ORTHO-SUBSTITUTED CHLOROBENZENES RELATED TO METAMECONINE[1]

J. A. McRae,[2] Marjorie Allen,[3] and R. Y. Moir[4]

ABSTRACT

Chlorinated derivatives of metameconine were formed for the first time. Partial demethylation of the derivatives with sulphuric acid occurred in highly selective fashion at the methoxyl ortho to the halogen, without regard to the relative position of the carbonyl group which is known to be highly directive for demethylations in the absence of halogen. The phenolic products of the demethylations are needed for the synthesis of sterically hindered diphenyl ethers. They showed a type of intermolecular hydrogen bonding in the crystal which was markedly subject to steric interference by the halogen atoms.

Our work with the chlorinated derivatives of metameconine (X) was first undertaken many years ago as a check upon the results we had obtained in the corresponding bromine series (1, 2, 3); these results had differed sharply from those reported by others (4). The need for a check was emphasized when our more recent work (5) led to somewhat surprising conclusions as to the direction of bromination, nitration, and selective demethylation in the metameconines. This paper reports the independent characterization of the chlorine series of compounds, shows that the chlorine series is an almost exact parallel to the bromine series, and therefore thoroughly verifies our previous results.

Two more reasons for proceeding with the chlorine series appeared later in our work. (*a*) A subject of continuing interest to us is the study of steric hindrance in diphenyl ethers (3, 6); obviously the ortho-chloro- and ortho-bromo-phenols obtained in this work will allow the preparation of corresponding diphenyl ethers with blocking groups of different sizes. (*b*) We hope to study the effect of crowding upon the quadrupole resonance frequency of the halogens; measurement of these frequencies is, of course, easier for chlorine compounds than for bromine or iodine compounds.

The main novelty of the present work lies in the description of an interesting steric hindrance of hydrogen bonding in the solid phase.

Synthesis and Structure

The most easily available of the chlorine derivatives was 7-chlorometameconine[5] (XII), made from metameconine (X) by nitration, reduction to the amine (XI) (1, 2, 4), diazotization of the amine, and the Sandmeyer reaction. No doubt the structure was obvious, since 7-bromometameconine (1, 2, 4) and 7-iodometameconine (1, 3), formed in corresponding ways, have had their structures thoroughly verified. Nevertheless the present work offered a quite independent proof that the new substance was indeed 7-chlorometameconine, its indirect formation from 2-chloroveratric acid (XIV), as shown in the chart, leaving no room for doubt as to its structure.

The isomeric 4-chlorometameconine (VII) was formed by the action of formaldehyde upon 5-chloroveratric acid (VI) in acid solution. The structure of the resulting phthalide

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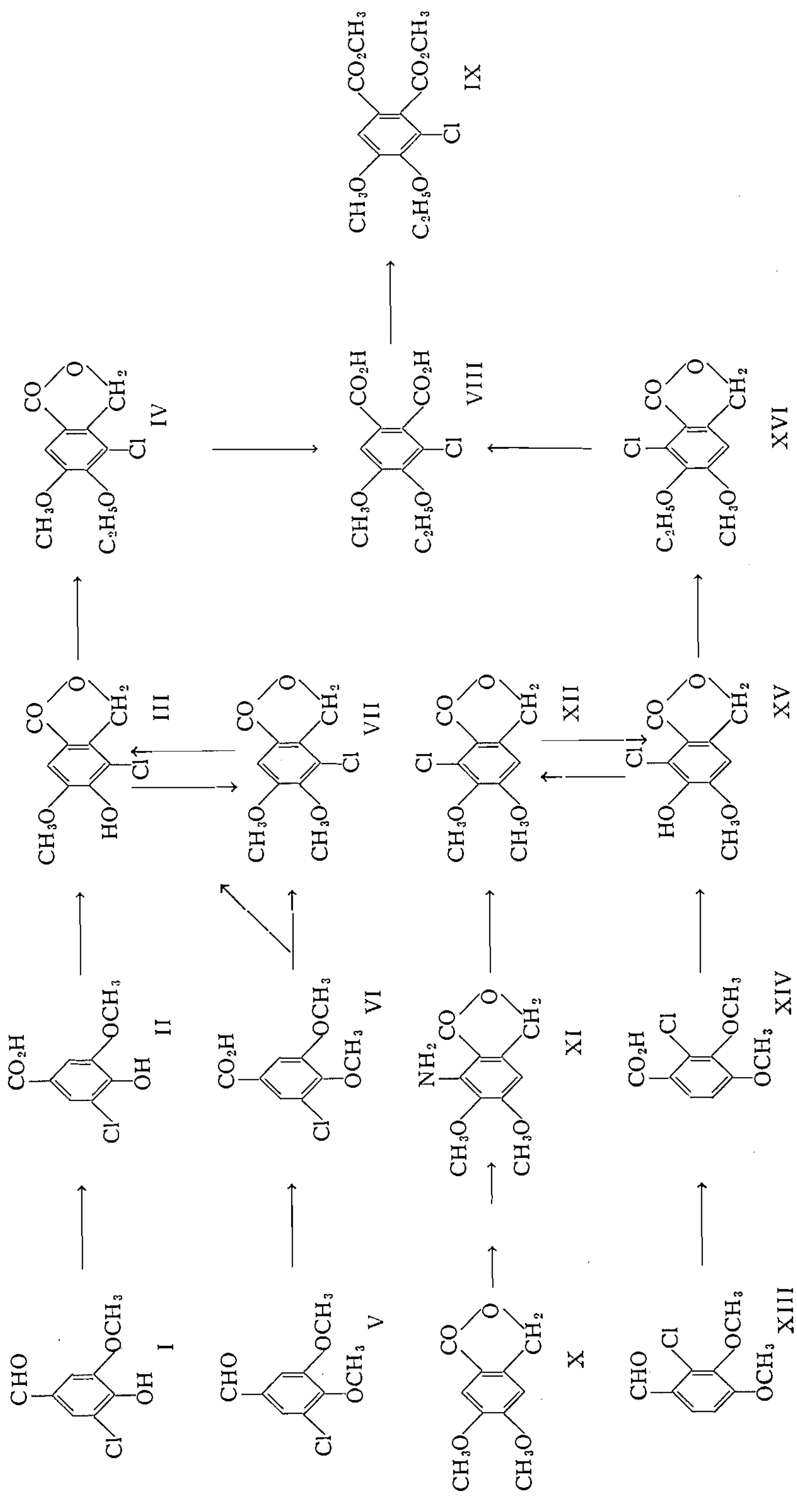
[2] *Died April 8, 1960.*

[3] *Holder of Canadian Industries Limited Fellowship 1958–60.*

[4] *Holder of Canadian Industries Limited Fellowship 1942–43.*

[5] *A different numbering scheme was used in some earlier papers.*


I
II
III
IV
V
VI
VII
VIII
IX
X
XI
XII
XIII
XIV
XV
XVI

was not immediately obvious, since the phthalide ring might have closed on either of the positions ortho to the carbonyl group in VI. That it did actually close as shown in structure VII followed from the fact that the phthalide could be converted to the phthalic ester IX which (as shown on the chart) could also be formed from metameconine (X) or from 2-chloroveratric acid (XIV).

Interesting phenolic compounds were obtained by selective demethylation of the chlorinated metameconines with sulphuric acid. Preparative yields were obtained of the easily purified products, much desired for future synthetic work. From 4-chlorometameconine (VII) there was obtained 4-chloro-5-hydroxy-6-methoxyphthalide (III), and from 7-chlorometameconine (XII) the isomeric 7-chloro-6-hydroxy-5-methoxyphthalide (XV). Just as in the bromine series, demethylation of both VII and XII occurred overwhelmingly at the methoxyl group ortho to the halogen, and without regard to the position of the carbonyl group, even though with veratraldehyde (7), veratric acid (7), and metameconine (5), highly selective demethylation occurred at the methoxyl meta to the carbonyl.

The methods used to show the structures of the phenolic compounds will be obvious from the transformations shown on the chart, the properties given in the experimental part, and the description of the corresponding bromine compounds (5).

Formaldehyde and 2-chloroveratric acid in acid solution gave none of the expected 7-chlorometameconine (XII); instead, very small amounts of 7-chloro-6-hydroxy-5-methoxyphthalide (XV) were obtained, along with large amounts of tars; the product was exceedingly difficult to purify. This miserable reaction was of central importance in our investigation, since it formed an exact parallel with the corresponding reaction of formaldehyde and 2-bromoveratric acid (1, 6), one of the main points in which our previous work disagreed with that of Rây and Robinson (4). Formaldehyde and 5-chloroveratric acid gave a mixture of the expected 4-chlorometameconine (VII) and the partially demethylated product, 4-chloro-5-hydroxy-6-methoxyphthalide (III). This too was an exact parallel with our experience with the corresponding 5-bromoveratric acid (2, 5). Even the infrared spectra of corresponding bromine and chlorine compounds are very similar throughout the two series, a further confirmation of the work in both. In fact the parallelism of the series broke down in only one respect: reductive dehalogenation, easy and convenient in the bromine series (5), in our hands failed completely in the chlorine series.

The correct orientation of the compounds of the metameconine series (1, 2, 3, 5, 6) has rested upon the correct orientation of the derivatives of vanillin used as reference compounds. It seems proper to point out how heavily we have relied upon the careful work of Dr. Raiford[6] and his students; of some 25 derivatives of vanillin needed in our structure proofs, only two (noted in the experimental part) have differed significantly from the descriptions given by these workers. One of the necessary intermediates, 5-chlorovanillic acid (II), has been made for the first time by Pearl's method (10), as shown in the experimental part.

Physical Properties

Jones, Angell, Ito, and Smith (12) reported that unsaturated lactones in solution sometimes show double peaks in the region of the carbonyl stretching frequency, though the two phthalides they investigated both showed single peaks. When their paper appeared

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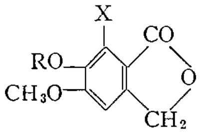
[6] *We especially wish to acknowledge the kindness of Professor Raiford in sending us an authentic sample of 2-chloroveratric acid nearly a year before its description was published (8), at a time when our work was delayed by the erroneous description of the acid then available (9), and not long before Professor Raiford's death (11).*

we had already observed, among the spectra of about 20 *solid* phthalides, a number of double peaks as well as some exceptionally large displacements of the carbonyl stretching frequency. A suggestion by Dr. R. N. Jones then enabled us to gain some understanding of the phenomena we had observed. Repetition of the spectra of the phthalides, but using solutions in tetrahydrofuran rather than solid samples in potassium bromide, immediately eliminated both the doubling of the peaks and the large displacements. Both factors were therefore due to intermolecular effects in the crystals; they were not due to impurities, incorrectly determined structures, or to unusual situations within the molecules.

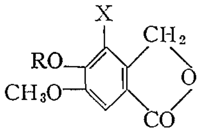
If one is interested in infrared spectra only for the determination of molecular structures, then the spectra of the crystals might simply be dismissed as inferior to the spectra of solutions. But the crystal effects are interesting in themselves, and had a special urgency for us, since quadrupole resonances *must* be observed in the solid state. We were able to make some progress in understanding the crystal effects because of the very large number of closely related phthalides at our disposal.

Spectra of Phthalides in Tetrahydrofuran

No double peaks were observed in the carbonyl stretching region, even in the acetylated derivatives (XVII A*d*, XVII C*d*, and XVIII C*d*) which have two different carbonyl groups. The peaks were all at positions normal for phthalides (13). In view of the results with the solid phthalides reported below, it was especially noteworthy that the phthalides bearing free phenolic groups had their peaks in the normal position, in agreement with previous work on related compounds (13, 14). Twelve halogenated phthalides (XVII and XVIII, with all possible combinations of B, C, *a*, *b*, and *c*) had their maxima in the region 1769–1773 cm^{-1}. Three unhalogenated phthalides (XVII A*a*, XVII A*b*, and XVIII A*a*) absorbed in the region 1766–1769 cm^{-1}. The available acetylated phthalides (XVII A*d*, XVII C*d*, and XVIII C*d*) showed absorption at the noticeably higher values of 1775–1777 cm^{-1}.



XVII



XVIII

Substituent code

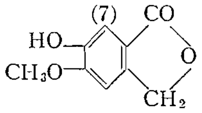
A: X = H   *a*: R = H
B: X = Cl   *b*: R = Me
C: X = Br   *c*: R = Et
D: X = I   *d*: R = Ac

Examples: XVII A*b* is structure X; XVII B*c* is XVI.

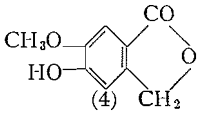
Spectra of Solid Phthalides in Potassium Bromide

We discuss only effects which are both large and reproducible, since the peaks were, of course, broader and had less sharply defined maxima than those obtained with solutions, and because of the well-known smaller spectral variations possible with this technique. Two remarkable phenomena were noticed.

(*a*) *Steric interference with intermolecular hydrogen bonding.*—The reality of this effect was evident because the effect was reproducible, extremely large, and beautifully correlated with structure. Two phthalides (XVII A*a* and XVIII A*a*) (5) both showed absorption at the abnormally low frequency of 1715 cm^{-1}. The displacement of the band was due to an intermolecular effect, since it vanished in solution; even phthalides having hydroxyl ortho to the carbonyl show but little intramolecular association (13, 14). Clearly too the displacement involved the hydroxylic hydrogen since methylation of the free hydroxylic group returned the maximum absorption (of solid XVII A*b*) to 1755 cm^{-1};



XVII A*a*



XVIII A*a*

acetylation of the free phenolic group brought the peak (in solid XVII A*d*) to 1753 cm^{-1}. Both values represent complete elimination of the effect. Direct hydrogen bonding from the phenolic group to the carbonyl group of another molecule would in any case be suspected from the great effect on the carbonyl stretching frequency, and confirmation of this was afforded by a most interesting steric effect. Substitution of either chlorine or bromine at position 7 in XVII A*a* also abolished the displacement effect, even though the hydroxyl group was still present, since solid XVII B*a* absorbed at 1760 cm^{-1}, and solid XVII C*a* at 1768 cm^{-1}. In view of our other results, by far the main effect of halogen at position 7 must have been due to steric blocking of the carbonyl group. Halogen at position 4 was very much less effective in interfering with the hydrogen bonding, solid XVIII B*a* absorbing at 1726 cm^{-1}, and solid XVIII C*a* at 1730 cm^{-1}, and this comparatively small increase from the values for unsubstituted XVIII A*a* may have been due to a combination of effects: a partial steric interference with the phenolic group, a general increase in lattice dimensions, and a small direct effect of halogen on the carbonyl group (see solution values, and reference 13). We have not yet been able to form phthalides having halogen ortho to carbonyl and meta to hydroxyl, so that these three effects cannot yet be separated from each other. Nevertheless, the displacement of the carbonyl peak in the solid phenolic compounds is so clear cut that it might have been used in the structure proofs to fix the relative positions of halogen and carbonyl. Eight solid phthalides in which intermolecular hydrogen bonding was absent showed a single peak in the carbonyl stretching region in the range 1753–1768 cm^{-1}. The rather wide range may be correlated with the lattice effects discussed in the next section.

(*b*) *Double carbonyl peaks with solid phthalides.*—Seven solid phthalides showed very distinct double carbonyl peaks; of the seven all were halogenated, none was phenolic, and none was acetylated. The lower peaks were all in the region 1748–1755 cm^{-1}, but the upper peaks were more variable in position. Four phthalides halogenated at position 4 (XVIII B*b*, B*c*, C*b*, and C*c*) had the upper peak at 1776–1782 cm^{-1}, and three phthalides halogenated at position 7 (XVII B*b*, C*b*, and D*b*) had the upper peak in the noticeably lower range of 1764–1767 cm^{-1}. The peaks varied considerably in relative amplitudes, without any obvious correlation with structure.

The double peaks were certainly due to effects of crystal structure, since only a single peak appeared in the spectra of solutions. For at least one phthalide, the double peak was associated with dimorphism. Fresh preparations of XVIII C*c* (5) consisted of feathery needles and showed peaks at 1753 and 1781 cm^{-1}. Older preparations consisted of heavy prisms and showed only a single peak at 1758 cm^{-1}. We have been unable to obtain a single peak in the spectrum of the less stable form. On the other hand the phthalide XVIII C*d* (5) showed only a single peak at room temperature, though it showed dimorphism at higher temperatures, the long needles melting at 140°, then resolidifying to small prisms which melted again at 165°. Although these have been our only direct observations of dimorphism, the phenomenon cannot be ruled out as the explanation of all the double peaks observed with our phthalides.

Double Carbonyl Peaks in the Phthalic Esters

The dimethyl ester of 3-chloro-4-ethoxy-5-methoxyphthalic acid showed double peaks both in solution (at 1730 and 1744 cm^{-1}) and in the solid state (at 1720 and 1735 cm^{-1}); the corresponding bromine compound (5) was very similar in its spectra. The corresponding phthalic acids showed double peaks in the solid state, and single, very wide peaks in solution.

EXPERIMENTAL

All identities claimed in this paper were checked by comparison of the infrared spectra. The spectra were obtained using potassium bromide disks containing 0.8% by weight of sample, and tetrahydrofuran solutions containing up to 6% depending on the solubility of the sample. The spectrometer (a Perkin–Elmer Model 21, using a sodium chloride prism) was repeatedly calibrated by the use of the polystyrene bands at 1802 cm^{-1} and 1603 cm^{-1}. Most melting points were determined in an instrument of high precision (15) and the rest were performed on a Koffler Micro Hot Stage and lowered 3–5° to agree with precision capillary melting points within less than 1° up to 250°.

5-Chlorovanillic Acid (II)

The oxidation of 5-chlorovanillin (I) (m.p. 162.6–163.2°) (16) was accomplished following the method described by Pearl (10) for the preparation of vanillic acid. The product melted at 252–254°. The recorded (17) melting point is 244–245°. Found: C, 47.58; H, 3.39; Cl, 17.25%. Calc. for $C_8H_7ClO_4$: C, 47.42; H, 3.48; Cl, 17.52%.

5-Chloroveratraldehyde (V)

The method described for veratraldehyde (18) was adapted to the methylation of 5-chlorovanillin. The product melted at 55–55.6°; the recorded (11) melting point is 48–49°. Found: Cl, 18.2%. Calc. for $C_9H_9ClO_3$: Cl, 17.69%.

5-Chloroveratric Acid (VI)

5-Chloroveratraldehyde (17.0 g) and sodium bicarbonate (3.0 g) in water (100 ml) were heated to 60°. With vigorous stirring a solution, also heated to 60°, of potassium permanganate (20.2 g) in water (200 ml) was slowly added over 30 minutes whilst the temperature was maintained at 60–80°. The reaction was allowed to proceed for another 30 minutes, and then the reaction mixture was cooled, saturated with sulphur dioxide, and strongly acidified with hydrochloric acid (20 ml, conc.). The white precipitate was recovered by filtration, washed with a small volume of cold water and crystallized from ethyl alcohol to yield the product (15.6 g) with a melting point of 189.0–189.6°. Two more crystallizations from ethyl alcohol raised the melting point to 189.8–190.4°. The recorded (11) melting point is 188–189°. Found: C, 50.14; H, 4.00; Cl, 16.38%. Calc. for $C_9H_9ClO_4$: C, 49.88; H, 4.19; Cl, 16.38%.

2-Chloroveratric Acid (XIV)

This acid was obtained from 2-chlorovanillin by methylation according to the procedure recorded for veratraldehyde (18) followed by oxidation by the method described above for the isomeric 5-chloroveratric acid. The product purified by crystallization from aqueous ethyl alcohol had a melting point of 202°–203°. A mixed melting point determination with an authentic sample supplied by Professor Raiford gave a melting point of 202.5–204.5°.

4-Chloro-5-hydroxy-6-methoxyphthalide (III)

(*a*) 5-Chlorovanillic acid (II) (2.0 g, m.p. 247–249°), glacial acetic acid (80 ml), hydrochloric acid (40 ml, conc.), and formaldehyde (20 ml, 36–38%) were mixed and heated at 80–85° for 2 days. The cooled reaction mixture was poured onto ice (200 g) and after 2 hours the resulting precipitate was recovered by filtration, washed with a little cold water, and dried. The product (1.18 g) had a melting point of 204–206° which was raised to 236.4–237.2° by three crystallizations from ethyl alcohol. Found: C, 50.55, 50.78; H, 3.55, 3.46; Cl, 16.21, 16.55; —OCH_3, 15.45, 15.37 and on the same sample by a different analyst 13.64%. Calc. for $C_9H_7ClO_4$: C, 50.37; H, 3.29; Cl, 16.54; —OCH_3, 14.46%.

(*b*) 5-Chloroveratric acid (VI) (10 g, m.p. 186–187°), glacial acetic acid (400 ml), hydrochloric acid (200 ml, conc.), and formaldehyde solution (100 ml, 36–38%) were combined and heated at 95–100° for 2 days. The white precipitate obtained after pouring the reaction mixture onto ice was extracted with sodium bicarbonate solution. The insoluble fraction yielded after one crystallization from ethyl alcohol 4-chlorometameconine (VII) (1.66 g) with a melting point of 168–171°. (For further details see below.) The sodium bicarbonate extract was acidified and the resulting precipitate recovered and crystallized from ethyl alcohol. The product (2.77 g) had a poor melting point of 168–220°, but a second crystallization raised the melting point to 234–235°. A mixed melting point with the product from method (*a*) showed no depression.

(*c*) 4-Chlorometameconine (VII) (0.13 g, m.p. 171.2–171.8°) was heated in sulphuric acid (1 ml, conc.) at 60° for 2 days. The solution was poured onto ice and the precipitate recovered by filtration and washed with water. The product after two crystallizations from ethyl alcohol melted at 234–235° and gave no depression in melting point when mixed with the product from method (*a*).

The infrared spectra of the three samples of 4-chloro-5-hydroxy-6-methoxyphthalide produced by these methods, are identical throughout the range 4000–600 cm^{-1}.

4-Chlorometameconine (VII)

(*a*) This method of preparation is the same as method (*b*) described for 4-chloro-5-hydroxy-6-methoxyphthalide. The product (1.66 g) was crystallized twice from ethyl alcohol to give the analytical sample with a melting point of 171.2–171.8°. Found: C, 52.77, 52.71; H, 4.11, 4.25; Cl, 15.62, 15.65%. Calc. for $C_{10}H_9ClO_4$: C, 52.50; H, 3.97; Cl, 15.52%.

(*b*) 4-Chloro-5-hydroxy-6-methoxyphthalide (III) (0.2 g, m.p. 234–235°) from method (*a*) above was added to an ether solution of diazomethane (20 ml, 2%) and the mixture was left to stand overnight. The solution was evaporated and the easily solidified residue crystallized from ethyl alcohol to give fluffy needles (0.13 g) which melted at 171.2–171.8°. A mixed melting point with the product from (*a*) gave no depression, and the infrared spectra of the two products were identical.

4-Chloro-5-ethoxy-6-methoxyphthalide (IV)

4-Chloro-5-hydroxy-6-methoxyphthalide (III) (1.63 g, m.p. 234–235°), from method (*a*) above, ethyl iodide (30 ml), and dry acetone (75 ml) were refluxed and stirred in dry apparatus protected from moisture by drying tubes. Drierite (1.0 g) was added and the mixture stirred for 30 minutes. Freshly prepared silver oxide (5.0 g) was added in portions (1.0 g) at intervals over 7 hours, the reaction was allowed to proceed for a further 2 hours, and then the reaction mixture was cooled and filtered to remove the silver compounds. The filtrate was evaporated to dryness and the solid residue crystallized from ethyl alcohol to give white crystals (1.48 g) which melted at 138–139°. Three more crystallizations raised the melting point to 141.4–141.8°. Found: C, 54.72, 54.67; H, 4.70, 4.45; Cl, 14.30%. Calc. for $C_{11}H_{11}ClO_4$: C, 54.44; H, 4.57; Cl, 14.63%.

7-Chlorometameconine (XII)

(*a*) 7-Aminometameconine (XI) (2) (15 g crude) was dissolved in hydrochloric acid (45 ml, conc.) and water (300 ml). The solution was mechanically stirred and cooled in an ice and salt bath to −5°. Sodium nitrite (7.5 g) in water (60 ml) was added from a dropping funnel over 20 minutes, and then the mixture was stirred and cooled for 3.5 hours longer. The excess nitrous acid was destroyed with urea and the reaction mixture was slowly poured, with stirring, into a well-cooled solution of cuprous chloride (from 19 g $CuSO_4.5H_2O$) in hydrochloric acid (21 ml, conc.) and water (8 ml). When the frothing had subsided, the reaction mixture was gently heated on a boiling-water bath. The precipitate which settled out of the cooled solution, was recovered by filtration, washed with water, and crystallized once from dilute acetic acid (3:2) and three times from *n*-butanol to yield white needles (5.0 g) with a melting point of 193–193.5°. Two more crystallizations of corresponding material from another preparation gave the analytical sample with a melting point of 195.8–196.6°. Found: C, 52.48, 52.32; H, 3.97, 3.96; Cl, 15.22, 15.37%. Calc. for $C_{10}H_9ClO_4$: C, 52.50; H, 3.97; Cl, 15.52%.

(*b*) 5-Methoxy-6-hydroxy-7-chlorophthalide (XV) (0.5 g, m.p. 234–235°) from method (*a*) below, when methylated with diazomethane yielded white needles (0.42 g), with a melting point of 194.2–195.2° after one crystallization from ethyl alcohol. The infrared spectra of these two samples of 7-bromometameconine are identical, and a mixed melting showed no depression. The material made by method (*b*) below was methylated with methyl sulphate and gave 7-chlorometameconine proved by mixed melting point determination and infrared spectra.

5-Methoxy-6-hydroxy-7-chlorophthalide (XV)

(*a*) 7-Chlorometameconine (XII) (2.0 g, m.p. 193–194°) was heated with sulphuric acid (10 ml, conc.) for 3.5 days at 60°. The cooled viscous solution was poured onto ice and the resulting precipitate recovered by filtration, washed with water, and dried. The solid (1.87 g) was extracted with sodium bicarbonate solution and the soluble fraction recovered by acidifying the extracts. This procedure yielded a solid (1.47 g) with a melting point of 230–231°, which was raised to 235–235.8° by three crystallizations from ethyl alcohol. Found: C, 50.66, 50.48; H, 3.42, 3.28; Cl, 16.23, 16.53; $-OCH_3$, 14.44%. Calc. for $C_9H_7ClO_4$: C, 50.37; H, 3.29; Cl, 16.54; $-OCH_3$, 14.46%. A mixed melting point with the isomer 4-chloro-5-hydroxy-6-methoxyphthalide (III) showed a large depression.

(*b*) 2-Chloroveratric acid (XIV) (5.0 g), formaldehyde solution (9.0 ml, 36–38%), hydrochloric acid (31 ml, conc.), and glacial acetic acid (45 ml) were heated at 80–90° for 76 hours and at 100° for 7 hours longer. The combined solutions from three similar experiments were cooled and decanted from a small amount of tar, diluted with water (85 ml), and filtered to remove more tar. A second dilution with water (50 ml) precipitated unchanged 2-chloroveratric acid which after successive crystallizations from ethyl alcohol, aqueous ethyl alcohol, *n*-butyl alcohol, and aqueous acetic acid melted at 200–201.5°. The filtrate was again diluted with water (500 ml) and the solution evaporated to less than 150 ml under a slight vacuum, neutralized with sodium bicarbonate, made very slightly acid with hydrochloric acid, and the resulting precipitate collected after 24 hours. The precipitate (1.95 g) was washed with hot and cold water, and crystallized three times from *n*-butanol to give a product with a melting point of 231–232.5°. Found: C, 51.98; H, 3.84; Cl, 16.85, 16.50%. Calc. for $C_9H_7ClO_4$: C, 50.37; H, 3.29; Cl, 16.54%.

Better material, m.p. 234.2–234.8°, was obtained by a further recrystallization from ethyl alcohol. The infrared spectra given by these two products from methods (*a*) and (*b*) were identical.

5-Methoxy-6-ethoxy-7-chlorophthalide (XVI)

5-Methoxy-6-hydroxy-7-chlorophthalide (XV) (2.0 g, m.p. 234–235°) was ethylated by the method described above for 4-chloro-5-hydroxy-6-methoxyphthalide. The product (1.59 g) after one crystallization from ethyl alcohol melted at 174–175°. Three more crystallizations raised the melting point to 177.2–177.6°. Found: C, 54.43, 54.52; H, 4.70, 4.56; Cl, 14.63%. Calc. for $C_{11}H_{11}ClO_4$: C, 54.44; H, 4.57; Cl, 14.63%.

3-Chloro-4-ethoxy-5-methoxyphthalic Acid (VIII)

(*a*) Potassium permanganate (2.5 g) was added over a period of 15 minutes to a well-stirred solution of 4-chloro-5-ethoxy-6-methoxyphthalide (IV) (1.0 g, m.p. 140.6–141.2°) in potassium hydroxide solution (110 ml, 5%) heated on a steam bath. The reaction was allowed to proceed another 45 minutes, and then cooled. Sulphur dioxide was passed until a clear solution was obtained. The solution was evaporated to half volume and after standing at room temperature, crystals with a poor melting point settled out of the solution. The product crystallized from water containing a few drops of hydrochloric acid in two modifications which were separated by hand: (A) long needles (0.2 g) with a melting point of 200–201° and a second melting point due to the anhydride of 133.5–134°; (B) small prisms (0.02 g) with a melting point of 203–207° and a second melting point of 133.5–134°. The infrared spectra in potassium bromide disks of these two modifications showed slight differences in the intensity of the peaks in the region 1500–1450 cm^{-1}, and differences in the positions of the peaks in the region 1000–850 cm^{-1}, which are probably due to variations in the crystalline structure. The two forms were methylated separately (see below) to give identical products as determined by infrared spectra and mixed melting points.

(*b*) 5-Methoxy-6-ethoxy-7-chlorophthalide (XVI) (1.0 g, m.p. 174–175°) was oxidized as above, and the product after one crystallization from water melted at 192–194° and the second melting point was 133.5–134°. This product appeared to be homogeneous, and the infrared spectrum was identical with that given by the modification B above.

Dimethyl 3-Chloro-4-ethoxy-5-methoxyphthalate (IX)

(*a*) 3-Chloro-4-ethoxy-5-methoxyphthalic acid (0.2 g, crystals A) were added to diazomethane solution (20 ml, 2% in ether) and left to stand overnight. The colorless solution was evaporated to dryness and the easily solidified residue was crystallized from petroleum ether (b.p. 30–60°) to give heavy needles which melted at 68.8–70.4°.

The product from crystals B melted at 70.4–70.6°, and a mixed melting point was 68.8–70.4°.

(*b*) 3-Chloro-4-ethoxy-5-methoxyphthalic acid (0.44 g from (*b*) above) yielded white needles (0.38 g) with a melting point of 70.4–71.4°, which did not depress the melting point of the above products. Found: C, 51.70, 51.66; H, 5.12, 4.86; Cl, 12.29, 12.42%. Calc. for $C_{13}H_{15}ClO_6$: C, 51.56; H, 4.99; Cl, 11.72%.

The infrared spectra given by the three samples of dimethyl 3-chloro-4-ethoxy-5-methoxyphthalate were identical.

Attempted Dechlorinations

5-Chlorovanillic acid (II) was used as a model compound in experiments designed to find the conditions for removal of the chlorine atom. The methods tried were: (*a*) sodium amalgam in aqueous medium, (*b*) zinc dust and potassium hydroxide, (*c*) preformed chromous chloride, (*d*) chromous chloride prepared *in situ*. All experiments failed, the only compound isolated being unchanged 5-chlorovanillic acid. The last two series of experiments were repeated with 4-chloro-5-hydroxy-6-methoxyphthalide (III) and once again there was no evidence that chlorine had been successfully removed.

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