A second crop amounted to 100 mg. and melted at 233–236°; $[\alpha]_D$ −35.2° (*c*, 0.53 ethanol).[7]

Anal. Calcd. for $C_{26}H_{40}O_5 \cdot 1/2CH_3OH$: C, 70.99; H, 9.44. Found: C, 71.01; H, 9.43.

A sample dried for 17 hr. at 100° (0.5 mm.) melted at 236–240°; $[\alpha]_D$ −38.6° (*c*, 0.57. ethanol).

Anal. Calcd. for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32; O, 18.49. Found: C, 71.81; H, 9.21; O, 19.04.

16α-Hydroxymethylprogesterone (IX).—A solution containing 320 mg. (0.000715 mole) of the solvated biscycloethylene ketal (VIII), 50 ml. of acetone and 10 ml. of 10% aqueous hydrochloric acid was warmed slightly to attain solution and allowed to stand at room temperature for 75 min. The acetone was removed in a stream of nitrogen and the residue diluted with water. The colorless needles thus obtained (228 mg.) melted at 160–161°. A sample purified by recrystallization from methanol and water melted at 161–162.5°; $[\alpha]_D$ +164° (*c*, 1.04, chloroform); reported m.p.[1] 163–164°; $[\alpha]^{25}_D$ +160° (chloroform).

16α-Hydroxymethyl-5-pregnene-3,20-dionebiscycloethyleneketal Tosylate (X).—A solution of 1.0 g. (0.0023 mole) VIII, 2.260 g. of triethylene diamine in 300 ml. of thiophene-free benzene was stirred at room temperature until complete solution was attained. To this was added 2.20 g. of *p*-toluenesulfonyl chloride in 75 ml. of benzene. After 5 min., the clear homogeneous solution became hazy and a finely divided solid separated; stirring was continued overnight. The suspension was decomposed with ice and water and the organic layer washed with water. Concentration (*in vacuo*) in the presence of pyridine followed by dilution with water gave 1.36 g. of colorless needles X; *decomposition point* 150–153°.

Anal. Calcd. for $C_{33}H_{46}O_7S$: C, 67.55; H, 7.90. Found: C, 67.42; H, 7.60.

16α-Iodomethyl-5-pregnene-3,20-dionebiscycloethyleneketal (XI).—A mixture of 200 mg. of X, (0.00034 mole) 400 mg. of sodium iodide, 125 ml. of methyl ethyl ketone and 25 mg. of anhydrous sodium bicarbonate was refluxed for 48 hr. The solution was concentrated *in vacuo* and the residue diluted with water giving 0.184 g. of XI melting at 165.5–167°. The analytical sample was obtained as colorless needles melting at 168–169.5°; $[\alpha]_D$ −51.0° (*c*, 0.4, ethanol).

Anal. Calcd. for $C_{26}H_{39}O_4I$: C, 57.56; H, 7.24; I, 23.39. Found: C, 57.79; H, 7.00; I, 23.50.

16α-Methylprogesterone (XII).—A solution 100 mg. of XI (0.000184 mole) in 10 ml. of diglyme (distilled from calcium hydride) was added to a stirred solution of 400 mg. of lithium aluminum hydride in 75 ml. of dry diglyme. After stirring overnight at 65°, 4.8 ml. of water was added dropwise. The inorganic salts were removed by filtration and the cake was washed well with ether. The solvents were removed *in vacuo*. The solid residue (70 mg.) gave a negative Beilstein test. This crude product was hydrolyzed by treatment with 40 ml. of acetone and 4 ml. of 10% aqueous hydrochloric acid at room temperature for 60 min. Concentration *in vacuo* followed by addition of water and filtering gave 33 mg. of colorless needles melting at 133–141°. Chromatography on silica gel using 4–6% ether in benzene as the eluting agent gave 14.7 mg. of colorless needles melting at 138–139° (Fisher–Johns block). A mixed melting point with an authentic sample (m.p. 136–137.5°) melted at 136–137°. The infrared pattern was identical with authentic material. A sample submitted for high temperature (237°) gas–liquid chromatography, using an 8-ft. glass column packed with 0.5% Pluronic F-68 on siliconized Chromasorb W (60–80 mesh), showed identical retention time when compared to authentic material.

Acknowledgment.—The author is indebted to Mr. E. F. Shelberg and Mr. W. Washburn and their associates for the microanalyses and infrared spectra, respectively, and to Dr. I. Merits for the gas–liquid chromatographic analysis of 16α-methylprogesterone. The autoclave reactions were carried out by Messrs. G. Stone and M. Freifelder. The clarifying discussions with Dr. W. Cole are gratefully acknowledged.

(7) The ethanol used in the rotation of ketals contained a trace of pyridine.

Prodigiosin[1a]

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In a preceding paper[2a] it was shown that the properties of model compounds do not support the Wrede and Rothhaas[3] 2,2′,2″-tripyrrylmethane structure for prodigiosin[2b,c] isolated from the Stanford Z-4 strain of *Serratia marcescens*. During our continuation of the structural study, the partial synthesis of prodigiosin was described and a formula essentially that considered as an alternate possibility earlier by Wrede and Rothhaas,[4] along with that of an analog, were suggested from an investigation[5] of a precursor derived from a colorless mutant of the bacterium. The complete synthesis of prodigiosin identifying it as 2,2′-[3-methoxy-4′-amyl-5′-methyl-5-(2″-pyrryl)] dipyrrylmethene (I), the formula favored from the precursor study, has been recently reported.[6] Interestingly, isomeric formulas have been proposed from a permanganate oxidation of a product derived from a particular strain of the bacterium.[7] The possibility of variations arising from aberrant strains exists. Our own results are hence of interest from this standpoint as well as for other reasons. The compound obtained from the Stanford Z-4 strain is evidently identical[8] with the synthetic product and

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(2) (a) A. J. Castro, A. H. Corwin, J. F. Deck, and P. E. Wei, *J. Org. Chem.*, **24**, 1437 (1959). For other comparisons see: (b) A. Treibs and K. Hintermeier, *Ann.*, **605**, 35 (1957); (c) A. Treibs and R. Zimmer-Galler, *Z. physiol. Chem.*, **318**, 12 (1960).

(3) F. Wrede and A. Rothhaas, *Z. physiol. Chem.*, **226**, 95 (1934).

(4) F. Wrede and A. Rothhaas, *ibid.*, **219**, 267 (1933).

(5) H. H. Wasserman, J. E. McKeon, L. Smith, and P. Forgione, *J. Am. Chem. Soc.*, **82**, 506 (1960).

(6) H. Rapoport and K. G. Holden, *ibid.*, **84**, 635 (1962).

(7) G. Narni and R. A. Nicolaus, *Rend. accad. sci. fis. mat.* (*Soc. naz. sci. Napoli*), **26**, 471 (1959).

(8) Chromic acid oxidation of the carefully purified natural product yielded maleimide and methoxymaleimide (the major product), and 2-methyl-3-amylpyrrole was obtained from a soda-lime distillation. The imides[9] and alkylpyrrole[3] were similarly derived earlier by Wrede and Rothhaas. However, because of the impure nature of their product and the low yields of the imides apparently obtained, conclusions reached therefrom have been questionable. It should be mentioned that permanganate oxidation at different conditions, including those of Narni and Nicolaus,[7] as well as the use of a variety of oxidants in addition to the application of other procedures to obtain products suitable for structure elucidation were unsuccessful. Hydrogenation with an Adam's catalyst in dioxane at room temperature resulted in the ready uptake of one mole of hydrogen followed by a subsequent slow hydrogenation in agreement with initial reduction of the dipyrrylmethene unit, indicated by salt formation[1,11] and zinc complex formation as concluded earlier,[12] followed by the more difficult hydrogenation of the pyrrole rings.[4,13,14] Zerevitinov analysis gave values of 0.45 and 0.46% active hydrogens corresponding to 1.47 active hydrogen per mole of monomer, although the proton magnetic resonance spectrum shows a typical low, broad absorption at $\tau = -0.98$, assignable to two pyrrole NH protons in a total of twenty-five.[15] Moreover, the synthetic product is described as identified by comparison with a reported authentic sample and *the properties of prodigiosin given by* Treibs and Zimmer-Galler.[2c] From the infrared and visible–ultraviolet absorption spectra of our compound and those reported by the latter workers, their product and ours are apparently the same, even though their product is described as decomposing at 90° and individual samples of our red, crystalline compound melt with decomposition near 150°.[16] Similarly, the visible–ultraviolet absorption for their hydrochloride and ours[11] appear to be the same, while they describe this derivative as dark violet needles melting at 135° and we find it is a magenta colored solid that melts with decomposition at 148.5–150.0°. Their per-

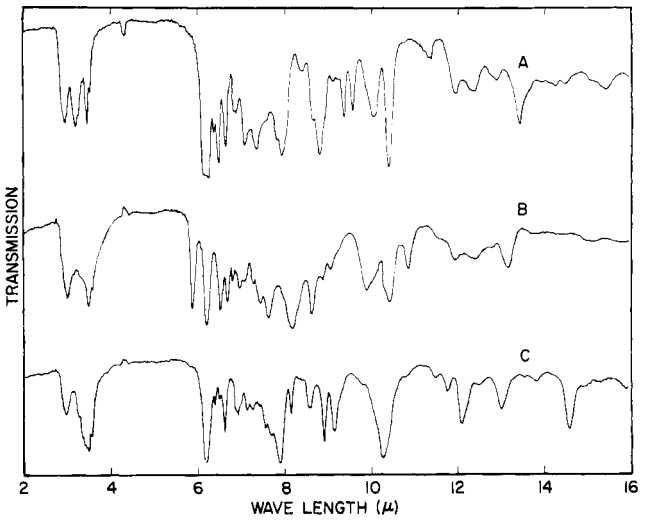


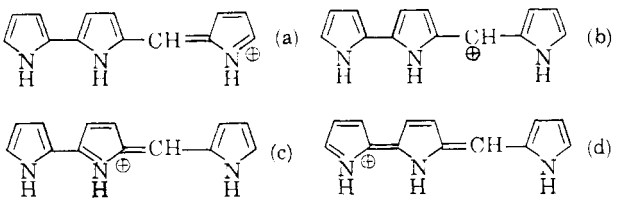
Fig. 1.—Infrared absorption spectra (KBr): A, prodigiosin hydrochloride; B, 2,2′-(3-methoxy-4′-amyl-5′-methyl-5-methoxycarbonyl)dipyrrylmethene hydrobromide; C, 2,2′-(4,4′-diamyl-5,5′-dimethyl)dipyrrylmethene hydrobromide.

the differences recorded elsewhere for properties of prodigiosin and observed by us are really not significant. In this connection it has been suggested[6] that differences in the visible spectra, presumably in methanol, can be used to distinguish prodigiosin (I) (main band, 470 mμ; low absorption peak near 532 mμ) from the isomeric compound 2,2′-[3-methoxy-4′-ethyl-5′-butyl-5-(2″-pyrryl)]dipyrrylmethene (II) (λ_{max} 475 mμ). The absorption noted at the longer wave length for I is actually probably due to a small amount of its protonated form, arising from a trace of acid.[10] Thus a careful examination of methanol and 95% ethanol solutions of I reveals a maximum at 537 mμ (I·$HClO_4$, $\lambda_{max.}^{95\%EtOH}$ 537–538 mμ[10]), which disappears entirely upon the addition of base yielding solutions with spectra otherwise not greatly changed.

The main absorption of prodigiosin at 466 mμ[10] is in the region defined[18] (400–500 mμ) for 2,2′-dipyrrylmethenes, but the range is so broad that this value alone is of little diagnostic value. In the present work 2,2′-(4,4′-diamyl-5,5′-dimethyl)- and 2,2′-(3-methoxy-4′-amyl-5′-methyl-5-methoxycarbonyl)dipyrrylmethene hydrobromide were synthesized for comparative purposes. This was accomplished by the hydrobromic acid-catalyzed condensation[17a] of 2-formyl-4-amyl-5-methylpyrrole and 2-formyl-3-methoxy-5-methoxycarbonylpyrrole, respectively, with 2-methyl-3-amylpyrrole. The first aldehyde was prepared from the reaction of 2-methyl-3-amylpyrrole with dimethylformamide and phosphorus oxychloride, and the second aldehyde was synthesized in a like manner starting with 1,2-diethoxycarbonyl-4-pyrrolidone and proceeding through a series of reactions patterned after those used by Kuhn and Osswald[19] to obtain 4-ethoxy-2-pyrrolecarboxylic acid. These involved: reaction with methyl sulfite and hydrogen chloride in methanol, bromination with N-bromosuccinimide, dehydrobromination with triethylamine, hydrolysis, and formylation. In one experiment, recrystallization of the crude hydrolysate yielded 2 - methoxycarbonyl - 4 - methoxypyrrole. It seems likely that the formation of the methoxycarbonyl derivative arose from alcoholysis during the first step in the sequence. Using more vigorous conditions for the hydrolysis gave 4-methoxy-2-pyrrolecarboxylic acid.

The accompanying Fig. 1 shows the infrared absorption spectrum of prodigiosin hydrochloride and those of the two methene hydrobromides. The similarity between the spectrum for prodigiosin hydrochloride and those for the methene hydrobromides in the region *ca.* 6.1–7.1 μ will be apparent. All three show NH bands at 2.94–3.01 μ, and prodigiosin hydrochloride shows a second strong NH band at 3.18 μ (shoulders at 3.22 and 3.33 μ). This extra band may find its counterpart in the spectra for the other two compounds in the broad absorption shown by both of these in this general region. The possibility also exists that the 3.18 μ band in the spectrum of the hydrochloride arises from the third pyrrole ring, which is not present in the two methene hydrobromides and the point is unsettled. However, this region of the hydrochloride spectrum is of further interest when compared with that of prodigiosin,[10] also in potassium bromide. The latter shows broad absorption at 2.78–3.32 μ. Examination of prodigiosin in carbon tetrachloride (0.165–0.521 g./100 ml.), using a lithium fluoride prism to obtain a greater degree of resolution, revealed the presence of a weak, free NH band at 2.87 μ accompanied by a much stronger, broad band at 2.89–3.26 μ due to association.

The visible–ultraviolet absorption spectrum of prodigiosin perchlorate in chloroform has its principal band at 540 mμ (log ε = 5.13). The main band for the unsymmetrical methene hydrobromide, in the same solvent, is at 489 mμ (log ε = 5.05); for the symmetrical methene hydrobromide, 492 mμ, (log ε = 5.08). This is understandable in terms of the increased opportunity for resonance in the cation of prodigiosin perchlorate due to the presence of the additional pyrrole ring in the prodigiosin derivative, which is not present in the two methene hydrobromides. Using the formula for the cation of the unknown, unsubstituted prodigiosin analog for the purpose of illustration and ignoring those forms that can be represented where a positive charge would reside on a ring carbon, the following resonant forms may be written:



chlorate and ours decompose in the same region. Both the methoxy- and the methyl, amyl- substituted ring of formula I has been ascribed the α-pyrrolenine structure.[5,6] Actually, the arbitrary assignment, which has been recognized as such,[6] remains for study. As far as we know there is no evidence for tautomerism such as this in 2,2,-dipyrrylmethenes, except for one possible but questionable case.[17b] The existence of such isomeric forms of prodigiosin has not been apparent to us in our investigation.

(9) F. Wrede and A. Rothhaas, *Z. physiol. Chem.*, **222**, 203 (1933).

(10) A. J. Castro, A. H. Corwin, F. J. Waxham, and A. L. Beilby, *J. Org. Chem.*, **24**, 455 (1959).

(11) A. J. Castro, J. F. Deck, M. T. Hugo, L. R. Williams, and M. R. Zingg, *ibid.*, **23**, 1232 (1958).

(12) F. Wrede, *Z. physiol. Chem.*, **210**, 125 (1932).

(13) B. Harrell and A. H. Corwin, *J. Am. Chem. Soc.*, **78**, 3135 (1956).

(14) F. Wrede and O. Hettche, *Ber.*, **22**, 2678 (1929).

(15) Dr. J. N. Shoolery, Varian Associates, Palo Alto, Calif., private communication.

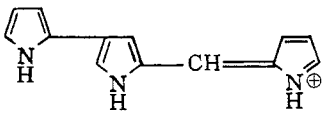
(16) *Cf.*, E. N. Morgan and E. M. Tanner, *J. Chem. Soc.*, 3305 (1955).

(17) H. Fischer and H. Orth, "Die Chemie des Pyrrols," Band II, I Hälfte, Akademische Verlagsgesellschaft, M. B. H. Leipzig, 1937, (a) p. 2; (b) p. 5.

(18) A. H. Corwin and K. W. Doak, *J. Am. Chem. Soc.*, **77**, 464 (1955).

(19) R. Kuhn and G. Osswald, *Chem. Ber.*, **89**, 1423 (1956).

Form d is not possible for the dipyrrylmethene salts. It will also be recognized that if the third pyrrole ring were in a β position resonance interaction involving all three rings as demonstrated by form d would no longer be possible and one would anticipate a spectrum more like those of the dipyrrylmethene hydrobromides by analogy with the case of the polyphenyls.[20]



The 2-methyl-3-amylpyrrole employed was synthesized *via* the route: 2-formylpyrrole → 2-methylpyrrole → 2-methylpyrrylmagnesium bromide → 2-methyl-5-ethoxycarbonylpyrrole → 2-methyl-3-valeroyl-5-ethoxycarbonylpyrrole → 2-methyl-3-amylpyrrole. The last step has been performed[21] by hydrogenolysis of the ketopyrrole followed by saponification and decarboxylation. We have found that replacement of the ethoxycarbonyl group and reduction of the keto grouping can be achieved in a single operation using the Huang-Minlon[22] modification of the Wolff–Kishner procedure resulting in formation of the methylamylpyrrole in a fair yield (52%).

Experimental[23]

Prodigiosin.—The compound was derived from a rapid pigment producing substrain isolated from the Stanford Z-4 strain of *Serratia marcescens*. It was purified by the magnesium oxide process already described[10] or by an alternate process to be described, which was proved to yield the same compound by comparison of infrared spectra and melting points. Individual samples melted, with decomposition, in the neighborhood of 150°.

A solution of 0.0492 mg. of prodigiosin and 1 drop of cyclohexylamine in 10.0 ml. of methanol showed the following maxima: 467 mμ (log ϵ 4.72), 335 (3.93), 282 (4.00). Using another solution exactly the same as the first, but containing 1 drop of 6 *N* sodium hydroxide instead of cyclohexylamine gave: 467 mμ (log ϵ = 4.71), 335 (3.96), 282 (4.00). A solution of 0.0427 mg. of prodigiosin and 1 drop of cyclohexylamine in 10.0 ml. of 95% ethanol exhibited the following maxima: 467 mμ (log ϵ = 4.67), 335 (3.92), 282 (4.00).

The isopropyl alcohol solution resulting from the reaction of 0.109 mg. of prodigiosin with 11 mg. of zinc acetate dihydrate and 0.1 ml. of concentrated ammonium hydroxide in 100 ml. of isopropyl alcohol was examined to determine the absorption characteristics of the zinc complex. Maxima were observed at 531 mμ (log ϵ = 5.57) and 501–506 mμ (log ϵ = 5.20). Wrede[12] reports maxima in ether at 517.3–550.8 and 490.8–504.4 mμ.

2-Methylpyrrole.—A mixture of 17.5 g. of 2-formylpyrrole,[24] 35 g. of potassium hydroxide, 25 ml. of 84% hydrazine hydrate and 235 ml. of ethylene glycol was heated. As the temperature was raised the solid that first formed began to decompose and dissolve while gas was evolved. The mixture then was refluxed for 2.5 hr. and distilled. The distillate, collected to 195°, was extracted with ether. The ether was removed, after drying the extract with calcium chloride, and distillation of the residue yielded 10.8 g. (72%) of 2-methylpyrrole, b.p. 147–148° (lit.,[25] b.p. 148°).

2-Methyl-5-ethoxycarbonylpyrrole.—This compound was synthesized by a method like that of Fischer, Beller, and Stern.[25] The conversion of 85 g. of 2-methylpyrrole to the Grignard reagent by reaction with 404 ml. of 2.76 *M* ethylmagnesium bromide followed by reaction of the resulting 2-methylpyrrylmagnesium bromide with 119.8 g. of ethyl chlorocarbonate yielded 56.1 g. (35%) of the cream colored, crystalline pyrrole, m.p. 99.0–101.1°, (lit.,[25] m.p. 100°) after crystallization from ethyl alcohol.

2-Methyl-3-valeroyl-5-ethoxycarbonylpyrrole.—This compound was obtained as a tan solid, m.p. 124°, from the reaction of 2-methyl-5-ethoxycarbonylpyrrole, valeroyl chloride, and aluminum chloride as described by Fischer and Gangl,[21] who report its melting point as 123°.

2-Methyl-3-amylpyrrole.—Thirty-three grams of 2-methyl-3-valeroyl-5-ethoxycarbonylpyrrole was mixed with a solution of 27.5 g. of potassium hydroxide in 204 ml. of diethylene glycol. Twenty-one milliliters of 85% hydrazine hydrate was added and the mixture was heated. As the temperature rose the evolution of gas noted at 125° and the mixture was refluxed for 6 hr. The water condenser was replaced with an air condenser and the temperature was raised to 195°, where it was held for 1 hr. The reaction mixture was steam distilled while admitting nitrogen to the apparatus to minimize air oxidation of the pyrrole, which had been noted to occur very readily. Upon distilling the residue from the ether extract of the steam distillate, after drying the extract with sodium sulfate, there was collected 11 g. (52%) of 2-methyl-3-amylpyrrole as a colorless liquid, b.p. 95–99°/4 mm. (lit.,[21] b.p. 119°/15 mm.). This compound has a characteristic odor.

Anal. Calcd. for $C_{10}H_{17}N$: C, 79.41; H, 11.33; N, 9.26. Found: C, 79.60; H, 11.27; N, 9.28.

2-Formyl-5-amyl-4-methylpyrrole.—One and one-half grams of 2-methyl-3-amylpyrrole was formylated by the method of Silverstein, Ryskiewicz, and Willard[24] for the synthesis of 2-formylpyrrole The quantities of other reagents were one-hundredth of those cited by these workers using 1 mole of pyrrole. The pyrrole in ethylene dichloride was added to the chilled phosphorus oxychloride–dimethylformamide complex during a 5-min. period and the resulting mixture was refluxed for 10 min. The crude aldehyde, 1.7 g. (96%), m.p. 20–25°, was decolorized with charcoal in ethanol and cream colored crystals of the aldehyde, m.p. 44.0–45.0°, were obtained.

Anal. Calcd. for $C_{11}H_{17}ON$: C, 73.70; H, 9.56; N, 7.81. Found: C, 74.01; H, 9.70; N, 7.98.

4-Methoxy-2-pyrrolecarboxylic Acid.—A mixture of 113.6 g. of 1,2-diethoxycarbonyl-4-pyrrolidone,[19] 59 g. of methyl sulfite,[26] 4 ml. of methanol saturated with hydrogen chloride, and 90 ml. of methanol was refluxed for 30 hr., during a period of 3 days. The methanol was removed at reduced pressure and the residue vacuum distilled yielding 112 g. of liquid, b.p. 151–164°/6–6.5 mm.

A solution of 25.2 g. of the methylation product in 160 ml. of carbon tetrachloride was cooled in ice and 17 g. of N-bromosuccinimide was added. The mixture was warmed until a vigorous reaction started and the reaction was moderated by cooling. The reaction mixture was finally refluxed until reddish-brown colored. A solution of 11 g. of triethylamine in 50 ml. of carbon tetrachloride was added and the mixture was refluxed for 1.5 hr. The mixture was filtered and the filtrate was washed twice with 50-ml. portions of 1 *M* sulfuric acid and twice with 50-ml. portions of a saturated solution of sodium bicarbonate. The solution was combined with like solutions from three other runs executed similarly with 25.2 g. of the methylation product in each case. The resulting solution was dried with sodium sulfate and distilled yielding 47.8 g. of light yellow colored oil, b.p. 144–156°/3.5 mm.

A mixture of 3.5 g. of the oil from the preceding operation, 3.5 g. of sodium hydroxide in several milliliters of water and 35 ml. of methanol was refluxed for 15 min., the methanol was evaporated and the remaining aqueous solution was refluxed for 15 min.

(20) L. N. Ferguson, "Electron Structures of Organic Molecules," Prentice-Hall, Inc., New York, N. Y., 1952, p. 279.

(21) H. Fischer and K. Gangl, *Z. physiol. Chem.*, **267**, 201 (1941).

(22) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(23) Melting points were determined with a Fisher–Johns or a Kofler melting point apparatus and are uncorrected. Infrared absorption spectra were obtained using a Beckman IR-5 spectrophotometer equipped with a sodium chloride prism, except for high resolution studies which were conducted with a Beckman IR-4 spectrophotometer having a lithium fluoride prism. Visible–ultraviolet absorption spectra were determined with a Cary 14 spectrophotometer. Analyses were performed by the Berkeley Analytical Laboratory, Berkeley, Calif., Micro-Tech Laboratories, Skokie, Ill., and by Drs. G. Weiler and F. B. Strauss, Oxford, England.

(24) R. M. Silverstein, E. E. Ryskiewicz, and C. Willard, *Org. Syn.*, **36**, 74 (1956).

(25) H. Fischer, H. Beller, and A. Stern, *Ber.*, **61**, 1078 (1928).

(26) W. Voss and E. Blanke, *Ann.*, **485**, 258 (1931).

followed by heating on a water bath for 45 min. Enough 6 *N* sulfuric acid was added to neutralize the base used and the 4-methoxy-2-pyrrolecarboxylic acid that formed was filtered from the solution. The crude acid was dissolved in chloroform, the insoluble material was separated, and the acid remaining in solution was crystallized from chloroform and ether. The resulting grey colored crystalline acid, 1.07 g., melted with decomposition at 164–167°. Recrystallization raised this to 175.0–175.5° (lit.,[27] m.p. 179–180°).

Anal. Calcd. for $C_6H_7O_3N$: C, 51.06; H, 5.00; N, 9.93; neut. equiv., 141. Found: C, 51.27; H, 4.85; N, 9.77; neut. equiv., 145.

2-Methoxycarbonyl-4-methoxypyrrole.—A mixture of 14.2 g. of the methoxypyrrole diester fraction, prepared as described above, 87 ml. of methanol and 3.3 g. of potassium hydroxide in 28 ml. of water was boiled for 10 min. To the mixture was added *ca.* 7% more 6 *N* sulfuric acid than equivalent to the potassium hydroxide used, the resulting mixture was diluted with water and extracted with ether. The ether solution was washed with sodium bicarbonate solution, dried with sodium sulfate, and the solvent evaporated. The dark colored oil was taken up in carbon tetrachloride and after two crystallizations 1.9 g. of purple-tinged crystals of 2-methoxycarbonyl-4-methoxypyrrole, m.p. 75–79°, remained. After decoloration of a portion with charcoal in ethyl alcohol and all in ether, which proved more effective, recrystallization from ether–petroleum ether mixture and finally benzene, beautiful white blades of the ester, m.p. 86.2 86.8° (lit.,[27] m.p. 85–86°), resulted.

Anal. Calcd. for $C_7H_9O_3N$: C, 54.25; H, 5.85; N, 9.02. Found: C, 54.33; H, 6.01; N, 9.10.

2-Formyl-3-methoxy-5-methoxycarbonylpyrrole.—A 0.75-g. sample of the crude ester derived from the hydrolysis of the methoxydialkoxycarbonylpyrrole fraction, b.p. 144–156°/3.5 mm., in a manner like that described as leading to 2-methoxycarbonyl-4-methoxypyrrole was formylated employing a procedure like that for the syntheses of 2-formyl-4-amyl-5-methylpyrrole. The crude aldehyde was crystallized from ethyl alcohol whereupon 0.52 g. (59%) of cream colored crystals, m.p. 164–165°, were obtained. A recrystallized sample melted at 166.5–168.2°.

Anal. Calcd. for $C_8H_9O_4N$: C, 52.46; H, 4.95. Found: C, 52.71; H, 5.16.

The 2,4-dinitrophenylhydrazone[28] of the aldehyde is a red, crystalline solid, which after crystallizing from ethyl alcohol was found to melt at 270° dec.

2,2′-(3-Methoxy-4′-amyl-5′-methyl-5-methoxycarbonyl)-dipyrrylmethene Hydrobromide.—To a solution of 0.36 g. of 2-formyl-3-methoxy-5-methoxycarbonylpyrrole and 0.28 g. of 2-methyl-3-amylpyrrole in 3 ml. of 95% ethyl alcohol, 1 ml. of 47.5% hydrobromic acid was added dropwise with cooling. Red crystals of the methene hydrobromide precipitated upon standing. These weighed 0.51 g. (69%) after separation, washing with water and air drying for a short time. Recrystallization from a mixture of chloroform and petroleum ether gave microscopic red crystals that exhibit a green reflex at 137.2–138.5° and melt dec.

Anal. Calcd. for $C_{18}H_{25}O_3N_2Br$: C, 54.41; H, 6.34; N, 7.05; Br, 20.11. Found: C, 55.19; H, 6.55; N, 6.70; Br, 20.47.

2,2′-(4,4′-Diamyl-5,5′-dimethyl)dipyrrylmethene Hydrobromide.—This compound was synthesized from 0.45 g. of 2-formyl-4-amyl-5-methylpyrrole and 0.53 g. of 2-methyl-3-amylpyrrole as in the preceding case. Red needles of the methene hydrobromide, 0.6 g. (61%), m.p. 126–128° dec., were obtained from alcohol. Two recrystallizations from benzene raised the melting point to 137.0–138.0° dec.

Anal. Calcd. for $C_{21}H_{33}N_2Br$: C, 63.61; H, 9.17; N, 7.07; Br, 20.15. Found: C, 63.64; H, 8.44; N, 7.33; Br, 20.30.

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Isopropyl Tetra-*O*-acetyl-α-D-glucopyranoside; A Synthesis of Kojibiose

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The chemical synthesis of α-D-glucopyranosides has proved very difficult. The β-D-anomers are readily synthesized by the use of the Koenigs–Knorr reaction[3] in which a tetra-*O*-acyl-α-D-glucopyranosyl halide reacts with a hydroxylic compound. Application of the Koenigs–Knorr reaction to the synthesis of α-D-glucopyranosides has been of limited success. Wolfrom, Pittet, and Gillam[4] introduced the use of stable, crystalline 3,4,6-tri-*O*-acetyl-2-*O*-nitro-β-D-glucopyranosyl chloride in a modified Koenigs–Knorr reaction leading to the successful synthesis of β-isomaltose octaacetate when 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose[5] was used as the alcohol component. Methyl tetra-*O*-acetyl-α-D-glucopyranoside was obtained in 86% yield when methanol was used as both the solvent and the reactant.[4] The 2-nitrate group does not participate in the displacement at C-1 and the condensation reaction proceeds with Walden inversion at C-1 to yield the desired α-D linkage.

It was of interest to investigate the reaction of this glucosyl chloride with secondary alcohols. Isopropyl alcohol was chosen for this purpose since it is the simplest secondary alcohol available. Isopropyl alcohol and 3,4,6-tri-*O*-acetyl-2-*O*-nitro-β-D-glucopyranosyl chloride were condensed in the presence of silver carbonate, silver perchlorate, and anhydrous calcium sulfate, the alcohol serving as both solvent and reactant. The nitrate group was removed by catalytic reduction, the sirup acetylated, and subjected to silicate chromatography whereby there was obtained a 4.7% yield of crystalline isopropyl tetra-*O*-acetyl-β-D-glucopyranoside[6] and a 35% yield of the crystalline α-D anomer.[7] This constitutes the first direct chemical synthesis of isopropyl tetra-*O*-acetyl-α-D-glucopyranoside which had been prepared[7] previously by anomerization with boron trifluoride, of a chloroform solution of isopropyl tetra-*O*-acetyl-β-D-glucopyranoside.

When the condensation reaction was carried out in an ether solvent with the isopropyl alcohol present in a fourfold excess, the yields of both the α- and β-D-glucoside tetraacetate were reduced to 15.3% and 3.18%, respectively. The addition of iodine[8] to the reaction mixture produced no noticeable effect on the yields of products.

Attempts to extend this condensation reaction to the preparation of a disaccharide involving reaction with a

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