid as a characteristic derivative; our main attention was accordingly given to the methyl ester.

(*b*) *Esterification*

The crystals "A" above (0.16 g) were almost dissolved in ether (5 ml) and an excess of an ethereal solution of diazomethane (20 ml) was slowly added, the mixture being cooled in ice. A vigorous reaction occurred;

after 3 hours, the ether was removed, the residue crystallized by solution in methanol followed by evaporation, and then recrystallized from aqueous methanol. Long needles, m.p. 116.0–116.5°, were obtained in a yield of 0.14 g. A second recrystallization gave the analytical sample, m.p. 115.6–116.2°. Found: C, 59.78, 59.65; H, 4.92, 5.16%. Calc. for $C_{20}H_{20}O_9$: C, 59.40; H, 4.99%. Faltis and Frauendorfer (1) reported that the substance sintered at 111° and melted at 113–114°; King (36) did not obtain a crystalline ester.

Attempted Resolution of 7-(4′-Carboxy-2′-iodophenoxy)metameconine (VAe)

7-(4′-Carboxy-2′-iodophenoxy)metameconine (0.6 g, m.p. 257–258°) suspended in chloroform (100 ml) was dissolved by the addition of ethanol (10 ml). Strychnine (0.44 g, m.p. 279–282°, from the nitrate) in chloroform (20 ml) was added to the solution. After 24 hours, the solution was concentrated to 20 ml and diluted with petroleum ether to precipitate a colorless oil which gradually hardened; the precipitate was recovered and recrystallized from ethanol to give a white product, m.p. 174–178°, in a yield of 0.82 g or 79%; three more recrystallizations from ethanol gave white crystals (0.38 g), m.p. 178.5–179.5°, and a fifth recrystallization left the melting point unchanged. Found: C, 57.34, 57.63; H, 4.97, 5.03; N, 3.51, 3.42%. Calc. for $C_{38}H_{35}O_9N_2I$: C, 57.73; H, 4.46; N, 3.54%. The ethanol mother liquors from the first three recrystallizations were combined and concentrated; they deposited crystals (0.31 g, m.p. 161–166°, mixture m.p. with the anal. sample 177–181°) which after one recrystallization had m.p. 176–177°; thus a second diastereoisomer did not seem to be present.

The strychnine salt (analytical sample, 0.3023 g) was dissolved in chloroform to give a solution volume of 5 ml. At age 3 minutes for the solution, a single reading showed a rotation of −0.49°; the mean for 10 readings taken before age 10 minutes was −0.470°, while that for 10 readings at 20 hours was −0.471°; sets of 10 readings at ages 1 hour, 2.25 hours, and 5 hours showed no deviation of the mean from these larger than 0.006°. The zero point was 0.032°. From these readings $[M]_D = -650°$ (0.077 M in chloroform). The lack of mutarotation showed that dynamic interchange of the stereoisomers did not occur at an observable rate, but time did not permit us to investigate further the following anomaly in our results. Strychnine itself has $[M]_D^{18} = -465°$ (0.067 M in chloroform) (37, 38), but while our salt showed a molecular rotation apparently significantly more negative than this, known salts of strychnine have much less negative molecular rotations than does the free base. Thus aqueous solutions of the salts of mineral acids (39) and organic acids (40) show molecular rotations close to −110°, while solutions of organic salts of strychnine in organic solvents show numerically very small molecular rotations, which may be either positive or negative in sign (39, 41, 42).

Nitration of Salicylaldehyde

(a) Preparation of the Crude Mixture of 3- and 5-Nitrosalicylaldehydes (VIIIb and VIIIc)

The method of von Miller (43) was followed, but the yield obtained (58%) was much less than those (90–100%) reported by others (43–47).

(b) Separation of the Mononitro Derivatives

(i) Via the sodium salts.—Von Miller (43) reported an easy separation by fractional crystallization of the yellow sodium salt of the 5-nitro derivative from the red salt of the 3-derivative. The method has often been used without comment; there are two reports (44, 46) of easy and almost quantitative separations (though the reported proportions of the isomers differed very greatly!), and three (47–49) in which the method was difficult or inefficient. In our work fractions enriched in one or other of the components were obtained, but in very prolonged, careful, and repeated fractional crystallizations of the sodium salts, only two small crops of the pure yellow salt of the 5-isomer; the other fractions were all mixtures of the yellow and red salt. There seemed to be little difference in their solubilities, and the successes reported previously presumably were based on the maintenance of suitably supersaturated solutions.

(ii) Via the sodium bisulphite addition compounds.—Taege (50) found that 5-nitrosalicylaldehyde formed a stable crystalline addition compound, and that the derivative of 3-nitrosalicylaldehyde did not crystallize. Our results did not agree with this. In fact, when a mixture of the sodium salts, enriched in the 3-isomer, was treated with sodium bisulphite, a small amount of a crystalline precipitate was obtained which on treatment with aqueous acid gave directly almost pure 3-nitrosalicylaldehyde, m.p. 108.5–110.5°. The 5-isomer could also be obtained almost pure (see below).

(iii) By partial acidification.—One quarter of a mother liquor saturated in both salts was treated cautiously with dilute hydrochloric acid until the color just changed; the rest of the mother liquor was then added with shaking, and next morning the precipitate was recovered; its melting point of 103–109° showed that it was almost entirely 3-nitrosalicylaldehyde. But later crops were mixtures much less rich in the 3-isomer. Presumably the selective precipitation of the 3-isomer was a solubility effect, since the difference in their acidity constants is small and in the wrong direction (51).

(iv) By a combination of methods.—The most elementary theory suggests that separations of this type are best carried out with at least two methods having different separation coefficients. The following work demonstrated that the intractable mixture of salts could be broken by the use of this principle, though the separation was tedious. Salicylaldehyde (100 g) was nitrated in the usual way (43) and the mixed product was treated at 70° with water (300 ml) and sodium bisulphite (88.4 g); all but a few milligrams dissolved. Next morning, the light yellow crystals which had separated from the chilled solution were recovered (from mothor liquor A), washed with sodium bisulphite solution, resuspended in water, treated with hydrochloric

acid and a stream of air, the crystals recovered, washed, and dried, yield 28.2 g (20% on salicylaldehyde) of almost pure 5-nitrosalicylaldehyde, m.p. 124.5–128.5°. The acid mother liquor B was subjected to an air stream for a long time, and four successive crops of mixed aldehydes were obtained. Thus the crystalline addition product must have been a mixture, and the recovery from it of 5-isomer was due at least as much to the faster decomposition in acid of the 5-derivative as to its lesser solubility in water. Mixed aldehydes were also recovered from mother liquor A; the mixed aldehydes from A and B were separately converted to their sodium salts and subjected to very long and careful fractional crystallizations from water. A gave two small crops of the pure yellow salt from which almost pure 5-nitrosalicylaldehyde was obtained directly by acidification; m.p. 126.5–127° and 126–126.5°, yield 7.8 g or 5.6% in all. All other fractions were mixtures; one of the mother liquors from B was used to establish the results in (iii) above (and therefore also confirmed the previous demonstration of the crystalline bisulphite addition product of the 3-isomer). The remaining salts and mother liquors from A and B were now united in one aqueous solution for the demonstration of the differential separation. The combined solution was treated as in (iii) with one quarter of the amount of hydrochloric acid required for neutralization, and the precipitate (B1) recovered. The filtrate was then concentrated until (as it was judged) enough water had been removed to bring it back to saturation, in the cold, in the 3-isomer; after being chilled, it deposited a salt (C1). The double separation was then repeated several times to obtain the "less soluble acids" B2, B3, and B4, and the "less soluble salts" C2 and C3. One recrystallization of C2 and C3 gave a pure yellow salt which on treatment with acid gave almost pure 5-nitrosalicylaldehyde, m.p. 125.5–125.8°, yield 3.2 g or 2.3%. The deep orange C1 gave mainly the 3-isomer. The fractions B1, B2, B3, and B4 were somewhat impure 3-isomer, yield 14.2 g or 10%. Two recrystallizations from aqueous acetic acid and one from ethanol of the united fractions of the crude 3-isomer, with charcoal, gave large, bright, sandy-yellow crystals, m.p. 108.5–109.5°, of pure 3-nitrosalicylaldehyde, yield 18.2 g or 13%. One recrystallization of its united fractions from aqueous acetic acid gave beautifully shaped, very light yellow crystals of pure 5-nitrosalicylaldehyde, m.p. 125.4–126.4°, yield 33.7 g or 24%. Mixed fractions (useful for further nitration) were also obtained in a yield of 15%.

(c) Dinitration

The crude mixture of mononitrosalicylaldehydes (43.4 g) obtained as in (*a*) part was treated according to the method of Lovett and Roberts (52) to give crude 3,5-dinitrosalicylaldehyde (VIII*a*) in a yield of 90%. Three recrystallizations from benzene and one from aqueous acetic acid gave 6.7 g of bright yellow crystals, m.p. 72.1–74.4°. A slightly better sample, m.p. 72.3–73.7°, was recovered from the mother liquors in a yield of 1.0 g. A second crop, 26.4 g, m.p. 72.9–73.4°, was obtained as a light yellow powder and a third crop, 0.78 g, m.p. 70.6–72.1°, as a darker powder. There was, therefore, little evidence of fractionation, supporting the correctness of our melting point, which was much higher than those recorded before, viz., 56° (53), 58–60° (52), and 62–63° (45).

Reactions of Dicyclohexylcarbodiimide

(a) With Methyl 2-Hydroxy-3,5-dinitrobenzoate (VII)

Dicyclohexylcarbodiimide (2.0 g) was added to a warm solution of methyl 2-hydroxy-3,5-dinitrobenzoate (54) (4.0 g, m.p. 124–125°) in dry ethyl acetate (40 ml). A precipitate began to form immediately. Next morning the precipitate was recovered and the solid residue from the evaporation of the mother liquor to dryness was added to it. One crystallization from methanol and two from benzene gave small bright yellow needles whose melting point of 205–207° was raised to 211–212° by two more recrystallizations from methanol and one from aqueous acetone. A final recrystallization from methanol gave the analytical sample of the 1:1 addition compound, m.p. 211.6–212.2°. Found: C, 56.08, 56.26; H, 6.21, 6.32; N, 12.46, 12.30%. Calc. for $C_{21}H_{28}O_7N_4$: C, 56.24; H, 6.29; N, 12.49%. Dicyclohexylurea could not be found in the mother liquors, though a little phenolic starting material was recovered.

(b) With Methyl 3,5-Dinitro-4-hydroxybenzoate (VI)

Methyl 3,5-dinitro-4-hydroxybenzoate (54) (10 g), dissolved in dry ethyl acetate (75 ml), was treated with dicyclohexylcarbodiimide (5 g). The mixture became warm and a precipitate began to form in a few minutes; after 2 days it was recovered and recrystallized from benzene to give a yellow product (6.89 g), m.p. 191–201°. Two more recrystallizations from benzene and one from methanol gave prisms which exhibited dimorphism at the melting point: the prisms partially melted at 190°, the melt resolidified as needles, the remaining prisms melted at 196–200°, and the needles sharply at 200°. Another recrystallization from methanol gave a mixture of needles (0.96 g) and prisms (0.34 g) which were separated by hand; the needles melted at 199–200° and the prisms behaved as before; in chloroform solution the infrared spectra of the two forms were identical. One more recrystallization from methanol gave a pure sample of the 1:1 addition compound, which separated originally as needles but which after 3 days had completely changed to prisms; they showed the same double melting point as before, and two more recrystallizations from methanol produced no change in the melting point. Found: C, 56.18, 56.26; H, 6.36, 6.20; N, 12.75, 12.69%. Calc. for $C_{21}H_{28}O_7N_4$: C, 56.24; H, 6.29; N, 12.49%. The reaction mixture filtrate and the mother liquors gave, after one recrystallization of the crude crystals from methanol, an excellent product showing the double melting point in the range 190–200°, in a yield of 8.39 g, as well as a fraction (m.p. 97–112°, 2.29 g) thought to be impure phenolic starting material since, when the reaction was repeated in dry benzene at the reflux temperature, 9.62 g of crude addition product, m.p. 195–198°, was obtained as well as 2.4 of

material, m.p. 107–111°, undepressed by admixture with methyl 3,5-dinitro-4-hydroxybenzoate. No dicyclohexylurea could be found in the mother liquor.

The addition product (2.25 g, m.p. 190–200°) was recovered unchanged in a yield of 1.85 g after it had been heated at 170° for 2 hours with methyl 3,5-dinitro-4-hydroxybenzoate and dimethylformamide, the mixture poured into water, and the precipitate recrystallized from methanol. No substituted diphenyl ether could be recovered.

(c) With Unactivated Phenols

When methyl 3,5-dinitro-4-hydroxybenzoate (2.4 g), dicyclohexylcarbodiimide (2.2 g), and methyl salicylate (20 ml) were heated 8 hours on the steam bath, the only insoluble compound produced was the same addition product observed in (*b*) just above, identified by melting point and infrared spectrum. Cyclohexylcarbodiimide failed to react on prolonged contact with methyl *p*-hydroxybenzoate in dry ethyl acetate.

(d) With 3,5-Dinitrosalicylaldehyde (VIIIa)

A solution of 3,5-dinitrosalicylaldehyde (8.4 g, m.p. 55–58°) and dicyclohexylcarbodiimide (4.4 g) in dry ethyl acetate (80 ml) was heated under reflux for 4 hours and then evaporated to dryness. Light-sensitive crystals, m.p. 186–206°, were obtained by recrystallization of the residue from benzene, yield 4.78 g. The benzene mother liquor was evaporated to dryness and the residual gum triturated with methanol; significantly, the mixture became quite warm. A solid (0.82 g, m.p. 171–186°) separated from the cooled methanol; it was added to the previous solid fraction, and efforts to purify these solids failed. The methanolic mother liquor, however, yielded prisms (2.47 g, m.p. 156–186°) which after two more recrystallizations from methanol and two from aqueous acetone gave the analytical sample, which seemed also to be dimorphic (m.p. 192.5–193.5° with a little previous melting and resolidification at 188°). Found: C, 58.46, 58.26; H, 6.59, 6.52; N, 12.98, 13.25%; mol. wt., 415. Calc. for $C_{21}H_{28}O_6N_4$: C, 58.32; H, 6.53; N, 12.96%; mol. wt., 432. In a second experiment, the methanolic mother liquors gave dicyclohexylurea as white crystals (0.7 g), separated by virtue of its low solubility in benzene; after one recrystallization it was pure. It was identified by its melting point (233.2–234.0°), mixture melting point, and infrared spectrum.

(e) With 5-Nitrosalicylaldehyde (VIIIb)

Two experiments very similar to those above, but using purified 5-nitrosalicylaldehyde as the phenolic component, were performed. From the first experiment, pure dicyclohexylurea (m.p. 233.0–233.4°, with an abrupt change of crystal form but no melting at 222°) was obtained. Found: C, 69.92; H, 10.64; N, 11.08%. $C_{13}H_{24}ON_2$ requires: C, 69.65; H, 10.72; N, 12.50%. In the second experiment, five recrystallizations of the entire solid reaction mixture from ethanol gave the analytical sample of the principal reaction product, m.p. 142–143°. Found: C, 62.94, 62.74; H, 6.54, 6.63; N, 11.12, 11.27%.

(f) With 3-Nitrosalicylaldehyde (VIIIc)

In two experiments using purified 3-nitrosalicylaldehyde as the phenolic component, small amounts of unchanged 3-nitrosalicylaldehyde were recovered and identified by mixture melting point. The only other pure product obtained was dicyclohexylurea (identified by m.p., mixture m.p., and infrared spectrum), which separated spontaneously from the dry ethyl acetate of the first experiment.

(g) Infrared Spectra

The values given are uncorrected. The addition products, A with methyl 2-hydroxy-3,5-dinitrobenzoate and B with methyl 4-hydroxy-3,5-dinitrobenzoate, showed bands at the same position (near 3320 cm^{-1}) as the N—H stretching band of dicyclohexylurea (C) in potassium bromide disks; in a chloroform solution of B, the band was weakened and raised to 3440 cm^{-1}. This band was completely absent in D, the condensation product with 3,5-dinitrosalicylaldehyde, and in E, the condensation product with 5-nitrosalicylaldehyde. A and B showed an ester carbonyl stretching band at 1730 and 1737 cm^{-1}, absent in the others; all the compounds showed bands in the "amide I" region; 1650 (A), 1640 (B), 1630 (C), 1682 (D), and 1660 cm^{-1} (E) in potassium bromide (aldehyde C—H stretching bands being absent in the spectra of D and E); in chloroform the band for B was *raised* to 1670 cm^{-1}, as would be expected for a band of this type. A, B, D, and E showed strong bands near 1620 cm^{-1}, extremely strong in the latter pair. The "amide II" region (near 1550 cm^{-1}) was occupied also by the nitro groups' frequency; in A and B the two sources overlapped to form a wide band, in potassium bromide disks, but in the spectrum of a chloroform solution of B the bands were resolved, one component moving to a lower frequency (as would be expected for a true "amide II" frequency). In agreement with the loss of the N—H stretching bands, the spectra of D and E both showed narrower bands (with potassium bromide disks) having the shape of the nitro groups' band alone. As expected, a strong, moderately broad band near 1290 cm^{-1} in the spectra of A and B was absent in that of D; the differences between D and E suggested by the elementary analysis were most clearly supported in the spectra by the presence in the spectrum of E, but not of D, of an extremely strong, broad band between 1330 and 1290 cm^{-1}, and by the presence in the spectrum of E of two moderately strong, very sharp, and well-resolved bands at 1480 and 1380 cm^{-1}, present at most as weak shoulders in the spectra of the other compounds.

ACKNOWLEDGMENTS

The present work was undertaken as a tribute to Professor J. A. McRae and to all the many research students at Queen's who have worked upon the problem. It is hard to have

to report that Dr. McRae died nearly a year before the completion of our own work. We wish to thank Dr. R. H. Manske for the suggestions which led to the beginning of this work nearly 25 years ago, for his advice as to the early concepts of the biosynthesis of cularine, and for his long continued interest in the problem. Miss Shelagh Courtney determined most of the infrared spectra, Miss Lorna Craig and Mr. Stephen Safe made our work possible by the production of very large amounts of the necessary intermediates, and Dr. C. A. Sankey gave us the large amounts of vanillin needed as starting material. The National Research Council of Canada supported the work by a research grant, and by the grant of a scholarship to one of us.

REFERENCES

1. F. Faltis and H. Frauendorfer. Ber. Sect. B, **63**, 806 (1930).
2. R. H. F. Manske. Can. J. Res. Sect. B, **16**, 81 (1938).
3. R. H. F. Manske. J. Am. Chem. Soc. **72**, 55 (1950).
4. M. Kulka. *In* The alkaloids. Vol. IV. *Edited by* R. H. Manske. Academic Press, New York. 1954. p. 199.
5. J. A. McRae, R. B. VanOrder, F. H. Griffiths, and T. E. Habgood. Can. J. Chem. **29**, 482 (1951).
6. H. King and E. V. Wright. J. Chem. Soc. 1168 (1939).
7. A. G. Davies and J. Kenyon. Quart. Rev. (London), **9**, 203 (1955).
8. R. H. Manske, J. A. McRae, and R. Y. Moir. Can. J. Chem. **29**, 526 (1951).
9. J. A. McRae, R. Y. Moir, J. J. Ursprung, and H. H. Gibbs. J. Org. Chem. **19**, 1500 (1954).
10. M. Allen and R. Y. Moir. Can. J. Chem. **37**, 1799 (1959).
11. M. Allen, A. L. Promislow, and R. Y. Moir. J. Org. Chem. **26**, 2906 (1961).
12. J. A. McRae, M. Allen, and R. Y. Moir. Can. J. Chem. **39**, 995 (1961).
13. F. Faltis, L. Holzinger, P. Ita, and R. Schwarz. Ber. Sect. B, **74**, 79 (1941).
14. E. Späth. Ber. Sect. B, **65**, 1778 (1932).
15. R. H. Manske and H. L. Holmes. J. Am. Chem. Soc. **67**, 95 (1945).
16. R. H. Manske, A. E. Ledingham, and H. L. Holmes. Can. J. Res. Sect. B, **23**, 100 (1945).
17. H. King. J. Chem. Soc. 1157 (1939).
18. H. King. J. Chem. Soc. 265 (1948).
19. E. T. Borrows, J. C. Clayton, B. A. Hems, and A. G. Long. J. Chem. Soc. S190 (1949).
20. J. Blair and G. T. Newbold. J. Chem. Soc. 3935 (1954).
21. J. R. Chalmers, G. T. Dickson, J. Elks, and B. A. Hems. J. Chem. Soc. 3424 (1949).
22. H. E. Ungnade. Chem. Rev. **38**, 405 (1946).
23. A. T. Bottini and J. D. Roberts. J. Am. Chem. Soc. **79**, 1458 (1957).
24. J. F. Bunnett. J. Chem. Ed. **38**, 278 (1961).
25. R. Y. Moir and C. B. Purves. Can. J. Res. Sect. B, **26**, 694 (1948).
26. J. Lowenthal and J. M. Pepper. J. Am. Chem. Soc. **72**, 3292 (1950).
27. V. E. Meharg and I. Allen. J. Am. Chem. Soc. **54**, 2920 (1932).
28. J. Trotter. Can. J. Chem. **39**, 1638 (1961).
29. H. C. Yuan and R. Adams. J. Am. Chem. Soc. **54**, 2966 (1932).
30. H. G. Khorana. Chem. Rev. **53**, 145 (1953).
31. M. Busch, G. Blume, and E. Pungs. J. Prakt. Chem. Ser. 2, **79**, 513 (1909).
32. C. Niemann and G. E. McCasland. J. Am. Chem. Soc. **66**, 1870 (1944).
33. C. M. Suter, E. J. Lawson, and P. G. Smith. J. Am. Chem. Soc. **61**, 161 (1939).
34. A. Roe. *In* Organic reactions. Vol. V. Wiley and Sons, New York. 1949. p. 193.
35. H. H. Hodgson and J. Walker. J. Chem. Soc. 1620 (1933).
36. H. King. J. Chem. Soc. 1276 (1936).
37. K. Warnat. Helv. Chim. Acta, **14**, 997 (1931).
38. A. C. Oudemans, Jr. Ann. **166**, 76 (1873).
39. F. L. Shinn. J. Phys. Chem. **11**, 201 (1907).
40. H. Tykociner. Rec. Trav. Chim. **I**, 144 (1882).
41. J. Minguin. Compt. Rend. **140**, 243 (1905).
42. T. C. James and J. J. Sudborough. J. Chem. Soc. **95**, 1538 (1909).
43. W. von Miller. Ber. **20**, 1927 (1887).
44. H. Biltz. Ann. **305**, 187 (1899).
45. P. Hill and R. Robinson. J. Chem. Soc. 486 (1933).
46. K. C. Pandya, O. S. Saxena, and J. D. Tinku. J. Indian Chem. Soc. **24**, 437 (1947).
47. C. C. Hach, L. M. Ligett, and H. Diehl. Iowa State Coll. J. Sci. **21**, 316 (1947); Chem. Abstr. **42**, 1240 (1948).
48. R. Stoermer. Ber. **44**, 637 (1911).
49. H. Ichibagase and S. Terada. J. Pharm. Soc. Japan, **72**, 878 (1952); Chem. Abstr. **47**, 6413 (1953).
50. C. Taege. Ber. **20**, 2109 (1887).
51. J. G. Jones, J. B. Poole, J. C. Tompkinson, and R. J. P. Williams. J. Chem. Soc. 2001 (1958).
52. A. B. E. Lovett and E. Roberts. J. Chem. Soc. 1975 (1928).
53. L. N. Gilliland, Jr., J. P. Hart, and M. R. Everett. Proc. Oklahoma Acad. Sci. **21**, 119 (1941); Chem. Abstr. **36**, 438 (1942).
54. G. W. K. Cavill. J. Soc. Chem. Ind. **64**, 212T (1945).