[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, QUEEN'S UNIVERSITY]

REACTIONS OF THE IODOMETAMECONINES[1]

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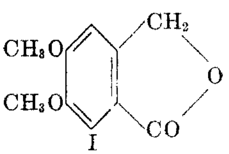
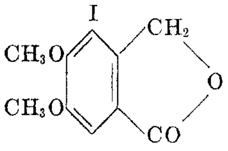
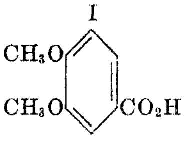
Metameconine has two possible derivatives in which one iodine atom is attached to the benzene ring. In a previous paper (1), we described the preparation of 7-iodometameconine (I)[4] from metameconine by nitration, reduction and the Sandmeyer reaction. Its isomer, 4-iodometameconine (II),[4] was first prepared about 15 years ago by Dr. Norah McGinnis in the reaction of formaldehyde with 5-iodoveratric acid (III). Our repetition of her unpublished work is recorded in the experimental part. The iodo-compounds have now been converted to phenols, alkyl ethers, aryl ethers, and various oxidation products which were formerly unobtainable.



I



II



III

The iodine atom was found to be easily replaceable by hydroxyl or alkoxyl groups in the Ullmann reaction. Thus with water, copper, and potassium hydroxide, 7-iodometameconine (I) gave good yields of 7-hydroxymetameconine (IVa), while 4-iodometameconine gave good yields of 4-hydroxymetameconine (Va). The phenol IVa was further characterized through its acetyl derivative. Similarly, with methanol, copper, and potassium methoxide, 4-iodometameconine (II) gave 4-methoxymetameconine (Vb) which was shown to be identical with the trimethoxyphthalide (Vb) of known structure made from trimethylgallic acid and formaldehyde (2). As reported previously (1), 7-iodometameconine (I) gave the isomeric 7-methoxymetameconine (IVb). Both methyl ethers have almost exactly the same melting point, and other possibly misleading coincidences in melting point are recorded in the experimental part.

One ethoxyl derivative (IVc) was prepared by the same general method, but in lower yields.

Vigorous oxidation of 7-ethoxymetameconine (IVc) gave 3-ethoxymetahemipinic acid, characterized as its dimethyl ester (VI), which should be of value as a

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[1] The material in this paper is taken from theses written by J. J. Ursprung (August, 1952) and H. H. Gibbs (August, 1953), in partial fulfilment of the requirements for the degrees of Master of Arts and Master of Science, respectively.

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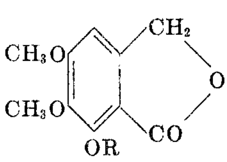
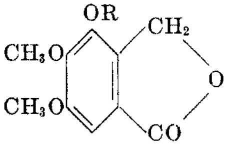
[4] The numbering scheme used in this paper is that suggested by Chemical Abstracts, and differs from the numbering used in our previous papers.

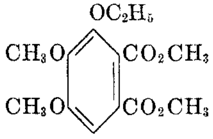
reference compound in the degradation of natural products. Similar oxidations of 7-iodometameconine (I) and of 7-methoxymetameconine (IVb) to the corresponding metahemipinic acids have already been reported (1). Of greater interest for synthetic work are the oxidations of the metameconines to the corresponding metaopianic acids. Brown and Newbold (3) reported that good yields of metaopianic acid are produced by the action of N-bromosuccinimide upon metameconine, followed by hydrolysis of the intermediate bromo-compound, and we find their method to be superior to the oxidation with lead tetraacetate reported previously by us (4). Oxidation of 7-iodometameconine with N-bromosuccinimide gave the formerly unknown 3-iodometaopianic acid (VIIa), and the Ullmann reaction with VIIa gave the much desired 3-hydroxymetaopianic acid (VIIb), also a new compound.



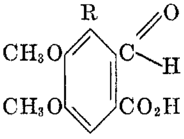
IVa R = H
IVb R = CH_3
IVc R = C_2H_5



Va R = H
Vb R = CH_3



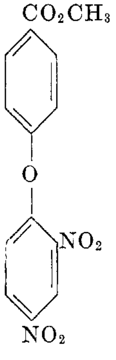
VI



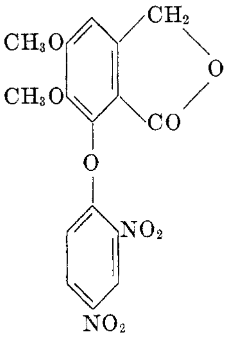
VIIa R = I
VIIb R = OH

The structures suggested for all these compounds appear to be firmly based. Thus the structures of the parent iodo-compounds (I and II) were verified (4) by methods not involving any displacement reactions, such as the Ullmann reactions described here. The methoxymetameconines (IVb and Vb) have their structures assigned to them on account of their relations to the known trimethoxyphthalide made from trimethylgallic acid (1, 2) independently of their formation in the Ullmann reaction by the displacement of an iodine atom with a methoxyl group. Furthermore, 7-hydroxymetameconine (IVa), produced by the displacement of iodine with hydroxyl, gave on ethylation the same 7-ethoxymetameconine (IVc) produced by direct displacement of iodine with ethoxyl. Since hydroxyl, methoxyl, and ethoxyl ions are in increasing order of nucleophilic strength, and since hydroxyl and ethoxyl both react in the same way, there seems no reason to doubt the assigned structures IVa, IVc, and Va. The rest of the compounds were produced by reactions known not to give rearrangements.

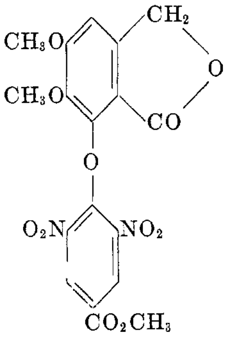
The total failure experienced in our attempts to form substituted diphenyl ethers in the Ullmann reactions of the iodometameconines is in great contrast to the ease with which phenols and alkyl ethers are formed from them. Some of these failures were described previously (1), and some others, of interest because of the observed side reactions, are described in the experimental part. A much more promising method for producing diphenyl ethers was discovered a few years ago by Borrows, Clayton, Hems, and Long (5), who found that phenylpyridinium compounds, activated by two *ortho* or *para* nitro-groups, attacked phenols in pyridine solution to give good yields of diphenyl ethers. This method gave excellent results when applied to the present series of compounds. Compound VIII was formed first, simply for practice. Compound IX was then formed by the action of 2,4-dinitrophenylpyridinium tosylate upon 7-hydroxymetameconine (IV a) in pyridine; compound X by the action of methyl 4-chloro-3,5-dinitrobenzoate (5) upon 7-hydroxymetameconine (IVa) in pyridine; and compound XI by the action of 2′-nitro-4′-carbomethoxyphenylpyridinium tosylate (XII) upon 7-hydroxymetameconine in pyridine. Structures IX, X, and XI were assigned to the resulting compounds largely because of the method of synthesis. Not a single example of rearrangement has been recorded in the large number of substituted diphenyl ethers made by the present method (6–10), but it should be added that the majority of the known derivatives of diphenyl ether, made not only by the present method but also by the related "activated" syntheses (11) and by the Ullmann reaction, have their structure resting on their method of synthesis alone, so that perhaps the synthetic methods have not been adequately checked for all cases. Some independent confirmation of the structures offered in this paper may be given. While very gentle alkaline hydrolysis of the compound thought to have structure XI merely removed the methyl ester group, moderately vigorous alkaline hydrolysis cleaved the molecule. Presumably this means that both the activating nitro and carbomethoxy groups are still in the *ortho* and *para* positions, since unactivated diphenyl ethers are very resistant to cleavage, and since known rearrangements in aromatic nucleophelic substitution occur at *ortho* positions only (11). Rearrangement of the metameconine portion of the molecule XI would of course not be expected.



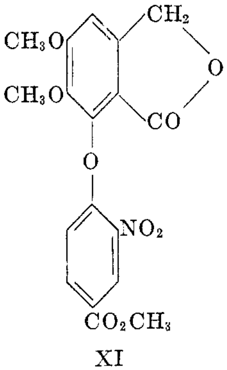
VIII



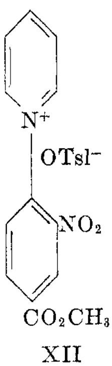
IX



X



XI



XII

Formation of all the compounds VIII, IX, X, and XI took place under mild conditions and in good yields, and the products were easily purified. It is reasonable to think that this method will be useful in the synthesis of bisbenzylisoquinoline alkaloids and of alkaloids of the cularine type (12). The work is also interesting (a) because compounds X and XI show, in wooden models, an unusually great degree of steric hindrance about the diphenyl ether linkage, and (b) because the activation required for the formation of compound XI (one nitro-group and one carbomethoxy group) is considerably less than that of two nitro-groups considered necessary by the discoverers of the reaction (5). Although this extension of their method is of small theoretical significance, the presence of two different activating groups will add considerably to the usefulness of the compounds in subsequent synthetic reactions.

EXPERIMENTAL

All melting-points are corrected.

5-Iodoveratric acid (III). 5-Iodovanillin (13, 14) was methylated in aqueous solution to give crude 5-iodoveratric aldehyde (15) in a yield of 73%. The crude aldehyde was then oxidized with warm, slightly alkaline, aqueous permanganate to give crude 5-iodoveratric acid (16), m.p. 182.5–184.6°, in a yield of 68%.

4-Iodometameconine (II). Crude 5-iodoveratric acid (18.0 g.) was stirred with warm glacial acetic acid (70 cc.) until solution was complete. Concentrated hydrochloric acid (22 cc.) and formaldehyde solution (36–38%, 15 cc.) were then added, and the mixture was heated under reflux on the steam-bath, with mechanical stirring, for 24 hours. Two volumes of water were then added, the mixture was chilled for 12 hours, and the cream-colored precipitate was recovered, washed with water, and extracted with 5% potassium carbonate solution for one hour, with mechanical stirring. The alkaline filtrate from the extraction on acidification gave unchanged 5-iodoveratric acid, while the alkali-insoluble precipitate, after being washed with water and thrice recrystallized from ethanol with charcoal, yielded large colorless needles of 4-iodometameconine, m.p. 173.0–174.0°.

Anal. Calc'd for $C_{10}H_9IO_4$: I, 39.65. Found: I, 39.58, 38.99.

In 24 runs, the average yield of pure 4-iodometameconine was 6.3%, and the average recovery of 5-iodoveratric acid was 63%. These experiments were based on the work of Dr. Norah McGinnis (Mrs. W. Glen) who obtained a similar product in these laboratories 15 years ago.

4-Hydroxymetameconine (Va). Pure 4-iodometameconine (3.0 g.) was dissolved in boiling potassium hydroxide solution (5 %, 150 cc.), copper bronze catalyst (Kahlbaum's No. 02219, 0.30 g.) was added and the mixture was heated under reflux for three hours. The cooled mixture was filtered, and the filtrate was acidified with concentrated hydrochloric acid, the liberated iodine being destroyed with bisulfite as it was formed, and the mixture was chilled overnight. White crystals were then recovered and washed with water, and a further crop was obtained on concentrating the filtrate. The average yield of crude material was 81%. Two crystallizations from water, charcoal being used once, gave colorless needles of m.p. 184.7–185.7°.

Anal. Calc'd for $C_{10}H_{10}O_5$: C, 57.14; H, 4.76.
Found: C, 57.10, 56.72; H, 4.76, 4.85.

4-Methoxymetameconine (Vb). Pure 4-iodometameconine (0.5 g.) and copper bronze catalyst (0.03 g.) were heated under reflux for 11 hours with a solution made from potassium (0.27 g.) and dry methanol (8 cc.). The catalyst and solvent were then removed, the residue taken up in a little water, acidified, and the precipitate recovered. Long white needles of 4-methoxymetameconine (0.2 g.) were obtained, and after three recrystallizations from water the beautifully crystalline, colorless product had m.p. 134.7–135.7°. This melting point was not depressed by admixture of the material with authentic 4-methoxymetameconine, made by Dr. R. H. Manske from trimethylgallic acid according to method of King and King (2), but it was markedly depressed on admixture of the sample with 7-methoxymetameconine (1).

3-Iodometaopianic acid (VIIa). The procedure was based on that used by Brown and Newbold (3) for the preparation of metaopianic acid. Pure 4-iodometameconine (5.0 g.) was dissolved in very dry, boiling benzene (125 cc.), treated with dry carbon tetrachloride (125 cc.) and N-bromosuccinimide (5.6 g.), and heated under reflux for 2 hours, the reaction flask being irradiated with a 60-watt light bulb. The mixture then was cooled, the insoluble succinimide was recovered by filtration and the filtrate was evaporated to dryness under reduced pressure. The residue was boiled with water (500 cc.) for 2 hours and the hot solution was filtered from a small amount of gum. On cooling, the filtrate deposited well formed colorless needles in an average yield of 74%. Two recrystallizations of the needles from water, charcoal being used once, gave the pure 3-iodometaopianic acid, m.p. 186.8–187.7°. Admixture of the material with metaopianic acid (m.p. 187.2–187.7°) gave a large depression of the m.p.

Anal. Calc'd for $C_{10}H_9IO_5$: I, 37.86. Found: I, 37.46, 38.08.

3-Hydroxymetaopianic acid (VIIb). Pure 3-iodometaopianic acid (2.3 g.) was heated under reflux for 3 hours with potassium hydroxide solution (5 %, 50 cc.) and copper bronze catalyst (0.23 g.). The mixture was cooled, filtered, and the filtrate acidified, a little solid sodium bisulfite being added to destroy the free iodine as it was formed. Long colorless needles were deposited from the solution after it had been chilled overnight; these were recovered and washed with water to give a 69% yield of crude product. Two recrystallizations from water gave the pure product, m.p. 154.9–155.4°, the mixture m.p. with metameconine (m.p. 157.0–158.1°) showing a large depression.

Anal. Calc'd for $C_{10}H_{10}O_6$: C, 53.10; H, 4.47.
Found: C, 52.88, 53.38, H, 4.49, 4.41.

Both of the substituted metaopianic acids just described reacted promptly with a solution of phenylhydrazine, acetic acid, and sodium acetate, to give precipitates.

7-Iodometameconine (I). 7-Aminometameconine hydrochloride was prepared in five steps from vanillin as previously described (1, 4), and then was converted to 7-iodometameconine largely as previously described (1). It was found (a) that the use of a large excess bisulfite in destroying free iodine lowered the yield of product and (b) that 95% alcohol with charcoal was a more satisfactory solvent for purification. Attention to these small details resulted in a yield of 71% of pure 7-iodometameconine, m.p. 171.3–171.6°.

7-Hydroxymetameconine (IVa). Pure 7-iodometameconine (3.798 g.) was heated under reflux for 2 hours with potassium hydroxide solution (25 %, 75 cc.) and copper bronze catalyst (0.1 g.). A side test showed that iodide ion had been produced. The mixture was cooled, filtered, and the filtrate was acidified, a little sodium bisulfite being added. Part of the product was recovered by filtration, the rest by ether extraction; it consisted of feathery crystals, m.p. 158–160°, in a yield of 2.0481 g. or 82%. The mixture m.p. (of another sample) with metameconine showed a large depression. Purification of the material was difficult. Recrystallization from hot water with charcoal followed by very slow cooling of the filtrate gave colorless white needles, m.p. 159.8–160.7°.

Anal. Calc'd for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80.
Found: C, 57.39; H, 4.70.

7-Acetoxymetameconine. Crude 7-hydroxymetameconine (0.5 g.) was acetylated either with aqueous potassium hydroxide and acetic anhydride (72% yield of once recrystallized product) or with acetic anhydride and a trace of concentrated sulfuric acid (95% yield of once recrystallized product). Two more recrystallizations from dilute acetic acid of a product made by the latter reaction gave small colorless crystals, m.p. 147.3–147.7°.

Anal. Calc'd for $C_{12}H_{12}O_6$: C, 57.14; H, 4.80.
Found: C, 57.23, 57.24; H, 4.64, 4.85.

The product from the former method was the same.

7-Methoxymetameconine was prepared largely as described before (1) from 7-iodometameconine, and the product was shown to be the same as that obtained previously by m.p. and mixture m.p.

7-Ethoxymetameconine (IVc). (*a*). Pure 7-iodometameconine (3.9 g.) and copper bronze (0.2 g.) were heated under reflux for 14 hours with a solution made from potassium (2.4 g.) and dry ethanol (200 cc.). The product was isolated in the usual manner and after two recrystallizations from water, characoal being used once, was obtained as colorless needles of m.p. 132.0–132.4°, yield 1.0 g. or 34%.

Anal. Calc'd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92.
Found: C, 60.90, 60.67; H, 5.93, 5.84.

A reaction time of 24 hours led to a yield of only 12.6%.

(b). Crude 7-hydroxymetameconine (1 g.) was ethylated with aqueous potassium hydroxide and diethyl sulfate to give a product which after one recrystallization from water melted at 131.1–132.2°, yield 0.1 g. One more recrystallization from water, using charcoal, gave colorless needles whose m.p. of 132.0–132.5° was not depressed by admixture with material made by method (*a*).

Dimethyl ester of 3-ethoxymetahemipinic acid (VI). 7-Ethoxymetameconine (0.3388 g.) was oxidized with warm aqueous potassium permanganate in the presence of a sodium bicarbonate buffer, and the product was recrystallized once from water to give colorless plates, m.p. 162.5° with frothing, yield 0.2655 g. or 69%, presumably 3-ethoxymetahemipinic acid. Acid (0.4327 g.) made in this way was then converted to its dimethyl ester by the use of ethereal diazomethane. The product was rubbed up several times with 95% ethanol to give a colorless granular solid of m.p. 59.8–60.3°.

Anal. Calc'd for $C_{14}H_{18}O_7$: C, 56.35; H, 6.08; O, 37.57.
Found: C, 56.24; H, 6.05; O, 37.54.

The anhydride of 3-ethoxymetahemipinic acid was prepared (in different ways) by Späth (22) in his study of pellotine, and by Manske and co-workers (26, 27) during their study of capaurine.

Methyl 4′-(2,4′-dinitrophenoxy)benzoate (VIII). 2,4-Dinitrophenol (0.5 g.) and *p*-toluenesulfonyl chloride (0.6 g.) were warmed on the steam-bath for 5 min. with dry pyridine (5 cc.); methyl *p*-hydroxybenzoate (0.7 g.) was then added and the mixture was heated under reflux for 90 min. The cooled reaction mixture was poured into dilute potassium hydroxide solution (1 %, 50 cc.), and the yellow precipitate was recovered, washed with water, and recrystallized from ethanol to give yellow needles, m.p. 150°, in a yield of 0.588 g. or 68%. One more recrystallization from ethanol with much charcoal gave large, stout, colorless prisms, m.p. 151–151.4°.

Anal. Calc'd for $C_{14}H_{10}N_2O_7$: C, 52.84; H, 3.17; N, 8.80.
Found: C, 53.23, 52.90; H, 3.30, 3.48; N, 9.07, 8.17.

The corresponding free acid, 4-(2′,4′-dinitrophenoxy)benzoic acid, was reported by Cook (23), but not fully characterized.

7-(2′,4′-Dinitrophenoxy)metameconine (IX). Pure N-(2,4-dinitrophenyl)pyridinium toluene-*p*-sulfonate (1.05 g., m.p. 254.0–255.5°) (23, 24) was heated on the steam-bath for 6 hours with 7-hydroxymetameconine (0.515 g., m.p. 159–160°) and dry pyridine (15 cc.). The cooled mixture was then poured into ice-water, and the precipitated solid was recovered and recrystallized to give 0.62 g. (67%) of reddish-yellow crystals. Two more crystallizations gave very slightly yellow hexagons, m.p. 183.5–183.7°.

Anal. Calc'd for $C_{16}H_{12}N_2O_9$: C, 51.07; H, 3.22; N, 7.45.
Found: C, 50.85, 51.09; H, 3.23, 2.99; N, 7.33, 7.66.

7-(2′,6′-Dinitro-4′-carbomethoxyphenoxy)metameconine (X). Methyl 3,5-dinitro-4-chlorobenzoate (3.3 g., m.p. 102–103°) (5) was warmed on the steam-bath for 5 min. with dry pyridine (20 cc.); 7-hydroxymetameconine (2.7 g.) was then added and the mixture was heated for a further 90 min. The mixture was poured onto ice, and the red precipitate was recovered and recrystallized from dilute ethanol to give reddish-yellow crystals, m.p. 199–201°, in a yield of 2.4 g. (42%). Two more recrystallizations from dilute ethanol and one from methanol gave faintly yellow rhombohedrons, m.p. 209.3–210.1°, which had to be analyzed immediately since they slowly decomposed in the air.

Anal. Calc'd for $C_{18}H_{14}N_2O_{11}$: C, 49.78, H, 3.25; N, 6.45.
Found: C, 49.81, 50.04; H, 3.35, 3.37; N, 6.04, 6.12.

3-Nitro-4-iodobenzoic acid. The following method may be more convenient than those previously described. *p*-Aminobenzoic acid was acetylated in 77% yield and then nitrated to give 3-nitro-4-acetaminobenzoic acid in 76% yield. The acetyl group then was removed by boiling the product for 90 min. with a mixture of dioxane and concentrated hydrochloric acid to give the free amino acid in 78% yield. Diazotization of the product had to be done according to the very vigorous general method developed by Witt (17). Sodium bisulfite

(15 g.) was pulverized with 3-nitro-4-aminobenzoic acid (15.7 g.) and the mixture was added over the course of an hour to fuming nitric acid kept at 5° in an ice-bath. After 90 min. longer, the mixture was poured onto ice (100 g.), treated with a solution of iodine (15 g.) and potassium iodide (30 g.) in water (40 cc.), and allowed to stand for 150 min. at room temperature. The dark mixture was then cautiously warmed for 1 hour, cooled, and the solid precipitate was recovered, treated with a solution of sodium bisulfite to remove iodine, and then recrystallized four times from ethanol with charcoal to remove unchanged amino-acid. In this way, yellow lances were obtained in a yield of 10 g. or 48%; their m.p. of 205–206° agreed with that reported by Slater (18), but was lower than those reported by Hübner and Glassner (210°) (19) and by Hodgson and Beard (213°) (20).

2-Nitro-4-carbomethoxyphenyl toluene-p-sulfonate. Methyl 3-nitro-4-hydroxybenzoate (21) (15 g.) and *p*-toluenesulfonyl chloride (15 g.) were shaken with dry pyridine (25 cc.) until solution had occurred, allowed to stand 10 min. longer, and poured into dilute hydrochloric acid (1%, 500 cc.) and ice (30 g.). The syrupy precipitate solidified after 1 hr., and was recovered, crushed, and recrystallized from methanol to give white needles in a yield of 14.1 g. or 53 %, m.p. 92–93°. After two more recrystallizations, the m.p. was 92.8–93.2°.

Anal. Calc'd for $C_{15}H_{17}NO_7S$: S, 9.12. Found: S, 8.98, 8.75, 8.97.

Sane and Joshi (28) reported m.p. 86° for this compound, which they made in diethylaniline solution rather than in pyridine.

N-(2-Nitro-4-carbomethoxyphenyl)pyridinium toluene-p-sulfonate (XII). Pure 2-nitro-4-carbomethoxyphenyl toluene-*p*-sulfonate (8 g.) was warmed on the water-bath with pyridine (20 cc.). The ester soon dissolved, and the quaternary compound begun to separate after about 20 min. Heating was continued 2 hr. altogether; the mixture then was cooled, and the precipitate was recovered and washed thoroughly with ether and with absolute alcohol. Short, stout, white needles were obtained in a yield of 9.0 g., or 92%, m.p. 220–221°. One recrystallization from absolute ethanol gave long transparent needles of m.p. 220.8–221.3°. The product was freely soluble in water.

Anal. Calc'd for $C_{20}H_{18}N_2O_7S$: S, 7.45. Found: S, 7.30, 7.56.

The same product was obtained directly from the ester, pyridine, and *p*-toluenesulfonyl chloride.

7-(2′-Nitro-4′-carbomethoxyphenoxy)metameconine (XI). (*a*). N-(2-Nitro-4-carbomethoxyphenyl)pyridinium toluene-*p*-sulfonate (4.6 g.), 7-hydroxymetameconine (2.3 g.), and dry pyridine (20 cc.) were heated together for 4 hr. on the steam-bath. The mixture was poured onto ice (200 g.) and water (50 cc.), the reddish-yellow precipitate was recovered and recrystallized to give 2.8 g. (66%) of small, slightly yellow crystals, m.p. 157–159°. Two more recrystallizations from ethanol with charcoal and one from methanol gave colorless rhombohedrons, m.p. 158.0–158.8°.

Anal. Calc'd for $C_{18}H_{15}NO_9$: C, 55.53; H, 3.88; N, 3.60.

Found: C, 55.86, 55.64, 55.70; H, 3.37, 3.54, 3.81; N, 3.22, 3.35.

(*b*). Methyl 3-nitro-4-iodobenzoate (1.55 g.) was heated with dry pyridine (10 cc.) for 4 hours on the steam-bath. Crude 7-hydroxymetameconine (m.p. 158°; 1 g.) was added, and the mixture was heated for a further 3 hours, cooled, and poured onto ice. The recovered precipitate was washed with water and recrystallized from dilute alcohol with charcoal to give a small yield of colorless rhombohedrons, m.p. 158°. No depression of the m.p. was caused by admixture of the product with that from the first method described just above, but large depressions of the m.p. resulted from admixture with metameconine or with 7-hydroxymetameconine.

7-(2′-Nitro-4′-carboxyphenoxy)metameconine. 7-(2′-Nitro-4′-carbomethoxyphenoxy)metameconine (0.25 g., m.p. 157–158°) was powdered and warmed gently for 30 min. with dilute potassium hydroxide solution (10 %, 20 cc.). The mixture was filtered and the filtrate was acidified to give a greyish solid (0.2 g., m.p. 220–230°). One recrystallization from methanol gave very pale yellow rhombohedrons, m.p. 236.2–237.2°, which were completely soluble in dilute caustic and in sodium carbonate solution. Treatment with diazomethane gave back the original ester, identified by m.p. and mixture m.p.

Very gentle warming was needed for this hydrolysis. When another run was heated under reflux for 2 hours, a small yield of a product, m.p. 120–140°, was obtained instead of the desired acid, probably due to cleavage of the diphenyl ether.

7-(2'-Amino-4'-carboxyphenoxy)metameconine. Crude 7-(2'-nitro-4'-carboxyphenoxy)-metameconine (0.4 g.) was suspended in water (20 cc.) and ammonia was added until the solid just dissolved. The solution was warmed to 80° and ferrous sulfate (tech.) was added in small portions, the green ferrous hydroxide being allowed to change to the reddish ferric compound before the next addition; ammonium hydroxide was added dropwise from time to time to keep the mixture alkaline. These additions were continued until the green ferrous compound persisted; the mixture was then made very alkaline, cooled, and filtered, the sludge being washed with dilute ammonia. The filtrate was slowly acidified with acetic acid until precipitation was complete; the amino acid was recovered and recrystallized from dilute methanol to give 0.264 g., or 72%, of almost colorless matted needles, m.p. 260.8–261.5°. Two more recrystallizations from dilute methanol gave the analytical material, m.p. 268.4–268.8°.

Anal. Calc'd for $C_{17}H_{15}NO_7$: C, 59.18; H, 4.38.
Found: C, 59.41, 59.50; H, 4.71, 4.51.

Brief summary of attempts to prepare diphenyl ethers by the Ullmann synthesis (Aryl halide, metal phenoxide, and copper catalyst). (*a*). Our previous attempts have been reported (1).

(*b*). Two further instances of the catalytic dehalogenation of the aryl halide by the copper catalyst were noted. (a) 7-Iodometameconine and the copper salt of methyl *p*-hydroxybenzoate, heated together with copper bronze under nitrogen at 200–210° for 4 hours, gave metameconine, identified by m.p. and mixture m.p., as well as unchanged starting materials. (b) The dry potassium salt of 7-hydroxymetameconine was heated under reflux with copper bronze and an excess of iodobenzene for 20 hr. Unchanged starting materials, as well as a little benzene and some free iodine, were recovered.

(*c*). Another instance of methylation of a phenol by an ester was noted. Methyl *p*-hydroxybenzoate (3.6 g.) was converted to its dry potassium salt, which was then heated for 90 min. at 165° under nitrogen with 7-iodometameconine (3 g.), copper bronze (0.1 g.), and the copper salt of methyl *p*-hydroxybenzoate (0.05 g.). The reaction mixture gave 0.255 g. of methyl anisate, identified by m.p. and mixture m.p. as well as unchanged starting materials.

SUMMARY

1. Hydroxy-, methoxy-, and ethoxy-metameconines have been made from the iodometameconines through the Ullmann reaction.

2. Ethoxyhemipinic acid, 3-iodometaopianic acid, and 3-hydroxymetaopianic acid have been obtained.

3. Further attempts to form diphenyl ethers from the iodometameconines in the Ullmann reaction have failed.

4. Some substituted diphenyl ethers have been formed indirectly from 7-iodometameconine in the Hems synthesis.

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