Reactions of Phosphorus Compounds. X. Preparation of Pyrrolizine Compounds from Allyl- and Substituted Allyltriphenylphosphonium Salts

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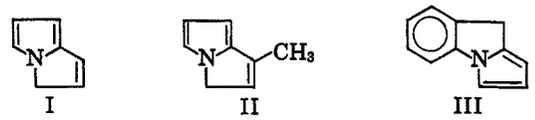
Received April 15, 1966

The use of allyl-, methyallyl-, cinnamyl-, and crotyltriphenylphosphonium salts in the synthesis of pyrrolizine compounds is reported.

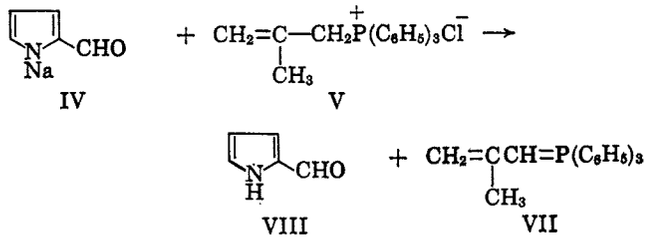
In previous papers in this series[1,2] we reported the synthesis of 3H-pyrrolizine (I), 1-methyl-3H-pyrrolizine (II), 9H-pyrrolo[1,2-*a*]indole (III),[2b] and their reduction products, by means of the general ring synthesis developed in these laboratories using vinyltriphenylphosphonium bromide.[3]



I II III

The first report of the usefulness of allylphosphonium salts in ring syntheses was published recently.[4] The mechanism has been shown to involve an intermediate butadiene followed by ring closure[5] in contrast to the Michael–Wittig aspects of the reactions of the vinyl salt.[3]

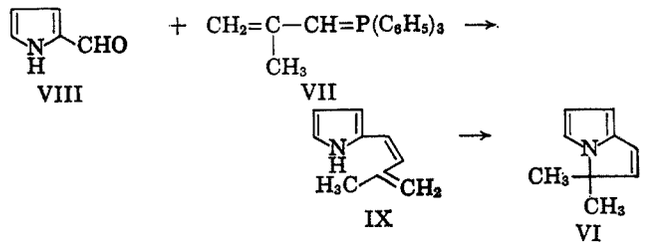
We now wish to report the preparation of some pyrrolizine compounds using allyl- and substituted allyltriphenylphosphonium salts. When the sodium salt of pyrrole-2-carboxaldehyde (IV) is allowed to react with methallyltriphenylphosphonium chloride (V), the only isolable product other than triphenylphosphine oxide is 3,3-dimethyl-3H-pyrrolizine (VI) in a yield of 66%. This reaction may first involve the formation of the ylide (VII) and pyrrole-2-carboxaldehyde (VIII) by reaction of the sodium salt (IV) and the methallyl salt



IV V

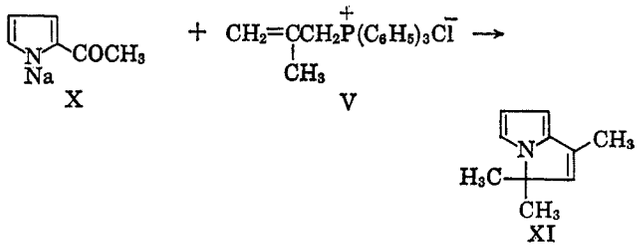
VIII VII

(V). Reaction of the ylide (VII) with the aldehyde (VIII) could then form a butadiene intermediate (IX) which in the presence of base could undergo ring closure to give the observed product, VI.



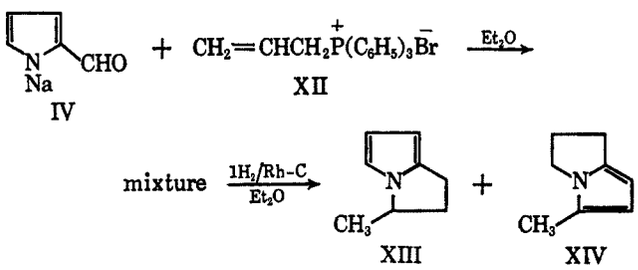
VIII VII IX VI

The reaction of the methallyl salt (V) with the sodium salt of 2-acetylpyrrole (X) gives a similar result. The only volatile product isolated was 1,3,3-trimethyl-3H-pyrrolizine (XI) in a yield of 36%. Formation of this compound may be rationalized in a manner similar to the one previously discussed.



X V XI

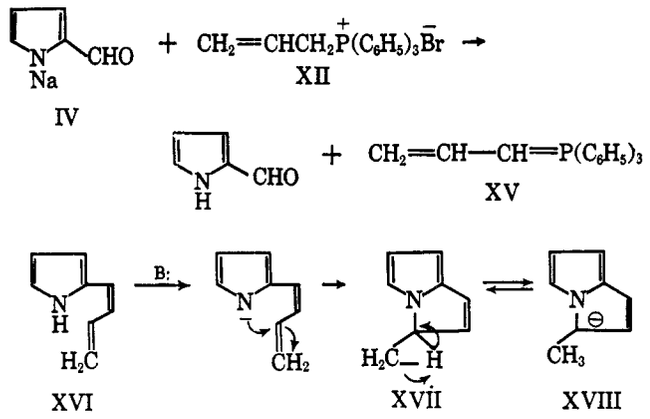
The reaction of allyltriphenylphosphonium bromide (XII), however, is somewhat more complicated. Reaction of XII with the sodium salt (IV) under identical conditions gives a mixture of compounds which cannot be separated by fractional distillation on a spinning-band column. Analysis by vpc is impossible, since the compounds decompose on the column and in the injection port even at low temperatures (column less than 80°). If the mixture obtained is hydrogenated in ether with a rhodium–carbon catalyst, 1 mole of hydrogen is absorbed and two products are formed, namely, 1,2-dihydro-3-methyl-3H-pyrrolizine (XIII) and 1,2-dihydro-4-methyl-3H-pyrrolizine (XIV).



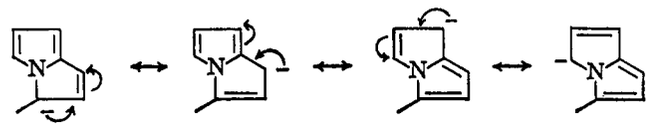
IV XII XIII XIV

This reaction may be rationalized as follows. Initially the ylide (XV) would be formed; then reaction with the pyrrole-2-carboxaldehyde would give an intermediate butadiene (XVI). Ring closure in base yields XVII which after a proton shift would result in the intermediate XVIII.

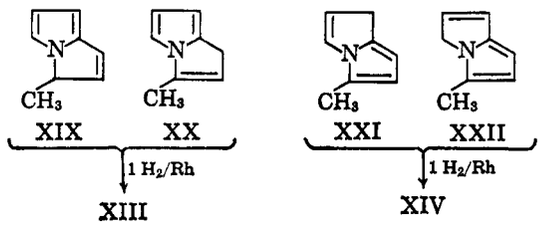
(1) E. E. Schweizer and K. K. Light, *J. Am. Chem. Soc.*, **86**, 2963 (1964).
(2) (a) E. E. Schweizer and K. K. Light, *J. Org. Chem.*, **31**, 870 (1966). (b) This last compound was erroneously reported as 3H-pyrrolo[1,2-*a*]indole in ref 2a. We wish to thank Professor R. W. Franck (Fordham University) for pointing to this error.
(3) E. E. Schweizer, *J. Am. Chem. Soc.*, **86**, 2744 (1964).
(4) E. E. Schweizer and C. J. Berninger, *Chem. Commun.*, (London), 92 (1965).
(5) E. E. Schweizer, E. T. Shaffer, C. T. Hughes, and C. L. Berninger, *J. Org. Chem.*, in press.



This is a ten π electron system and should be capable of aromatic resonance as shown below.

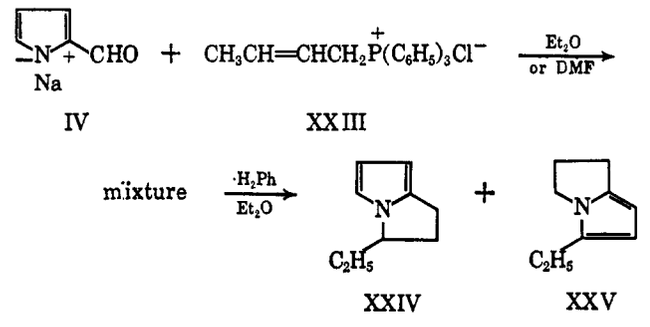


If this system is now neutralized, four products should be obtained: XIX, XX, XXI and XXII. The elemental analysis of the mixture obtained is in agreement with the formula, C_8H_9N, which could correspond to any mixture of these compounds. The yield obtained in this reaction was 67%. Partial hydrogenation of either XIX or XX would give the observed 1,2-dihydro-3-methyl-3H-pyrrolizine (XIII), while partial hydrogenation of XXI or XXII would give the observed 1,2-dihydro-4-methyl-3H-pyrrolizine (XIV). The ratio of the two products is XIII, 64%; XIV, 36%. The



nmr spectrum of XIV is identical with that of 1,2-dihydro-3H-pyrrolizine[2] except for the addition of a single methyl peak in place of one of the aromatic hydrogens. The spectrum shows τ^{neat} = 8.00 (s, 3, CH_3), 7.71 (cm, 4), 6.62 (d, 2), 4.50 and 4.30 ppm (m, 1, pyrrole H). The spectrum of XIII shows τ^{neat} = 8.83 (d, 3, CH_3), 7.83 (cm, 4), 6.15 (m, 1), 4.37, 3.95, and 3.72 ppm (m, 1, pyrrole H).

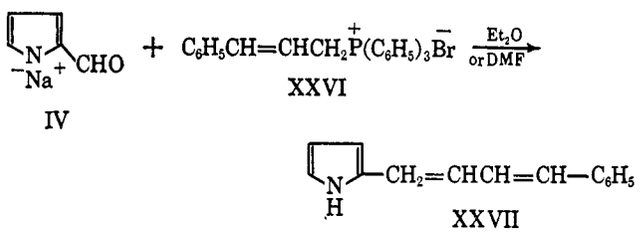
Reaction of the sodium salt (IV) with crotyltriphenylphosphonium chloride (XXIII) in ether or dimethylformamide also gave a mixture of compounds which could not be separated. Partial hydrogenation



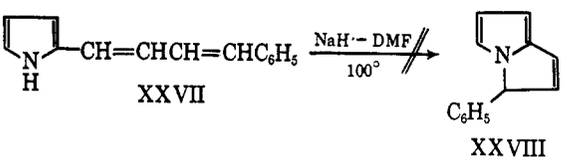
gave two compounds, 1,2-dihydro-3-ethyl-3H-pyrrolizine (XXIV) and 1,2-dihydro-4-ethyl-3H-pyrrolizine (XXV) in a yield of 43.5%. This reaction may be explained in a manner similar to that of the allyl salt. The relative percentages of products obtained in this case are XXIV, 67%; XXV, 33%. The nmr spectrum of XXIV shows τ^{neat} = 9.32 (t, 3, CH_3), 7.2 to 9.0 (cm, 6), 6.25 (q, 1), 4.38, 3.95, and 3.64 ppm (m, 1, pyrrole H). The spectrum of XXV shows τ^{neat} = 8.89 (t, 3, CH_3), 7.66 (m, 4), 6.56 (t, 2), 4.45 and 4.25 ppm (m, 1, pyrrole H).

The partially reduced compounds obtained from the allyl- and crotylphosphonium salts could not be reduced to the saturated amines in methanol solution with rhodium–carbon, even when hydrogen pressures of up to 1000 psi and temperatures of 100° were used. The unsubstituted 3H-pyrrolizine and the 1-methyl-3H-pyrrolizine on the other hand were able to be reduced with this system at an atmospheric pressure of hydrogen.[2]

The reaction of cinnamyltriphenylphosphonium bromide (XXVI) with the sodium salt (IV) in ether or dimethylformamide at ice bath temperature gave only the butadiene (XXVII) in 34.3% yield, thus lending



support to the mechanism proposed above. Reaction at higher temperatures gave smaller amounts of products. Heating a sample of the butadiene (XXVII) in dimethylformamide at 100° in the presence of sodium hydride failed to convert any of the compound to the pyrrolizine (XXVIII). The starting material was recovered unchanged. The nmr spectrum of the butadiene showed τ (d_5-pyridine) = 3.8–2.5 (cm, 13), −1.86 ppm (s, 1, NH).



Further work involving the reactions of other than alkyl-substituted allylphosphonium salts with substituted pyrrole derivatives is in progress and will be reported shortly.

Experimental Section[6]

Reaction of Methallyltriphenylphosphonium Chloride with Pyrrole-2-carboxaldehyde.—In a 500-ml, two-neck, round-bottom flask fitted with a reflux condenser and a magnetic stirrer was placed 3.98 g of a 52.6% dispersion of sodium hydride in mineral oil (2.08 g NaH, 0.087 mole) and 100 ml of anhydrous ether. To the stirred slurry was added 16.5 g of pyrrole-2-carboxaldehyde[7] (0.174 mole). After stirring for 2 hr, 28.0 g of the meth-

(6) All melting points taken on a Fisher-Johns melting point apparatus, uncorrected. Analyses were done by Micro Analysis, Wilmington, Del. Nmr spectra were obtained on a Varian A-60A spectrometer.

(7) "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963–1964, p 831.

allyltriphenylphosphonium chloride (V)[8] was added and the stirring was continued for 4 hr. After this time the solution was filtered and the ether was distilled. Vacuum distillation of the residue gave a liquid with boiling range 60–94° at 7 mm. Redistillation on a spinning-band column gave 6.95 g (65.5%) of the product, 3,3-dimethyl-3H-pyrrolizine (VI), bp 50° at 6 mm.

Anal. Calcd for $C_9H_{11}N$: C, 81.15; H, 8.33; N, 10.53. Found: C, 81.15; H, 8.47; N, 10.71.

The nmr spectrum showed τ^{neat} = 8.85 (s, 6, CH_3), 4.12 (m, 2), 3.78, 3.36 ppm (m, 1).

Preparation of 2-Acetylpyrrole.—In a 1-l., three-neck flask fitted with a stirrer, a reflux condenser, and a dropping funnel was placed 12 g (0.5 g-atom) of magnesium turnings and 25 ml of anhydrous ether. To this was added with stirring 70 g (0.5 mole) of methyl iodide in 250 ml of anhydrous ether at a rate such that gentle reflux was maintained. When addition was complete and the mixture had stirred for an additional 15 min, 33.5 g (0.5 mole) of pyrrole in 50 ml of anhydrous ether was added slowly. After standing overnight under a nitrogen blanket, 39 g (0.5 mole) of acetyl chloride in 100 ml of ether was added to the solution with cooling. When addition was complete, 250 ml of water was added dropwise to hydrolyze the mixture. The ether layer was separated and the water was extracted with 100 ml of ether. The combined ether layers were dried over anhydrous magnesium sulfate and then allowed to evaporate. Sublimation of the resulting crystalline mass gave 27.6 g (51%) of 2-acetylpyrrole, mp 87–90° (lit.[9] mp 90°).

Preparation of 1,3,3-Trimethyl-3H-pyrrolizine (XI).—Into a 500-ml, three-neck flask fitted with a stirrer and a reflux condenser were placed 4.56 g of a 52.6% dispersion of sodium hydride in mineral oil (2.4 g of NaH, 0.1 mole) and 150 ml of anhydrous ether. To the slurry was added 10.9 g of 2-acetylpyrrole (0.1 mole). The mixture was stirred for 1 hr to ensure complete conversion to the sodium salt. Then 35.1 g of the methallyltriphenylphosphonium chloride[8] was added, along with 150 ml of anhydrous ether. The mixture was stirred for 1 hr at room temperature, and then at ether reflux temperature for 3 hr. The mixture was cooled and the amber colored liquid was decanted from the gummy residue. The ether was removed by distillation and the residue was vacuum distilled, yielding a yellow liquid, bp 63–68° at 6 mm. Redistillation of this liquid on a spinning-band column gave 5.30 g (36%) of 1,3,3-trimethyl-3H-pyrrolizine (XI), $n^{24.5}D$ 1.5205, bp 65° (6 mm). The nmr spectrum showed τ^{neat} = 8.80 (s, 6), 8.08 (d, 3), 4.42, 4.10, 3.75, and 3.40 ppm (s, 1).

Anal. Calcd for $C_{10}H_{13}N$: C, 81.58; H, 8.90; N, 9.52. Found: C, 81.44; H, 8.76; N, 9.52.

Hydrogenation of 1,3,3-Trimethyl-3H-pyrrolizine (XI).—To 2.4 g of the trimethyl pyrrolizine (XI) was added 35 ml of Spectrograde methanol and about 0.1 g of a rhodium-on-carbon catalyst. The mixture was placed in a Parr hydrogenation bottle at a pressure of 30 psi of hydrogen. An uptake of 2 psi of hydrogen was observed after 1 hr. The solution was filtered and the methanol was distilled. The residue was vacuum distilled, yielding 1,2-dihydro-1,3,3-trimethyl-3H-pyrrolizine, a colorless liquid with bp 60° (6 mm), $n^{24.5}D$ 1.4880. The nmr showed τ^{neat} = 8.81 (s, 3, CH_3), 8.80 (d, 3, CH_3), 8.63 (s, 3, CH_3), 7.96 (m, 2), 6.95, 4.38, 3.92, and 3.69 ppm (m, 1).

Anal. Calcd for $C_{10}H_{15}N$: C, 80.48; H, 10.13; N, 9.39. Found: C, 80.41; H, 10.36; N, 9.33.

Reaction of Pyrrole-2-carboxaldehyde with Allyltriphenylphosphonium Bromide (XII).—Into a two-neck, 500-ml flask fitted with a magnetic stirrer and a condenser was placed 300 ml of anhydrous ether. To this was added 10.0 g of a 53.6% dispersion of sodium hydride in mineral oil (5.36 g of NaH, 0.23 mole). To the stirred mixture was added slowly 20.0 g of pyrrole-2-carboxaldehyde (0.21 mole). When reaction was complete, 80.0 g of the allylphosphonium salt (XII)[10] (0.21 mole) was added at once with stirring and cooling in an ice bath. The mixture was allowed to react for 2 hr, after which the resulting salts were removed by filtration, and the ether was distilled. Vacuum distillation of the residue gave 19.5 g (67%) of product, bp 65–71° (6 mm). An nmr spectrum of this crude product indicated that a mixture was present, but no separation could be achieved by vpc since the compounds seemed to decompose while in the instrument, even when the column temperature was under 80°.

Anal. Calcd for C_8H_9N: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.64; H, 7.44; N, 11.88.

A portion of the mixture was placed in a Parr bottle with 30 ml of anhydrous ether and 0.1 g of a rhodium-on-carbon catalyst, and the mixture was hydrogenated at 50 psi. The catalyst was removed by filtration, and the ether was distilled. Vpc now showed only two components, 1,2-dihydro-3-methyl-3H-pyrrolizine (XIII) and 1,2-dihydro-4-methyl-3H-pyrrolizine (XIV). The two components were separated by vpc (20-ft Carbowax 20M column, 200°) yielding slightly colored liquids which were purified by short-path distillation. The 1,2-dihydro-3-methyl-3H-pyrrolizine (XIII) was obtained as a water-white liquid, $n^{23}D$ 1.5112, with the nmr spectrum showing τ^{neat} = 8.83 (d, 3, CH_3), 7.83 (cm, 4), 6.15 (No. 6, 1), 4.73, 3.95, and 3.72 ppm (m, 1, pyrrole H).

Anal. Calcd for $C_8H_{11}N$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.30; H, 8.97; N, 11.64.

The 1,2-dihydro-4-methyl-4H-pyrrolizine (XIV) was obtained as a water-white liquid, $n^{22}D$ 1.5252, with nmr spectrum showing τ^{neat} = 8.00 (s, 3, CH_3), 7.71 (cm, 4), 6.62 (d, 2), 4.50 and 4.30 ppm (m, 1, pyrrole H).

Anal. Calcd for $C_8H_{11}N$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.20; H, 9.06; N, 11.59.

A 5.62-g portion of the original reaction mixture was placed in an autoclave in 250 ml of anhydrous methanol with 0.1 g of a 5% rhodium-on-carbon catalyst. A hydrogen pressure of 1000 psi was applied at 100° for 4 hr. A slight drop in hydrogen pressure was noted. The solution was cooled and filtered, and most of the methanol was removed by distillation. Vpc analysis of the remaining liquid (20% DEGS on Chromasorb, 190°) showed that the only products formed were the previously prepared dihydropyrrolizines (XIII, XIV).

Preparation of Crotyltriphenylphosphonium Chloride (XXIII).—To 290 g of triphenylphosphine (1.11 moles)[11] in 300 ml of ethyl acetate was added 100 g of crotyl chloride (1.11 moles). The mixture was stirred and refluxed for 48 hr. The white salt was filtered and refluxed with fresh ethyl acetate for 12 hr. The salt was again filtered and washed with ethyl acetate. The salt was air dried to remove most of the solvent and then dried at 100° overnight in a vacuum oven, yielding 234 g (60%), mp 226–228° (lit.[12] mp 222–224°).

Reaction of Pyrrole-2-carboxaldehyde with Crotyltriphenylphosphonium Chloride (XXIII).—In a 250-ml, three-neck flask fitted with a stirrer, a condenser, and a gas inlet tube was placed 100 ml of anhydrous dimethylformamide. To this was added 4.8 g of a 52.6% dispersion of sodium hydride in mineral oil (0.104 mole of NaH). To the stirred mixture was added slowly 9.5 g of pyrrole-2-carboxaldehyde (0.10 mole). When reaction was complete 31.9 g of the crotyltriphenylphosphonium chloride (XXIII) was added while the flask was cooled in a water bath. After 5 min the water was replaced by an oil bath which was heated to 85°. The mixture was stirred at this temperature for 8 hr under a constant flow of dry nitrogen. Heating was discontinued and the reaction mixture was allowed to cool slightly and was then poured into 300 ml of water. This solution was extracted with four 100-ml portions of ether. The combined ether extracts were extracted with three 100-ml portions of water, and the ether layer was dried overnight with magnesium sulfate. The ether solution was filtered and distilled. The residue was distilled under vacuum, yielding 5.71 g of a material, bp 40–45° (0.4 mm) (43.5% based on $C_9H_{11}N$). Nmr showed that a mixture of compounds was present, and separation by vpc was not effective.

Partial Hydrogenation of the Crotyl Mixture (from XXIII).—Into a Parr hydrogenation bottle was placed 9.83 g of the mixture and 100 ml of anhydrous ether. About 0.1 g of a 5% rhodium-on-carbon catalyst was added, and the mixture was hydrogenated on a Parr shaker apparatus for 3 hr. An uptake of 5 psi of hydrogen was noted (49–44 psi). No further uptake occurred after 1 hr. The catalyst was removed by filtration, and the ether was distilled. Distillation of the residue gave 8.92 g of a material, bp 64° (1.5 mm) (91% recovery). Vpc separation of the material (Dow 210, 5-ft, 200°) gave two compounds, 1,2-dihydro-3-ethyl-3H-pyrrolizine (XXIV), and 1,2-dihydro-4-ethyl-3H-pyrrolizine (XXV). Distillation of the slightly dis-

(8) C. F. Hauser, T. W. Brooks, M. L. Miles, M. A. Raymond, and G. B. Butler, *J. Org. Chem.*, **28**, 372 (1963).

(9) R. Schiff, *Ber.*, **10**, 1500 (1877).

(10) G. Wittig and V. Scholkopf, *ibid.*, **87**, 1318 (1954).

(11) Obtained from Metal and Thermit Corp., Rahway, N. J.

(12) C. T. Hughes, unpublished results.

colored liquids gave water-white liquids. The 3-ethyl compound (XXIV) had $n^{24}D$ 1.5072, with the nmr showing τ^{neat} = 9.32 (t, 3, CH_3), 7.2–9.0 (cm, 6), 6.25 (q, 1), 4.38, 3.95, 3.64 ppm (m, 1, pyrrole H). *Anal.* Calcd for $C_9H_{13}N$: C, 79.95; H, 9.69; N, 10.36. Found: C, 80.11; H, 9.79; N, 10.29.

The 4-ethyl compound (XXV) had $n^{24}D$ 1.5205, with the nmr showing τ^{neat} = 8.89 (t, 3, CH_3), 7.66 (m, 4), 6.56 (t, 2), 4.45 and 4.25 ppm (m, 1, pyrrole H).

Anal. Calcd for $C_9H_{13}N$: C, 79.95; H, 9.69; N, 10.36. Found: C, 80.02; H, 9.64; N, 10.16.

Preparation of Cinnamyltriphenylphosphonium Bromide (XXVI).—In a three-neck, 1-l. flask fitted with a stirrer and a reflux condenser was placed 500 ml of anhydrous benzene. To this was added 50 g of cinnamyl bromide (0.25 mole). To the stirred mixture was added 66 g (0.25 mole) of triphenylphosphine. The mixture was stirred at room temperature and a slight heating accompanied by slow precipitation of the salt was observed. After stirring overnight, the mixture was refluxed for 2 hr, followed by filtration, washing with benzene, and refluxing with an additional 500 ml of benzene for 1 hr. The salt was filtered, washed with benzene, and air dried overnight, yielding 90 g (77.5%), mp 256–258° (lit.[13] mp 240°).

(13) K. Friedrich and H. Mirback, *Chem. Ber.*, **92**, 2756 (1959).

Reaction of Pyrrole-2-carboxaldehyde with Cinnamyltriphenylphosphonium Bromide (XXVI).—Into a 500-ml flask fitted with a magnetic stirrer, a condenser, and a drying tube was placed 2.29 g of a 52.6% dispersion of sodium hydride in mineral oil (1.2 g of NaH, 0.05 mole) and 200 ml of anhydrous ether. To the stirred suspension was added 4.75 g of pyrrole-2-carboxaldehyde (0.05 mole). When evolution of hydrogen ceased, 23 g of the cinnamyl salt (XXVI) (0.05 mole) was added. Reaction occurred immediately, and it was necessary to temper with a cool water bath. The mixture was allowed to stir overnight. The salts were removed by filtration, and the ether was allowed to evaporate, leaving a dark oil which was chromatographed on alumina with hexane–benzene (1:5), resulting in an oily solid. This was chromatographed again using a 2:1 mixture of benzene–hexane, resulting in a light yellow solid which when sublimed at 100° at 0.3 mm gave 3.36 g of 1-(2-pyrryl)-4-phenylbutadiene (XXVII), mp 192–195°. The nmr spectrum showed τ(pyridine-d_5) = 3.8–2.5 (cm, 13), −1.86 ppm (s, 1, NH).

Anal. Calcd for $C_{14}H_{13}N$: C, 86.12; H, 6.71; N, 7.18. Found: C, 86.12; H, 6.78; N, 7.00.

Acknowledgment.—This investigation was supported in part by a Public Health Service Grant GM12692-01 and a Public Health Service Predoctoral Fellowship (to K. K. L.) for which we are most grateful.

Studies on the Anomalous Linkages in Glycogen and Amylopectin[1]

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Received January 31, 1966

The problem of anomalous linkages in glycogen and amylopectin has been investigated by studying the periodate oxidation products of these polysaccharides. Glycogen and amylopectin polyaldehydes having degrees of oxidation 96.8 and 98.5%, respectively, have been reduced with sodium borohydride to the corresponding polyalcohols. After a complete methylation of the polyalcohols, the resulting methylated derivatives have been hydrolyzed. The major components, namely, methoxyacetaldehyde, 1,3-di-*O*-methylglyceritol, 1,4-di-*O*-methylerythritol, and 1-*O*-methyl-D-erythritol, and the minor components 2,3,4,6-tetra-*O*-methyl-D-glucose, 2,3,6-tri-*O*-methyl-D-glucose, 2,6-di-*O*-methyl-D-glucose, 2,3-di-*O*-methyl-D-glucose, and mono-*O*-methyl-D-glucose have been separated, identified, and quantitatively determined. The proportion of 2,6-di-*O*-methyl-D-glucose from both glycogen and amylopectin polyaldehydes amounting to only 0.02% is very small and does not favor the presence of the so-called anomalous linkages of (1→3) type.

Glycogen and amylopectin have long been recognized as high molecular weight polymers having branched-chain structures composed of D-glucopyranose residues. These residues are joined by (1→4)-α-D-glucosidic linkages and the branch points are located at position 6 of one out of about 12 residues in the case of glycogen and one of about 20 glucose residues in the case of amylopectin. The number of glucose units in the inner and outer branches amounts to 4 and 8 for glycogen and 12 and 8 for amylopectin, respectively. These structural concepts have emerged from the application of various techniques such as methylation,[3] periodate oxidation,[4] enzymic degradation,[5] and partial acid hydrolysis.[6] Although the general structures of glycogen and amylopectin stated above have been accepted by most investigators, there remains a difference of opinion as to the presence of linkages other than those of (1→4) and (1→6) types. The evidence that has so far accumulated from various studies discussed below indicates the possible existence of (1→3)-α-D linkages in both glycogen and amylopectin.

The original suggestion as to the presence of (1→3) linkages came from the methylation studies. Bell[7] obtained, from the degradation products of methylated glycogen, 2,3,4,6-tetra-*O*-methyl-D-glucose (I), 2,3,6-tri-*O*-methyl-D-glucose (II), and di-*O*-methyl-D-glucose in a molar ratio of 1:9:2. Subsequently, this di-*O*-methyl-D-glucose fraction was found to contain an appreciable amount of 2,6-di-*O*-methyl-D-glucose[8] (III) in addition to 2,3-di-*O*-methyl isomer (IV), a finding which prompted the suggestion that (1→3) linkages were present in glycogen. It was, however, found later[9] that most of the component III resulted from incomplete methylation and some by demethylation of the higher methyl ethers of glucose during hydrolysis.[10] Similar studies in our laboratory have also confirmed that the hydroxyl groups at positions C-3 are more difficult to methylate than those at C-2 and C-6. Evi-

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