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Reductive *C*-alkylation[1]

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At 95–115°, paraformaldehyde and hydriodic acid completely *C*-methylate aromatics such as benzene and phenol. Pyrroles are *C*-methylated similarly, carbethoxy and acetyl groups being lost. In hydriodic acid at 15–45°, typical pyrroles retain these groups and all free positions are *C*-alkylated, methylated by paraformaldehyde, or otherwise alkylated by the appropriate carbonyl compound. The alkylation of a 2-free- by a 2-formylpyrrole led to a dipyrrylmethane. With pyrroles, hydriodic acid may be replaced by another strong acid and a reducing agent. This was necessary when a β-free pyrrole gave the iodo–alkyl derivative rather than the expected product.

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Introduction

Not infrequently, two or more general reactions of organic chemistry are carried out under similar conditions; the reagents involved would be compatible and the product of one reaction would be the substrate for another. New or improved methods have been developed by combining such reactions in one-step procedures, but only sporadically. For example, it is frequently possible to avoid the isolation of intermediates, a real advantage if these are unstable or are mixtures, or one reagent may be continuously regenerated; both are illustrated by the oxidation of olefins with permanganate and periodate (1).

An approach so clearly defined was ripe for more systematic treatment. In the first instance, it had suggested to us that acids would be quite generally reduced to methyl derivatives by a combination of the McFadyen–Stevens and Wolff–Kishner reductions, if the limitations on the former method were due to the lability of aldehydes in alkali. However, although the benzenesulfonylhydrazides of 2,4-dimethyl-5-carboxypyrrole and (contrary to the report (2) from this laboratory) of benzoic acid were reduced to 2,4,5-trimethylpyrrole and toluene respectively, using the Huang modification in the latter case, the generality of the method was limited.

In a second and more fruitful application, we have regarded reductive *C*-alkylation as possible whenever the substrate would condense with a carbonyl compound to an intermediate known to be reducible in a compatible medium.[5] Although less developed than analogous reductive *N*-alkylations (3–6), some of the possibilities here had already been exploited. Others, however, were readily derived.

Ethyl cyanoacetate, for example, had been alkylated by catalytic hydrogenation in acetic acid – piperidine with aldehydes or ketones (8). The reduction of isoquinoline and benzaldehyde to 4-benzyltetrahydroisoquinoline was interpreted as the reductive *C*-alkylation of an enamine (9). More frequently, *C*-alkylations had been carried out like *N*-alkylations, by alcohols, alkali alcoholate, and/or Raney nickel at about 200°, and similarly interpreted. 2-Naphthol was thus monoalkylated at the 1-position (10), fluorene at the 9-position (11), oxindole (12), and indoles at the 3-position, and indoles also gave indole-3-acetic acids with α-hydroxy acids (13). Pyrroles

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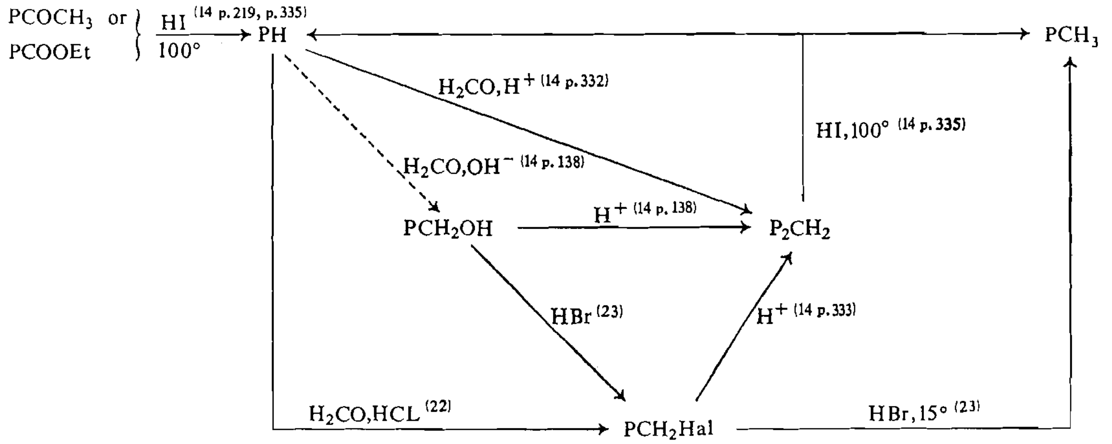
[5] The term "reductive *C*-alkylation" has also been applied to a quite unrelated method wherein sodium adducts of aromatic compounds are alkylated with methyl iodide (7).



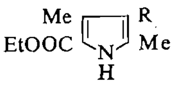
Scheme 1
P = α- or β-pyrryl

were *C*-alkylated by this method, carbethoxy and acyl groups being lost (see ref. 14, p. 33, 55, 58). The self-alkylation of alcohols under similar conditions (Guerbet reaction) has been assumed to involve dehydrogenation, the reductive *C*-alkylation of an aldehyde by an aldehyde, and further reduction (15). The scope of these reactions is largely determined by the requirement for basic conditions. We have found complementary methods employing acid catalysts. These had been most nearly represented by the Friedel–Craft alkylation of benzene with dichloroalkanes in the presence of a hydrogen donor—a saturated hydrocarbon with a tertiary carbon atom (16).

The iodomethylation of aromatic compounds to benzyl iodides with formaldehyde and hydrogen iodide, although seldom employed (17), is presumably as effective as their chloromethylation. Benzyl iodide, however, is evidently reduced to toluene by hydriodic acid at 140° (18). These two reactions suggest the reductive methylation of benzene by formaldehyde and hydriodic acid at the higher temperature. The result would be the same if diphenylmethanes were formed and then reduced to a mixture of methylated and unmethylated products, and this is not improbable in view of the reduction of triphenylmethane (19) and of 4,4′-dihydroxydiphenylmethanes (20). In either case the concurrent condensation and reduction would recycle incompletely methylated products. As methyl groups unlike chloromethyl groups (17) favor further substitution hexamethylbenzene should result, unless demethylation intervened, for 1,2,3,5-tetramethyl benzene is demethylated to 1,3,5-trimethylbenzene by hydriodic acid at 160° (21).

We found that *p*-xylene, tetralin, and phenol were converted into hexamethylbenzene (82%), 5,6,7,8-tetramethyl-1,2,3,4-tetrahydronaphthalene (73%), and pentamethylphenol (25%) respectively by paraformaldehyde, hydriodic acid (*d* 1.95), acetic acid or acetic anhydride, and hypophosphorous acid at 90–115°. Hexamethylbenzene was also obtained from benzene (35%) under conditions which minimized losses by volatilization, and from *o*-dichlorobenzene under conditions chosen to illustrate the use of immiscible solvents. As the chloromethylation of phenols usually leads to tars (17), the behavior of phenol here suggests that reductive *C*-alkylations are not necessarily limited by the stability of the unreduced intermediates.

Scheme 1 is a composite of pyrrole condensations and reductions, which had been carried out only on derivatives bearing carbethoxy or acyl groups. Where not directly involved as indicated, these groups are essential to stabilize the carbinols, halomethylpyrroles, and dipyrrylmethanes. In all these reactions, except one leading to an acid-labile product, only formaldehyde and a halogen acid are required, and the only terminal product is the methyl derivative. Formaldehyde and hydriodic acid should then replace all α- or β-hydrogen, carbethoxy, or acyl groups by methyl,



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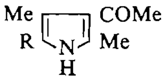

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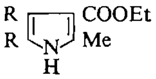

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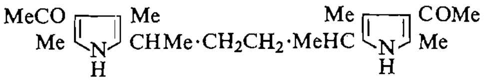
a) R = H
b) R = Me
c) R = Et
d) R = CH_2Et
e) R = CH_2CMe_3
f) R = $CHMe_2$
g) R = $CHEt_2$
h) R = $CHMe{\cdot}CH_2CHMe_2$
i) R = $CH_2C_6H_5$
j) R = $CHMeC_6H_5$
k) R = $CH < (CH_2)_5$
l) R = CH_2COOH
m) R = $CHMe{\cdot}COOH$
n) R = $CHMe{\cdot}CH_2CH_2COOH$
o) R = CH_2CHMe_2
p) R = $CHI{\cdot}CHMe_2$



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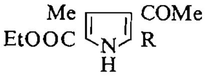

a) R = CHO
b) R = CH_2Cl

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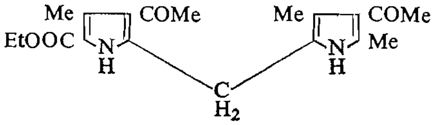

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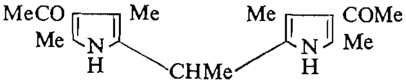

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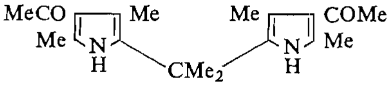

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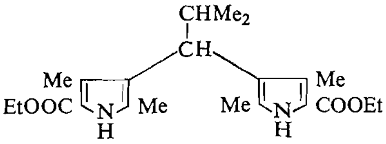

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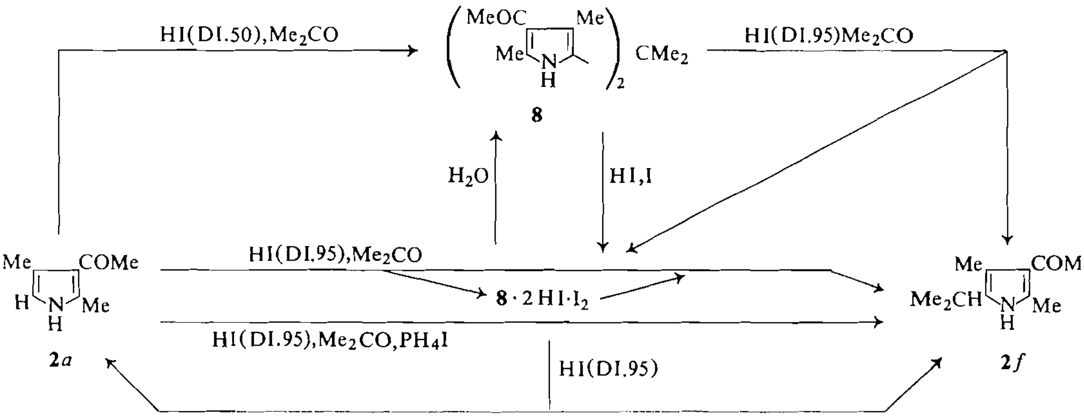
if the unstabilized intermediates did not suffer their usual degradation to unrecognizable products.

We did obtain 2,3,4,5-tetramethylpyrrole from 2,4-dimethylpyrrole and from its 5-carbethoxy-, 3,5-dicarbethoxy- , and 3-acetyl derivatives (37, 50, 35, and 68%), using paraformaldehyde with hydriodic, acetic, and hypophosphorous acids at about 100°. Presumably the intermediates are stabilized here by their complete protonation in the strong acid or, if oxidation initiates the side-reactions, by the reducing conditions.

Tetramethylpyrrole had previously been obtained from 2,4-dimethyl-3,5-dicarbethoxypyrrole with sodium in methanol at about 220° (24), a general method referred to above. Its further development was not promising. The yields were variable, carbethoxy and acetyl groups were first lost (25*a*), the subsequent alkylation of the α-position preceded that of the β (25*b*), and ethyl (25*a*) or propionic acid (25*c*) groups might be replaced. Some α,α′- and β,β′-dipyrrylmethanes were converted to tetramethylpyrrole but the bridges, at least when substituted, were lost (25*c*).

We found, however, that the paraformaldehyde – hydriodic acid reagent was effective at room temperature, *C*-methylating the free positions of pyrroles while leaving carbethoxy and acetyl groups intact. Thus **1***a*, **2***a*, and **3***a* were converted to **1***b* (64%), **2***b* (73%), and **3***b* (75%).

To determine the range of alkyl groups which might be introduced by carbonyl compounds and hydriodic acid in favorable cases, we used 2,4-dimethyl-3-acetylpyrrole, **2***a*, for which an improved preparation is given. This was stirred magnetically at about 35° with the carbonyl compound, hydriodic acid, hypophosphorous acid, and (usually) acetic anhydride. In general, the reaction and its end were indicated by the iodine color and its disappearance. An intermediate sometimes separated then, although only under modified conditions when benzaldehyde was used, redissolved. Most of the crude products could be precipitated by water and were then substantially pure and free of halogen. The



Scheme 2

5-alkyl derivatives **2c**–**2o** resulted, as did **4** when 2,5-hexandione was used (60–90%). Chloroacetone, like acetone, gave **2f**. The alkylation of **2a** with the pyrrole aldehyde **5a** required more definite conditions but at 45° **6** resulted (73%). The same product had been obtained conventionally from **2a** and **5b** in 21% yield (32). Another pyrrole, **3a**, was ethylated to **3c** (54%).

As might be expected, hydriodic acid could be replaced by another strong acid and a reducing agent. This proved necessary for the alkylation of **1a** with isobutyraldehyde for, when hydriodic acid was used, the intermediate 3-(1-iodoisobutyl) derivative **1p** (see below) was not reduced. However, **1a** was alkylated to **1o** (82%) by isobutyraldehyde, hydrogen chloride in acetic acid, and amalgamated zinc at 20°. The pyrrole **2f** was obtained from **2a** and acetone using hydriodic acid as above (92%), using hydrogen bromide in acetic acid and stannous bromide (77%), or using sulfuric acid in acetic acid and zinc amalgam (<24% crude). Formic acid, so useful in the reductive alkylation of amines, has not proved useful here although, with sodium formate, it will reduce crystal violet to dimethylaniline and bis-(*p*-dimethylamino-phenyl)methane (26).

We were interested in the intermediates which sometimes separated then redissolved when hydiodic acid was used in the alkylations, particularly after isobutyraldehyde failed to alkylate **1a**. The behavior of 3-(1-iodoalkyl)-pyrroles was unknown but 3,3′-dipyrrylmethanes could not be intermediates for, with hydriodic acid at 100°, their bridges were incompletely reduced if methylene or split off if substituted (25*c*). Either 2-(1-iodoalkyl)pyrroles or 2,2′-dipyrrylmethanes might be intermediates. The former should be easily reduced (Scheme 1). The latter, whether or not their bridges were substituted, had been reduced to 2-free and 2-alkyl pyrroles at 100° (25*d*) and their reduction at lower temperatures had not been attempted.[6]

The methylation of **1a** with paraformaldehyde and hydriodic acid in acetic acid at 20° suggested then that the 3-iodomethyl derivative was the intermediate, particularly as the chloromethyl derivative had been prepared by chloromethylation (22). There is now no doubt that 3-iodoalkyl derivatives can be formed, but they may not be easily reduced. When **1a** was stirred with isobutyraldehyde, hydriodic acid, hypophosphorous acid, and acetic anhydride at about 35°, **1p** crystallized out. More vigorous conditions resulted in unidentified products, and there was no evidence that the dipyrrylmethane 9, which was prepared for comparison, was involved.

When **2a** was alkylated with acetone and

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[6] *Note added in proof*:—As will be reported later with R. A. Chapman, we have reduced porphyrins (e.g. 1,3,5,7-tetramethyl-2,6-diethyl-4,8-di-*n*-propyl-porphin) with hydriodic and acetic acids at 100° as usual, then added paraformaldehyde and continued the heating. Instead of mixtures of homologous pyrroles ill-suited to g.l.p.c. (cf. 35), the products were then easily separated and identified tetra-substituted pyrroles. Porphyrins are converted into these tetra-substituted pyrroles equally directly by potassium methylate at 220° (36). However, the behavior of meso-substituted α, α′-dipyrrylmethanes with hydriodic acid (see above) and with potassium methylate (p. 3293) suggests that *meso-substituents on porphyrins will be retained on the pyrroles* when hydriodic acid, but not when potassium methylate is used.

hydriodic acid in the same way, a complex of the dipyrrylmethane **8**, presumably **8**·2HI·I_2 (see Experimental), separated then redissolved more slowly. Further experiments, summarized in Scheme 2, showed that **8** was indeed the intermediate or, when weaker hydriodic acid was used, the final product. When strong hydriodic acid was used, the dipyrrylmethane initially formed was reduced to a mixture of **2***a* and **2***f*, the former being recycled in the presence of acetone. However, unless the iodine liberated in the reduction was rapidly removed by phosphonium iodide, it combined with the dipyrrylmethane to form the less soluble complex.

We did not attempt to isolate the dipyrrylmethane **7** as an intermediate in the alkylation of **2***a* by paraldehyde and hydriodic acid. However, **7** was converted into **2***c* by the same mixture. In the absence of the aldehyde, **7** had been reduced by hydriodic acid at 100° to 2,4-dimethylpyrrole and its 5-ethyl derivative (25*d*). It is thus reasonable to assume that in the alkylation of **2***a*, the critical intermediates are easily reduced dipyrrylmethanes.

Experimental

The hypophosphorous acid used was 50%. The hydriodic acid was of density about 1.94 or 1.95–1.96 and was stored at 0° over phosphonium iodide (for which a convenient preparation is given).

The hydriodic acid – acetic anhydride mixture was best made by adding the acetic anhydride slowly to the hydriodic acid, cooled with water and stirred magnetically, then adding the hypophosphorous acid; otherwise, a yellow solid might form. When the reaction temperatures are not specified, there was a rise to 35–45° due to magnetic stirring.

Melting points were determined on a hot-stage and are corrected. The products gave negative Beilstein tests for halogen, their assigned structures were consistent with their nuclear magnetic resonance (n.m.r.) spectra, and the pyrroles gave positive Ehrlich's reactions hot.

Phosphonium Iodide (cf. ref. 34)

Hydriodic acid (d = 1.95, 115 ml) and red phosphorus (50 g) were stirred magnetically in a 250 ml flask, surmounted by a 6 in. air condenser under a reflux condenser and heated by an oil bath. The bath temperature was slowly raised to 80° (frothing!), held at that temperature for 1½ h, then slowly raised to 105°. The phosphonium iodide was periodically removed from the air condenser and stored at 0° under hydriodic acid (d 1.95); yield 74 g.

2,4-Dimethyl-3-acetyl-pyrrole (2a)

2,4-Dimethyl-3-acetyl-5-carbethoxypyrrole (8 g) and 40 ml of 10% aqueous sodium hydroxide were heated for 4 h at 175° in a Teflon lined brass tube. The contents of the tube were ground up and filtered. The solid was washed with water and distilled (125°, 1 × 10^{-3} mm) to give a colorless product (4.72 g, 90%), m.p. 140–140.5° (lit. (14, p. 185) 137°).

Anal. Calcd. for $C_8H_{11}O$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.22; H, 8.21; N, 9.99.

Hexamethylbenzene

(a) From Benzene

Hydrogen iodide in acetic acid (20 ml, density 1.6, about 50%), 3 g of paraformaldehyde and 1 ml of benzene were stirred at 20° for 18 h in a stoppered flask (an oil separated, presumably diiodomethyl ether (27)), then heated for 18 h at 90° under a reflux condenser. The mixture was cooled, 5 ml of hypophosphorous acid and 20 ml of acetic anhydride were added, and heating continued for 4 h at 110°. It was again cooled, 5 ml of hypophosphorous acid added, and again heated for 18 h at 115°. The mixture was cooled somewhat, decolorized with hypophosphorous acid, and poured into water. The solid which separated was dried, boiled with 10 ml of pyridine, recovered by pouring the mixture into water (this removed any halogen), ground and washed with 20 ml of methanol, dried, sublimed (about 100°, 0.1 mm), and crystallized from 25 ml of methanol as colorless plates (589 mg), m.p. 165–166.5° (lit. (28) 166.6°) after changing to needles or prisms at ca. 105° and to plates at ca. 145°. A further 45 mg were obtained from the methanolic mother liquor (total 635 mg, 35%). No aromatic protons were apparent in the n.m.r. spectrum when the intensity was increased 100 times.

Anal. Calcd. for $C_{12}H_{18}$: C, 88.82; H, 11.18. Found: C, 88.63; H, 11.10.

(b) From p-Xylene

Hexamethylbenzene, m.p. 165.5–166.5° was obtained similarly but more conveniently and in 82% yield, from *p*-xylene (1 ml), 10 ml of hydriodic acid (d = 1.95), 40 ml of acetic anhydride, and 2 g of paraformaldehyde, at 90 °C then at a gentle reflux (116°), using hypophosphorous acid.

Anal. Found: C, 88.74; H, 11.04.

(c) From o-Dichlorobenzene

A mixture of *o*-dichlorobenzene (1.47 g), hydriodic acid (20 ml), paraformaldehyde (2.4 g), and *n*-heptane (20 ml) was stirred (Vibromischer) at 95° (bath temperature) under reflux for 10 h, decolorizing it periodically with phosphonium iodide. The heptane layer was separated and washed with 20% aqueous pyridine (2 × 25 ml), with 10% hydrochloric acid, and with water. It was then dried and the heptane was evaporated. The residue was recrystallized from pentane as colorless crystals (621 mg, 38%). For analysis, it was sublimed (65°, 1 × 10^{-2} mm), m.p. 164–165°.

Anal. Found: C, 88.64; H, 11.31.

5,6,7,8-Tetramethyl-1,2,3,4-tetrahydronaphthalene

1,2,3,4-Tetrahydronaphthalene (1 ml) was added to a mixture of paraformaldehyde (2 g), hydriodic acid (10 ml), and acetic anhydride (40 ml). The mixture was then stirred and heated under reflux for 4½ h at 90–100° then at ca. 116° for 5 h. During the heating, the solution was periodically cooled to 60° and decolorized with hypophosphorous acid (total 7 ml). The warm solution was added to 125 ml of water, the resulting mixture was cooled, and the crystalline crude product was separated. This was boiled for 5 min with pyridine and the hot solution poured into boiling water (125 ml) containing 10 ml of acetic acid. The mixture was cooled and the product was separated, dried, sublimed (75°, 1 × 10^{-4} mm), and extracted into 20 ml of methanol. When the solution was concentrated then allowed to cool, 925 mg of the product separated and a further 94 mg (total 74%) were obtained by concentrating the mother liquors. The product formed large colorless plates, m.p. 81.5–82° (lit. (29) 79–79.5°).

Anal. Calcd. for $C_{14}H_{20}$: C, 89.29, H, 10.71. Found: C, 89.43; H, 10.49.

Pentamethylphenol

To phenol (4.06 g) in acetic acid (40 ml) was added hydriodic acid (43 ml) and paraformaldehyde (6.47 g). The mixture was kept at 95° under nitrogen and stirred for 6 h, adding hypophosphorus acid periodically to decolorize it. Ammonium hydroxide was then added dropwise to the cooled (0°) and stirred solution until it was basic (pH ~8). The product was extracted with ether (3 × 30 ml), which was dried over anhydrous magnesium sulfate, filtered, and then removed *in vacuo* to leave the crude product (2.1 g). Several recrystallizations from *n*-hexane gave the product, 1.64 g (25%), m.p. 127–129°. (lit. (30) 125°). The infrared spectrum had the hydroxy absorption at 3625 cm^{-1}.

Anal. Calcd. for $C_{11}H_{16}O$ (mol. wt., 164): C, 80.44; H, 9.83. Found (mol. wt., 160 (vapor pressure), 164 (mass spectroscopy)): C, 80.12; H, 9.91.

2,3,4,5-Tetramethylpyrrole

(a) From 2,4-Dimethyl-5-carbethoxypyrrole (1a)

2,4-Dimethyl-5-carbethoxypyrrole (1.64 g), acetic acid (25 ml), hydriodic acid (25 ml), and paraformaldehyde (0.589 g) were heated at 95–100° for 3 h under nitrogen with stirring. The solution was decolorized with hypophosphorous acid, made alkaline with ammonia at 0°, and extracted with ether (2 × 75 ml). The ether was removed from the dried extract ($MgSO_4$) at 20° in a rotary evaporator to leave the crude product, avoiding its exposure to air. The product was purified by distillation (10 mm, 60°) to give 0.628 g (52%), m.p. 106–108° (lit. (14, p. 44) 110°).

Anal. Calcd. for $C_8H_{13}N$: C, 77.99; H, 10.64; N, 11.37. Found: C, 77.88; H, 10.51; N, 11.22.

(b) From 2,4-Dimethyl-3,5-dicarbethoxypyrrole

2,4-Dimethyl-3,5-dicarbethoxypyrrole (2.4 g), acetic acid (35 ml), hydriodic acid (35 ml), and paraformaldehyde (1.2 g) were heated at 100° for 4 h under a stream of nitrogen. The crude product was obtained as in (*a*) above, then distilled (15 mm, 65°) to yield 0.44 g (36%), m.p. 107–109°.

(c) From 2,4-Dimethyl-3-acetylpyrrole (2a)

2,4-Dimethyl-3-acetylpyrrole (1.58 g) in 25 ml of acetic acid was added in five portions during 1 h to a stirred mixture of paraformaldehyde (2.07 g), hydriodic acid (25 ml), and hypophosphorous acid (3 ml) maintained at 115° under nitrogen. The mixture was heated at 115° for a further 3 h, and the crude product then isolated as in (*a*) above. Distillation (65°, 10 mm) gave 996 mg (68%) of colorless crystals, m.p. 108–110°.

Anal. Found: C, 77.74; H, 10.59; N, 11.19.

(d) From 2,4-Dimethylpyrrole

2,4-Dimethylpyrrole (2.06 g) in acetic acid (50 ml) was added over 2 h to a stirred solution of paraformaldehyde (5.21 g) in hydriodic acid (75 ml), acetic acid (25 ml), and hypophosphorous acid (6 ml) at 105° under nitrogen. The solution was heated 4 h longer, then brought to pH 9 with ammonium hydroxide at 0°. Isolated as in (*a*) above and washed with a little pentane, the colorless product (0.996 g. 37%) melted at 107–109°. The analytical sample, m.p, 109–111°, had been redistilled (60°, 8 mm).

Anal. Found: C, 77.94; H, 10.56; N, 11.29.

2,3,4-Trimethyl-5-carbethoxypyrrole (1b)

2,4-Dimethyl-5-carbethoxypyrrole (**1***a*) (0.83 g), acetic acid (10 ml), hydriodic acid (10 ml), and paraformaldehyde (0.60 g) were stirred for 3 h at 25° under nitrogen. Hypophosphorous acid (about 1 ml) was added dropwise to decolorize the solution. The cooled solution (0°) was made basic with ammonium hydroxide and the product was extracted with ether (2 × 20 ml). The extract was dried over magnesium sulfate, filtered, and the ether removed in a rotary evaporator at 20°. Recrystallization from benzene gave the product, 0.58 g (64%), m.p. 125–126° (lit. (14, p. 239) 128°).

Anal. Calcd. for $C_{10}H_{15}O_2N$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.35; H, 8.18; N, 7.90.

2,3,5-Trimethyl-3-acetylpyrrole (2b)

2,4-Dimethyl-3-acetylpyrrole (**2***a*), (0.68 g), acetic acid (15 ml), hydriodic acid (15 ml), and paraformaldehyde (0.6 g) were stirred for 3 h under nitrogen at 25°. The solution was decolorized with hypophosphorous acid, made alkaline with ammonium hydroxide at 0°, and extracted with ether. The ether was evaporated from the dried extract ($MgSO_4$) leaving the crude product which was crystallized from benzene as colorless elongated prisms (0.55 g, 73%), m.p. 204–207° (lit. (14, p. 188) 207–209°).

Anal. Calcd. for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.29; H, 8.68; N, 9.38.

2,4,5-Trimethyl-3-carbethoxypyrrole (3b)

2-Methyl-3-carbethoxypyrrole (**3***a* (33), 0.99 g), acetic acid (15 ml), hydriodic acid (20 ml), and paraformaldehyde (0.78 g) were stirred for 3 h at 25°. The crude product was isolated as was that of the 3-acetyl derivative (above) and sublimed (82°, 4 × 10^{-3} mm) as fine colorless needles (75%), m.p. 103–103.5° (lit. (14, p. 248) 104–105°).

Anal. Calcd. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.35; H, 8.17; N, 7.88.

2,4-Dimethyl-3-isobutyl-5-carbethoxypyrrole (1o)

Acetic anhydride (20 ml) was slowly added to 5 ml of concentrated hydrochloric acid with stirring and cooling, and 668 mg of 2,4-dimethyl-5-carbethoxypyrrole (**1***a*) were dissolved in the resulting solution. Amalgamated zinc (10 g, 20 mesh) and 0.75 ml of isobutyraldehyde were then added at 20°, and the mixture was stirred for 15 min at 20–25°. The zinc was separated, washed with acetic acid, and the liquids were poured into water to precipitate the crude product. It was dried and extracted into pentane (thimble), the pentane was evaporated, and the residue was recrystallized from aqueous ethanol (13 ml of 55%) as colorless needles (681 mg), m.p. 115–117° (lit. (31), 116–117°) after changing to fine needles at about 112°, and to plates at about 115°. A further 51 mg were obtained from the mother liquors (total 732 mg, 82%). The n.m.r. spectrum and the X-ray powder photograph were identical with those of authentic material, and the mixed m.p. was 115–117°.

Anal. Calcd. for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 70.08; H, 9.67; N, 6.25.

2,4-Dimethyl-3-acetyl-5-ethylpyrrole (2c)

A solution of 2,4-dimethyl-3-acetylpyrrole (**2***a*, 548 mg) in 10 ml of hydriodic acid containing a little solid phosphonium iodide was cooled in an ice–salt bath. Paraldehyde (0.35 ml) was added and the solution was stirred for $4\frac{1}{2}$ h without further cooling. The solution was then added to 100 ml of ice water to precipitate the light-brown product (385 mg, 58%), m.p. 153–160°. For analysis, it was sublimed *in vacuo* then recrystallized from ether (thimble) as grey needles, m.p. 163° after changing to plates at 140°.

Anal. Calcd. for $C_{10}H_{15}O$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.67; H, 8.88; N, 8.69.

2,4-Dimethyl-3-acetyl-5-n-propylpyrrole (2d)

2,4-Dimethyl-3-acetylpyrrole (**2***a*, 1.02 g), acetic acid (15 ml), hydriodic acid (25 ml), and propionaldehyde (1.74 g), were stirred at 25° for 3 h under nitrogen. The crude product was isolated as was that of the 2,4,5-trimethyl derivative, **2***b*, except that 2 × 50 ml ether were used. Recrystallization from benzene gave the product 0.786 g (59%), m.p. 157–158°.

Anal. Calcd. for $C_{11}H_{17}ON$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.73; H, 9.39; N, 7.79.

2,4-Dimethyl-3-acetyl-5-isobutylpyrrole (2o)

(*a*) 2,4-Dimethyl-3-acetylpyrrole (**2***a*, 548 mg) was dissolved in hydriodic acid (10 ml), acetic anhydride (10 ml), and hypophosphorous acid (2 ml). Isobutyraldehyde (0.75 ml) was added and the solution was stirred for 35 min. No precipitate formed. Water precipitated a yellow iodine complex (864 mg), m.p. unsharp from 90°, Beilstein test for halogen positive. This was converted into the desired product by dissolving it in ethanol and adding ammonium hydroxide. For analysis it was recrystallized from aqueous ethanol, m.p. 152° after changing to smaller crystals at 125°.

Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.40; H, 9.73; N, 7.43.

(*b*) When the above reaction was run in the presence of a little added phosphonium iodide, the color faded within 1 min and after 5 min water precipitated the colorless product (0.7 g, 91%). It melted at 150–152° (phase change at 125°) after being recrystallized from ethanol.

2,4-Dimethyl-3-acetyl-5-neopentylpyrrole (2e)

2,4-Dimethyl-3-acetylpyrrole (**2***a*, 548 mg) was warmed to solution in a mixture of 10 ml of hydriodic acid, 10 ml of acetic anhydride, and 2 ml of hypophosphorous acid. The solution was cooled to 35° and 0.85 ml of pivalaldehyde (Columbia Organic Chemicals Co.) was added. The solution was stirred for 10 min, by which time the initially dark brown color had changed to yellow, and then it was poured into 125 ml of water. The product separated as a colorless powder (769 mg, 93%), m.p. 156–163°. For analysis, it was recrystallized from ether–pentane, sublimed at 115° (10^{-4} mm), and again recrystallized by extraction into hexane (thimble) as long colorless plates, m.p. 166–167° after changing to prisms below 130°.

Anal. Calcd. for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76. Found: C, 75.13; H, 10.30; N, 6.58.

2,4-Dimethyl-3-acetyl-5-isopropylpyrrole (2f)

(a) Using Hydriodic Acid

Hydriodic acid (10 ml) and 2 ml of hypophosphorous acid were cooled and stirred while 10 ml of acetic anhydride was slowly added. 2,4-Dimethyl-3-acetylpyrrole (**2***a*, 548 mg) was dissolved in the solution, 0.6 ml of acetone added, and the mixture was stirred for $\frac{1}{2}$ h by which time a yellow precipitate had formed and redissolved and the solution had turned yellow; the final temperature was 37°. The solution was poured into 100 ml of water and 30 ml of ammonium hydroxide kept at 20°. The nearly colorless product separated as plates (662 mg, 92%). At 138° these changed to cubes which either melted at 165° or turned to irregular needles, m.p. 171–173°. For analysis, it was recrystallized from aqueous ethanol as colorless plates, m.p. 165.5° or 171.5–173°.

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.59; H, 9.48; N, 7.76.

(b) Using Hydrogen Bromide and Stannous Bromide

Anhydrous stannous bromide (5 g) was stirred to solution in 20 ml of hydrogen bromide in acetic acid (30–32%). 2,4-Dimethyl-3-acetylpyrrole (**2***a*, 548 mg) was added and the mixture was warmed to dissolve this, then cooled to 30°. Acetone (0.6 ml) was added and the solution was stirred at 35° for $2\frac{1}{2}$ h. then poured into water at 10°. The product was separated and washed with dilute hydrochloric acid then with water. It formed colorless micro-prisms (549 mg, 77%), m.p. 166–167° or 173–174.5° after changing to cubes at about 136°. For analysis it was recrystallized from aqueous ethanol as prismatic rods, m.p. 172°, 172–173° when mixed with the product of (*a*) above.

Anal. Found: C, 73.92; H, 9.23; N, 7.88.

(c) Using Sulfuric Acid and Zinc

2,4-Dimethyl-3-acetyl-pyrrole (**2***a*, 548 mg), 1 ml of acetone, and 10 g of amalgamated zinc (20 mesh) were added to a solution of 1 ml of concentrated sulfuric acid in 20 ml of acetic acid. The mixture was stirred for 1 h at 45°. The liquid was decanted from the zinc into 100 ml of water forming a solution from which the crude product separated at 15° (174 mg, m.p. 164–169°, after the usual solid phase changes). For analysis, it was extracted into ether (thimble) then recrystallized from 3 ml of aqueous ethanol as nearly colorless elongated prisms, m.p. 170–172° (171–173° when mixed with the product of (*a*) above) after a solid phase change at 142°.

Anal. Found: C, 73.60; H, 9.40; N, 7.92.

2,4-Dimethyl-3-acetyl-5-(3-pentyl)pyrrole (2g)

3-Pentanone (0.85 ml) was added to a solution of 548 mg of 2,4-dimethyl-3-acetylpyrrole (**2***a*), in 10 ml of hydriodic acid, 10 ml of acetic anhydride, and 2 ml of hypophosphorous acid. The solution was stirred for $1\frac{3}{4}$ h then poured into 200 ml of water to precipitate the product as tiny nearly colorless prisms (651 mg, 79%), m.p. about 186–189°. For analysis it was recrystallized from ethanol as colorless plates, m.p. 188.5° after a solid phase change at 135°.

Anal. Calcd. for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76. Found: C, 75.13; H, 10.04; N, 6.78.

2,4-Dimethyl-3-acetyl-5-(4-methyl-2-pentyl)pyrrole (2h)

Methyl isobutylketone (1.1 ml) was added to a solution of 548 mg of 2,4-dimethyl-3-acetyl-pyrrole, **2***a*, in hydriodic acid (10 ml), acetic anhydride (10 ml), and hypophosphorous acid (2 ml). The solution was stirred for 4 h then poured into a mixture of 150 ml of water and 30 ml of ammonium hydroxide. The product separated as tiny colorless prisms (709 mg, 80%), m.p. 140–141.5°. For analysis, it was recrystallized from aqueous ethanol (charcoal) as tiny colorless prisms, m.p. 142–143°, some changing to plates at 120°.

Anal. Calcd. for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.81, H, 10.37; N, 6.38.

2,4-Dimethyl-3-acetyl-5-benzylpyrrole (2i)

A solution of 10 ml of hydriodic acid, 10 ml of acetic anhydride, and 2 ml of hypophosphorous acid containing 548 mg of 2,4-dimethyl-3-acetylpyrrole, *2a*, was stirred magnetically while a solution of 0.6 ml of benzaldehyde in 5 ml of acetic anhydride was slowly added over 20 min. The solution was stirred for 10 min then poured into water. The crude product which separated was recrystallized from acetone (thimble) as nearly colorless irregular plates (85%), m.p. 165.5–167° after a partial change to prismatic rods above 165°.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.22; H, 7.50; N, 6.18.

2,4-Dimethyl-3-acetyl-5-(1-phenyl-ethyl)pyrrole (2j)

A solution of 0.6 ml of acetophenone in 5 ml of acetic anhydride was slowly added to a stirred mixture of 10 ml of hydriodic acid, 10 ml of acetic anhydride, and 2 ml of hypophosphorous acid containing 548 mg of 2,4-dimethyl-3-acetylpyrrole, *2a*. The mixture was allowed to stand for two days at room temperature then poured into water. The crude product which separated was recrystallized from acetone (thimble) as nearly colorless rhombic plates (75%), m.p. 146–148.5°.

Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.47; H, 7.78; N, 5.79.

2,4-Dimethyl-3-acetyl-5-cyclohexylpyrrole (2k)

A solution of 10 ml of hydriodic acid, 10 ml of acetic anhydride, and 2 ml of hypophosphorous acid was stirred magnetically at 40° while 548 mg of 2,4-dimethyl-3-acetylpyrrole, *2a*, were dissolved in it; 0.5 ml of cyclohexanone was then added, and an additional 0.5 ml of cyclohexanone was added after a few minutes. The solution was stirred at 40° for 1½ h then poured into water. The crude product which separated, m.p. 186–188° was recrystallized from ethanol as colorless rhombic prisms (82%), m.p. 188.5–189° after changing to flat prisms above 153°.

Anal. Calcd. for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.39. Found: C, 76.49; H, 9.50; N, 6.30.

2,4-Dimethyl-3-acetyl-pyrrole-5-acetic Acid (2l)

Glyoxylic acid monohydrate (500 mg) was added to a solution of 548 mg of 2,4-dimethyl-3-acetylpyrrole *2a*, in 10 ml of hydriodic acid and 2 ml of hypophosphorous acid. The solution was stirred for 1 h at 15°. A yellow crystalline solid containing iodine was removed by filtration, washed with ether, dried, then slurried with 5 ml of water. The solid (Beilstein test for halogen now very weak) was again separated, washed with 5 ml of water, dried, and extracted into 40 ml of ether (thimble). When the ether solution was concentrated the product separated as yellow prisms (550 mg, 70%), m.p. 195–205°. For analysis, it was recrystallized by dissolving it in 40 parts of cold 50% aqueous acetone, boiling off the acetone, and cooling. It separated as nearly colorless prismatic rods, m.p. 206–210°, after changing to prisms at 155° and evolving gas at 175°. Before melting, it evidently decarboxylated to the 5-methyl derivative (see above), the m.p. of which was not depressed by the resolidified melt.

Anal. Calcd. for $C_{10}H_{13}NO_3$ (eq. wt., 195): C, 61.52; H, 6.71; N, 7.18. Found (eq. wt., 197): C, 61.35; H, 6.90; N, 7.10.

2,4-Dimethyl-3-acetyl-5-(1-carboxyethyl)pyrrole (2m)

A solution of 548 mg of 2,4-dimethyl-3-acetylpyrrole *2a*, in 10 ml of hydriodic acid and 2 ml of hypophosphorous acid was treated with 0.4 ml of pyruvic acid and stirred for 10 min at 40° when yellow crystals containing iodine formed. After 2 days at 0° the crystals were separated, dried, and slurried with 5 ml of water. They dissolved and a colorless product then separated which gave a very weak Beilstein test for halogen. This was washed with water, dried, and recrystallized from ether (thimble) as tiny colorless rods (493 mg, 59%), m.p. 156–158° (decomp.).

Anal. Calcd. for $C_{11}H_{15}NO_3$ (eq. wt., 209): C, 63.14; H, 7.23; N, 6.69. Found (eq. wt., 207): C, 63.11; H, 6.98; N, 6.80.

2,4-Dimethyl-3-acetyl-pyrrole-5-(4-pentanoic) Acid (2n)

A solution of levulinic acid (0.6 ml) in 5 ml of acetic anhydride was slowly added to a solution of 548 mg of 2,4-dimethyl-3-acetylpyrrole, *2a*, in hydriodic acid (10 ml), acetic anhydride, and hypophosphorous acid (2 ml). The solution was stirred for 12 h then the volatile solvents were removed in a vacuum desiccator over potassium hydroxide. Water (10 ml) was added to the residue to yield the product as an oil which soon solidified to salmon colored prisms which were washed with water to yield 742 mg (78%), m.p. 175–177°. For analysis, it was recrystallized from acetone (thimble) as nearly colorless prisms, m.p. 175–180°.

Anal. Calcd. for $C_{13}H_{19}NO_3$ (eq. wt., 237): C, 65.80; H, 8.07; N, 5.90. Found (eq. wt., 234): C, 66.03; H, 8.20; N, 5.91.

2,5-Bis-(3,5-dimethyl-4-acetyl-2-pyrryl)hexane (4)

2,5-Hexandione (1 ml) was added to a solution of 548 mg of 2,4-dimethyl-3-acetylpyrrole *2a* in 10 ml of hydriodic acid, 10 ml of acetic anhydride, and 2 ml of hypophosphorous acid. The solution was stirred for 1½ h then poured into 150 ml of water to precipitate the nearly colorless product (442 mg, 62%), m.p. 263–268°. For analysis it was twice recrystallized from acetone (thimble) as a colorless crystalline powder, m.p. 275–279° after changing to needles at 271°.

Anal. Calcd. for $C_{22}H_{32}N_2O_2$: C, 74.12; H, 9.05; N, 7.86. Found: C, 74.01; H, 9.04; N, 7.94.

3,5,4′-Trimethyl-4,3′-diacetyl-5′-carbethoxydipyrrylmethane (6)

Hydriodic acid (10 ml) was stirred and cooled while 10 ml of acetic anhydride were added slowly. Hypophosphorous acid (2 ml) and 548 mg of 2,4-dimethyl-3-acetylpyrrole, *2a*, were added and the mixture was stirred at room temperature until the latter dissolved. 2-Formyl-3-acetyl-4-methyl-5-carbethoxypyrrole (*5a*, 892 mg) was added and the mixture was stirred at 40–45° for 2 h, then poured into 150 ml of water. The precipitate was separated, dried, slurried with 15 ml of ethanol, and then filtered, dried, and extracted into 40 ml of acetone (thimble). The product (781 mg) crystallized from the acetone as colorless plates, m.p. 209–212° and concentrating the acetone gave a further 219 mg (total, 73%). The X-ray powder photograph and the n.m.r. spectrum were identical with those of authentic material (32) for which we found the m.p. to be 210–213°; the mixed m.p. was 209–213°.

Anal. Calcd. for $C_{19}H_{24}O_4N_2$: C, 66.26; H, 7.02; N, 8.13; OEt, 13.08. Found: C, 66.11; H, 7.23; N, 8.18; OEt, 12.97.

2-Methyl-4,5-diethyl-3-carbethoxypyrrole (3c)

A solution of 612 mg of 2-methyl-3-carbethoxypyrrole **3***a* (33) in 10 ml of hydriodic acid, 10 ml of acetic anhydride, and 2 ml of hypophosphorous acid was stirred while 0.35 ml of paraldehyde was dropped in. Stirring was continued for $\frac{1}{2}$ h and the solution was then poured into water. For analysis, the pale-yellow micro-crystals which separated (0.45 g 53%, m.p. 104–106°) were recrystallized from aqueous ethanol.

Anal. Calcd. for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.67. Found: C, 68.73; H, 9.09; N, 6.85.

Experiments Relating to the Intermediates

2,4-Dimethyl-3-(1-iodo-isobutyl)-5-carbethoxypyrrole (1p)

2,4-Dimethyl-5-carbethoxypyrrole (**1***a*, 668 mg) in hydriodic acid (10 ml), acetic anhydride (10 ml), and hypophosphorous acid (2 ml) was treated with 0.75 ml isobutyraldehyde. The solution was stirred for 15 min while the solution turned dark then lightened as a precipitate formed. This was separated and washed well with water, leaving the product as colorless crystals (1 g), m.p. 119–121°. For analysis it was recrystallized from heptane.

Anal. Calcd. for $C_{13}H_{20}NO_2I$: C, 44.71; H, 5.77; N, 4.01; I, 36.33. Found: C, 44.55; H, 6.15; N, 4.13; I, 36.29.

meso-Isopropyl-2,2′,4,4′-tetramethyl-5,5′-dicarbethoxy-dipyrrylmethane (9)

2,4-Dimethyl-5-carbethoxypyrrole (**1***a*, 668 mg) and isobutyraldehyde (0.75 ml) were refluxed for 15 min in ethanol containing two drops of hydrochloric acid. Water was added to the cooled solution to precipitate colorless crystals, m.p. 120–125° after being recrystallized from heptane.

Anal. Calcd. for $C_{22}H_{32}N_2O_4$: C, 68.01; H, 8.30; N, 7.21. Found: C, 67.99; H, 8.37; N, 7.35.

The Complex of meso-Dimethyl-3,3′,5,5′-tetramethyl-4,4′-diacetylpyrromethane (8) with HI and Iodine

(*a*) The pyrrole **2***a* (548 mg) was stirred with hydriodic acid, acetic anhydride, hypophosphorous acid, and acetone as in the preparation of **2***f* (above). After 5 min the precipitated complex (723 mg, 45%) was separated and well washed with acetic acid, m.p. 167° (decomp.), KI–starch test positive.

Anal. Calcd. for $C_{19}H_{26}O_2N_2.2HI.I_2$: C, 27.70; H, 3.40; N, 3.42; I, 61.60. Found: C, 28.18; H, 3.46; N, 3.48; I, 61.56.

(*b*) The above experiment was repeated giving 470 mg of the complex, m.p. 157–159° (decomp.), further identified by its n.m.r. spectrum. The acid mother liquors were poured into water (100 ml) and ammonium hydroxide (30 ml) to precipitate 370 mg of **2***f*, identified by m.p., mixed m.p., and n.m.r. spectrum.

(*c*) The experiment was again repeated in the presence of a little added phosphonium iodide. The color appeared more slowly, disappeared more rapidly, and no precipitate formed. After 15 min the pale solution was poured into water and ammonium hydroxide to precipite **2***f* (604 mg, 85%) identified by m.p., mixed m.p., and n.m.r. spectrum.

(*d*) The complex prepared as in (*a*) was treated with water or ethanol to give **8** (see below).

(*e*) The complex (548 mg) prepared as under (*a*) was stirred in 10 ml of hydriodic acid, 10 ml of acetic anhydride, and 2 ml of hypophosphorous acid. No acetone was added. When the solution became clear, water precipitated 310 mg of a product, m.p. 152–160°, a 1:1 mixture of **2***a* and **2***f* as indicated by the n.m.r. spectrum.

(*f*) No precipitate was obtained by adding either iodine or hydriodic acid to **8** (see below) in acetic acid. However, the complex separated when both were added, m.p. 145–150° (decomp.), mixed m.p. with the complex obtained as above 153–155° (decomp.). Found: C, 28.48; H, 3.61; N, 3.26; I, 62.10.

meso-Dimethyl-3,3′,5,5′-tetramethyl-4,4′-diacetyl-pyrromethane, 8

(*a*) The pyrrole **2***a*, hydriodic acid, acetic anhydride, hypophosporous acid, and acetone were stirred together as in the preparation of **2***f* but hydriodic acid (d = 1.50) was used. After 5 min the yellow precipitate of **8** was separated from the pale-yellow solution (no iodine color). The product (75%), m.p. 225–227°, melted at 235–237° alone or mixed with authentic material (32) after it was recrystallized from ethanol.

Anal. Calcd. for $C_{19}H_{26}O_2N_2$: C, 72.58; H, 8.34; N, 8.91. Found: C, 72.67; H, 8.44; N, 8.78.

(*b*) The pyrromethane **8** was stirred with hydriodic acid (d = 1.50), acetic anhydride, hypophosphorous acid, and acetone. Warming was necessary to bring it into solution. Water precipitated nearly pure **8**, m.p. 215–217°, identified by its n.m.r. spectrum.

(*c*) The pyrromethane **8** (548 mg) was stirred in hydriodic acid (10 ml, d = 1.95), 10 ml of acetic anhydride, 2 ml of hypophosphorous acid, and 0.3 ml of acetone. The solution darkened, a yellow precipitate appeared, then the solution lightened and the precipitate redissolved. After $\frac{1}{2}$ h water and ammonium hydroxide precipitated 535 mg (86%) of **2***f*, identified by its m.p., mixed m.p., and n.m.r. spectrum.

2,4-Dimethyl-3-acetyl-5-ethyl-pyrrole (2c) from meso-Methyl-3,3′-5,5′-tetramethyl-4,4′-diacetyl-pyrromethane (7)

meso-Methyl-3,3′,-5,5′-tetramethyl-4,4′-diacetylpyrromethane (**7** (14, p. 351), 548 mg) in 10 ml of hydriodic acid, 10 ml of acetic anhydride, 2 ml of hypophosphorous acid, and 0.34 ml of acetaldehyde was stirred for 15 min. The solution was then poured into water to precipitate the product as pale-yellow crystals (400 mg 66%), m.p. 161–162°.

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