RECENT ADVANCES IN THE CHEMISTRY OF PYRROLE

EVAN BALTAZZI

IIT Research Institute, Chicago, Illinois

LEWIS I. KRIMEN[1]

Nalco Chemical Company, Chicago, Illinois

Received December 7, 1962

CONTENTS

I. INTRODUCTION

Spectacular advances have been made in the chemistry of pyrrole which in recent years culminated in the synthesis of chlorophyll by Woodward and his school. This article reviews the most significant advances made in this field within the last ten years.

Because of the vast literature involved, the present review will encompass only pyrroles and pyrrole derivatives with noncondensed rings. Porphyrins and porphyrin synthesis intermediates will not be included, since they should be treated separately as a whole.

II. HISTORICAL BACKGROUND

Runge (357) gave the name of pyrrole (from the Greek πυρρός meaning red and ἔλαιον meaning oil) to certain coal tar fractions which were presumably responsible for the reddening by hydrochloric acid of a pine shaving previously dipped in them. Anderson (23) characterized this substance, and Bayer (40) determined its constitution. Pyrrole and several

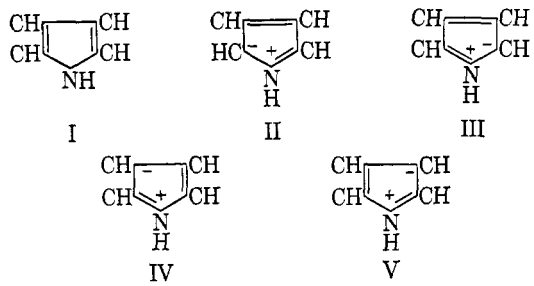
(1) Abbott Laboratories, North Chicago, Ill.

pyrrole derivatives, especially the methyl homologs, are found in coal tar and bone oil. The biological importance of pyrrole and its derivatives cannot be overemphasized, because several natural pigments, such as heme, chlorophyll, bile pigments, or enzymes like the various cytochromes, include the pyrrole nucleus. Many alkaloids and at least two amino acids, namely, proline and hydroxyproline, also contain the reduced pyrrole ring (pyrrolidine).

A description of the various positions in the pyrrole ring can be achieved either by the use of numbers or by the use of Greek letters. Both are common in the chemical literature; however, the numbering system tends to supplant the older system, which used Greek letters.

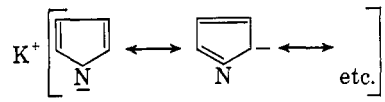
III. Structure of Pyrrole

Pyrrole can be represented by several resonating formulas, proposed by Pauling and Scherman and almost simultaneously by Ingold.



Unsaturated five-member ring compounds all possess molecular weights and molecular volumes and shapes close to that of benzene. They are planar, and the π-orbitals of the double bonds and those of the heteroatoms overlap to form doughnut-shaped molecular orbitals above and below the plane of the nuclei. The resulting resonance stabilization amounts to 31 kcal. per mole in the case of pyrrole. Pyrrole is more acidic than basic and has a pronounced resemblance to resonating benzenoid systems of the phenolic type. The basic properties of pyrrole are extremely weak, and its salts with strong acids are not stable. However, it forms picrates stable under conditions under which the salts with stronger acids are unstable. The formation of picrates by certain pyrroles should not, however, be regarded as a true salt formation, since similar derivatives are formed with aromatic hydrocarbons which are not considered to be basic in the usual sense. The acidic properties of pyrrole, on the other hand, are evidenced by their frequent value in preparative work which makes use of pyrrole salts with bases.

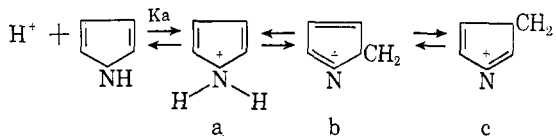
The conjugate base of pyrrole is stabilized by delocalization of the negative charge. The resulting anion is probably the intermediate involved in a number of nucleophilic substitutions.



It appears, therefore, that the Bayer formula (I), in which the nitrogen is said to have an unshared pair of electrons, cannot adequately represent pyrrole in its reactions. The similarity of benzenoid systems and the absence of basic properties, usually associated with secondary amines, due to the unshared pair of electrons on the nitrogen also indicate the presence of resonance.

The pK_a of pyrrole has been determined spectrophotometrically using the Hammett Ho indicator and was found to be -0.27. The problems caused by the acid-catalyzed polymerization of pyrrole were overcome by a back-extrapolation method and a differential plot (307).

The lack of basicity can be ascribed to a fractional positive charge on the nitrogen atom—in other words, a deficiency in electrons. The result of this deficiency is little tendency to accept a proton. However, in the presence of an acid strong enough to form a salt, the unshared pair of electrons originally present is no longer free to shift to other positions in the ring and the aromatic character is destroyed. The high reactivity, similar to that of dienes, being exhibited by pyrroles in acid solutions can be explained by this hypothesis. The protonated species (a), (b), or (c) are unstable and undergo polymerization. The main product of this is 2,5-dipyrrolylpyrrolidine (334). The application of many electrophilic substitution reactions to pyrrole is prohibited by this fact.



Reduced pyrroles, or pyrrolidines, behave as typical secondary amines.

IV. Pyrrole Ring Closure

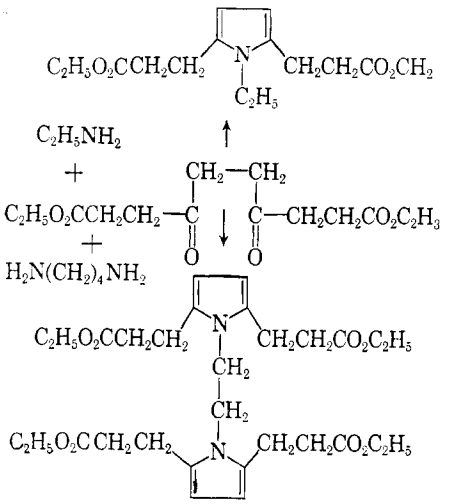
Generally speaking, five-member heterocyclic rings can be synthesized from noncyclic compounds *via* the following general routes.

1. Only carbon heteroatom bond formation.
2. Formation of a 2,3 bond.
3. Formation of a 3,4 bond.
4. Formation of a 2,3 and a 4,5 bond.

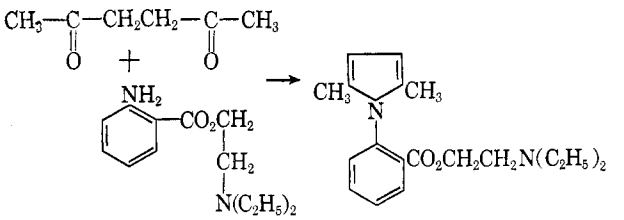
In the second and third approaches simultaneous C–N bond formation may or may not occur.

A. FORMATION OF CARBON HETEROATOM BONDS

A large variety of ways have been used to establish one or both carbon–nitrogen bonds. Typical examples are the well known pyrrole formation from 2,5-diketones with primary amines or ammonia. A variety of amines were used to effect this type of ring closure with primary amines. N-Substituted pyrroles result; conversely, when diamines were used, bispyrroles are formed (63, 178, 211).

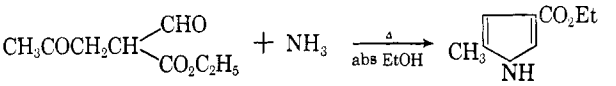


A large number of 2,5-disubstituted pyrroles bearing an aromatic or heterocyclic substituent in position 1 have been prepared, many of them for evaluation for their antispasmodic activity (351). The Knorr–Paal condensation of hexane-2,5-dione, 4-benzoylbutane-2-one, phenacylacetone, and 1,2-dibenzoylethane with the three isomeric picolylamines and 2-aminomethyl-6-methylpyridine was effected with good yields. (1,4-Diketones condense with aromatic amino carboxylic esters.) Thus β-diethylaminoethyl ester of 1-*o*-carboxyphenyl-2,5-dimethylpyrrole was prepared (351).



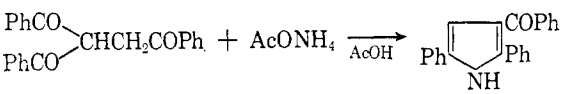
Aromatic and heterocyclic amines with various substituents, such as *p*-trifluoromethyl aniline, have also been used (65, 285, 350, 463, 468). With hydrazine, N-amino-substituted pyrroles were obtained (423).

Other carbonyl compounds such as ketoaldehydes, afforded nonsubstituted pyrroles at the aldehyde point of ring closure. Thus, 2-methyl-4-carbethoxypyrrole was prepared by the use of the following ketoaldehyde with ammonia in absolute ethanol (217).



When amino derivatives of sugars were used in this type of synthesis, pyrrole with polyhydroxy chains resulted (172). Pyrroles with quinoline or isoquinolyl substituents on the nitrogen were prepared from the corresponding amino quinolines or amino isoquinolines and dicarbonyl compounds (96, 155, 167, 169).

Amines such as ammonia or ammonium acetate were used successfully for the preparation of pyrroles nonsubstituted on the nitrogen. For instance, 2,5-dimethylpyrrole has been obtained in 36% yield from 2,5-pentanedione and ammonia over alumina at 325°. With aniline, 43% of N-phenylpyrrole was obtained under similar conditions (494). Another instance where ammonium acetate was the source of nitrogen is illustrated by the preparation of 2,5-diphenyl-3-benzoylpyrrole from the corresponding carbonyl compound (396).



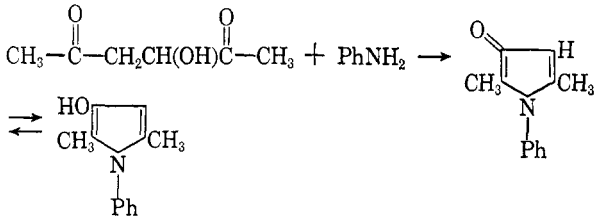
Ammonium acetate or ammonium chloride in acetic acid was also used for the cyclization of the monoacetal of a dialdehyde dicarboxylic ester to give the 3,4-dicarbethoxypyrrole (218). The same compound was obtained with ammonia in absolute ethanol.

Similarly, ammonium acetate in acetic acid afforded various polyphenylpyrroles from the corresponding dicarbonyl compounds. When ammonium acetate was replaced by the hydrochlorides of primary amines, aniline, or phenylene diamine, the corresponding N-substituted triphenylpyrroles were obtained (255). Diethyl-2,3-di-(2-ketopyrridyl) succinate was similarly obtained (466).

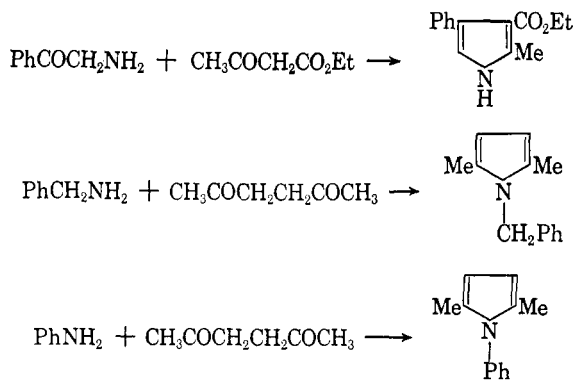
A dicarbonyl compound is not necessary as starting material. A monocarbonyl alcohol can be dehydrated over alumina in the presence of palladium at 450° and give the corresponding pyrrole in the presence of ammonia. Thus, 2-methylpyrrole has been obtained in 20% yield from 1-hydroxypentane-4-one and ammonia over alumina in the presence of palladium (418).

It was mentioned before that the reaction of 1,4-dicarbonyl compounds with diamines affords bispyrroles; this reaction was tried with aromatic amines and did not appear to be sensitive to steric hindrance (63). Acetylaminophenyl sulfohydrazine was condensed with 2,5-hexanedione in boiling glacial acetic acid, to give the acetyl derivative of 1-(*p*-aminophenylsulfamido)-2,5-dimethylpyrrole in excellent yield (472).

When 2,4-diketohexan-3-ol was treated with aniline it afforded 1-phenyl-2,5-dimethyl-3-hydroxypyrrole. It was shown that this pyrrole, as do most 3-hydroxypyrroles, exists in the oxopyrroline form. However, the derivatives of 3-hydroxy-1-phenylpyrrole in which the alpha positions are substituted so that interannular conjugation is possible, appear to be in the enolic hydroxypyrrole form (115).



The condensation of ω-phenacylamine with acetyl acetate as a function of the pH of the solution was studied in order to relate the influence of the pH on condensations involving the linking of carbon to nitrogen. It was found that at a pH of 6.9–8.2 a 63% yield of 2-methyl-3-carbethoxy-4-phenylpyrrole was obtained. When the pH dropped to 6.1, there was a sharp decrease in the yield which was then 14%; when the pH dropped further, to 3.9, the yield was only 2%; however, when benzylamine was treated with 2,5-hexanedione over a period of several days, the optimum yield was obtained around pH 10.9–11.5. When the pH dropped to 5.8 or below, the yield was insignificant. Over a period of seven days, aniline with the same 2,5-diketone gave a 70% yield in 2,5-dimethyl-1-phenylpyrrole at a pH of 4.4–5.5. When the pH became 8.2, the yield dropped to zero. It appears, therefore, that the influence of the pH on the formation of carbon–nitrogen bonds is extremely important, depending on the amine used (64).

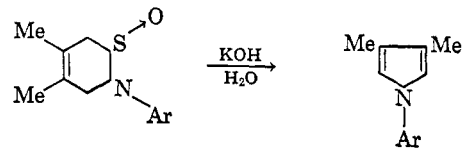


The Browning reaction of sugars with amino acids was studied by means of simple hydroxyketones. The reaction of benzoin with 2-amino acids at 165–170° generates evolution of CO_2 and formation of tetraphenylpyrrole *via* an aldolization process; tetraphenylpyrazine is also formed *via* an oxidative path. Benzoin, acetophenone, and glycine at 175° yielded 1-methyl-2,3,5-triphenylpyrrole (207).

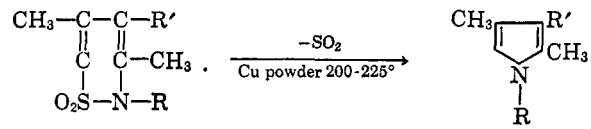
A number of novel cyclizations to pyrroles involving only formation of nitrogen–carbon bond have been developed in recent years.

1,2,4-Trihydroxybutane with aniline, over a catalyst of mixed thoria and alumina at 300°, yielded N-phenylpyrroline (348). The treatment of glutamic acid with nitrogen suboxide in the presence of nitrogen at 230–250° afforded pyrrole (209). N-Phenylpyrrole was obtained in 56% yield upon treatment of pyromucic acid with aniline for a few days and then distillation over alumina (29).

An interesting reaction yielding pyrroles involves a ring contraction of 1,2-thiazine 1-oxides. Thus, 4,5-dimethyl-2-(4′-carbomethoxyphenyl)-3,6-dihydro-1-oxo-1,2-thiazine refluxed for 1.5 hr. with a solution of potassium hydroxide in ethanol afforded 1-(4′-carboxyphenyl)-3,4-dimethylpyrrole in 100% yield. This reaction seems to be fairly general, since it has been used for the preparation of various substituted pyrroles (354).

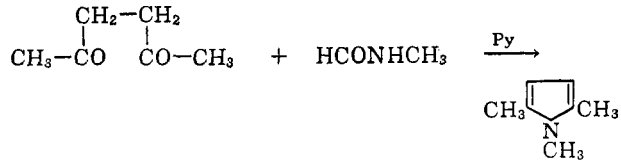


The pyrolysis of substituted 1,3-butadiene sultams gives pyrroles in good yield by ring contraction.



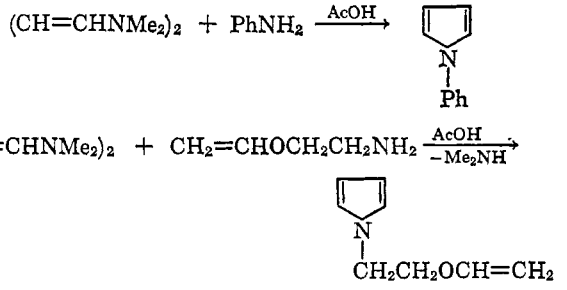
R = *p*-tolyl; R′ = CH_3
R = *m*-dimethylaminophenyl; R′ = CH_3

Formamide and substituted formamides have been used as nitrogen sources for the pyrrole nucleus in the presence of pyridine. Thus when formamide was reacted with 2,5-diketo-3,4-dicarbethoxyhexane, 2,5-dimethyl-3,4-dicarbethoxypyrrole resulted. Similarly, 2,5-hexanedione and N-methylformamide yielded the 1,2,5-trimethylpyrrole (407).

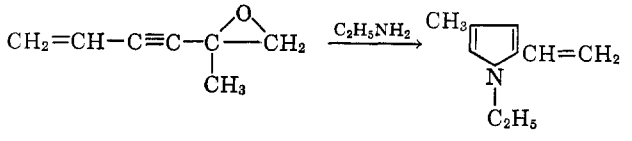


An interesting and versatile pyrrole synthesis involves enamines. For instance, 1,4-bis-(N,N-dimethyl)-1,3-butadiene treated with aniline in the presence of acetic acid afforded N-phenylpyrrole. Similarly, 1-(2-vinyloxyethyl)-pyrrole was obtained from 1,4-bis-(N,N-dimethylamino)-1,3-butadiene by

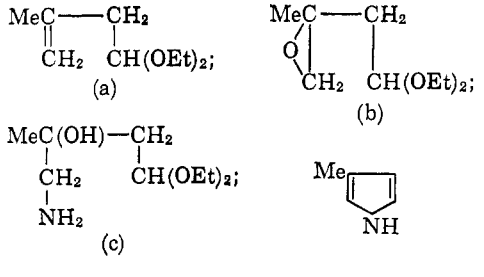
treatment with 2-vinyloxyethylamine in acetic acid. A wide variety of substituted pyrroles were obtained by this method (52, 133).



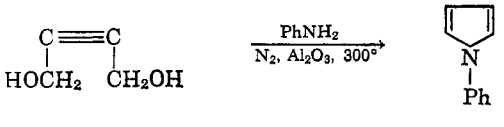
Another interesting and versatile method to close pyrrole rings uses vinyl acetylene epoxides with various amines (329, 331). Apparently this reaction involves two steps: first, the addition of the amine across the oxirane ring with concomitant ring opening; then, the addition of the substituted terminal amine on the ethylenic carbon atom next to the vinyl group. A number of pyrroles (including dipyrroles), such as 1-ethyl-4-methyl-2-vinylpyrrole, were obtained by this method (330).



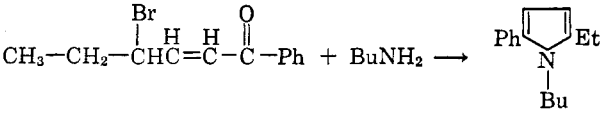
3-Methylpyrrole has been synthesized in four steps from methylallyl chloride. 2-Methylallylmagnesium chloride reacts with ethyl orthoformate to form 3-methylbut-3-en-1-al diethylacetal (a); upon epoxidation of the latter with perbenzoic or, better, perphthalic acid the corresponding epoxide is obtained (b); this is in turn reacted with aqueous or methanolic ammonia. The resulting aminoacetal (c) was dissolved in aqueous citric acid and steam distilled; 3-methylpyrrole was isolated in 39% yield (101).



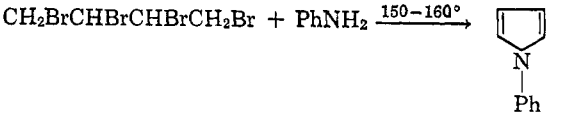
Another method proceeding *via* acetylenes is similar to that developed by Reppe. Thus, butyne-1,4-diol with aniline in the presence of alumina at 300° affords 1-phenylpyrrole (491).



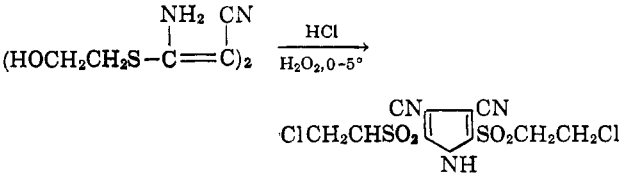
Some interesting pyrrole ring closures use halogen derivatives. For instance, haloketones with unsaturation between the keto and the halogen group were cyclized to give substituted pyrroles (371).



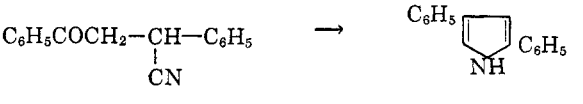
Similarly, 1,2,3,4-tetrabromobutane has been reacted with various amines at high temperatures to give pyrroles substituted on the nitrogen. Thus, 1-anilino-, benzylamino-, and methylamino-substituted pyrroles were obtained in high yields (439). 5-Bromopentan-2-one was cyclized with liquid ammonia to the corresponding pyrrolidine (460).



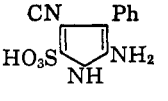
Unsaturated nitriles are interesting starting materials for pyrrole synthesis (238).



The catalytic reduction of ketonitriles with Raney nickel also gives pyrroles. For instance, when 2-phenyl-3-benzoylpropionitrile was reduced catalytically, with Raney nickel in methanol or ethyl acetate at room temperature and atmospheric pressure, 2,4-diphenylpyrroline was obtained in 95% yield. Upon treatment with selenium at 250° the latter afforded 2,4-diphenylpyrrole in 55% yield. A slightly lower yield was obtained with Raney nickel as dehydrogenation catalyst at 350°. Conversely, a much better yield was obtained in the vapor phase with a nickel pumice catalyst (83%).

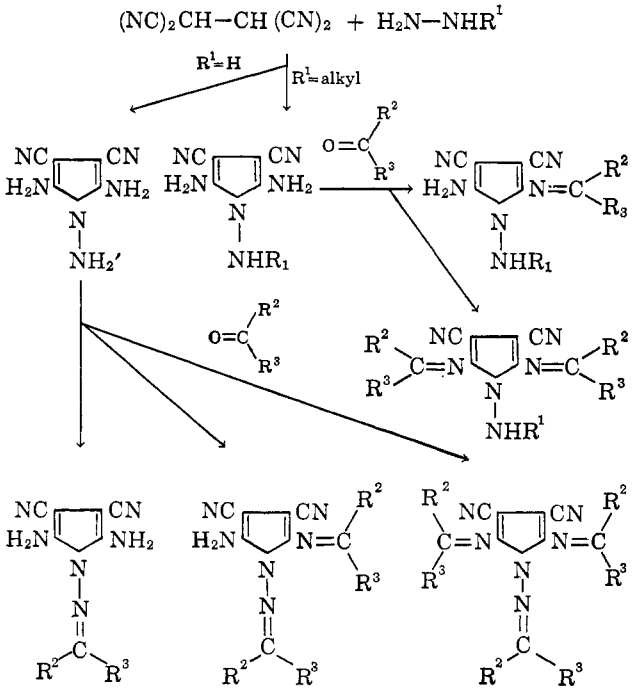


Polycyanohydrocarbons, namely, derivatives of ethane such as 1,1,2-tricyanoethane or 1,2,2-tricyanoethylbenzene, were cyclized with sodium bisulfite in water at reflux temperature. They yielded 5-amino-3-cyano-2-pyrrolesulfonic acid derivatives. These salts proved useful as fungicides and for removing copper compounds from petroleum hydrocarbons (284).

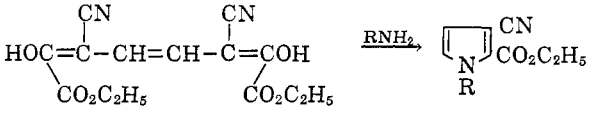


A new class of penta-substituted aminopyrroles

and alkylidene derivatives thereof was obtained from tetracyanoethane and monosubstituted hydrazines (285).

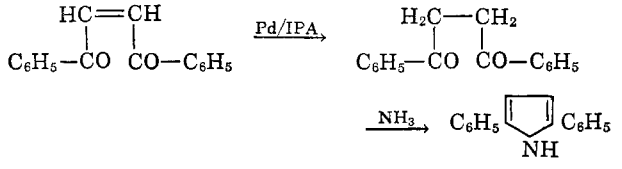


Another instance where unsaturated nitriles were used for the preparation of pyrrole derivatives is given below (203).



R = aliphatic or aromatic

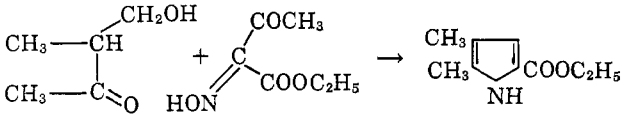
An interesting reaction yielding N-benzylpyrrole proceeds *via* α,α-dibromoadipic dinitrile. This upon heating for 4 hr. with benzylamine in glycol at 150° with frequent shaking affords N-benzylpyrrole in 40% yield (447). The synthesis of 2,5-diphenylpyrrole from *trans*-1,2-benzoylethane has been elaborated. Optimum conditions for the conversion of the former to the latter consist in the palladium-catalyzed pressure hydrogenation of the former in isopropyl alcohol solution at room temperature. The pyrrole ring is most effectively formed from 1,2-dibenzoylethane with ammonia under pressure at 140–145° (235).



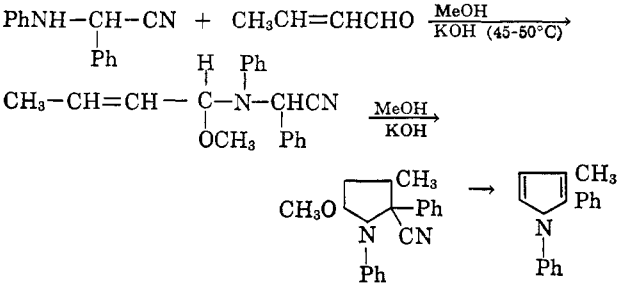
B. FORMATION OF 2,3 ALONE OR WITH C–N BONDS

This type of pyrrole ring closure has been used less frequently than the previous ones. β-Ketoaldehydes in the form of their acetals were used and 3- or 3,4-dimethylpyrroles were obtained with 40% yield (333).

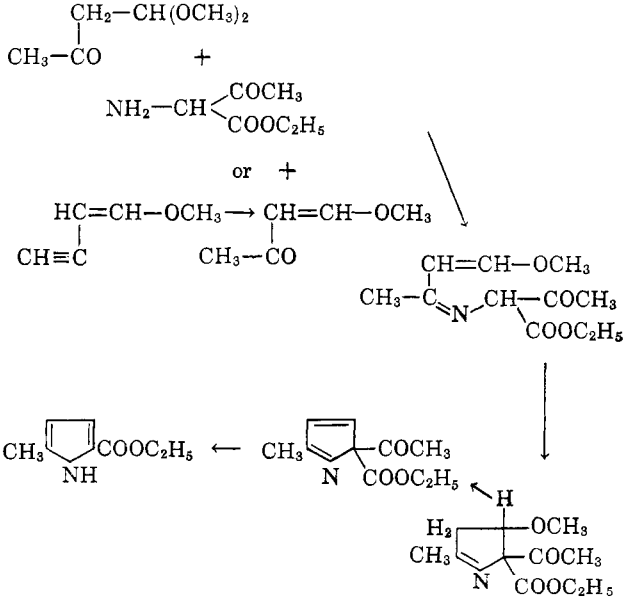
Another method involving ketoaldehydes and developed by Fischer and Fink makes use of sodium hydroxymethylenemethyl ethyl ketone in 50% acetic acid and the isonitroso derivative of acetylacetic ester; the mixture is reduced with zinc dust (146).



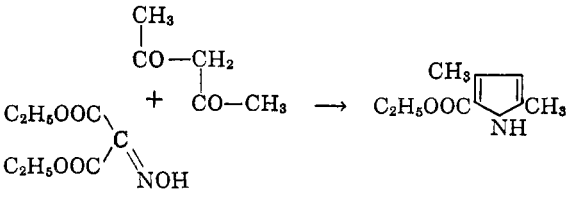
The von Miller–Plöchl pyrrole synthesis was studied and evidence that it proceeds as follows was found (427).



To the Fischer–Fink synthesis has been ascribed the following mechanism.

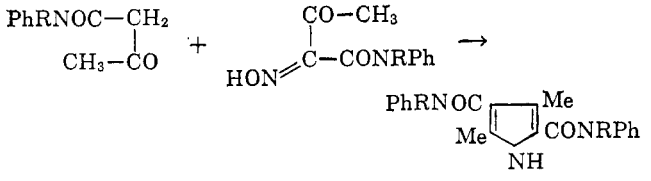


A novel route to pyrroles from β-diketones and α-oximinocarboxylic acid esters involves reductive ring closure and simultaneous formation of 2,3 and C–N bonds. For instance, when 2,4-pentanedione was treated in acetic acid with diethyloximino malonate in the presence of anhydrous sodium acetate and zinc dust, 2-carbethoxy-3,5-dimethylpyrrole resulted in 60% yield (227).

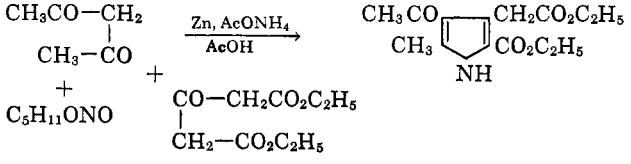


C. FORMATION OF 3,4 AND C–N BONDS

This approach has found wider use than the previous one. β-Ketoamides reduced in the presence of α-oximinoamides with zinc and acetic acid yielded pyrrolecarboxamides (36).



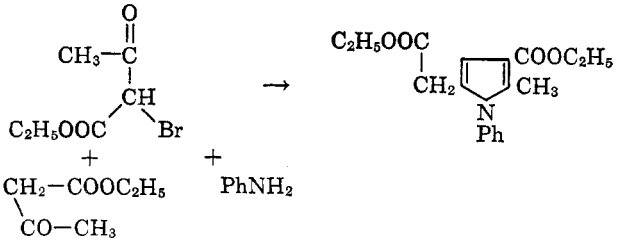
β-Diketones or β-ketodiesters reacted with amyl nitrite and reduced with zinc in acetic acid in the presence of ammonium acetate afford pyrroles (483).



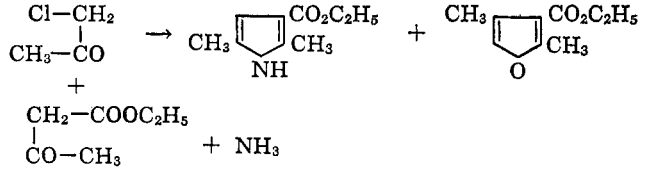
Similarly, β-ketoesters afforded pyrroles when reduced in the presence of α-oximino-β-ketoesters (89, 115).

The reductive condensation of α,γ-diketo-β-oximino compounds with β-diketones was carried out in the presence of zinc dust and acetic acid to yield acetylpyrroles (229).

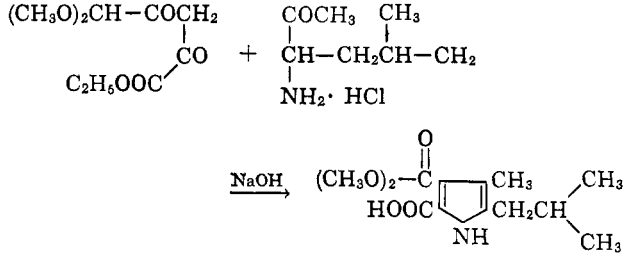
The reaction of β-ketoesters with α-halo-β-ketoesters in the presence of amines affords substituted pyrroles according to the scheme (301).



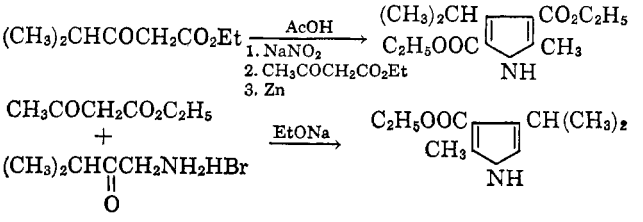
α-Haloketones reacted with β-ketoesters or their sodio derivatives in the presence of ammonia to yield substituted pyrroles (16, 123) together with some furan derivatives.



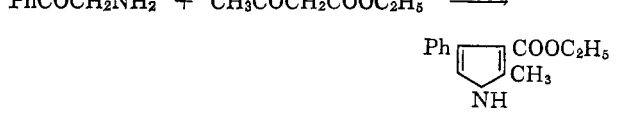
Reactions using various aminocarbonyl compounds fall into this category. For instance, α, γ-diketoesters treated with α-aminoketone hydrochlorides in the presence of sodium hydroxide gave substituted pyrroles in high yields (16, 299).



α-Amino-β-ketoester hydrochlorides reacted with β-ketoesters afforded pyrrole carboxylic acid esters in good yields (99, 141, 234, 412, 466, 485). The amino compound resulting from the reduction of the corresponding oximino derivative need not be isolated (141, 412).

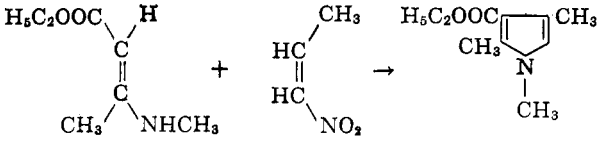


As mentioned previously the influence of the pH on condensations involving the formation of C–N bonds is important. Apparently, in the case of the simultaneous formation of 3,4 and C–N bonds, a relatively lower pH is not deleterious to the yield. For instance, in the reaction



the yield was 63% at pH 6.9–8.2. However, the optimum yield obtained from 2,5-hexanedione and benzylamine at pH 10.9–11.5 was 68–70%, whereas at pH 7.1 it dropped down to 1%. Aniline with the same diketone gave a yield of 70% at pH 4.4 to 5.5; the yield was nil above pH 8.2 (179).

The Michael type addition of 1-nitropropane to the N-substituted esters of β-aminocrotonic acids leads directly to the alkylcarbethoxypyrroles in good yields (174).



Pyrroles with polyhydroxy side chains are obtained

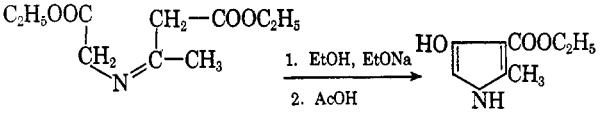
from amino sugars such as, *e.g.*, D-glycosylamines, upon heating, or at room temperature for long periods of time with β-dicarbonyl compounds in the presence of piperidine as catalyst (361). The main products, which are of the type $RC(O)\overline{C:CMeNHCH:C}-(CHOH)_3CH_2OH$, result apparently from an Amadori rearrangement of the glycosylamines to the corresponding 1-amino-1-deoxyketose (or aldose) followed by a Knorr type cyclization of the amino sugar with the dicarbonyl compound.

A novel approach to the synthesis of 3-methylpyrrole involves the formation, *in situ*, of aminoacetone generated *via* the hydrolysis of N-acetonylphthalimide (247).

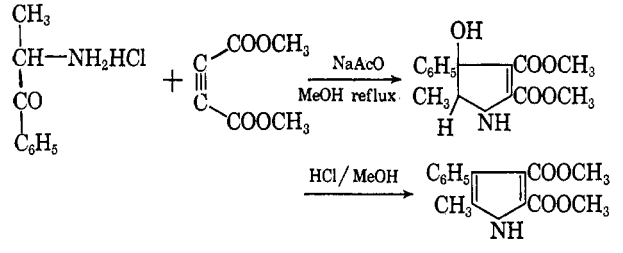
Reduction of the Knorr synthesis by sodium dithionate gave high yields of 2,4-dimethyl-3,5-dicarbethoxypyrrole. This method offers the advantage that it can be performed in aqueous solution or suspension. The isonitroso derivatives can be replaced by benzeneazo derivatives with zinc/acetic acid as the reducing agent (456).

Ethyl 4-acetyl-3-ethyl-5-methylpyrrole-2-carboxylate was obtained in 55% yield by a reverse Knorr type reaction of acetonylacetone and the 2-hydroximino derivative of ethyl-3-oxopentanoate.

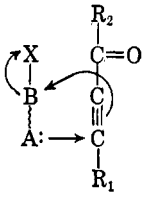
β-Hydroxypyrroles were prepared *via* a novel route involving Schiff bases from α-amino acid esters with β-ketoacid esters, β-diketones, or β-ketoaldehydes. This reaction creates a 3,4 bond but no C–N bond (448).



α-Aminoketones with acetylenic ketones cyclize and dehydrate to give pyrroles in high yield *via* a Michael type addition.

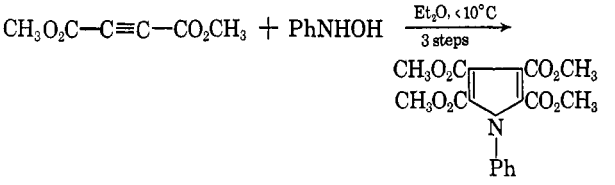


The mechanism of this reaction can be illustrated as



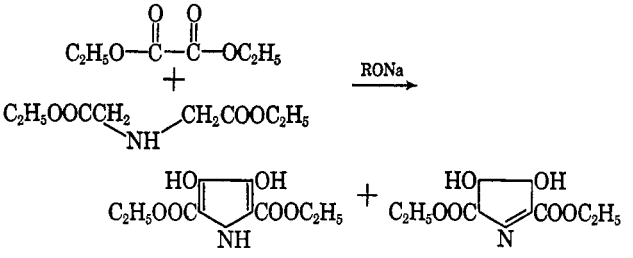
Since the acetylenic carbonyl reactant provides assymetric directionality, only one isomer is formed. This synthesis can be extended to other heterocyclic systems (190).

Another route to N-arylpyrrole proceeds *via* substituted phenylhydroxylamines and acetylenedicarboxylic esters (206).



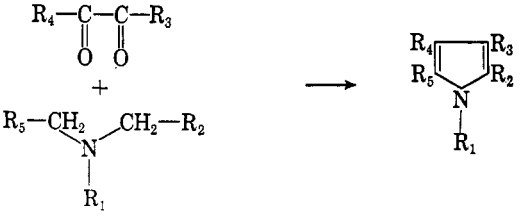
D. FORMATION OF 2,3 AND 4,5 BONDS

There are relatively few examples of such ring closures; 2,4-dihydroxy-4,5-dicarbomethoxypyrrole results from the reaction of the diethyl ester of iminodiacetic acid and diethyloxalate in the presence of metal alcoholates. The corresponding pyrroline, which is also formed, gives the enediol reaction (467).



In a more general way, N-alkyl-, N-aryl-, or N-acylamines with two ester or nitrile groups activating the α,α′-positions condense with α-diketones in the presence of bases, *e.g.*, potassium *t*-butylate, to give 1-alkyl-, aryl-, or acyl-3,4-diphenylpyrroles with carboxy carbalkoxy, cyano, or amido residues in the 2- and 5-positions.

The free α-carboxylic acids are easily decarboxylated and the 1-acylpyrroles are easily hydrolyzed to the free pyrroles (119).



R_1 = alkyl, aryl, acyl
R_2 = R_5 = CO_2CH_3, CN, etc.
R_3 = R_4 = alkyl, aryl, H

This general approach applies also to furan and thiophene derivatives.

V. CONVERSION OF FURANS AND OXIRANES TO PYRROLES

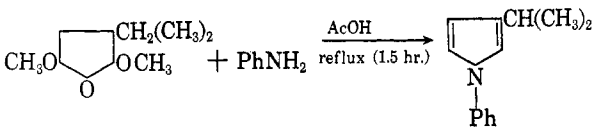
The conversion of furans to pyrroles was first reported by Yurev and Levi. A series of pyrroles and

N-substituted pyrroles were prepared by passing furans and a large excess of ammonia or amine in the vapor phase over aluminum oxide at approximately 400°. Water and the corresponding pyrrole were formed. Yields were moderate and were around 40% at best. Several examples of such conversions were given (493).

Furan reacted with ammonia over alumina to give pyrrole in yields ranging from 18–30% (51, 278, 488, 492). Other amines, such as methylamine (51) and aniline (492), reacted to give the corresponding N-substituted pyrroles. Steam (51) improved the yields substantially, and catalysts such as sulfuric acid, activated bentonites, and synthetic aluminum silicates (352, 493) proved satisfactory.

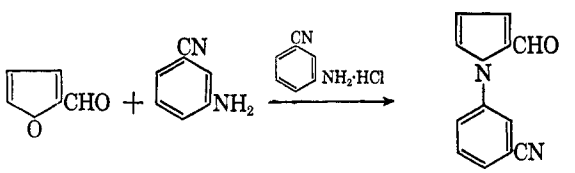
The reaction of 2,4-dimethylfuran and ammonia over alumina at temperatures around 330° afforded the corresponding pyrrole in reasonable yields (492). This temperature is well below the 400° required for the previous reactions.

2,5-Dihydrofuran reacted with aniline to give the corresponding N-phenylpyrrolidine (492). The reaction of 2,5-dimethoxytetrahydrofuran with various amines, however, produced substituted pyrroles. For instance, 1-phenyl-3-isopropylpyrrole has been obtained from 2,5-dimethoxy-3-isopropyltetrahydrofuran and aniline in refluxing acetic anhydride. In this case the elimination of the methoxy groups brought about aromatization.

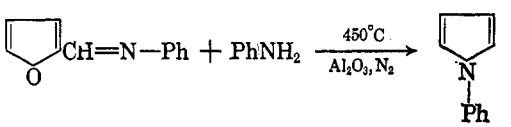


On the other hand, 2,5-diethoxytetrahydrofuran was dehydrogenated with Raney nickel catalyst in the presence of ammonia to yield pyrrole and pyrrolidine (132).

Furfural reacted with various amines of aromatic nature in the presence of the corresponding hydrochlorides and gave N-substituted arylpyrrole aldehydes according to the following scheme (253).

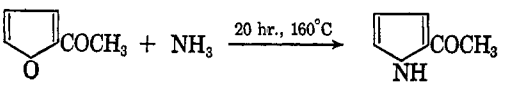


Similarly, furfuryl anil and aniline reacted at 450° to form N-phenylpyrrole (497).



Furyl and methylfuryl ketones reacted in liquid ammonia in the presence of ammonium chloride to afford the corresponding α-pyrryl ketones (408).

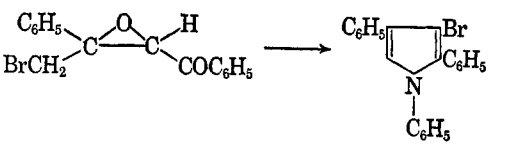
Upon treatment of α-methylfuryl ketone with ammonia in ethanol, α-methylpyrryl ketone was obtained in 38% yield. When butylamine (124) or methylamine (352, 356) was used, the corresponding N-substituted pyrroles resulted. With ethylenediamine, 1-methyl-2,4-dihydropyrrolo-1,2-*a*-pyrazine was the ultimate product (124).



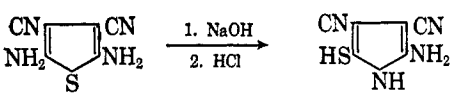
α-Methylfuryl ketone reacted with aniline over alumina gave N-phenylpyrrole in moderate yield (497).

The methyl ester of furylcarboxylic acid reacted with aniline in the presence of alumina at 475° under nitrogen yielded N-phenylpyrrole. The maximum yield (35%) was obtained at 400°.

Miscellaneous methods of obtaining the pyrrole ring from the reaction of ethylene oxide with ammonia or amines at high temperatures over various catalysts, such as uranyl oxide, chromium oxide, aluminum oxide, and chromium oxide yielded pyrroles. Styrene gave a trace of pyrrole derivatives (268, 271, 308). Pyrroles were also formed from α,β-oxido ketones (282).



Methods using acetylenic epoxides are mentioned elsewhere in this review. S-Heterocyclics of the thiophene series yielded pyrroles by rearrangement, as shown in the following scheme (282).

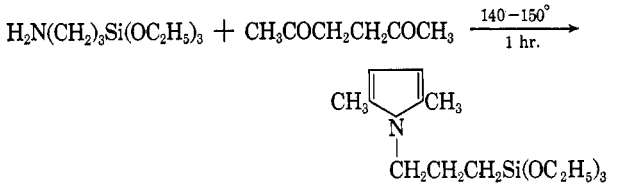


A new method of synthesizing the pyrrole ring was described by Novikov and Belikov (320).

Pyrrole ring closure has been achieved under stereospecific conditions. When, for instance, a mixture of α-diphenacyl bromide and aniline was heated until effervescence took place, then refluxed for 15 min., 3-bromo-1,2,4-triphenylpyrrole was obtained in 77% yield. The β-isomer in which the phenyl and benzoyl group are *trans* to each other affords 3-hydroxy-1,2,4-triphenylpyrrole (473).

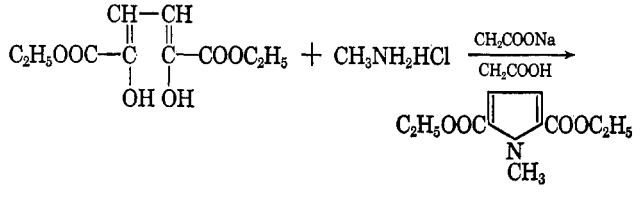
An interesting reaction involves substituted amines such as bromoethylamine as its hydrochloride in acetic acid in the presence of potassium acetate. Under such conditions, cyclization with hexane-2,5-dione gave 2,5-dimethyl-1-(2-bromoethyl)-pyrrole (226). Silicon-containing amines, for instance, 3-aminopropyltriethoxysilane, afford with 2,5-hexanedione, a 2,3-

dimethylpyrrole-1-(propyl-3-triethoxysilyl) group. An interesting intermediate containing the pyrrole ring and a silicone side chain thus was obtained (332).



One way of characterizing 1,4-diketones makes use of their cyclization to pyrroles with *p*-nitroaniline to yield typical derivatives (135).

A variation of the old pyrrole synthesis *via* muconic acid yielded 2,5-dicarbethoxy-1-methylpyrrole. When diethyl α,δ-dihydroxymuconate and methylamine hydrochloride reacted together in sodium acetate–acetic acid solutions, diethyl 1-methyl-2,5-pyrroledicarboxylate was obtained in 83% yield (237).

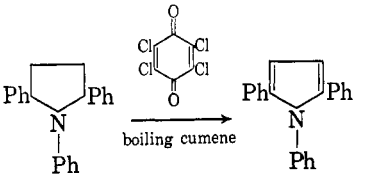


VI. Preparation of Pyrroles *via* Dehydrogenation, Hydrogenation, and Oxidation Reactions

Pyrrole has been prepared *via* dehydrogenation of pyrrolidine with various catalysts generally used for dehydrogenation of cyclic amines, *e.g.*, platinum or palladium on asbestos; oxides of magnesium, calcium, or zinc, or their mixtures; and nickel–nickel chromite. The effectiveness of rhodium on alumina in reducing nitrogen heterocyclic systems suggested that it might be a superior dehydrogenation catalyst for cyclic amines. Indeed, pyrrole was obtained in a 45% yield from a reaction over rhodium on alumina at 650° (326). Apparently, in this reaction pyrrolidine is converted to pyrrole *via* 1-pyrroline. Some 2-(2-pyrrolidyl)-pyrrole is found as a by-product.

1-Pyrroline is also an intermediate in the vapor-phase dehydrogenation of pyrrolidine over 5% palladium on charcoal. Rapid dehydrogenation of pyrrolidine at low pressure and room temperature with rhodium on alumina catalyst gives 1-pyrroline in 30% yield. 2-(2-Pyrrolidyl)-pyrrole results from the nucleophilic addition of pyrrole at the double bond of 1-pyrroline. 2-Methyl-, 3-methyl-, and 2,4-dimethylpyrroles also give this reaction in refluxing butanol (155).

In the course of investigations on aromatization of hydroaromatic compounds over nickel or platinum catalysts with benzene as a hydrogen acceptor, various substituted pyrrolines were dehydrogenated to the corresponding pyrroles (5). Other dehydrogenation catalysts, such as ferric oxide–chromic oxide–aluminum oxide mixture in ratios of 20, 1, and 79%, respectively, also were successful in dehydrogenating N-phenylpyrrolidines or pyrrolines. N-Phenylpyrrole with small amounts of 2-phenylpyrrole thus were obtained from the corresponding pyrrolidines (100). Pyrrolidines and pyrrolines were dehydrogenated to pyrroles by various oxidizing agents including manganese tetroxide (29), silver oxide (262), hydrogen peroxide (233), and 2,3,4,5-tetrachloro-1,4-benzoquinone (392). When Raney nickel (104, 105, 216, 364) or nickel–aluminum alloy and hydrogen were used (262), pyrrole and 2-pyridylpyrroles were obtained along with piperidine. Hydrogenation of pyridine over various nickel catalysts yielded, besides other products, small amounts of pyrrole (104, 106, 216, 364, 380).



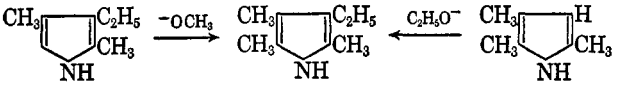
A review of hydrogenation of pyrroles was given by De Cat (116).

VII. Substitution Reactions of Pyrroles

Several substitution reactions, such as alkylation, acylation, halogenation, dehalogenation, introduction of aldehyde and keto groups, diazo coupling, nitration, nitrosation, and coupling to yield methene dyes, have been extensively studied. We shall review here the most important developments in these areas.

A. ALKYLATION

As we have seen previously, upon reaction of pyrrole with methyl iodide, alkylation of the carbon results rather than alkylation of the nitrogen. This reaction is analogous with the C alkylation of derivatives of resorcinol and phloroglycinol (188, 189). One reaction which has no analogy in the phenol series is the alkylation of the pyrrole nucleus with alkoxide ion, as illustrated below (143). This involves a nucleophilic attack of the alkoxide ion on an activated pyrrole ring.



Alkylpyrroles are normally obtained *via* the Knorr synthesis; however, there are a number of other approaches involving the pyrrole nuclei as such.

When, for instance, pyrrolealdehyde semicarbazone was treated with potassium hydroxide in water 2-methylpyrrole was obtained in 75% yield (36, 69).

The reaction of allyl bromide on the potassium salt of pyrrole gave 2-allylpyrrole. The same results were obtained when the corresponding N-Grignard reagent was used. However, when pyrrole was treated with potassium and propargyl bromide, N-propargylpyrrole was obtained; 2-crotyl bromide gave 2-crotylpyrrole under similar conditions (70). Several N-methylpyrroles were prepared by the use of sodium and methyl sulfate (106).

Reaction of sodamide with 2,5-dimethylpyrrole affords the N-sodio derivative which upon treatment with methyl iodide yields 1,2,5-trimethylpyrrole. The sodium atom and not the amino group enters the ring.

It has been generally conceded that the reaction of pyrrylmagnesium halides affords carbon-alkylated pyrroles and that pyrrylsodium or pyrrylpotassium yields 1-alkylpyrroles. However, this generalization is not always true; for example, the reaction of pyrrylpotassium with allyl or crotyl bromide gave 2-alkylpyrroles predominantly.

In an attempt to gain an insight into the behavior of pyrrylmetal salts in alkylation reactions, the effect of reaction media, cation, and reaction temperatures on the reaction of pyrrylmetal salts with benzyl halides was studied. Reactions were carried out under both heterogeneous and homogeneous conditions. It was found that the products of the reaction were 1-benzylpyrrole, 2-benzylpyrrole, and dibenzylpyrroles. The latter were shown to be formed by further alkylation of 2-benzylpyrrole.

The ratio of 1-benzylpyrrole to 2-benzylpyrrole was increased by the use of more polar solvents, by a change from heterogeneous to homogeneous media, by use of lower concentrations of the pyrrylmetal salt, and by lower reaction temperatures. Alkylation at the nitrogen also increased as the cation was varied in the following order: lithium, sodium, potassium, trimethylphenylammonium.

The substitution of benzyl bromide for benzyl chloride increased the yield of monobenzylated products but did not appreciably affect the ratio of 1-benzylpyrrole to 2-benzylpyrrole. It was shown that the monobenzylpyrroles do not rearrange under the reaction conditions.

The results are best explained on the basis of the degree of dissociation of the pyrrylmetal salt. It is proposed that the anion of the dissociated salt attacks the halide in a normal S_N2 reaction, giving N-alkylpyrroles and that carbon-alkylation occurs by reaction of the undissociated pyrrylmetal salt with the halide, possibly through a transition state in which the alkyl residue is adjacent to the α-carbon of the pyrrole ring and the halide ion is adjacent to the cation. Thus, polar solvents would be expected to favor the dissociation of the salt and thereby favor alkylation at the nitrogen. Also, the degree of dissociation of pyrrylmetal salts should increase as the cation is varied from lithium to sodium, to potassium, and to trimethylphenylammonium; this is the order of increasing nitrogen alkylation.

Since the polarity of the reaction media affects the alkylation ratio under homogeneous conditions as well as under heterogeneous conditions, and since dilution of the salt under homogeneous conditions favors nitrogen benzylation, the degree of homogeneity of the reaction media appears to have little or no importance in determining the position of alkylation.

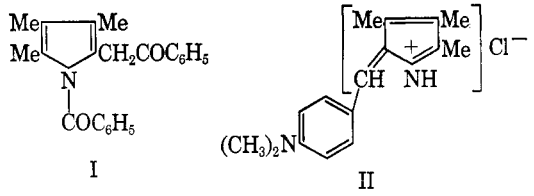
It would be expected that the reaction of the undissociated salt with the halide would be a higher energy process than that of the dissociated salt. This was borne out by the experimental data. The yields of monobenzylpyrroles increased with the increasing polarity of the medium and the increasing size of the cation.

In addition, higher reaction temperatures should favor the higher energy process more than the lower energy process. The fact that the relative amount of 2-benzylpyrrole increased with the increasing reaction temperature is consistent with this hypothesis (201).

A study of the alkylation of pyrrole metal salts with benzyl halides was undertaken, and it was proved, contrary to the general belief, that the reaction of pyrrylmagnesium halides with alkyl halides affords carbon-alkylated pyrrole and that pyrrylsodium or pyrrylpotassium yields 1-alkylpyrroles (73). In theory, the reaction of pyrrylpotassium with allyl or crotyl bromide was assumed to give 2-alkylpyrroles predominantly.

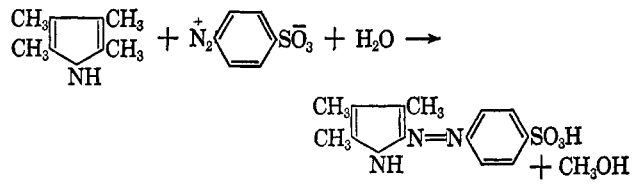
The action of alkyl iodides on the Grignard derivatives of 2,3,4- and 2,3,5-trialkylpyrroles and 2,3,4,5-tetraalkylpyrroles was shown to afford tetra- and pentaalkyl-2,4-pyrroles (pyrrolenines) with 2,2-*gem*-dialkyl groups. This reaction was inhibited by the presence of ester substituents on the pyrrole ring (50).

Upon reaction of 2,3,4,5-tetramethylpyrrole with benzoyl chloride, an adduct $C_{22}H_{21}O_2N$ (I) was obtained which with hydroxylamine gave a substance $C_{22}H_{27}O_4N_3$ which was not an oxime. When carefully purified, the above tetramethylpyrrole gave the Ehrlich reaction, and the resulting compound has the probable structure II.

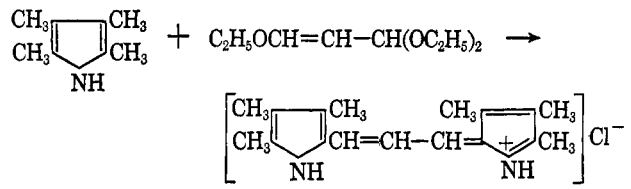


I II

The reactivity of the 2-methyl group offers certain peculiarities, in particular its elimination under the action of diazobenzenenesulfonic acid to yield the same azo dye as the 3,4,5-trimethylpyrrole.

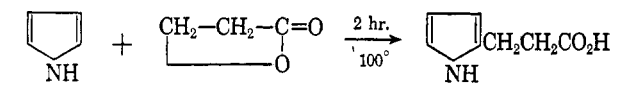


A similar elimination occurs upon reaction with the acetal of β-ethoxyacrolein.



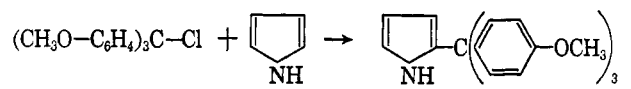
The same dye results from 2,3,4-trimethylpyrrole with the same acetal. To explain these and similar reactions the theory has been advanced that the driving force resides in the tendency toward the formation of a pyrrolenine cation the α-H of which condenses, as in several other pyrrole reactions (429).

Upon treatment of pyrrole with propiolactone at 100°, 2-carboxyethylpyrrole was obtained (180).

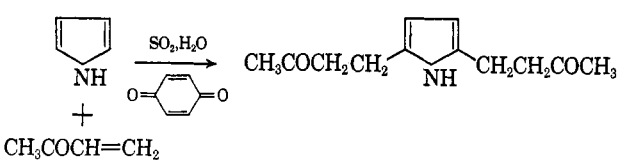


Treatment of pyrrole with ethyl diazoacetate at 95–100° yielded 2-carboxymethylpyrrole. After the usual sequence of reactions, 2-pyrrolealdehyde treated with malonic acid gave a hydrazide of (2-pyrryl)-propionic acid (244).

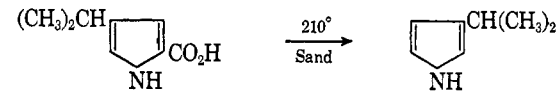
Reaction of the tri-(*p*-methoxyphenyl)-chloromethane with pyrrole in benzene introduced the tri-(*p*-methoxyphenylmethyl) radical on the 2-position of the pyrrole ring (411).



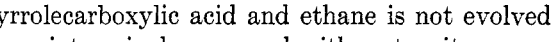
Upon reaction of the methyl vinyl ketone with pyrrole in sulfur dioxide, the corresponding methylethyl keto group was introduced in the 2- and 5-positions (476). Treatment of pyrrole with methyl vinyl ketone in the presence of sulfur dioxide and quinone in water at 60° afforded 2,5-methylethyl pyrryl ketone in 90% yield (475).



Alkylpyrroles could be obtained by decarboxylation of the corresponding alkylpyrrole carboxylic acid in the presence of sand at 210° (413).



The nature of the Grignard reagent formed from N-methylpyrrole was elucidated. Since carbonation of the mixture of N-methylpyrrole and ethylmagnesium bromide does not result in the formation of N-methylpyrrolecarboxylic acid and ethane is not evolved until the mixture is decomposed with water, it appears that the reaction is not due to interaction of N-methylpyrrole with the Grignard reagent; furthermore, the 2-acyl-N-methylpyrrole which is formed upon reaction with acid chlorides is the result of a Friedel–Crafts type acylation catalyzed by magnesium bromide.



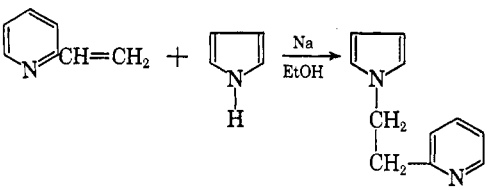
2-Acetyl-N-methylpyrrole was also obtained when acetyl chloride was reacted with N-methylpyrrole in ether in the presence of magnesium bromide (193). This reaction did not occur in the absence of magnesium bromide or Grignard reagent.

B. REACTIONS ON THE NITROGEN ATOM

Generally speaking, the direct substitution on the pyrrole nitrogen can be accomplished only if the hydrogen on the nitrogen has been replaced previously by a basic reagent. Thus, N-methylpyrrole can be prepared by the reaction of methyl iodide with potassium pyrrole. The reaction of potassium pyrrole with chloroformic ester introduces the carbethoxy group on the nitrogen of the pyrrole nucleus.

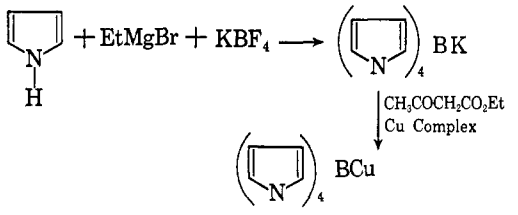
Upon treatment of potassium pyrrole with phosphorus trichloride in ether under nitrogen, a tripyrrylphosphine was obtained which was converted to the corresponding thiophosphite by reaction with sulfur (210).

Sodium salts of pyrrole have also been used. 2-Vinylpyridine reacted with pyrrole in the presence of sodium and ethanol to give the N-2-ethylpyridylpyrrole (346).

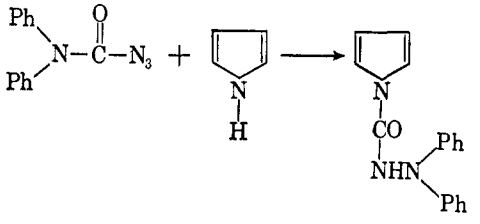


When a Grignard reagent was used to secure activation of the pyrrole ring, the reaction was not confined to nitrogen. In this case, alkyl halides alkylate on carbon instead of nitrogen and chloroformic ester re-

acted in both positions. A special case was treatment of pyrrole with ethylmagnesium bromide and potassium perfluoborate to give a pyrrole boron potassium salt which could be converted to a copper salt by means of ethyl acetoacetate–copper complex (367).



An unusual reaction of the acylation type occurred when pyrrole was treated with N,N-diphenylaminocarbazide. The N,N-diphenylhydrazide of 1-pyrrolecarboxylic acid was formed (373).



When N-benzoylpyrrole was reduced with lithium aluminum hydride in ether, pyrrole was obtained in high yields. Similar results were obtained when N-acetylpyrrole was treated with the same reagent (280). However, upon reduction of N-acetylpyrrole with lithium aluminum hydride in the presence of aluminum chloride, N-ethylpyrrole resulted (322).

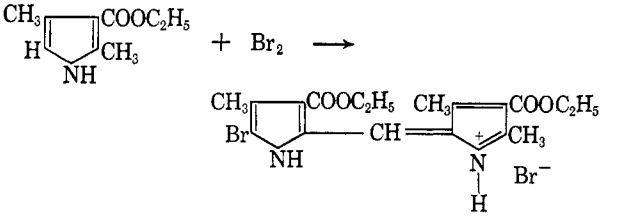
N-Alkylation occurred when 4-nitropyrrole-2-carboxylic esters were reacted with alkyl bromide in the presence of sodium methoxide in ethanol (477). N-Vinylation was carried out by reacting pyrrole with acetylene in the presence of potassium hydroxide (349).

The relative lability of the N-hydrogen was demonstrated by treating pyrrole with deuterium oxide to give the N-deuterated pyrrole (242).

C. HALOGENATION, DEHALOGENATION, THIOCYANATION, AND SELENOCYANATION

The usual reagents for the introduction of a halogen group in the pyrrole series are: sulfuryl chloride, elementary bromine (305), and the triiodide ion (145). The latter reaction proceeds with great rapidity, which illustrates the reactivity of the pyrrole nucleus. For instance, tetraiodopyrrole may be prepared conveniently from pyrrole and the triiodide ion (91).

A complication which sometimes arises in the bromination of pyrroles which have a methyl group and a free hydrogen group in the α-position is a condensation which leads to dipyrryl methenes (138).



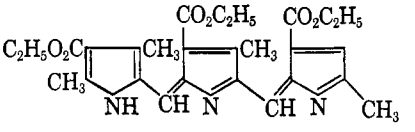
A further complication which occasionally causes difficulties in halogen is the substitution of halogen for groups other than hydrogen. For instance, the elimination of acetyl groups by bromine has been observed (110, 144).

The introduction of the halogen atom to replace a carboxylic group on the pyrrole nucleus with simultaneous decarboxylation is a common method for the preparation or halopyrroles. Bromine and iodine have thus been introduced (224).

Replacement of carboxyl groups by bromine occurs frequently in the pyrrole series and constitutes a standard method for preparing reactive dipyrryl methenes for porphyrin synthesis. This reaction accomplishes decarboxylation when other means fail (110, 140). Replacement of a carboxyl group by iodine has been achieved with iodine in bicarbonate (30).

Bromine and iodine on the pyrrole ring can be removed readily. Tetraiodopyrrole can be reduced with zinc and alkali (93) and catalytic hydrogenation readily removes ring-bound bromine (102). Iodopyrroles can be reduced to pyrroles with hydriodic acid or catalytically (120). Halogen atoms serve, therefore, to protect the pyrrole ring while other reactions are performed and can then be easily removed.

Bromination of ethyl 2,4-dimethylpyrrole-3-carboxylate gives a blue dye to which the following formula has been assigned (426).



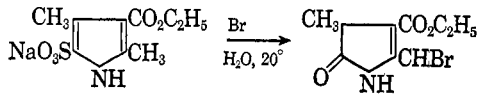
The unstable α-chloropyrrole was obtained by treatment of pyrrole with sulfuryl chloride in ether at 0°. However, upon treatment of the first reaction mixture with pyridine–SO_3 adduct in a sealed tube and then neutralization with barium carbonate, 2-chloro-5-pyrrolesulfonic acid was isolated in the form of its barium salt (415).

The reaction of sulfuryl chloride with methylpyrroles gives both dichloro- and trichloromethylpyrroles. This has been utilized as a method of preparing the corresponding aldehydes and acids which were obtained by hydrolysis of the dichloro- and trichloromethyl derivatives, respectively (317, 397).

The reaction of N-bromosuccinimide upon aromatic substituents of N-pyrrole derivatives was studied.

Halogenation was found to proceed in the *para* position (256).

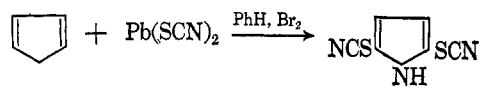
When the pyrrole ring is substituted with sulfonic acid residues, treatment with halogen eliminates and replaces the sulfonic group by a keto group (426).



Since the iodine in the iodo derivatives of pyrrole is easily replaced by hydrogen, bromine, chlorine, aryl, azo, NO_2, and CH_2R groups, the preparation and reactions of several iodo derivatives of pyrrole have been carefully investigated (30, 440). A halogenation of limited applicability with hydroxylamine has been reported (30).

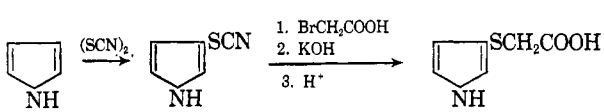
The kinetics of iodination of certain pyrrole derivatives was studied; it was found that the rates are dependent upon the concentration of the pyrrole derivative and the free iodine in the solution. Another species, perhaps hypoiodous acid, was active in iodination. Approximate values for the equilibrium constant of the iodination reaction were obtained. The reaction is affected very little by a structural change in the pyrrole and the α-position was found to be 25 times as reactive as the β-position. N-Methyl groups increased the reactivity of the pyrrole ring toward iodine by 8–15% (120).

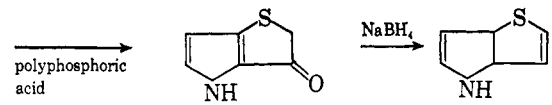
Thiocyano or selenocyano groups have been introduced in the pyrrole nucleus. For instance, the 3-thiocyanopyrrole has been obtained from pyrrole and thiocyanogen in methanol at −75° (276), or with cupric thiocyanate at 0° (277). Thiocyano derivatives were obtained upon treatment of pyrrole with lead thiocyanate in benzene in the presence of bromine (390).



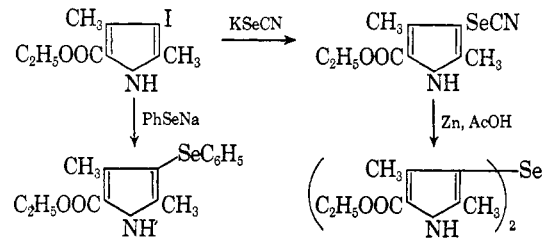
Pyrrole is converted to 3-cyanopyrrole in 50% yield with methanolic thiocyanogen at −70° or with cupric thiocyanate at 0°.

Addition of excess dilute potassium hydroxide to a cold methanolic solution of bromoacetic acid and 3-thiocyanopyrrole leads to (3-pyrrolylthio)-acetic acid. Similarly, methyl iodide and 3-cyanopyrrole yielded 3-methylthiopyrrole. Ring closure of the above acetic acid with polyphosphoric acid yielded 2H,3H-thieno-(3,2-b)-pyrrol-3-one. Desulfurization of the latter with Raney nickel afforded 2-acetylpyrrole whereas reduction with sodium borohydride led to thieno-3,2-b-pyrrole (277).

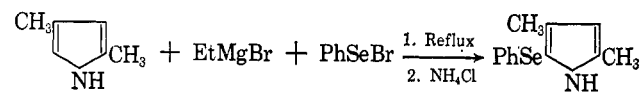




The selenocyano group was introduced in the pyrrole nucleus by treating the corresponding iodopyrrole with potassium selenocyanate. Similar reactions afforded other seleno derivatives (77, 78).



Another method for introducing the phenylseleno group into the pyrrole ring *via* Grignard reagents is outlined below (68).

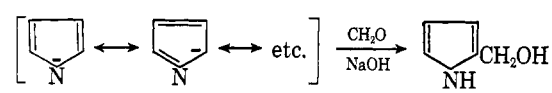


VIII. Preparation of Hydroxy- and Mercaptopyrroles

Generally speaking, three main types of pyrroles with hydroxy or mercapto groups can be considered.

(1) Pyrroles with the OH or SH group on a side chain attached on the nitrogen. Such pyrroles were obtained by the classical Knorr–Paal cyclization using, besides the diketo compound, an amino alcohol, aminophenol, or thiophenol (67, 482).

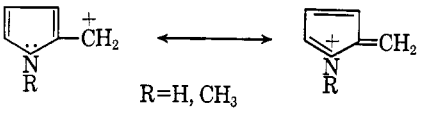
(2) Pyrroles containing the hydroxy group on a carbon side chain. These are obtainable by the reduction, usually with $LiAlH_4$ or $NaBH_4$, of an appropriate carbonyl compound. Treatment of the pyrryl anion with formaldehyde resulted in 2-pyrrolyl alcohol *via* nucleophilic addition of the anion to the carbonyl group.



Upon reduction of 2-pyrrolealdehyde with either of the above-mentioned reducing agents, a substance was obtained which by its analytical and physicochemical properties was in accord with the expected 2-hydroxymethylpyrrole. No derivative of this compound could, however, be prepared by the usual analytical procedures. N-methyl-2-hydroxymethylpyrrole behaved similarly. In this case, however, the compound was unequivocally identified by a crossed Canizzaro reaction of N-methyl-2-pyrrolealdehyde and *via* the alkaline hydrolysis of the methiodide of N-methyl-2-dimethylaminomethylpyrrole (383). Similar confir-

mation in the case of 2-pyrrolealdehyde was obtained from the methiodide of 2-dimethylaminomethylpyrrole.

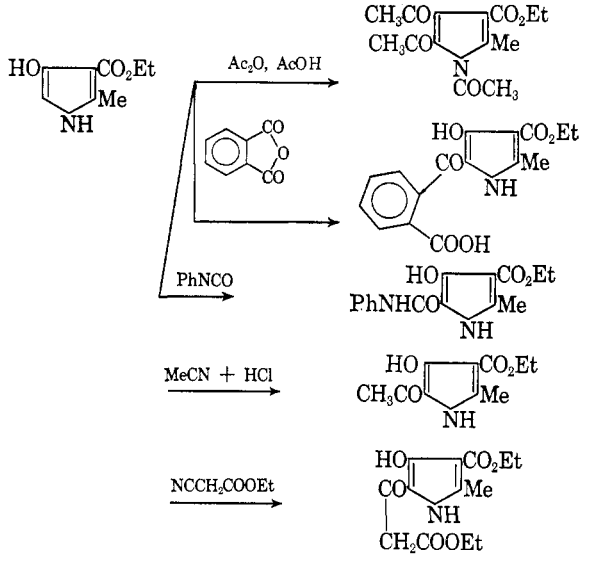
The failure of both these pyrrole alcohols to behave as primary alcohols can be accounted for by the ready formation of resonance-stabilized cations.



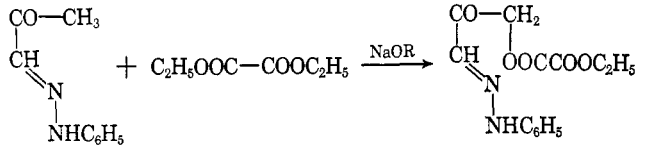
(3) Pyrroles with the hydroxy group on the nucleus. The 3-hydroxypyrroles (I) are best represented by the formula (II)

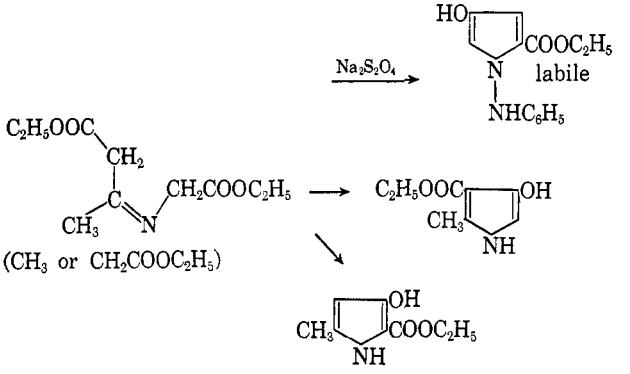
I II

3-Hydroxypyrrole gives a strong $FeCl_3$ test if carbonyl groups are present in the 2- or 4-position. The behavior of 3-hydroxy-5-methyl-4-carbethoxypyrrole was studied to some extent, and it was found that the 2-position is particularly activated and can be easily substituted by various groups, including acetyl, *o*-phthaloyl, carbamido, phenyl, etc. (448). Illustrations of these substitutions are

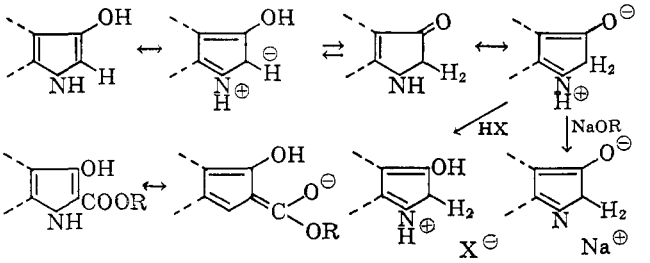


Schiff bases from β-ketoesters cyclize with α-aminoesters to form β-hydroxypyrroles *via* ester condensation. The Schiff bases of β-diketones and β-ketoaldehydes cyclize with α-aminoesters to give pyrroles *via* an aldol reaction.



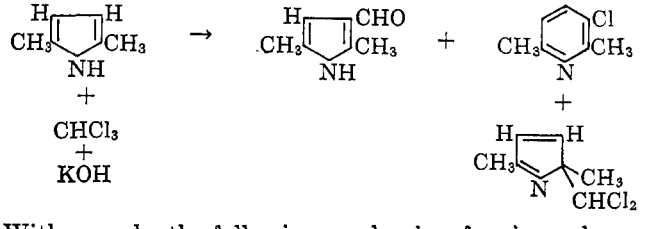


β-Hydroxypyrroles are very reactive. From their reactions and physical properties it appears that polar formulas best represent their constitution. They give some reactions of hydroxy compounds but no ketone reactions. Upon reaction with β-dicarbonyl compounds, dipyrryltrimethine dyes, pyrrolopyrrylium compounds, and α- and γ-pyranopyrroles can be obtained in analogy with the formation of benzopyrrylium, coumarin, and chromone derivatives from phenols.

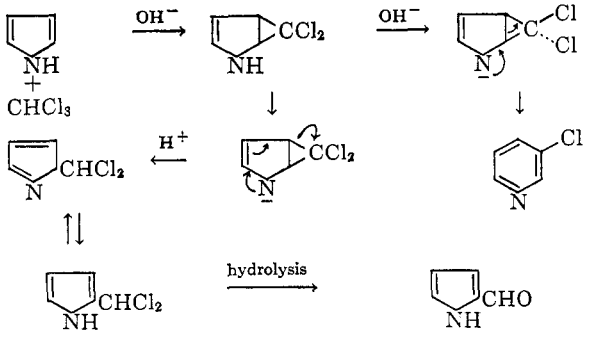


IX. Introduction of Aldehyde and Ketone Groups

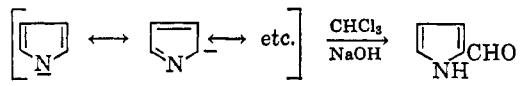
Pyrrole-α-aldehyde was first prepared by the Reimer–Tiemann method. The results, however, were very unsatisfactory and the yields poor. The number of by-products which were formed could account for the poor yields of aldehyde (35).



With pyrrole, the following mechanism for ring enlargement was proposed.



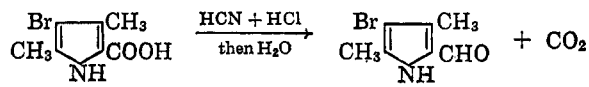
The nucleophilic substitution at saturated carbon resembles the Reimer–Tiemann reaction and affords 2-pyrrolealdehyde.



Another reaction with chloroform and alkali led to the formation of tripyrrylmethanes (142).

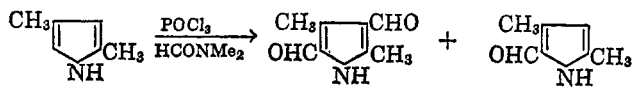
The most convenient method for introducing the aldehyde group in the pyrrole nucleus is the Gattermann synthesis, as first introduced by Fischer and Zerweck. Apparently it involves intermediate formation of chloromethylene formamidine (ClCH=NCH—NH). This reaction was greatly improved in terms of value and safety by the modification of Adams and Levine, which makes use of anhydrous zinc cyanide instead of anhydrous hydrogen cyanide (2, 4, 11, 104, 112, 148, 152, 449).

The Gattermann reaction, like halogenation, is capable of displacing carboxyl groups from the pyrrole ring (145), thus transforming a carboxylic acid to the corresponding aldehyde.

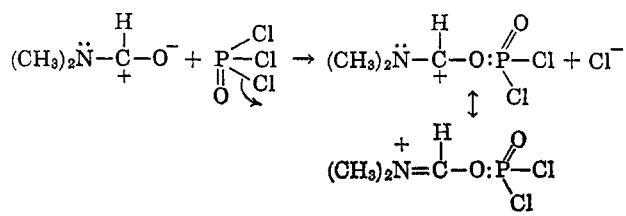


Houben–Hoesch synthesis, in which either an aliphatic or aromatic nitrile is substituted for the hydrogen cyanide in the Gattermann reaction, serves to introduce keto groups in the pyrrole nucleus (139). The method which, however, has been employed most frequently is the Friedel–Crafts reaction (150). In this reaction, the reactivity of the pyrrole ring is so great that it is frequently unnecessary to add aluminum chloride as catalyst. Thus, α-acetylpyrrole was prepared simply by heating pyrrole with acetic anhydride. The most common way of preparing pyrryl ketones which are of value in synthesis is ring closure. Usually when this is possible it is also desirable.

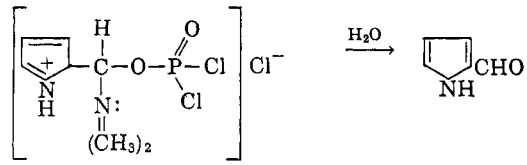
The introduction of the aldehyde group was achieved in various other ways. Phosphorus oxychloride and dimethylformamide conveniently introduced one or more aldehydic groups in the pyrrole nucleus (28, 163, 383).



It was suggested that a 1:1 complex is formed with the phosphorus oxychloride functioning as a Lewis acid.

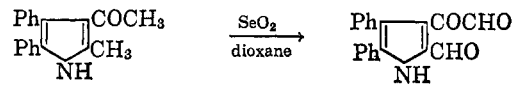


This resonance-stabilized cation reacts with the more active 2-position of the pyrrole nucleus to give an intermediate, which, upon hydrolysis, yields the aldehyde (383).

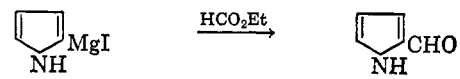


Ketones were prepared by a similar method using phosphorus oxychloride and the appropriate amide (28).

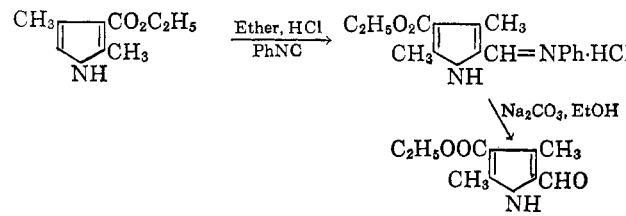
A keto aldehydic derivative of pyrrole was prepared upon oxidation with selenium dioxide of the corresponding methyl ketone (13, 402).



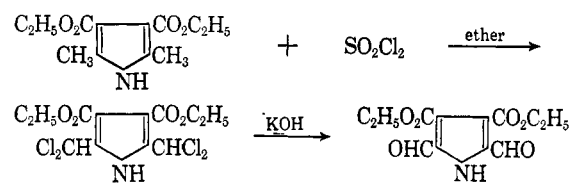
Introduction of the aldehyde group was also achieved with the Grignard reagents and ethyl formate as (417)



The addition of isonitriles to α-methylpyrroles yielded Schiff bases which, upon hydrolysis, afforded the corresponding aldehydes (430).



Attack of the methyl group on the pyrrole ring with sulfuryl chloride affords a dichloro derivative which upon hydrolysis with potassium hydroxide gives the corresponding aldehyde (265, 311, 317, 397). This classical method has been mentioned previously.

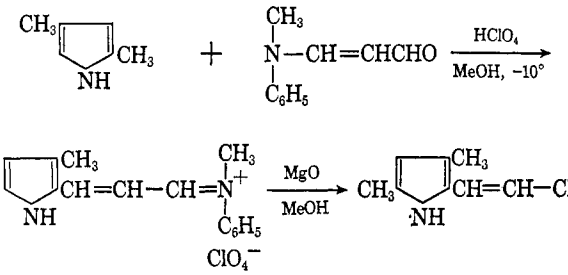


A new synthesis of pyrrolealdehyde devised by Treibs and Fritz consists of treatment of a quaternary Mannich base with a nitroso compound (432).

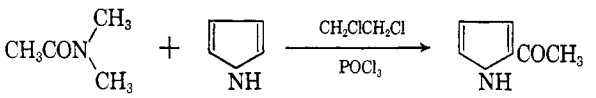
The reaction of α,γ-diketones and α,γ-keto aldehydes with ethyl β-oximinomalonate has been described above (229).

It was shown that 2-dichloromethyl-3,5-dicarbethoxy-4-methylpyrrole reacts with glacial acetic acid to form pyrrylaldehyde and acetyl chloride (108).

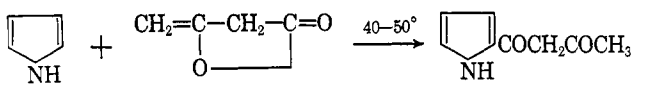
Several vinylogs of pyrrole aldehydes were prepared according to the general scheme (405)



α-Pyrrole methyl ketone was prepared from pyrrole, phosphorus trichloride, and dimethylacetamide in dichloroethane, a method similar to the preparation of pyrrole aldehydes from dimethylformamide (28, 165).

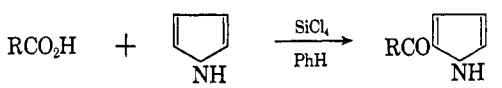


2,4-Dimethylpyrrole was acylated with benzochloride to yield the 1-acyl derivative. The reaction of benzonitrile in the presence of hydrochloric acid produced the 5-benzoyl derivative. A number of acyl derivatives were prepared by the use of diketene (442, 443).

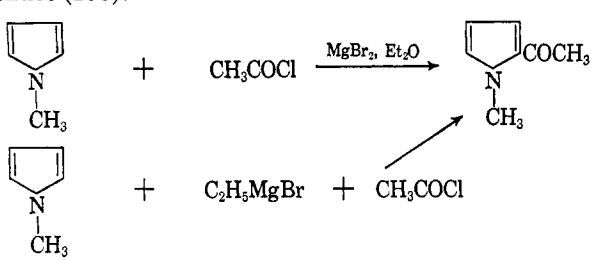


Ketocarboxylic acids were prepared from pyrroles and ethyl cyanoacetate in the presence of hydrochloric acid. The carbonyl group was reduced to CH_2 in a $AcOH–H_2SO_4$ mixture with palladium black and hydrogen (8).

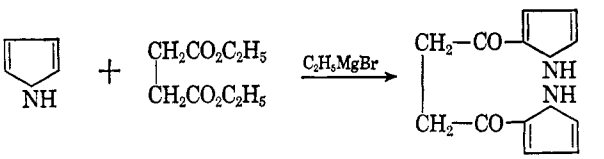
Silicon tetrachloride was used as a dehydrating agent in the condensation of pyrrole with carboxylic acids to yield pyrrole ketones. Generally speaking, silicon anhydrides of monobasic organic acids are useful for the synthesis of ketones (489).



N-Substituted pyrroles yielded pyrrole methyl ketones when treated with acyl halides and magnesium bromide in ether. Such experiments fully substantiated the hypothesis that the reaction of the so-called pyrrole Grignard reagents with acid chlorides are in reality acylations of the α-position catalyzed by magnesium halides (193).



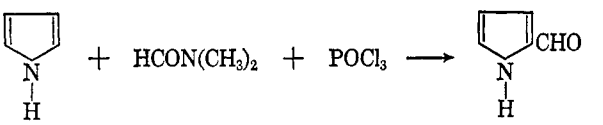
Di-(α-pyrrole)-1,4-butanediones were prepared according to the following scheme (80).



Acylation of N-methylpyrrole with acetic anhydride in the presence of zinc chloride in ether produced the 2-acyl derivative. Acylation of aromatic hydrocarbons such as benzene and toluene with 1-*n*-butyl-2,5-dimethylpyrrole-3,4-dicarboxylic acid chloride and anhydride in the presence of aluminum chloride gave quinone type compounds.

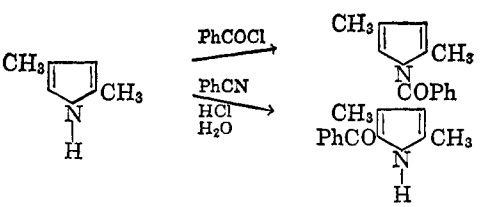
X. PREPARATION OF PYRROLE ALDEHYDES AND KETONES

The reaction methods used to prepare pyrrole aldehydes and ketones rely heavily on acylation. These reactions have been reported using a wide range of reagents and conditions. One improved procedure for the formylation of pyrrole and N-methylpyrrole employed an equimolecular mixture of phosphorus oxychloride and dimethylformamide (28).

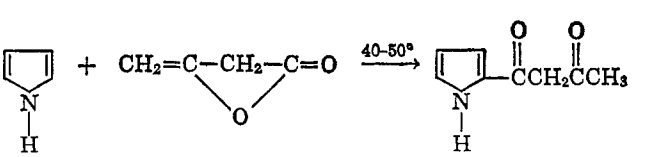


All attempts to acylate β-ethoxymethylene, thiophene, dimethylaniline, and fluorene by this method failed.

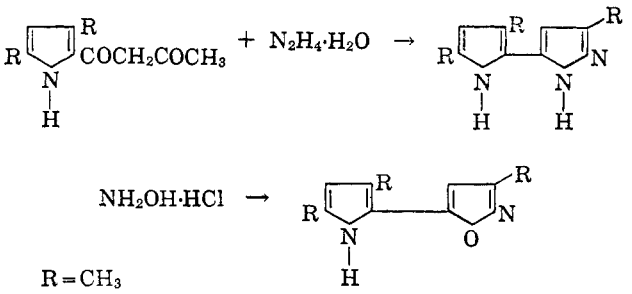
The classical reactions, such as the Schotten–Baumann and the Gattermann synthesis, were employed by Treibs and co-workers to prepare aryl pyrryl ketones (442). For example, 2,4-dimethylpyrrole gave the N-benzoyl derivative when reacted with benzoyl chloride; by contrast, the same compound yielded the 5-benzoyl compound when subjected to the Gattermann reaction.



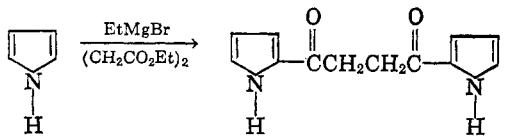
Treibs extended this work by employing diketene to give pyrryl 2,4-diketones (443).



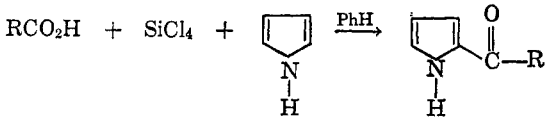
These ketones reacted with hydrazine and related carbonyl reagents to give cyclic derivatives.



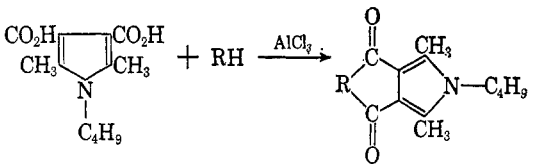
The initial hypothesis that N-methylpyrrole Grignard reagent reacted with acid chlorides to give ketones was shown to be an acylation catalyzed by magnesium bromide (193). The ethyl Grignard reagent, however, was employed to react pyrrole with diesters to give di-(α-pyrryl)-1,4-butanediones.



The acylation of pyrrole using the silicoanhydrides of monobasic organic acids as a ketone preparative method was reported in the Russian literature (489).



The use of the novel acylating agents, 1-*n*-butyl-2,5-dimethylpyrrole-3,4-dicarboxylic acid chloride and anhydride, in the well defined Friedel–Crafts reaction, gave quinone-type compounds with aromatic hydrocarbons by reacting twice with the same molecule when R is benzene, toluene, and *o*-, *m*-, and *p*-xylene.



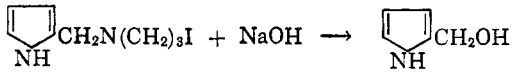
If R is mesitylene, two mesitylene nucleii were acylated forming a diketone (159).

The reactions of pyrrole aldehydes and ketones are those common to the carbonyl functional group. These embrace reduction (160, 341, 429), oxidation (402), and derivative formation (233, 403, 442, 443).

XI. Reactions of Pyrrole Aldehydes and Ketones

The behavior of pyrrole aldehydes and their derivatives was studied in various solvents. On the basis of the similarity of N-methyl-2-pyrrolealdehyde to 2-pyrrolealdehyde in chemical behavior and physical properties, the N-methyl derivative was assigned a structure to which a dipolar form contributes materially (194).

α-Pyrrolealdehyde, obtained *via* reaction of phosphorus trichloride with dimethylformamide, was transformed into the corresponding quaternary Mannich-base ammonium salt, which upon treatment with sodium hydroxide gave α-pyrrylcarbinol (383). However, N-methylpyrrole did not give this reaction.



Pyrrole aldehydes could be reduced with sodium borohydride or lithium aluminum hydride to the corresponding carbinols (350, 383). Pyrrole aldehydes could be transformed into the corresponding carboxylic acids *via* treatment with 2–10% sulfuric acid in alcohol (9). This reaction is believed to be general. Upon dehydration of the pyrrole aldoximes with acetic anhydride, the corresponding nitriles were obtained (22).

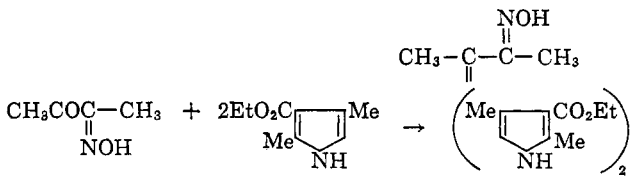
Derivatives of pyrrole aldehydes, like the thiosemicarbazones, isonicotinylhydrazones (21, 263, 464), as well as a number of azomethine (117, 118) bases, were prepared in order to study their chemical or biological properties. For instance, the azomethine derivatives of a number of aromatic or heterocyclic aminosulfonamides were obtained.

Pyrrole aldehydes were condensed with compounds containing active methyl groups, such as hydantoins (181), hippuric acid (191), cyanoacetic acid (171), acetophenone, malonic acid (214), nitromethane (243), and phenylacetonitrile (194), to give the corresponding pyrrylal derivatives.

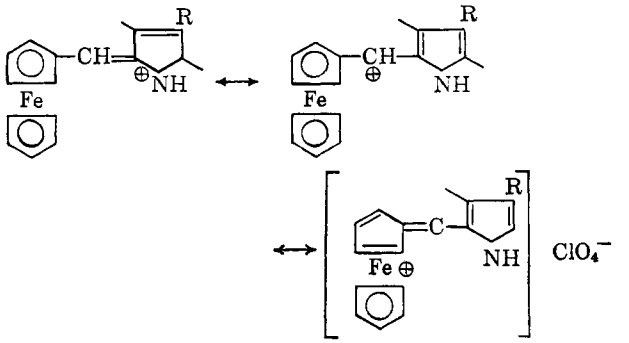
2,4,5-Triphenyl-3-pyrrolealdehyde reacted with ammonia under the influence of radiation to give *sym*-triphenyl-*sym*-triazine (74).

2-Pyrrole carbinols are obtained in excellent yield by the inverse $LiAlH_4$ reduction of 2-pyrrole ketones. 2-Ethylpyrrole is mainly obtained upon "normal" reduction. Dehydration of the carbinols furnishes homologs of 2-vinylpyrrole in fair yields (195). 2,4,5-Trimethyl-3-ethylpyrrole results from the reduction of 2,4-dimethyl-3-ethyl-5-carbethoxypyrrole or 2,4-dimethyl-3-acetyl-5-carboxypyrrole with $LiAlH_4$ (428). Alkyl groups on the pyrrole nucleus can also result from the reduction of aldehyde groups (429).

2,4-Dimethyl-3-carbethoxypyrrole was condensed with α-diketones or their monoximes to yield *gem*-pyrrolyl derivatives (450).



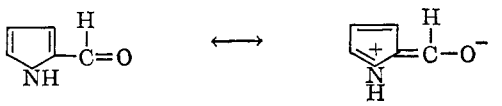
Pyrrole aldehydes condensed with forecene, and, conversely, ferrocenealdehyde condensed with pyrrole derivatives to yield ferrocenyl pyrryl dyes (314).



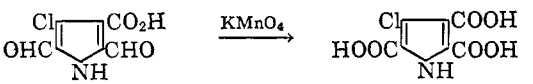
The perchlorates of these dyes were stable.

The Pomeranz–Fritsch reaction was studied in the pyrrole series. Cyclization of amino acetals of 2-pyrrolealdehyde and 2-acetylpyrrole resulted in two types of compounds, namely, pyrrolo-(2,3-c)-pyridines and pyrrolo-(1,2-a)-pyrazines; the pyrrole-(1,2-a)-pyrazines were obtained in larger amounts. Pyrrole-substituted acrylonitriles were prepared from 2-pyrrolealdehyde and arylacetonitriles with Triton B as catalyst. These compounds could not be hydrolyzed satisfactorily (194).

On the basis of its similarity of 2-pyrrolealdehyde in chemical behavior and physical properties, N-methyl-2-pyrrolealdehyde was assigned a structure to which a dipolar form contributes materially (194).

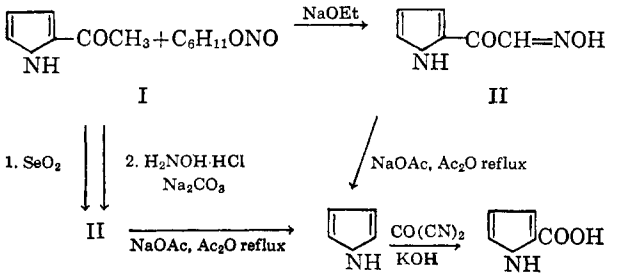


The permanganate oxidation of aldehyde groups on the pyrrole nucleus without attack of the heterocyclic ring is possible (310).



The reductive condensation of 2-pyrrolealdehyde with diethyl malonate using Raney nickel and hydrogen gave α-(2-pyrrylmethyl) malonate. Platinum oxide as catalyst yielded the corresponding pyrrolidyl compound (161).

The two routes to 2-pyrrole carboxylic acids *via* 2-pyrryl methyl ketone are (12)



2,4,5-Triphenyl-3-acetyl-pyrrole was oxidized with selenium dioxide to form the corresponding ketoaldehyde, and several derivatives of the latter, such as dioximes and quinoxalines, were prepared (402).

2-Propionylpyrrole readily formed a phenylhydrazone but failed to yield a semicarbazone, in contrast to 3-propionylpyrrole which gave a semicarbazone but no phenylhydrazone. 2-Propionylpyrrole yielded a hydrazone and oxime, but 3-propionylpyrrole failed to give either. The C-propionylpyrroles did not react with acetylene in ammonia in the presence of an alkali metal. Mixed acyloins, such as α-hydroxybenzyl-2-pyrryl ketone and the 4-chlorobenzyl and the 2,4-dichlorobenzyl acyloins, were prepared (161).

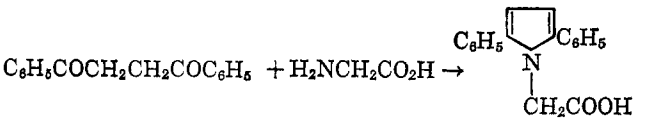
The reactivity of 2,4,5-triphenyl-3-methyl ketopyrrole with hydroxylamine hydrochloride was studied (8).

XII. Preparation of Pyrrole Carboxylic Acids and Derivatives

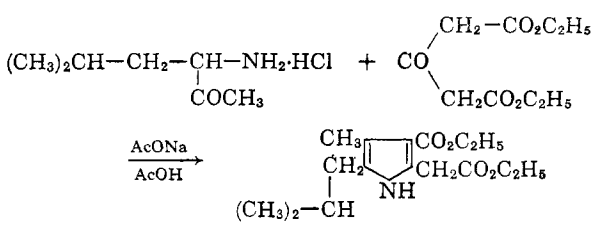
Pyrrole carboxylic esters are usually obtained by cyclization of appropriate compounds according to the general reactions outlined in the chapter on pyrrole ring formation. Selective reactions, based on the difference of reactivity of the substituents at the α- and β-positions, allow for the preparation of position isomers. Methods of direct carboxylation of the pyrrole ring exist, but they are relatively less used than cyclization reactions. Oxidation of side chains or degradation of various naturally occurring compounds, mainly porphyrins, also yields pyrrole carboxylic acids. A few other special methods of preparation are outlined below.

The well known Knorr–Paal and Hantzsch syntheses with various modifications were extensively used for the preparation of pyrrole carboxylic acid esters.

The condensation of various amino acids with 1,4-diketones yielded substituted N-pyrrole carboxylic acids (370); for instance

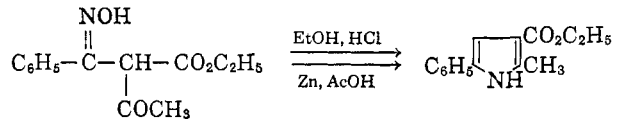


When diamines were used with diketones, bis-(1,1′-substituted pyrrole carboxylic esters) were obtained (212). Amino ketone salts with ketodiesters offered another route to pyrrole carboxylic esters (486).

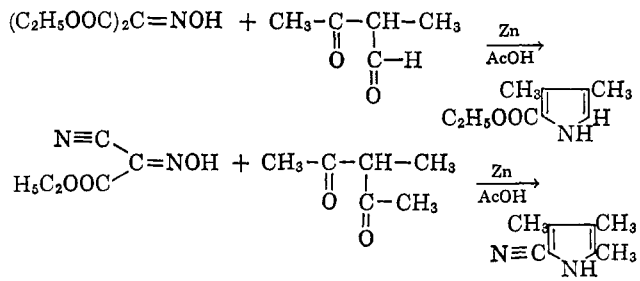


Amino ketone salts were also reacted with ketoacetals to yield pyrrole carboxylic esters (299). Thus, several 2-dialkoxyacetyl-2-pyrrole carboxylic acid derivatives were obtained. For instance, 5-methyl-3-aminohexan-2-one hydrochloride and $(MeO)_2CHCOCH_2COCO_2Et$ yielded 3-dimethoxyacetyl-4-methyl-5-isopropyl-2-pyrrolecarboxylic acid.

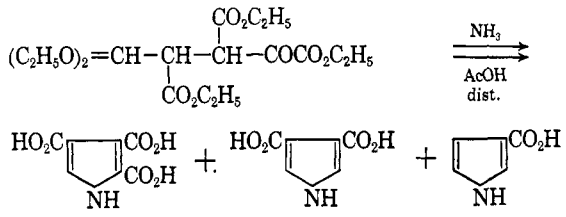
Monooximes of diketocarboxylates afforded pyrrole carboxylic esters upon treatment with ethanol saturated with hydrochloric acid and subsequent reduction with zinc and acetic acid (404).



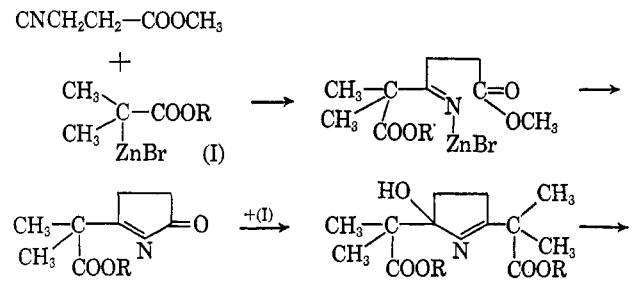
Methyl oximinomalonate underwent reduction and condensation with certain β-diketones and a β-ketoaldehyde to yield 2-pyrrole carboxylic esters. Similarly, ethyl oximinocyanoacetate and certain β-diketones afforded 2-pyrrole carbonitriles (227, 229).

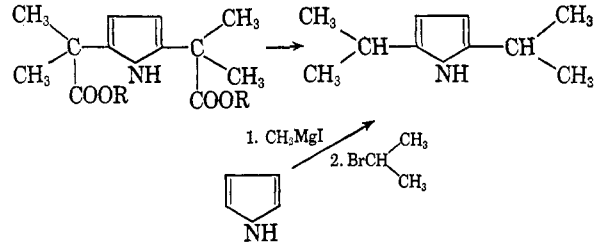


Mixtures of pyrrole carboxylic acids were obtained from the cyclization of the monoacetal of a dioxopolycarboxylate with ammonia (314).



The reaction of ethyl or methyl α-bromoisobutyrate on methyl β-cyanopropionate in the presence of zinc yielded an α,α′-disubstituted pyrrole (250).



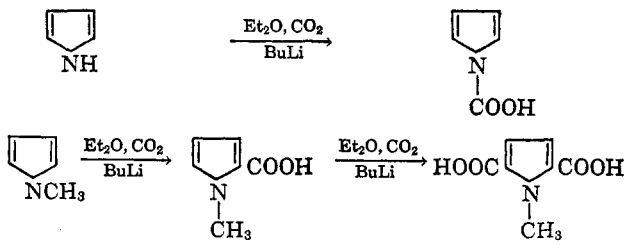


The synthesis of several pyrrole carboxylic acids related to porphyrins was achieved *via* well trodden paths (264). Trichloromethylpyrroles yielded the corresponding carboxylic acids with relative ease upon hydrolysis (265, 317, 397). A modification of the Knorr synthesis consisted in substituting benzyl acetoacetate for ethyl acetoacetate. The benzyl residue could be eliminated by catalytic hydrogenation over Raney nickel. *t*-Butylacetyl acetate can be generally used in the Knorr synthesis of pyrrole carboxylic acids. As can the benzyl group, the *t*-butyl group can be eliminated catalytically to yield the resulting pyrrole carboxylic acids; the latter then can be thermally decarboxylated (463).

Dialkyl - 1,6 - dioxo - 2,5 - dicyano - 3 - hexene - 1,6-dicarboxylate cyclizes when heated with ammonia or primary amines in organic solvents to yield 3-cyano-2-pyrrole carboxylic esters. These can be hydrolyzed subsequently to the corresponding acids (204).

All the C-methylpyrrole mono-, di-, and tricarboxylic acids, except the 2-methylpyrrole-2,4,5-tricarboxylic acid, were described; their chromatographic behavior was studied (315).

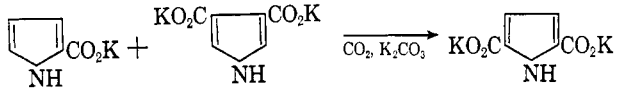
The preparation of pyrrole carboxylic acids by direct carbonation of the pyrrole nucleus has been achieved. Butyllithium has proved a satisfactory means for the carbonation of the pyrrole nucleus with carbon dioxide in ether. Grignard reagents can be used also. Pyrrole itself yields 1-carboxylic acid; however, if the 1-position is blocked, the 2- and 5-positions react to yield 2-carboxy- and 2,5-dicarboxypyrroles (379). Carbon dioxide acts as the electrophile.



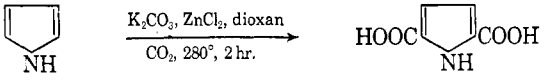
Apparently, this lack of reactivity of pyrrole toward C-metalation is quite different from the behavior of the 1-methyl derivative. Similarly, 1-phenyl-2-pyrrolecarboxylic acid was obtained from 1-phenylpyrrole (379).

Direct carbonation of pyrrole with carbon dioxide in the presence of potassium carbonate under pressure resulted in 2-pyrrolecarboxylic acid (386).

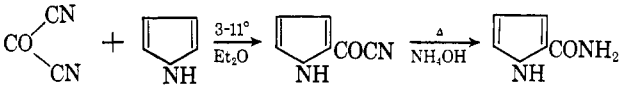
The potassium salts of pyrrole carboxylic acids rearranged under high temperature conditions (338).



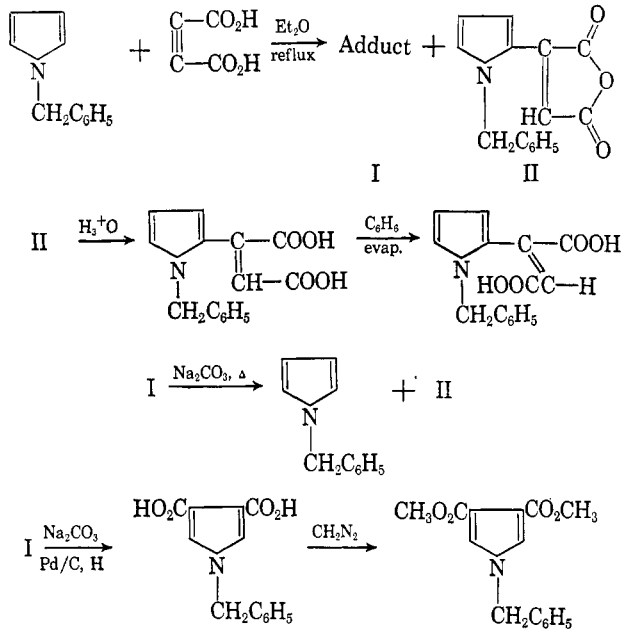
Pyrrole, α-carboxy, β-substituted, and β,β′-disubstituted pyrroles were converted to the corresponding α,α′-dicarboxylic acids by treatment with carbon dioxide under anhydrous conditions at elevated temperatures and pressures (372).



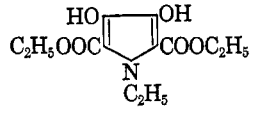
The following unusual reaction yielded a 2-pyrrole carboxamide (267).



N-Benzylpyrrole with acetylenedicarboxylic acid afforded some interesting adducts (272).



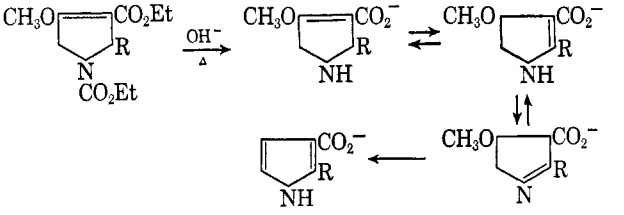
2-Benzylamino-3-(2′-pyrrole)-acrylic acids were obtained from the azlactone of 2-pyrrolecarboxaldehyde (191). Hydroxypyrrole carboxylates of the following structure have been patented as antistain agents for color photography (17).



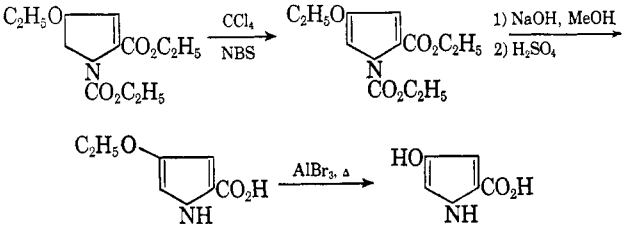
The reaction of pyrrole with propiolactone were described previously (180).

Pyrrole carboxylic acids were also obtained from oxidative attack on side chains attached to the pyrrole nucleus. Such groups can be, *e.g.*, polyhydroxy (164) or aldehyde (316, 484) or methyl (318). Silver nitrate, potassium permanganate, and hydrogen peroxide were used as oxidation agents.

When 3-carbethoxy-4-methoxy-δ^3-pyrrolines were heated with alkali, elimination of the methoxyl group occurred and pyrrole carboxylic acids were formed (342). A reasonable path for this reaction is as follows.

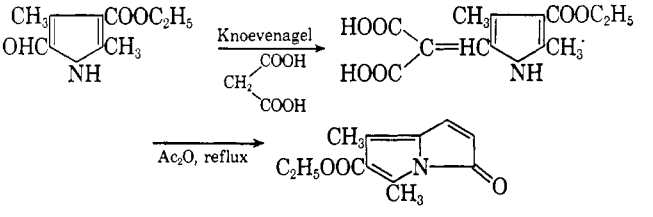


Another route to hydroxypyrrole carboxylic acids goes *via* δ^2-pyrrolines (240).



α- and β-pyrrole carboxylic acids were obtained synthetically from hydroxyaminopyridines through ring contraction (410).

A pyrrole acrylic lactam was synthesized in connection with the possibility of an "azapentalene" structure (6). The first step involved a Knoevenagel condensation *via* a nucleophilic addition of the malonic carbanion to the unsaturated carbon atom of the aldehyde, followed by dehydration.



It appeared that this compound had no extra stability attributable to "azapentalene" resonance, as evidenced by chemical and spectral data.

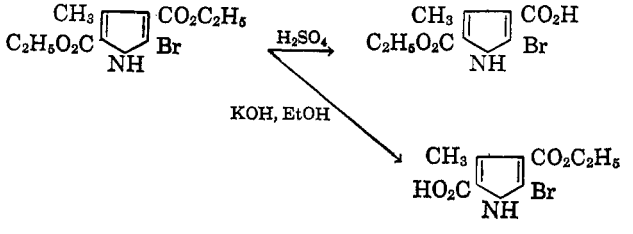
Acrylic acid derivatives added to the pyrrole nucleus in the presence of boron trifluoride etherate yielded α- and α′-pyrrole propionic acid derivatives. Aluminum chloride can also be used successfully for this reaction,

but boron trifluoride is superior due to its solubility in organic media. A pyrrolenine intermediate with activated hydrogen atoms is postulated. As expected, the β-position is less reactive than the α-position.

Acrylamide adds to the pyrrole nucleus although with less ease than the esters and the free acid (445).

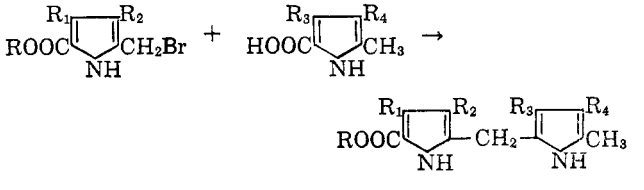
Various reactions of pyrrole carboxylic acids, such as esterification (121), alkoxide with lithium aluminum hydride of esters and amides to the corresponding carbinols and amines (121, 271, 272, 462), are to be found in the literature. In some instances, lithium aluminum hydride reduction yielded the corresponding alkyl substituent (428); thus 3,5-dimethyl-4-acetylpyrrole was reduced to the corresponding ethyl derivative (452). The catalytic transformation of benzyl- and *t*-butylpyrrole carboxylic esters to the free acids has already been mentioned.

Selective hydrolysis of carboxylic ester groups as related to their position has been used extensively (228, 313, 316, 413).



Amino-1-substituted pyrrole carboxylic acids and several of their derivatives on the amino group were prepared from the corresponding nitropyrrole carboxylic esters (469).

Unsymmetrical pyrromethanes were prepared from 5-bromomethylpyrroles and pyrrole-2-carboxylic acids (182).

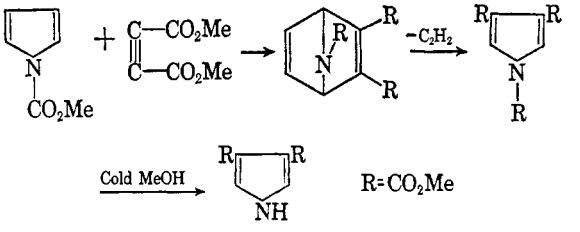


Carboxylic acids lose carbon dioxide at elevated temperatures (200°) or even in boiling water (105).

Carboxyl ester groups hinder decarboxylation in the pyrrole series. Selective freeing of ring positions on tricarboxylpyrrole derivatives can be attained by replacement of the first carboxyl group with bromine followed by selective degradations of the resulting dicarboxy derivatives (108).

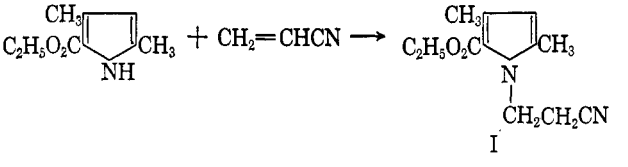
It was shown that selective degradation of pyrrole carboxylic esters can be achieved with sulfuric acid. The formation of an acyl cation preferentially in the α-position has been postulated (109).

Although the dissimilarity of the diene system of pyrrole to that of butadiene had been demonstrated by Diels and Alder (they showed that the dienophile, maleic anhydride, does not add to pyrrole but gives substitution reactions instead), a reaction was reported between acetylenedicarboxylic acid dimethyl ester and N-carboxymethylpyrrole at room temperature. The product, 1,3,4-tricarbomethoxypyrrole, was saponified and decarboxylated to the 3,4-dicarboxylic acid (1).

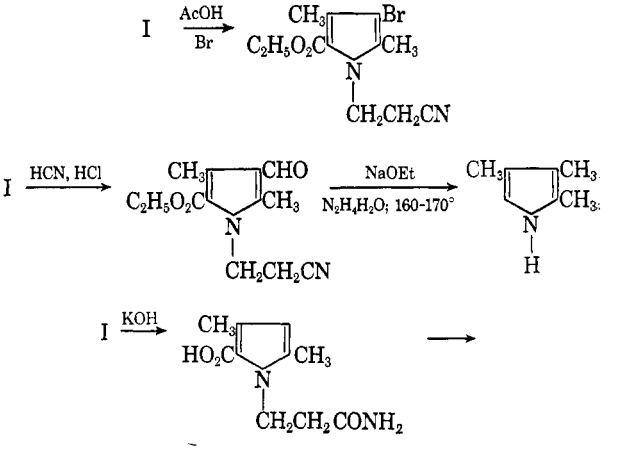


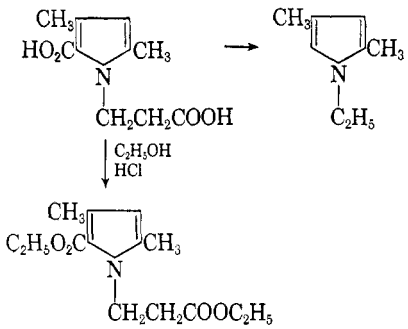
The synthesis and study of the chemical and chromatographic behavior of C-ethylpyrrolecarboxylic acid was carried out, and various novel derivatives of β-ethylpyrrole were synthesized in this conjunction; their synthesis followed well trodden paths involving selective hydrolysis of esters and decarboxylation (316).

Various nitriles from the pyrrole series have been described. The cyanoethylation of a number of 2,4,5-trisubstituted pyrroles was found to proceed smoothly in the presence of sodium ethoxide to yield 3-(1-pyrryl)-propionitriles.

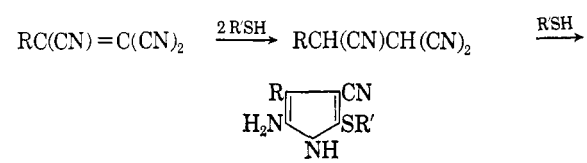


An interesting variety of reactions was carried out on this intermediate.

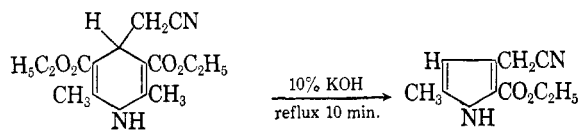




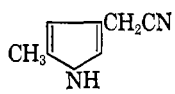
Tricyanovinyl compounds reacted readily with mercaptans, but the corresponding α-thiol derivatives were not obtained. Instead, the product isolated was a substituted pyrrole. Apparently, the reduction of the double bond was the first step of the reaction (366).



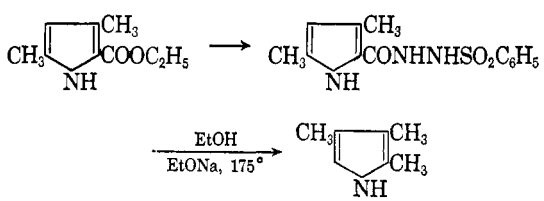
An improved procedure for the preparation of certain cyanomethylpyrroles from pyridine derivatives by ring contraction was devised.



Prolonged refluxing in 10% alkali simultaneously hydrolyzed and decarboxylated the pyrrole ester (112) to yield



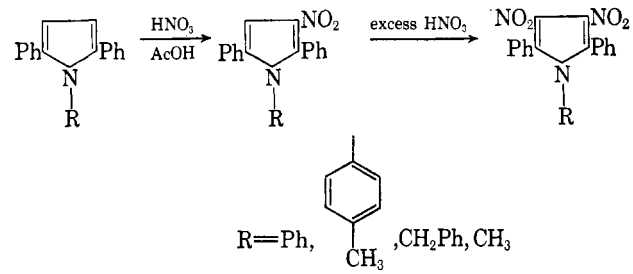
An α-pyrrole carboxylate can be directly reduced to the corresponding methyl derivative by conversion to the phenylsulfohydrazide in a modified McFadyen–Stevens reaction (36).



XIII. PREPARATION OF NITROPYRROLES AND NITROSOPYRROLES

The classical method of nitration, *i.e.*, the use of mixed sulfuric and nitric acids, continues to be the principal route to mono- and dinitropyrroles; however, in recent years there has been a trend toward the substitution of acetic anhydride for sulfuric acid (21, 297, 360). For instance, 2-propionylpyrrole was nitrated in acetic anhydride at $-10°$ in the presence of fuming nitric acid (d = 1.5) (161). Similarly 1,2,5-triphenylpyrrole was nitrated in acetic acid with nitric acid (d = 1.4) (166).

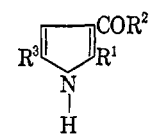
A study of nitration of 1,2,5-trisubstituted pyrroles showed that the mononitro derivative was obtained when an equivalent of nitric acid in acetic acid was employed, but an excess of nitric acid yielded the dinitro compound (397).



The structures of 4-nitro- and 5-nitro-2-propionylpyrroles were proved. Apparently nitration occurs preferentially in the 4-rather than in the 5-position. Since the 4-nitro derivative is less acidic than the 5-nitro derivative, separation was achieved by extraction at different pH values. The difference in acidity of the two nitropyrroles is assigned to the promixity of the nitro group to the NH of the pyrrole ring: the closer the nitro group, the more acidic the compound (162). Both these pyrroles fail to give the Ehrlich reaction given by the parent compound; in this they behave similarly to the corresponding acetylpyrroles. The practical identity of the ultraviolet spectra of 4-nitro-2-propionylpyrrole and 4-nitro-2-acetylpyrrole, the structure of which was proven unequivocally, identified the structure of the former.

The behavior of 1-methylpyrrole during nitration was investigated and it was noted that the substituent has a lesser α-directing effect as compared to pyrrole itself (21).

A recent investigation of Sprio and Fabra (399) showed that amyl nitrite could be employed as the nitrating agent in pyrrole derivatives of the following type to give the 4-nitro derivative.

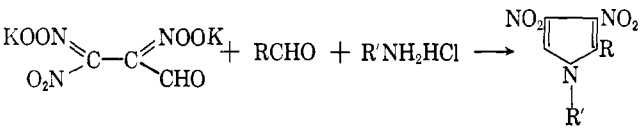


Several derivatives of pyrrole carboxylic acids were prepared, especially 1-lower alkyl-4-nitro-2-carbonyl pyrroles or polyamides therefrom, showing antibacterial activity (470).

2-Cyano- and 2-cyano-1-methylpyrrole were nitrated to the 4- and 5-nitro derivatives. The yields of products suggests that the cyano group is less strongly *meta*

directing (toward the 4-position) during nitration in the pyrrole series than in the benzene ring.

A novel and interesting synthesis of dinitropyrroles by cyclization and not by direct nitration was devised by Novikov, *et al.* (321).



(I) R = H, R′ = $CH_2C_6H_5$
(II) R = H, R′ = CH_2CH_2OH
(III) R = H, R′ = $CH_2COOC_2H_5$
(IV) R = R′ = CH_3
(V) R = C_2H_5, R′ = CH_3

Not all amines can be used for this reaction; for instance, ammonia, hydrazine, and ethylenediamine did not react, and aniline gave two substances of unidentified structure: $C_{16}H_{13}N_3O_2$ and $C_{13}H_{11}N_3O_2$.

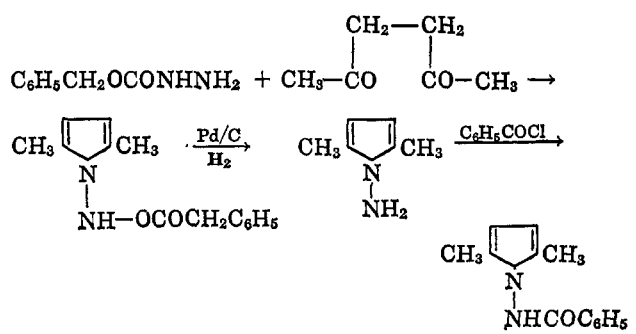
4- And 5-nitropyrrolyl-2-aldehydes were methylated on the nitrogen with sodium ethoxide and dimethyl sulfate (153).

Nitrosation is still conducted through the employment of nitrous acid prepared *in situ* from sodium nitrite and aqueous sulfuric acid (111, 398). We believe that some attention should be given to the use of nitrosyl chloride in the preparation of nitrosopyrrole derivatives.

2,5-Diphenylpyrrole was nitrosated at 3- with isoamylnitrite in the presence of sodium ethoxide (236).

XIV. PREPARATION OF AMINOPYRROLES

Pyrroles with an amino group attached onto the nitrogen directly or by the intermediate of an alkyl or aryl group can be obtained *via* appropriate cyclization reactions. Thus, carbobenzyloxyhydrazine can react with 2,5-hexanedione and the resulting carbobenzyloxyaminopyrrole can be reduced catalytically to yield the 2,5-dimethyl-1-aminopyrrole (325).



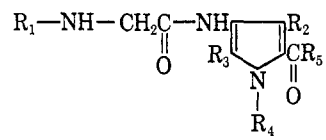
Amino derivatives of 2,5-dimethylpyrrole were prepared from primary dialkyldiamines such as N,N-diethyl-1,3-diaminopropane. It was found that when the primary amino group was attached to a secondary carbon atom the reaction was sluggish and amino groups attached to a tertiary carbon atom failed to react. Diprimary amines or primary aminohydroxy compounds reacted with ease, and isonicotinic hydrazide could also be used in the Knorr–Paal synthesis and afforded 1-isonicotinylamino-2,5-dimethylpyrrole and higher homologs (66). Reduction of 2,5-diphenyl-3-nitrosopyrrole with hydrogen and Raney nickel afforded the corresponding amino compound (236).

Reaction of potassium pyrrole with chloroacetonitrile, α-bromopropionitrile, and β-chloropropionitrile gave the appropriate nitriles; upon reduction, they, in turn, afforded the corresponding amines. Secondary amines were obtained *via* formylation followed by reduction. Tertiary amines were conveniently prepared by alkylating pyrrole with 2-dialkylamino alkyl chlorides (197). 1-Pyrrolepropionitrile can also be prepared by cyanoethylation of the pyrrole nucleus (148).

Mono- and dialkylaminomethyl pyrroles are readily accessible through the Mannich reaction. Acylations of 2-(2-aminoethyl)-pyrrole followed by reduction with lithium aluminum hydride yielded, successively, secondary and tertiary amines (197).

Preparation of 2-(2-aminoethyl)-pyrrole in fair to good yields has been achieved by reduction of 2-pyrroleacetamide with lithium aluminum hydride in ether or tetrahydrofuran (246).

Pyrroles of the general structure



where

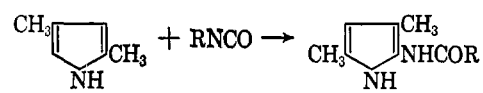
R_1 = H or amidino
R_2, R_3, R_4 = H or lower alkyls
R_5 = alkoxy, amino, -carbonyl, or lower alkylamino

where prepared from the corresponding aminopyrroles and mixed carbonic anhydrides resulting from the reaction of an alkyl carbonate and carbobenzyloxyglycine in the presence of triethylamine.

The carbobenzyloxy radical could be recovered then either by anhydrous hydrogen bromide in glacial acetic acid or by catalytic hydrogenation over palladium (18).

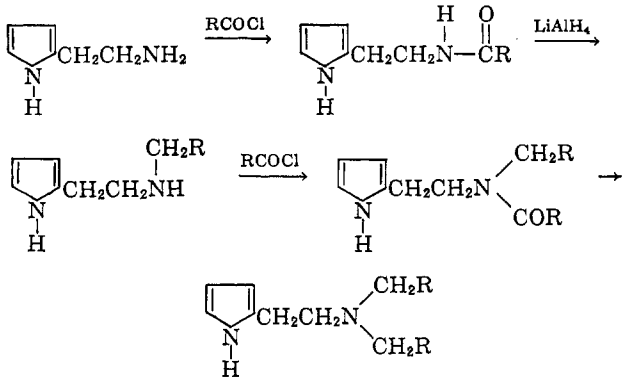
Catalytic reduction of nitropyrroles over palladium on carbon proceeded smoothly, and various derivatives on the amino group including sulfonamides, ureas, thioureas, amidines, etc., were prepared (369, 470).

The reaction of pyrroles with esters of isocyanic acid afforded carbamates (449).

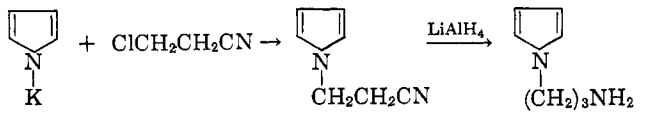


Pyrrole alkylamines were acylated and then reduced with lithium aluminum hydride to furnish a simple route to secondary pyrrole alkylamines. Reacylation

and similar reduction of these secondary amines resulted in tertiary amines (197).



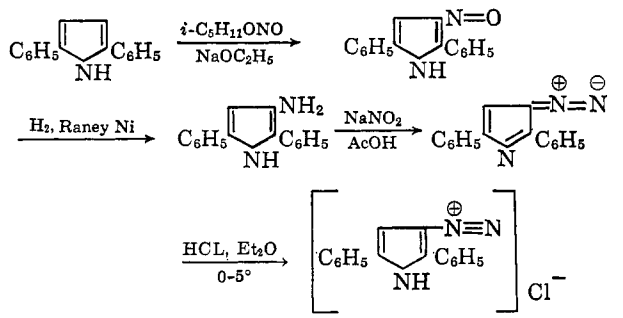
Reaction of chloropropionitrile and analogous haloalkylnitriles with potassium pyrrole yielded the N-alkyl-γ-nitrile, and upon reduction, the corresponding amine was produced (225).



XV. PREPARATION OF AZOPYRROLES

Azo coupling is the most accessible method for the synthesis of azo compounds. Heterocyclic compounds containing nitrogen afforded azo derivatives, the stability of which is related to the number of heterocyclic nitrogens present. Thus, azotetrazole could not be isolated (420), but azotriazoles could be prepared (422). Azopyrroles are stable compounds of easy access. Chichibabin's method of aminating heterocycles fails with pyrroles (76, 323).

3-Amino-2,5-diphenylpyrrole is prepared according to the following scheme and upon reaction with nitrous acid in acetic acid gives diazo-2,5-diphenylpyrrole (25), a resonance hybrid, which when treated with hydrochloric acid in ether at 0–5° gives 2,5-diphenylpyrrole-3-diazonium chloride (236).



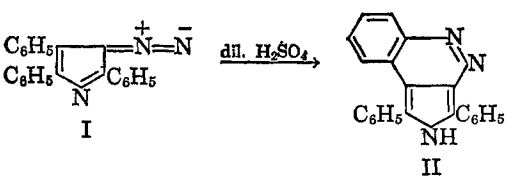
It was found that 2,5-diphenylpyrrole, 1-phenylpyrrole, and 1-methylpyrrole couple with *p*-sulfobenzenediazonium chloride under very mild conditions in inert solvents. The *p*-pyrroleazobenzenesulfonic acids obtained are red to blue solids undergoing color changes dependent on the pH when dissolved in dimethylformamide. They were proposed as indicators in alkalimetric titrations (236). The same conditions used with 2,5-diphenyl-3-diazonium chloride over 36 hr. gave satisfactory results.

Diazotized aromatic amines couple with pyrrole. This reaction was discovered by Fischer and Hepp (147). Numerous azo dyes containing the pyrrole ring have been prepared subsequently. As with phenols, the tendency to couple was so marked that the reaction takes place in acidic medium. With pyrrole itself, a mono azo dye is formed in the presence of acid and a bis azo dye is formed in basic media.

It has been shown that the α-position is more reactive to coupling then the β-position. However, the α azo dyes are less stable to light and air than the corresponding β azo dyes.

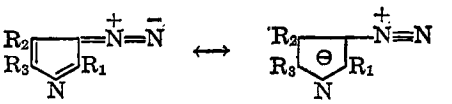
The coupling reaction is recommended for the separation and characterization of a mixture of pyrroles. Thus, tetrasubstituted pyrroles will not generally couple. β-Pyrryl azo dyes can be readily isolated from the coupling mixture by crystalization, and α pyrryl azo dyes can be recognized by the peculiar spot-test reaction with diazotized *p*-nitroaniline. In this test, the azo dye solution is treated with carbonate and placed on a filter paper on which diazotized *p*-nitroaniline is subsequently added. If an α-azo dye is present, the filter rim becomes purple and then the whole surface turns to an intense blue shade. β-Pyrryl azo dyes do not give this reaction. The reliability of this test is, however, questionable (37, 236).

A useful method to prepare pyrrylamines is the catalytic reduction of pyrryl azo dyes in the presence of palladium (149). The diazotization and coupling of pyrrylamines has yielded some interesting results. For instance, 2,4,5-triphenyl-3-diazopyrrolidine (I) is a stable compound. However, upon heating with dilute sulfuric acid for a prolonged period, it isomerizes to a substance, probably II (26, 27)



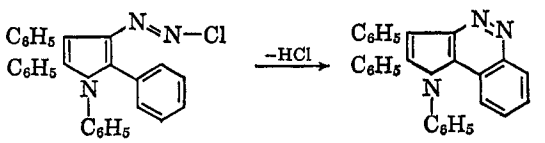
A most conveniently prepared diazonium salt is that from 2,4-dimethyl-2-amino-5-carbethoxypyrrole, which readily couples with phenols (151).

3-Diazopyrroles have received some attention. They can be best represented by the following resonating formula

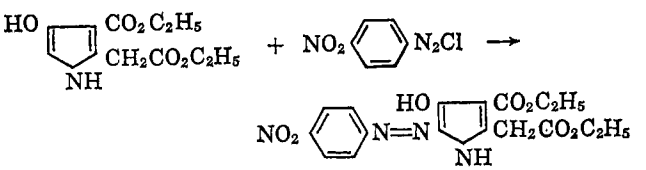


Three different methods have been used to synthesize 3-diazopyrrole, including the normal diazotization of 3-aminopyrrole (10, 166, 414), the direct introduction of the diazo group with nitrous acid, and the reaction of nitrosopyrrole with nitric oxide (414). The last reaction is a variation of the second reaction insofar as the nitroso compound which is first formed is isolated and then reacted with nitric oxide. These two reactions are successful only if the α-positions are blocked; attempts to prepare 2-diazopyrroles were unsuccessful. 3-Diazopyrrole salts do not couple even with resorcinol. However, azo dyes can be prepared by adding diazopyrrole to fused β-naphthol or by refluxing a neutral solution of β-naphthol with the diazo compound. 3-Azopyrroles exhibit a strong infrared band at 2020–2150 cm.$^{-1}$.

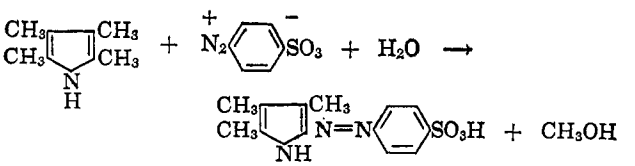
The comportment to diazotation of 3-amino-1,2,5-triphenylpyrrole was studied. The chloride of this diazopyrrole presents the same reactive characteristics as were observed previously for the pyrroles with the NH function free, or blocked, with regard to the instability, oxidative power, loss of nitrogen, and lack of coupling tendency. Unlike a diazonium salt, it failed to couple and lost a hydracid molecule with alkali metal hydroxides and ammonia to give a red substance for which the following structure was suggested (10, 166).



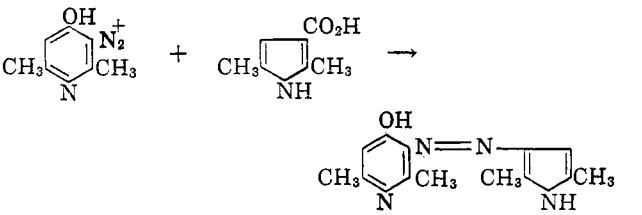
β-Hydroxypyrroles couple with *p*-nitrobenzenediazonium chloride in acetic medium to give the corresponding azo dyes (448).



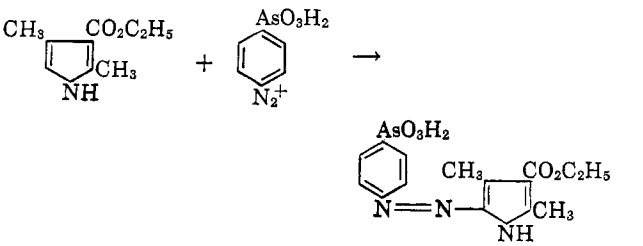
Tetramethylpyrrole couples with diazonium salts. Up to now this reaction was useful for a specific conversion of pyrroles with free methine groups; it was known that only carboxy groups could be thus eliminated. It was found, however, that 2,3,4,5-tetramethylpyrrole couples with diazonium salts under simultaneous elimination of a methyl group to yield the same diazo compound as 2,3,4-trimethylpyrrole (429).



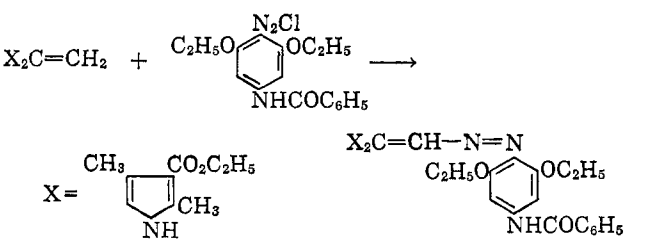
An instance of coupling of a diazonium salt with simultaneous decarboxylation under the influence of irradiation is given below (409).



Diazoarsanilic acid and 2-hydroxyarsanilic acids were coupled with pyrroles to yield arsenic-containing azo pyrroles (302).



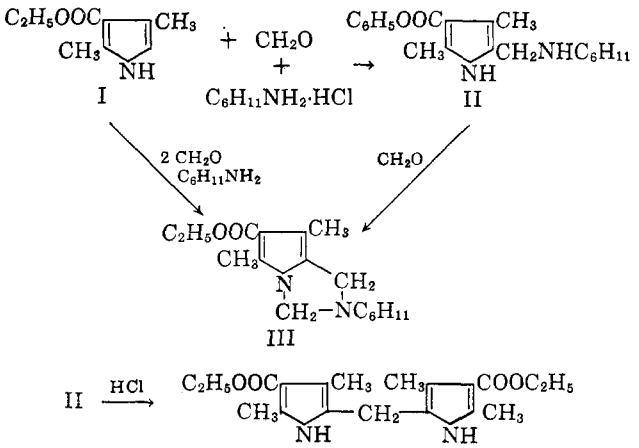
Dipyrryl ethylenes react with diazonium salts to yield blue azo dyes. They show greater reactivity than tripyrryl ethylenes, which, besides coupling reactions, do not undergo further substitution (451).



XVI. MANNICH REACTIONS

The Mannich reaction can be used to introduce a substituent on a pyrrole ring directly (241); thus the reaction of formaldehyde with primary and secondary amines with pyrroles at the α- and β-positions was studied (182). Formaldehyde is used as a substrate in a two-stage condensation reaction. It reacts first with an α-active methylene in an acid-catalyzed reaction. The resulting unsaturated intermediate reacts with the amine by conjugate addition. Interest in Mannich bases formed from pyrrole was stimulated by the work of Snyder and Smith (388, 389) on the reactions of gramine methiodide with the sodium derivative of acetaminomalonic ester and potassium silver cyanide (61).

Pyrrole reacted smoothly with equimolar proportions of formaldehyde and cyclohexylamine hydrochloride to yield 2-cyclohexylaminomethylpyrrole hydrochloride. The corresponding crystalline free base was readily obtained (61).



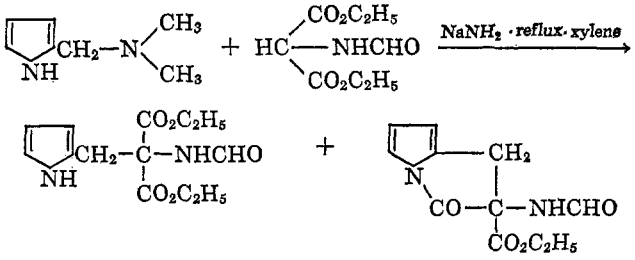
Use of 2 moles of formaldehyde resulted in a bicyclic 1H-imidazo-(1,5-a)-pyrrole (III). Formaldehyde and the hydrochloride of (II) yielded a dipyrryl methane in refluxing ethanol (61). 2-(N-Substituted)-aminomethylpyrroles produced from pyrrole formaldehyde and various heterocyclic (196) and aliphatic (321) bases have been reported. Thus, 2,5-dimethylpyrrole forms a 3,4-bis-(N-piperidinomethyl) derivative. On the other hand, 2-methylaminomethyl- and 2-ethylaminomethylpyrroles were obtained in 15 and 27% yields, respectively (61).

The Mannich bases formed from α-hydrogen atoms of pyrrole and substituted pyrroles resembled gramine in their ability to alkylate a variety of substances containing active halogen and became valuable intermediates in the synthesis of new pyrrole derivatives (53, 187). Mannich bases of 2,5-substituted pyrroles are easily prepared. In contrast to the indole series, where the order of reactivity in the Mannich reaction is $\beta > N > \alpha$, the order of substitution in the pyrrole series is $\alpha > \beta$; apparently, the nitrogen is not substituted at all.

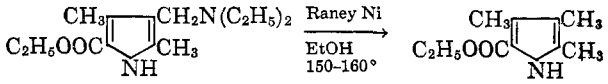
2,5-Dimethyl-3-dimethylaminomethylpyrrole was used for the alkylation of diethylacetamido malonate and diethyl malonate in refluxing toluene and in the presence of catalytic amounts of sodium hydroxide; however, the corresponding 1-methyl and 1-phenyl-2,5-dimethyl Mannich bases could not be brought into reaction.

1,2,5-Trimethylpyrrole and 1-phenyl-2,5-dimethylpyrrole form mono and bis Mannich bases at somewhat lower yields as compared with the corresponding N-unsubstituted pyrroles. The suitability of the β-substituted pyrrole Mannich bases for alkylation reactions was explored. In contrast to the nitrogen-substituted bases, which are able to react only *via* a substitution mechanism, the nitrogen-unsubstituted compounds react by elimination, addition, or substitution mechanism (199).

In base-catalyzed condensations of 2-dialkylaminomethylpyrroles with acylaminomalonic esters, mixtures of 2-pyrrylmethyl acylaminomalonic esters and the corresponding lactams (involving the N of the ring) were formed (245).

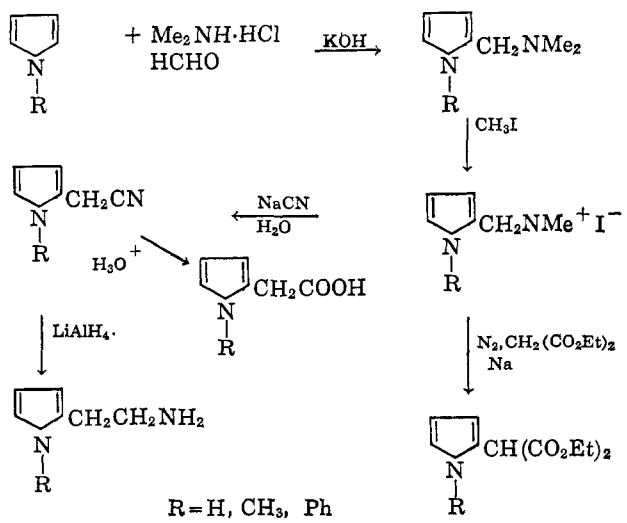


Mannich bases of the pyrrole series were catalytically reduced to the corresponding methylpyrroles (457).



The reaction of pyrrole with formalin, ammonium chloride, and sodium hydrogen sulfite offered an extremely simple method of preparing the 2-aminomethyl derivative (369).

3-Hydroxymethylindole could be considered as an intermediate in a Mannich reaction, and as such could be reacted with amines. Similarly, 2-hydroxymethylpyrrole afforded a Mannich base with piperidine; 1-methyl-2-hydroxymethylpyrrole, however, could not be brought to react with this base. These results are in accord with observations made on the relative reactivities of gramine and 1-methylgramine toward nucleophiles. It has been postulated that gramine may suffer amine elimination followed by a Michael type addition of the nucleophile (*e.g.*, NaCN), in contrast to 1-methylgramine, which cannot undergo this type of base-catalyzed amine elimination. The same hypothesis could be used to explain the reactivity of 2-hydroxypyrrole *via* a mechanism not permitted to 1-methyl-2-hydroxymethylpyrrole. It was mentioned elsewhere that the failure of these pyrrole alcohols to



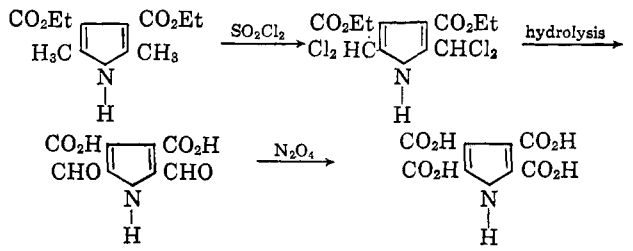
behave as primary alcohols could be accounted by the ready formation of resonance-stabilized cations (383).

Mannich bases were prepared as intermediates in the preparation of pyrrole nitriles, their corresponding acids (198), and pyrrole ethylamines (192). These bases also reacted with malonic ester to give pyrrolemalonic acids (198, 303).

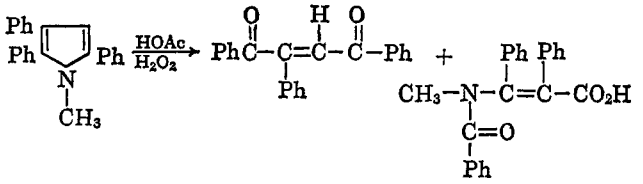
Mannich bases were formed when secondary amines such as piperidine, morpholine, and pyrolidine entered into, rather than catalyzed, the condensation of 2-pyrrolealdehyde with acrylonitrile (194).

XVII. OXIDATION

With the exception of the preparation of the novel compound, pyrrole-2,3,4,5-tetracarboxylic acid from the corresponding 2,5-dimethyl-3,4-dicarbethoxypyrrole as outlined below, most of the studies were concerned with the behavior of the pyrrole ring and particularly that of various polyphenylpyrroles (317).

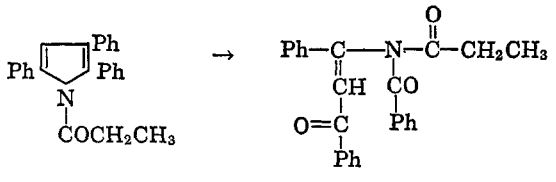


Peroxide oxidation in acetic acid converted N-methyl-2,4,5-triphenylpyrrole to α,β-dibenzoylstyrene and the corresponding amido acid (401).

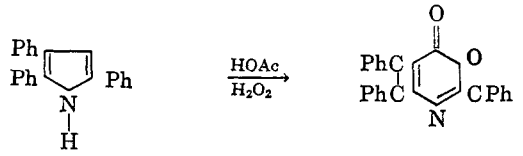


Further oxidation of polyphenyl pyrroles with potassium dichromate gave *cis*-dibenzoylstyrene in every case (400).

2,4,5-Triphenyl-3-nitropyrrole was not attacked by perchromic acid; however, hydrogen peroxide–acetic acid mixture yielded some benzaldehyde and benzoic acid along with unreacted triphenylnitropyrrole. Nitric acid oxidation of 1,2,4,5-tetraphenylpyrrole gave the 3-nitro derivative and 1,2,4-triphenyl-1,4-butadiene (7). Upon potassium dichromate oxidation, the ring of a triphenylpyrrole was opened between C-2 and C-3 to give a ketone (8).



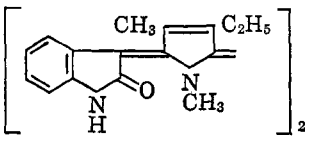
When 2,4,5-triphenylpyrrole was treated with hydrogen peroxide in acetic acid a lactone resulted from ring enlargement (395).



The photooxidation of 2,3,4,5-tetraphenylpyrrole in methanolic solution was studied and its decomposition products identified (474).

The oxidation of tri-α-pyrryl methanes with potassium permanganate yielded the corresponding dipyrryl ketones. Apparently, the other pyrrole nucleus was eliminated (75).

Polyphenylpyrrole oxidation studies were carried out, generally speaking, to aid in the structure determination of the complex pyrroles such as pyrrole blue, cryptopyrrole blue, and the melanins. According to such investigations, it seems that cryptopyrrole blue can be assigned the formula



The formation of this compound could involve the migration of a methyl group from the α-position to the nitrogen atom; however, this was not confirmed by experimental data. It was demonstrated that "pyrrole blue" has an indophenenic structure, and the experimental results of the oxidation were explained by the fact the pyrrole nucleus becomes stabilized in the pyrrolenic form (335).

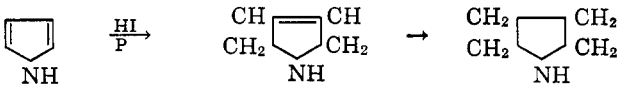
Permanganate oxidation of melanins (231) gave an acid similar to the pyrrole-2,3,4-tricarboxylic acid obtained by a similar method from violacein (368).

XVIII. REDUCTION

The reduced pyrrole ring is found in several naturally occurring pigments, and it is also widely distributed in alkaloidal systems. Since the various naturally occurring substances with reduced pyrrole rings are beyond the scope of this article, only the relationships between pyrrole and its reduction derivatives will be dealt with.

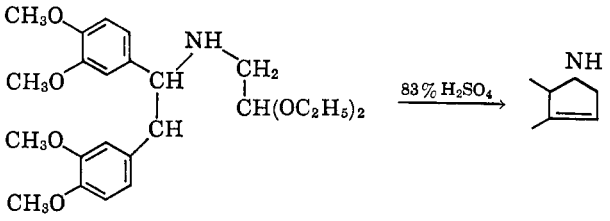
A. PYRROLINES

Unlike pyrrole, its reduction derivatives are basic and react to give salts with acids which can be isolated. Theoretically the reduction of the pyrrole ring can form either δ^2-pyrroline or δ^3-pyrroline; however, only the latter results from such reaction.



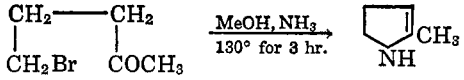
This method, due to Ciamician, *et al.* (17, 90, 92, 231, 249), affords mainly pyrrolidine and brings about partial ring opening; such cleavage products as *n*-butylamine, ammonia, and butane are obtained. Zinc and hydrochloric acid give a better yield of pyrroline (431). Ozonolysis followed by oxidation with hydrogen peroxide affords iminodiacetic acid; this established the structure of δ^3-pyrroline.

Although δ^3-pyrrolines are usually obtained by direct reduction of the pyrrole ring, cyclization reactions using acetals can also form these compounds. Irradiation of *n*-butyl and *n*-octyl azide yielded pyrrolidine and 2-butylpyrrolidine. The results could be explained by the assumption that photolysis of azides affords "activated" nitrenes R–$\ddot{N}$:; when conformation and constitution permit, these can rearrange to pyrrolidines (287).

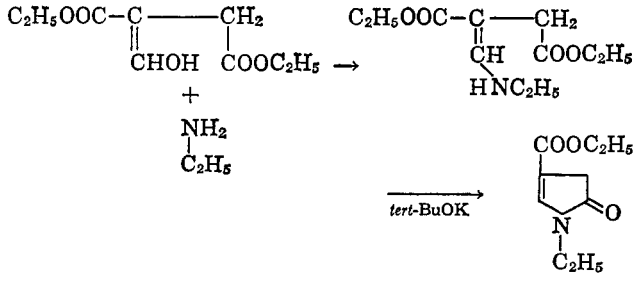


δ^2-Pyrrolines are obtained by ring closure rather than by hydrogenation of pyrroles (205), although cases where direct reduction affords δ^2-pyrrolines are known (71). Since the reduction of the pyrrole ring to the pyrrolinic state can proceed in two different ways, it is important that the structures of the pyrrolines obtained should be established by independent synthesis.

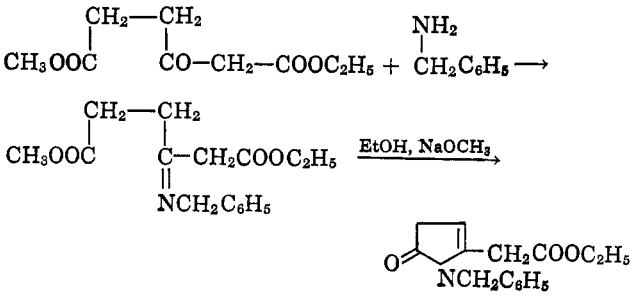
1-Bromo-4-pentanone in dry methanol saturated with ammonia formed 2-methyl-δ^2-pyrroline in good yield (460).



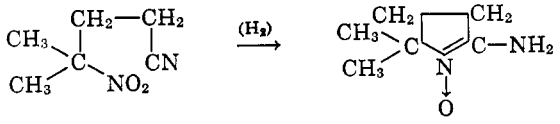
1-Ethyl-4-carbethoxy-δ^2-pyrroline-2-one could be obtained from diethyl formylsuccinate and ethylamine in high yields (173).



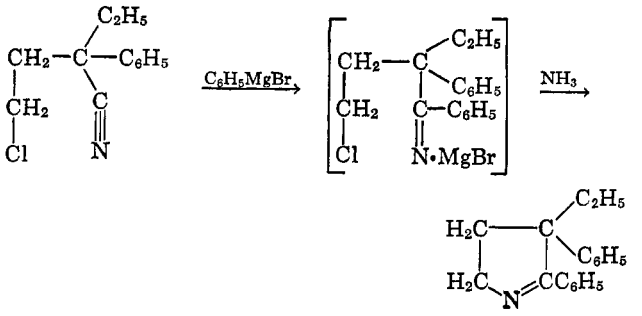
δ^2-Pyrroline-2-ones were obtained *via* azomethines (35).



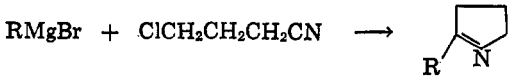
δ^1-Pyrrolines can be obtained *via* cyclization reactions. Thus, reduction of 3-nitro-3-methyl-*n*-butylcyanide in methanol with Raney nickel yielded 5-amino-2,2-diethyl-δ^1-pyrroline N-oxide (58).



2,3-Diphenyl-3-ethyl-δ^1-pyrroline was obtained in high yield from the action of phenylmagnesium bromide on γ-chloro-α-ethylphenylbutyronitrile and treatment of the resulting adduct with ammonia (304).

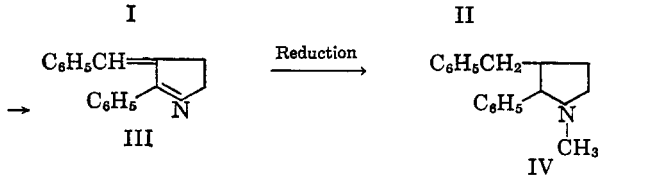


Another method, which has, however, the disadvantage of low yields, involved the reaction of a Grignard reagent on γ-chlorobutyronitrile to give a δ^1-pyrroline (60, 94, 257).



Grignard reagents reacted with 2-pyrrolidone to produce pyrrolines in low yields (60, 259).

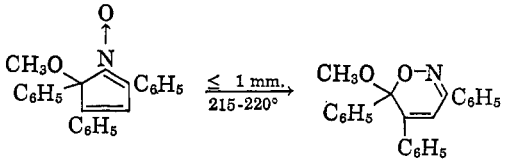
Acyl derivatives of 4-phenyl-but-3-enylamine gave pyrrolidines in good yield on treatment with phosphoryl chloride. Pyridine derivatives were not obtained.



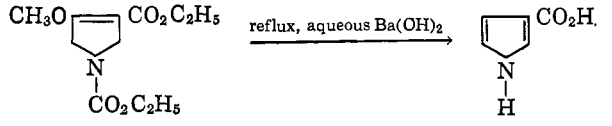
The structure of δ^1-2-phenyl-3-benzalpyrroline could be proved by exhaustive methylation. The

catalytic reduction of the methiodide of III afforded the corresponding N-methyl tetrahydrobase (406).

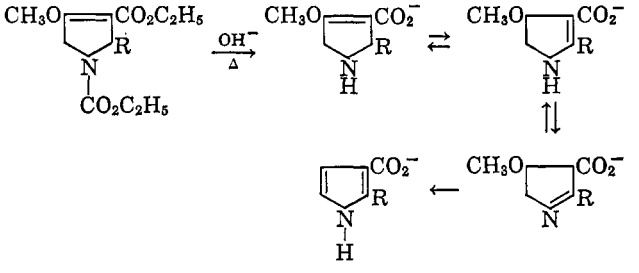
An interesting ring enlargement reaction involved the vacuum distillation of 2,3,5-triphenyl-2-methoxy-2(H)-pyrrolenine 1-oxide, whereupon 6-methoxy-3,5,6-triphenyl-1,2-oxazine results (43).



When 3-carbethoxy-4-methoxy-4-δ^3-pyrrolines are heated under reflux with alkali, elimination of the methoxyl group occurs and pyrrole-3-carboxylic acids are formed (342).



Possible mechanism

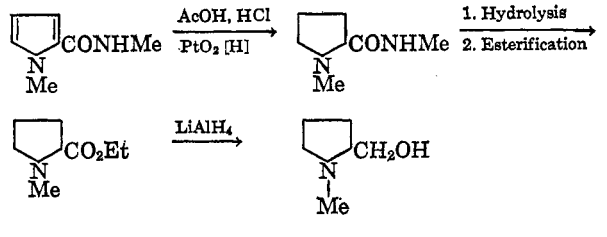


Increased acidity of the hydrogen α to the carboxyl facilitates elimination of β-methoxyl group.

XIX. PREPARATION OF PYRROLIDINES

Pyrrolidines are strong bases possessing ammoniacal odors and easily yielding salts which serve for their identification. They can be prepared either by reduction of pyrroles and pyrrolines or by ring closure.

Pyrrolidines can be prepared by reduction of pyrroles with phosphorus and hydrogen iodide or, most conveniently *via* catalytic hydrogenation. For instance, 1-methyl-2-pyrrolidylcarbinol has been prepared *via* the route (260)

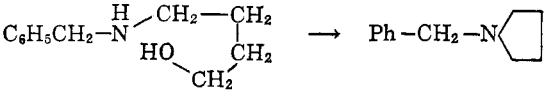


1,2,4-Trimethylpyrrolidine was obtained *via* catalytic hydrogenation with Raney nickel of the sodium salt of the 1,2,4-trimethyl-2,5-dicarboxypyrrole followed by decarboxylation (324).

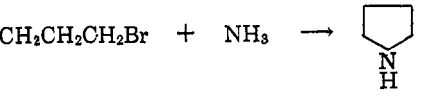
Reduction of N-methylpyrrole afforded a substance $C_{10}H_{18}N_2$, the structure of which has not been determined (261).

Pyrrolines can be reduced to pyrrolidines by low-pressure hydrogenation with Raney nickel. Lithium aluminum hydride is also capable of performing this reduction. The pyrrolidines can be converted to the N-methyl derivatives by the formaldehyde–formic acid method (208). They have also been prepared by electrolytic reduction of substituted succinamides.

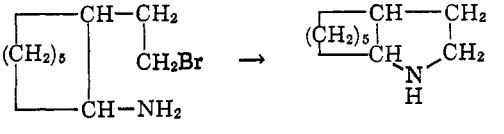
Cylization reactions offer convenient routes to pyrrolidines. Ring closures involving an amine nitrogen are most common. The following examples illustrate the varied conditions under which they are applicable. N-benzylpyrrolidine was formed in 61% yield when N-benzyl-4-hydroxybutylamine was heated in methyl trichloroacetate (254).



A very convenient method for obtaining certain pyrrolidines involves reaction of the commercially available 1,4-dibromobutane or 1,4-dibromopentane with ammonia or a primary amine, according to the scheme (127).

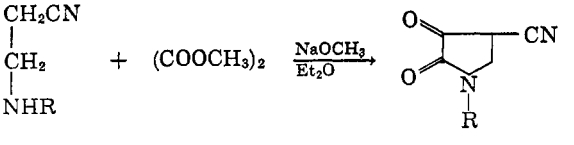


Treatment of two diastereoisomeric 1-(β-bromoethyl)-2-aminocycloheptanes with caustic gave the corresponding cycloheptane-2,3-pyrrolidines in high yields (337).



More recently 1,4-dichlorobutane has been used with long-chain primary amines to give 1-alkylpyrrolidines and 1,1-dialkylpyrrolidium chlorides (129).

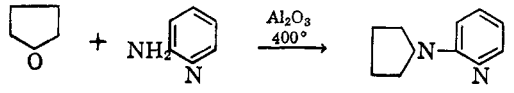
The synthesis of 2,3-dioxopyrrolidines and derivatives *via* condensation of oxalic esters with β-aminopropionic esters was first reported by Southwick, *et al.* (392, 394). Recently, N-substituted β-aminopropionitrile was condensed with diethyloxalate to yield N-substituted 4-cyano-2,3-dioxopyrrolidine (2).



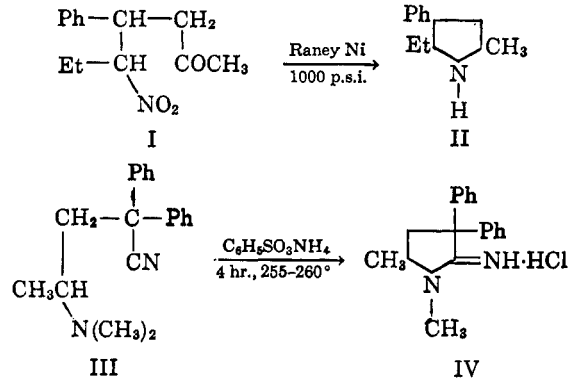
The conversion of dibutylamine *via* the corresponding chloramine to N-butylpyrrolidine offers a general

procedure for the preparation of N-substituted pyrrolidines from N-butylalkylamines (98).

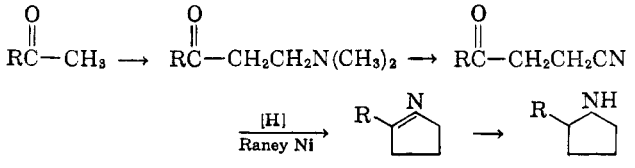
The reaction of tetrahydrofuran with 2-aminopyridine to give N-(2-pyridyl)-pyrrolidine (495) can be extended to include the aminoquinolines (487).



In addition to the ring syntheses involving an amine moiety, three rather interesting procedures have been described. The catalytic hydrogenation of the γ-nitroketone (I) gave pyrrolidine (II) in high yield (230), and upon treatment of 4-dimethylamino-2,2-diphenylvaleronitrile (III) with ammonium benzenesulfonate, 2-imino-1,5-dimethyl-3,3-diphenylpyrrolidinium chloride (IV) was obtained in 50% yield (114).



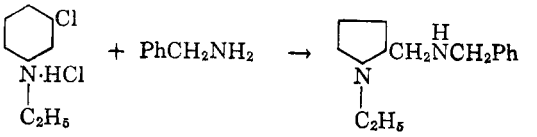
Preparation of pyrrolines and pyrrolidines can be attained by a method developed by Rupe and Gisiger (358) and Knott (232). This method depends upon the reductive cyclization of a β-aroylpropionitrile to a pyrroline or pyrrolidine (60). The nitrile is obtained *via* a Mannich base reaction with potassium cyanide according to the scheme



The reduction can be interrupted at the 1-pyrroline stage since the first two moles of hydrogen are absorbed much faster than the third.

In addition to these ring closures, a rather unusual photolysis method and a ring contraction have been described.

The irradiation of *n*-butyl azide, using a mercury arc lamp, produces pyrrolidine; similarly, *n*-octyl azide gives 2-butylpyrrolidine (39). It is suggested that the reaction proceeds *via* the activated nitrene R–N: which when confirmation and constitution permit, can arrange to form pyrrolidines. This reaction involves a free radical, and the preferred course is hydrogen abstraction—five atoms removed from the radical *via* a quasi-six-membered transition state.

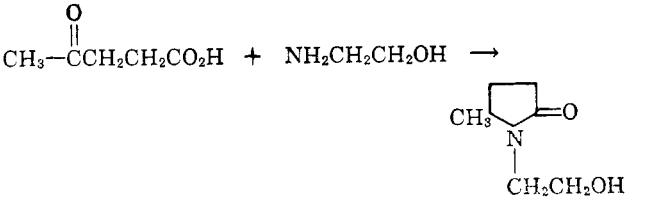


Treatment of 1-ethyl-3-chloropiperidine hydrochloride with benzylamine afforded 1-ethyl-2-benzylaminomethylpyrrolidine (15, 347).

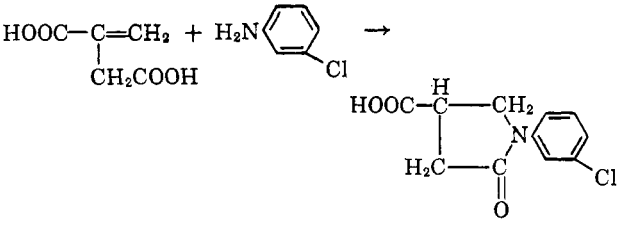
XX. Preparation of Pyrrolidones

In addition to the reduced pyrroles, or pyrrolidines, the chemistry of pyrrolidones has been extensively investigated. Since it is beyond the scope of this paper to treat these compounds in great detail, this discussion will be limited to representative procedures encountered in the synthesis of pyrrolidones, pyrrolidine diones, and pyrrolidine triones.

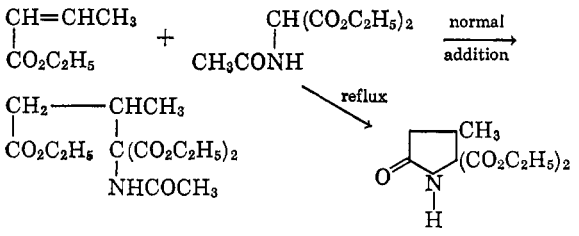
Both intermolecular and intramolecular ring closures to form 2-pyrrolidines have been described. The condensation of γ-ketocarboxylic acids with amines under reducing conditions gives 2-pyrrolidones in good yields. Moffett (300) treated levulinic acid with ethanolamine in platinum oxide–ethanol media for 4 hr. at 50 p.s.i. to give 1-(2-hydroxyethyl)-5-methyl-2-pyrrolidone in 95% yield.



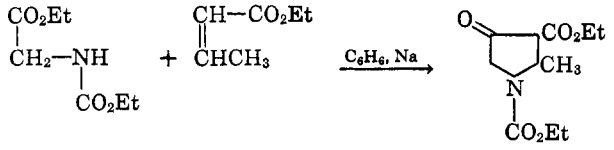
Another intermolecular route to N-substituted 2-pyrrolidones was reported by Paytash (327) and Evans (131). Fusion of itaconic acid with *m*-chloroaniline, afforded 4-carboxyl-1-(*m*-chlorophenyl)-2-pyrrolidone.



The Michael addition of diethyl acetamidomalonate to ethyl crotonate gave the normal product under mild conditions; refluxing, however, gives the abnormal adduct, 5,5-dicarbethoxy-4-methyl-2-pyrrolidinedione in 88% yield (97).

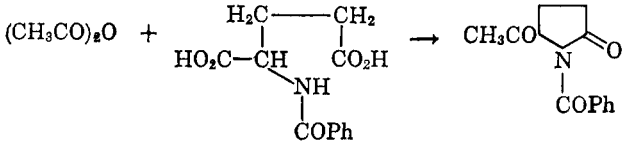


Ethyl crotonate was also employed in the preparation of 1,3-dicarbethoxy-2-methyl-4-pyrrolidone by addition to a mixture of N-carbethoxyglycine ethyl ester and sodium in benzene (240).

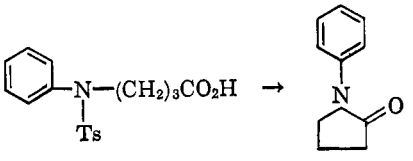


Intermolecular condensations make use of an amine or amide to form the desired pyrrolidone by ring closure. α, β-ethylene α-amino ketones provide a simple method of preparing various 3-pyrrolidones. Thus, refluxing 1-(*p*-chloroanilino)-1,4-diphenyl-3-buten-2-one in a sulfuric acid–ethanol–water mixture gave 1-(*p*-chlorophenyl)-2,5-diphenyl-3-pyrrolidone in 60% yield (393).

Ring closure to a 2-pyrrolidone was accompanied by decarbonylative acylation when benzoyl-DL-glutamic acid was heated in pyrridine with acetic anhydride. 5-Acetyl-1-benzoyl-2-pyrrolidone thus was obtained (59).

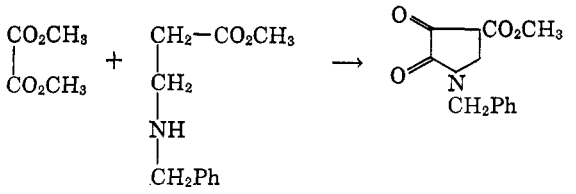


An unusual ring closure occurred when a solution of N-tosyl-γ-anilinobutyric acid was heated to 100° in polyphosphoric acid. Instead of ring closure to an aromatic ring, cyclization on the nitrogen was predominant and afforded 1-phenyl-2-pyrrolidone in 94% yield (31).

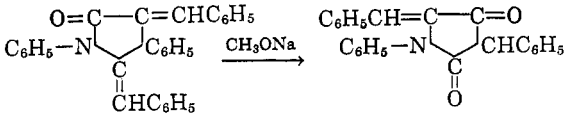


Similar methods have been employed in the synthesis of pyrrolidine diones and pyrrolidine triones. The base-catalyzed condensation of methyl oxalate and methyl α-benzylaminopropionate yielded 4-carboxymethyl-1-benzyl-2,3-dioxopyrrolidine (392).

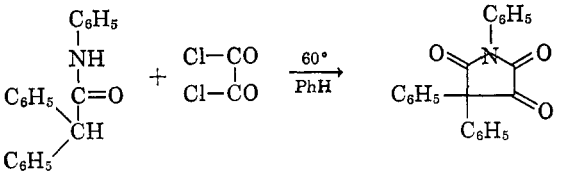
The addition of aniline to benzylidenepyruvic acid gave a 79% yield of 1,5-diphenyl-2,3-pyrrolidinedione (465).



An unusual ring opening and subsequent closing was reported by Sarsen and Bernstein (365), who isolated 1,4-diphenyl-2-benzylidene-3,5-pyrrolidinedione in quantitative yield after treating 2,4-dibenzylidene-1,3-diphenyl-5-oxazolidone with sodium methoxide.



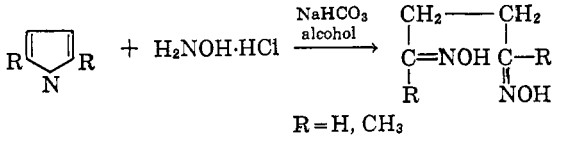
Condensation of oxalyl chloride with diphenylacetanilide gave 1,4,4-triphenyl-2,3,5-pyrrolidinetrione in 86% yields (385).



XXI. PYRROLE RING OPENING AND ENLARGEMENT

The opening of the pyrrole ring can be achieved by various means, and, as to be expected, the fission takes place at the C–N bond.

When hydroxylamine hydrochloride and sodium bicarbonate was refluxed for 24 hr. in alcohol with pyrrole or its 2,5-dimethyl derivative, α, δ-alkanedione-dioximes were obtained (137).

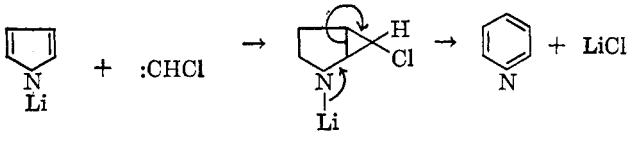


It is noteworthy that hydroxylamine and its hydrochloride are ineffective if used alone. Phosphorus pentachloride opened isonitroso triphenylpyrrole to yield a diamide (72). Ring cleavage of N-phenyl-2,5-dicarbomethoxy-3,4-dihydroxypyrrole by means of Tillmans' reagent yielded a polyhydroxy compound of linear configuration (334).

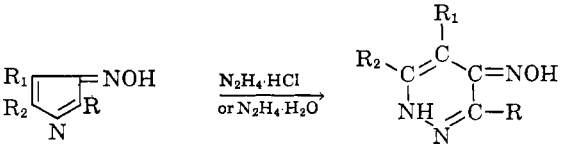
cis-Dibenzoylstilbene was obtained in 40% yield when tetraphenylpyrrole was heated at 80° with sodium nitrite in acetic acid, the same pyrrole underwent ring expansion to give 2,3,5,6-tetraphenylpyrazine when reacted with lead tetraacetate in chloroform (238). The behavior of 2,4,5-triphenylpyrrole upon oxidation with hydrogen peroxide in acetic medium was treated elsewhere (395).

Upon standing a long time, ranging from several months to one year, in the presence of amines or ammonia in ethanol, N-methyl- or N-aryltriphenylpyrrole gave the corresponding substituted triphenylpyrimidine. No change was observed using ultraviolet light and ammonia (73). However, under the sole influence of ultraviolet light, 2,4,6-triphenylpyrimidine was obtained from 2,3,5-triphenylpyrrole in 15 days (72).

Recent work by Closs and Schwartz (95) showed that pyridine is formed in 32% yield when methyllithium is added to a solution of pyrrole in methylene chloride. This reaction represents a chlorocarbene addition to pyrrole with subsequent rearrangement



Treatment of isonitrosopyrrole with hydrazine hydrochloride or hydrazine hydrate resulted in ring enlargement and the formation of the corresponding isonitrosodihydropyridazines (14).



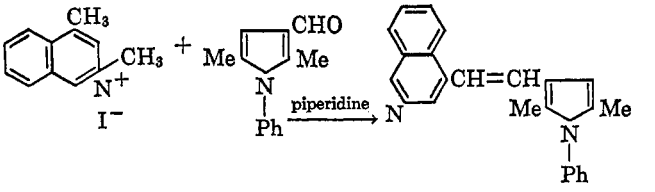
XXII. PREPARATION OF PYRROLE DYES

The extensive studies of dyes containing the pyrrole nucleus which are reported in the scientific and patent literature indicate the commercial importance which has been given to pyrrole chemistry. An excellent introduction ot this segment of pyrrole chemistry appears in Elderfield's "*Heterocyclic Chemistry*," and we believe that a summary of the recent work will furnish the reader with sufficient references for a more thorough examination.

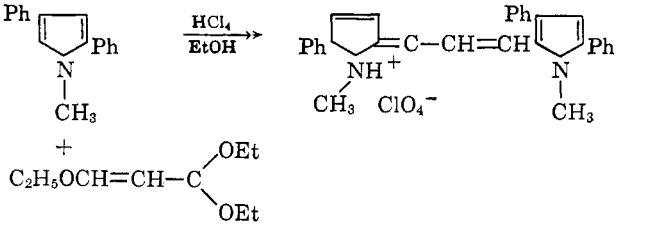
The pyrrolocarbocyanine dyes are polynuclear molecules containing the pyrrole nucleus. The pyrryl moiety is introduced by means of a pyrrole aldehyde or its vinylog. This condensation, involves substituted pyrroles with molecules having the structure $R_1OCH{=}CH{-}CH(OR_2)_2$, where R_1 and R_2 are alkyl groups containing 1 or 2 carbon atoms, or with carboxylic acid chlorides, anhydrides, and aralkyltrihalogenides.

Pyrrole aldehyde condensations were carried out with heterocyclic quaternaries (308, 311), barbituric acid (315), ferrocene (314), azulenes (313), and other pyrroles (317).

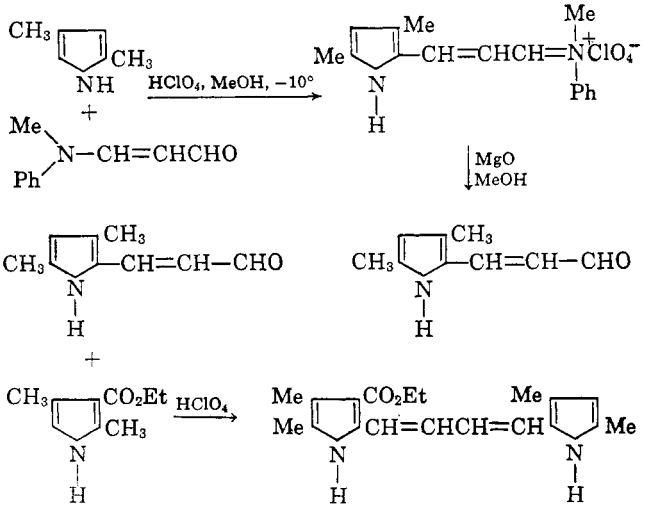
The 3,5-diarylpyrrole cyanine dyes are best prepared by treating a 3,5-diarylpyrrole with a compound having a general formula, $R_1O(CH{=}CH)_n{-}CH(OR)_2$ (345); for example, 1-methyl-3,4-diphenylpyrrole reacts with β-



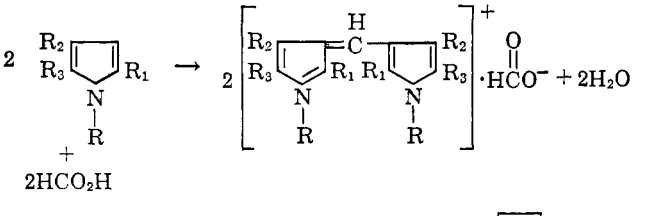
ethoxyacrolein diethylacetal to give bis-[-2-(1-methyl-3,5-diphenylpyrrole)].

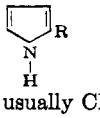


A similar condensation was reported by Strell and co-workers, who condensed di- and trisubstituted pyrroles with acrolein derivatives to give vinylogous aldehydes which could be further reacted to give trimethine derivatives.



Monomethine cyanine dyes were also obtained when alkyl substituted pyrroles were condensed with formic acid (33, 344); for example



R = primary alkyl group, 1–18 carbon atoms or 

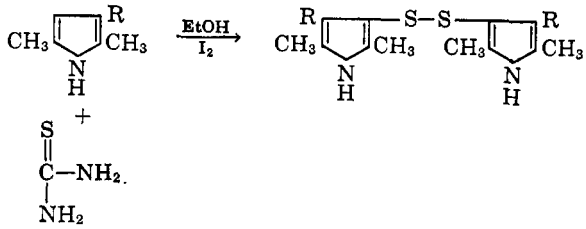
R_1, R_3 = primary alkyl group 1–4 carbon atoms, usually CH_3
R_2 = R or H
R_1 = Ph

In recent years Treibs and co-workers have investigated, rather extensively, the preparation of pyrrole

methine dyes using various compounds to form the carbon skeletal bridge. These syntheses employed β-unsaturated aldehydes and ketones (423), acyl chlorides (437), orthoformates (448), pyrrole acid chlorides and dipyrryl ketones (438), dipyrrylaldehydes (453), and aromatic aldehydes (434). Pyrrole blue and green dyes were obtained by condensing substituted pyrroles with ninhydrin, siloxan, 1,3-indandione, and perinaphthenone (453).

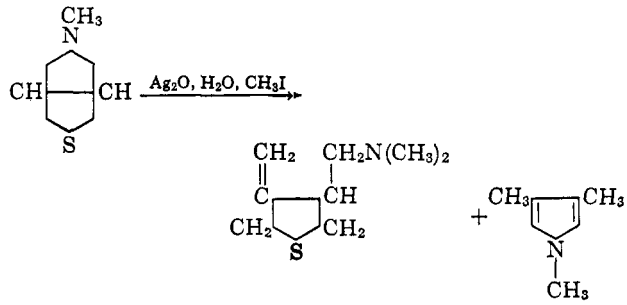
XXIII. MISCELLANEOUS

The syntheses of sulfur derivatives of pyrroles described in the literature were limited to the reaction of 2,3,5-trisubstituted pyrroles with thiourea and iodine to give disulfides (481), the reactions of various substituted aromatic sulfinyl compounds with aminopyrrole to give arylsulfonamidopyrroles (248), and the sulfonation of 2-chloropyrrole (419).



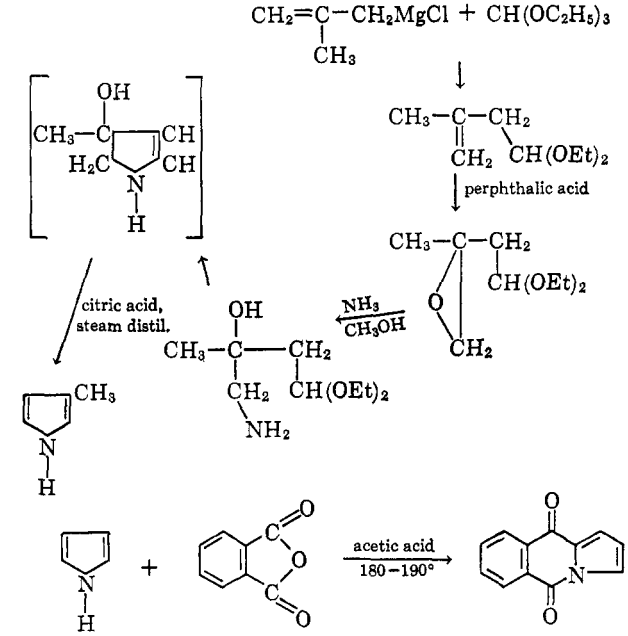
R = CH_3 or CO_2Et

An unusual synthesis of 1,3,4-trimethylpyrrole was reported by Marvel and co-workers. They treated N-methylthieno-(3,4-c)-tetrahydropyrrole with silver oxide and methyl iodide and obtained the trisubstituted pyrrole in 23.5% yield (275).

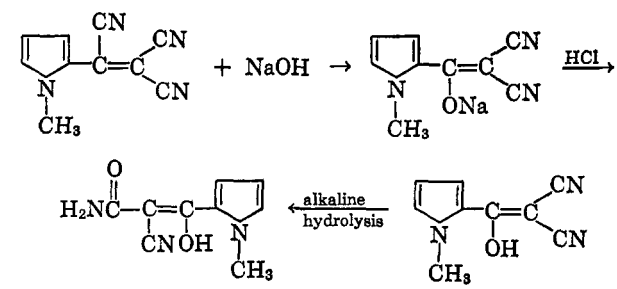


The substance producing most of the color with the Ehrlich reagent in the Elson–Morgan assay of hexaldamines was shown to be 2-methylpyrrole. 3-Acetyl-2-methylpyrrole is also formed. A synthesis of 3-methylpyrrole in four steps from 2-methylallyl chloride was described. Infrared spectra indicated that the condensation products of pyrrole with phthalic anhydride are benzopyrrocoline-5:10-diones. Several of these diones were described (101).

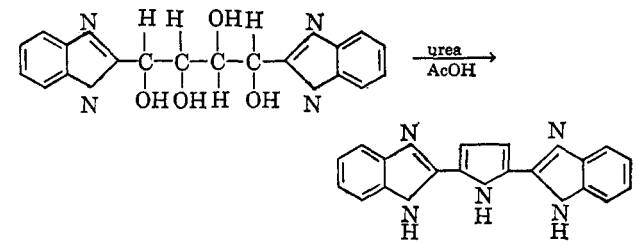
Solutions of free radicals were obtained by the action of dehydrogenating substances on tetraphenylpyrrole, and it was suggested that tetraphenylpyrrolyl with bivalent nitrogen was involved. The free radicals were obtained with lead dioxide in benzene (239).



The cyanoethylation of pyrroles was studied by Fischer (148). Pyrrole derivatives of cyanoethylene were prepared and from them a number of derivatives containing varied numbers of cyano and hydroxyl groups (281).

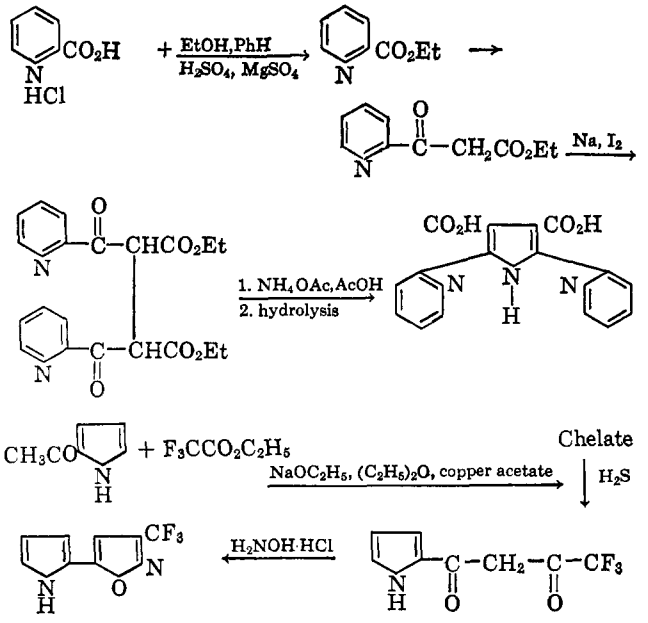


2,5-Di-(substituted benzimidazolyl)-pyrroles were prepared as follows (160, 381)

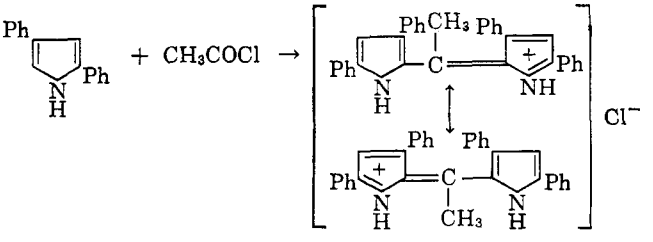


The preparation and study of the chemistry of the complexes of 2,5-di-(α-pyridyl)-pyrrole-3,4-dicarboxylic acid was studied (184).

2-Pyrryl methyl ketone was treated with methyl trifluoroacetate in the presence of sodium ethylate in ether and the trifluoromethyldione obtained further cyclized to the corresponding isoxazole with hydroxylamine hydrochloride (251).

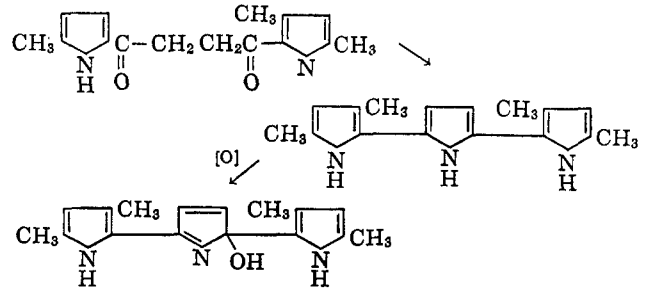


Upon treatment of 2,4-diphenylpyrrole with acetyl chloride, bis-(3,5-diphenylpyrrole)-*meso*-methyl methine hydrochloride was obtained (213).

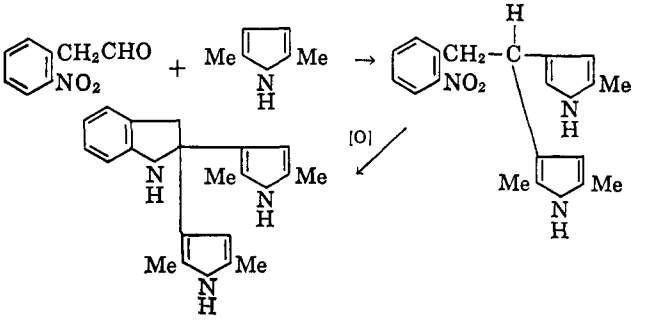


Pyrrole-containing polymers have been prepared and well characterized. The pyrrole monomers include N-vinylpyrrole (68, 301), pyrroledicarboxylic acid (302), and tetraphenylpyrroles (303). N-Vinyl and N-vinyltetraphenylpyrroles were homopolymerized while the dicarboxylic acid was condensed with diols to give polyesters.

In an attempt to prepare a tripyrrole from 1,4-bis-(3,5-dimethyl-2-pyrryl)-1,4-pentanedione-3,5-dimethyl, γ-oxo-2-pyrrolebutyric acid, its ethyl ester, and "pyrrole green" were obtained. It is believed that tripyrrole is formed, but immediately oxidizes to give I, then II (79).

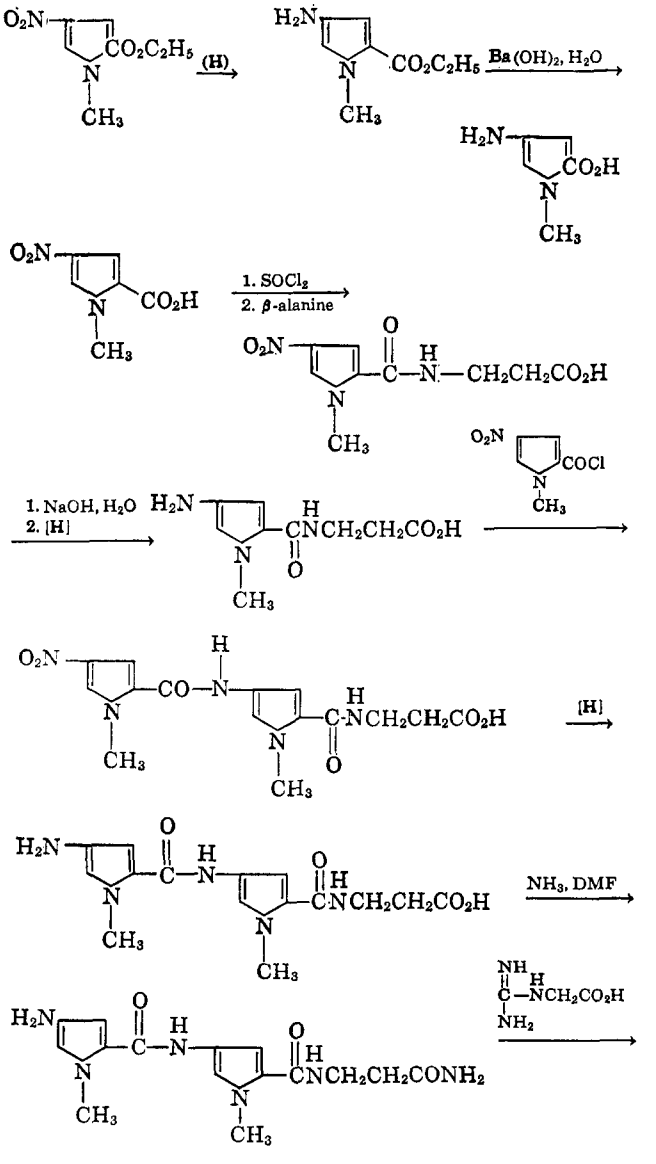


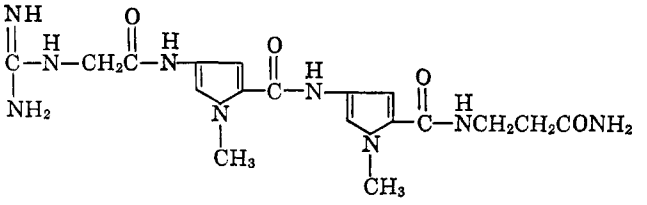
The synthesis of indole pyrrole trimers was achieved (317).



The structure of pyrrole derivatives, earlier observed to fluoresce like lubricating oil, has been investigated; these substances seemed to belong to a new heterocyclic system and were called dipyrrolopyridones (103).

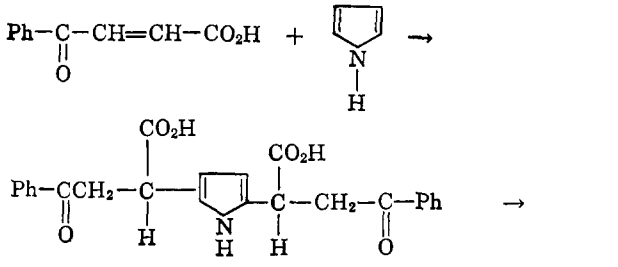
Synthesis of the degradation products of T-1348 (47) was carried out. The products were 4-amino-1-methyl-2-pyrrolecarboxylic acid, the tripeptide derived from two moles of the latter with β-alanine, β-[4-(4-amino-1-methyl-2-pyrrolecarboxamido)-1-methyl-2-pyrrole-car-



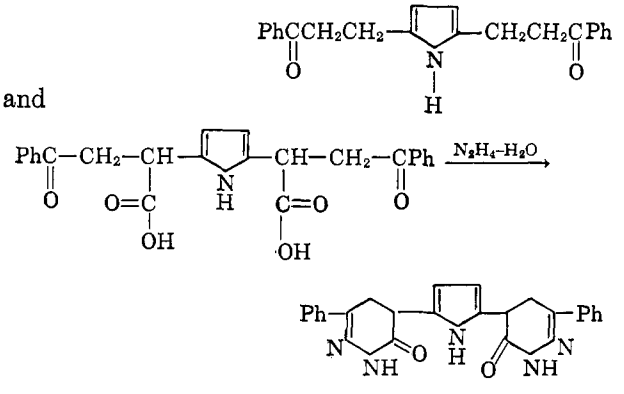


boxamido]-propionic acid, its amide, and the corresponding N-guanidinoacetyl derivative (478).

Pyrrole and methyl-substituted pyrroles were added in the conjugate manner to β-aroylacrylic acids (56).

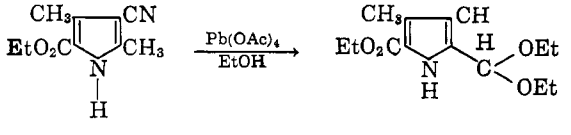


and

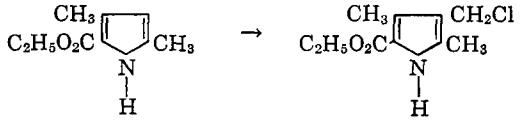


2-Methyl-4-cyanomethyl-5-pyrrolealdehyde was prepared from 2-methyl-4-cyanomethyl-pyrrole by means of the Adams–Montgomery (4) modification of the Gattermann aldehyde synthesis (112).

2,4-Dimethyl-3-cyano-5-carbethoxypyrrole, after treatment with lead tetraacetate and ethanol, gave the 2-formyldiacetal (112).

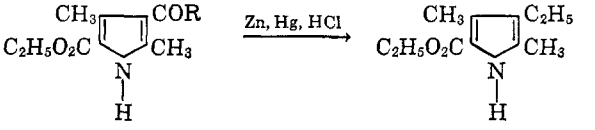


Chloromethylation was used for the first time to prepare 2,4-dimethyl-3-chloromethyl-5-carbethoxypyrrole (112).

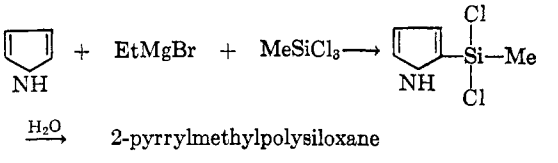


An attempt at using the Willgerodt reaction with 2,4-dimethyl-3-propionyl-5-carbethoxypyrrole and the corresponding 3-*n*-butyrylpyrrole was unsuccessful (112).

Clemmensen reduction of 2,4-dimethyl-3-acetyl-5-carbethoxypyrrole gave the 3-ethyl compound. Similarly, the 3-propyl and 3-butyl derivatives were also prepared (112).

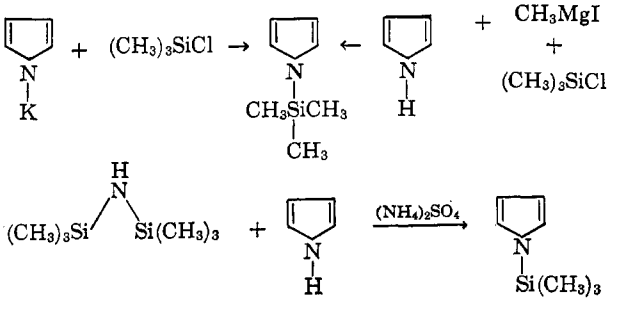


Several pyrrole compounds containing silicon were prepared. N-Trimethylsilylpyrrole was synthesized by the reaction of potassium pyrrole and trimethylchlorosilane. An exchange reaction between hexamethyldisilazone and pyrrole yielded the same product (42, 134). N-Triethylsilylpyrrole was prepared by similar methods (42). No evidence for the formation of 2-trimethylsilylpyrrole in this reaction was obtained. However, under different conditions, pyrrole in the presence of ethylmagnesium bromide and chlorosilanes afforded 2-pyrrylsilanes. Those of the latter which have two chlorines on the silicon atom can be hydrolyzed to yield 2-pyrrylmethylpolysiloxanes (154).



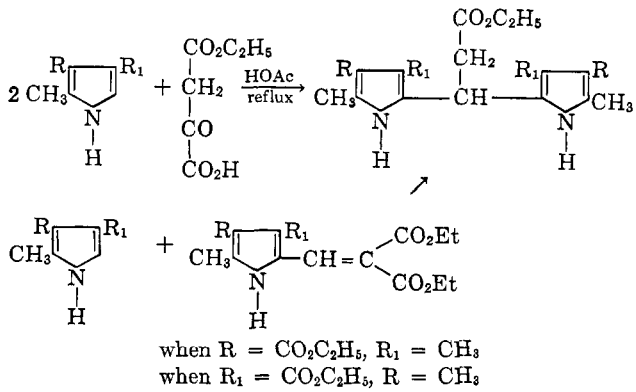
N-Trimethylsilylpyrrole has been found to be stable in ethanol. However, in boiling water or refluxing ethanol it is cleaved to pyrrole and silicon derivatives such as trimethylsilanol, hexamethyldisiloxane, or trimethylethoxysilane, depending upon the reaction conditions. N-Trimethylsilylpyrrole undergoes decomposition when heated in a sealed tube at 225° (42). 5-Amino-3-cyano-2-pyrrolesulfonic acid and its derivatives and salts were prepared and their properties studied (322).

N-Trimethylsilylpyrrole was synthesized by the reaction of potassium pyrrole and trimethylchlorosilane and by an exchange between hexamethyldisilazane and pyrrole (134).



This was the first "amine"–disilazane exchange reaction utilizing a secondary "amine."

β, β-Dipyrrylpropionic esters were prepared (9).



when R = $CO_2C_2H_5$, R_1 = CH_3
when R_1 = $CO_2C_2H_5$, R = CH_3

XXIV. PHYSICAL PROPERTIES OF PYRROLE AND ITS DERIVATIVES

The physical properties of pyrrole and its derivatives have been intensely studied by many investigators. To elucidate the contributions made in this field is beyond the scope of this review; indeed, the subject deserves treatment as a separate review.

However, we believe that an outline of the work described in recent literature would be of aid to those interested in the particular techniques used, the results, and their interpretation.

A. ULTRAVIOLET SPECTRA STUDIES

The study of the ultraviolet spectra has been centered on the effect of phenyl derivatives (136, 225) and various carbonyl groups, *ortho* to the nitrogen atom, where they are in conjugation with the pyrrole ring (24, 46, 47, 290, 340, 375). A quantitative spectrographic study has shown that variations in the electronic structure do not depend on the nitrogen atom but are related to the functional groups and their positions (291, 339). The relation between absorption spectra and chemical reactivity was discussed in a recent review (286).

B. INFRARED SPECTRA

The infrared spectra of various pyrroles were studied in the vapor phase, in the liquid state, and in solution (156, 293). Similar to the ultraviolet spectral studies, the investigation of the infrared spectra has centered on the effect of carbonyl groups adjacent to the NH group. The carbonyl group was present as an ester (278, 375) and aldehyde (48, 49, 294, 296, 297).

The N–H band in the region of 3458 $cm.^{-1}$ (49) has been studied thoroughly (157, 158, 175, 220, 252, 374, 377, 384) and ring substituents such as 2- and 3-methyl and 2,4- and 2,5-dimethyl gave a slight increase in the frequency (374). This work was extended to deuterated pyrroles and the effect of the solvent on this vibration. The infrared spectra of the newly synthesized N-trimethylsilylpyrrole and tetrapyrrylsilane have also been recorded (134).

C. OTHER PHYSICAL MEASUREMENTS

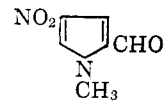
In addition to the numerous data dealing with the absorption spectra, the recent literature describes investigations of the dipole moment (57, 176, 295), polarographic measurements (44, 71, 336, 420), cryoscopic data (87, 221, 363, 421), and measurements of dielectric constants (202, 273, 459).

Quantum mechanical studies have not been overlooked, and indeed, the molecular orbital treatment has been employed by numerous investigators (34, 41, 83, 84, 85, 306, 328, 343, 362, 376), also its measurements such as valence vibration frequency (219), coulombic integral (177), nuclear magnetic resonance (353), and microwave (88) and emission spectra (287, 289).

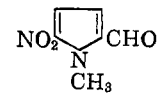
The pK_a of pyrrole, determined spectrophotometrically using the Hammett H_0 indicator method, was found to be −0.27. A back extrapolation method and a differentiation plot were used to overcome the problems caused by the acid-catalyzed polymerization of pyrrole (307). This study has shown that pyrrole is a weaker base than had been expected.

Unfortunately, no pK_a values exist for related compounds, and comparison is not possible. It would be of interest to determine the pK_a values of substances such as indole or carbazole which should also be very weakly basic and the acid dissociation constants of substituted pyrroles, namely, N-methylpyrrole.

The polarographic and spectral behavior of the isomeric N-methylnitropyrrolealdehydes I and II and their derivatives was studied in comparison with that of the nonmethylated compounds.



I



II

The nonmethylated aldehydes show anomalous polarographic behavior attributed to hydration. 5-Nitro-2-pyrrolealdehyde gives spectral evidence for the presence of two forms in acid and alkaline media in contrast to the 4-nitro isomer which does not show the same anomalies (153).

XXV. REACTIVITY IN THE PYRROLE SERIES

Pyrrole and its derivatives form one of the most reactive classes of organic compounds. In spite of the high reactivity of the pyrrole nucleus, however, its character is decidedly aromatic. Typical olefinic reactions generally do not occur. For instance, hydrogenation of the pyrrole nucleus is not easy. Furthermore, pyrrole does not react as a typical diene in Diels–Alder reactions, but rather as an RH compound.

The absence of double-bond frequency in the Raman spectra, as well as the behavior upon ozone degradation, lends support to the concept of its aromatic character,

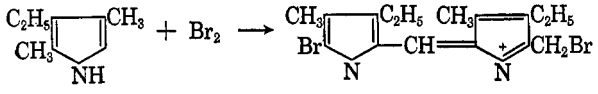
and the resonance structures which can be written for the pyrrole nucleus already have been given. The analogy between the reactivity of substituents on the pyrrole ring and those of the substituted aromatic hydrocarbons is not immediately apparent. This probably is due to the fact that the bulk of the work on pyrroles has been carried out on compounds in which most of the ring positions are blocked, in contrast to the benzene series, where the greatest number of reactions was studied on substances in which more than one ring position is available. This is apparent by the study of side-chain halogenation.

This reaction is facile in the benzene series under certain conditions; it is difficult, however, in the pyrrole series. Indeed, unless the other positions of the ring are blocked, the pyrrole nucleus halogenates prior to any substituent group. The halogens on the pyrrole nucleus can be easily replaced, as we have already seen, especially the iodo groups (30).

It has been mentioned previously that one of the most convenient methods of introduction of the aldehyde group in pyrrole derivatives is the reaction of sulfuryl chloride on methylated pyrroles. This reaction has been widely exploited for the preparation of pyrrole aldehydes and acids.

The contrast between the reactivity of the α-position and the β-position is brought out most strikingly by this reaction, which is usually performed in ether at 0°, since it yields itself only to the preparation of α-aldehydes and acids. In certain derivatives, however, in which the carbethoxy substituents make the α-methyl group less reactive, the use of glacial acetic acid allows trichlorination of the α-methyl group. In this case, as in the case of bromination, the reaction is limited by the ability of 2-methylpyrroles with an open 5-position to condense to the corresponding dipyrryl methenes.

In contrast to sulfuryl chloride, bromine tends to monohalogenate the α-methyl group. For this reason, it has been even more widely used than sulfuryl chloride for the preparation of dipyrryl methenes.



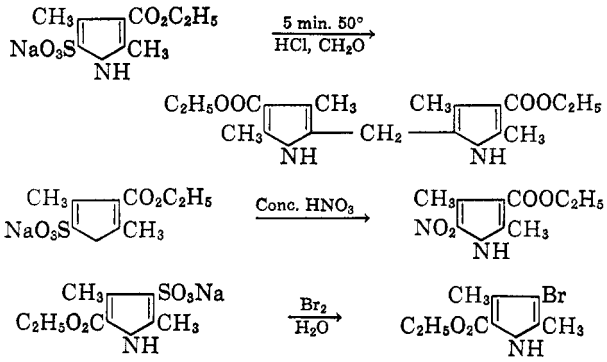
The fact that pyrryl methyl groups have not been iodinated demonstrates clearly that the methyl groups are substantially less active than nuclear positions in the ring since ring iodination takes place readily.

Another illustration of the distinctive property of the pyrrole ring to impart different reactivities to the α- and β-substituents is to be found with ester groups. This leads to the characteristic selective hydrolysis of pyrryl esters. Selective hydrolysis with alkali has been first accomplished by Knorr (231). Not only is the α-position more sensitive to attack by alkalies, but also ester interchange takes place preferentially at this position. The β-position in a pyrrole polyester can be attacked only by alkali in excess of the amount required to hydrolyze all esters in the α-positions. However, concentrated sulfuric acid is capable of selective attack on the β-position in the pyrrole ring.

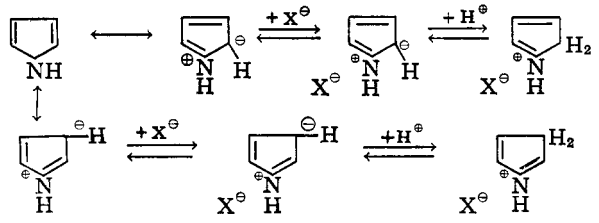
Pyrrole ketones undergo cleavage by both acidic and basic catalysts. For instance, sulfuric acid removes keto groups in what could be regarded as a reverse Friedel–Crafts synthesis.

Substituted pyrroles, dipyrryl methanes, and dipyrryl methenes containing the cyano group are well known. It was proven, however, that reactivity of the nitrile group in these substances varies markedly depending on its location with respect to the pyrrole ring. It becomes considerably lower than normal when the nitrile group is attached directly to the pyrrole nucleus.

The mechanism of certain exchange reactions on the pyrrole ring was studied in the case of pyrrole sulfonic acids. It was observed that electrophilic reagents add to the carbon atom carrying the exchangeable substituent to form intermediates in which the sulfonic group is subsequently replaced.



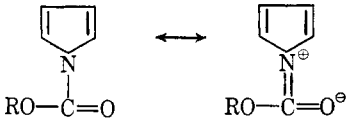
In order to explain the reactivity of the pyrrole nucleus the existence of α- and β-pyrrolenine forms has been postulated. According to this hypothesis, the pyrrolenine salts possess active methylene groups, which accounts for the activated forms of the pyrrole nucleus (441, 444, 446). This hypothesis also explains the fact that most substitution reactions are accelerated, or at least made possible, by acids or anionic catalysts. Essentially, the pyrrole nucleus has a tendency to accept an acid anion. The reaction is undoubtedly stimulated by the proton of the acid.



Whether the α- or β-position is preferred depends on the type of substituents present. On the basis of the inductive and mesomeric effects of the substituents, some theoretical rules for the substitution reactions of pyrrole and its derivatives were formulated. The reactivity of a given pyrrole depends on the character and location of its substituents and can be comparatively estimated by means of ease of coupling with azo dyes. An "activity series" of substituted pyrroles was thus obtained. The facile elimination of substituents and the formation and dissociation of polynuclear pyrroles (pyrrole exchange reactions) were classified accordingly as simple substitution reactions dependent upon the substituents on the pyrrole nucleus and their capacity for salt formation. The necessity for acid catalysis is thus recognized (430).

The effect of the substituents on the ring is to be viewed from the standpoint of their electropositive or electronegative character. The former increases the basicity of the ring, while the latter has the opposite effect. α-Methyl groups activate the α'-position and to a lesser extent, the β-position. β-Methyl groups activate only the neighboring α-position. Inactivation by electronegative groups occurs similarly.

Methyl groups on the nitrogen have little effect. However, negative substituents have a pronounced effect due to the fact that they render the participation of the pyrrolenic form difficult. This influence should be greater than that of a negative residue on the carbon, because the ring effect is suppressed.



Concerning other substituents, it should be mentioned that vinyl derivatives obtained by the condensation of aldehydes with active methylene compounds act as strong stabilizing negative residues, and the reactivity is partly shifted to the side chain. Carboxylic groups separated from the ring by one or more methylene groups, as in pyrrole acetic and propionic acids, have little influence on the alkyl residue.

XXVI. REFERENCES

(1) Acheson, R. M., and Vernon, J. M., *J. Chem. Soc.*, 457 (1961).
(2) Adams, R., and Levine, I., *J. Am. Chem. Soc.*, **45**, 2573 (1923).
(3) Adams, R., Miyano, S., and Nair, M. D., *J. Am. Chem. Soc.*, **83**, 3323 (1961).
(4) Adams, R., and Montgomery, E., *J. Am. Chem. Soc.*, **46**, 1518 (1924).
(5) Adkins, H., and Lonsted, L. G., *J. Am. Chem. Soc.*, **71**, 2964 (1949).
(6) Agosta, W. C., *J. Am. Chem. Soc.*, **82**, 2258 (1960).
(7) Aiello, T., and Giambrone, S., *Gazz. chim. ital.*, **81**, 276 (1951).
(8) Aiello, T., and Giambrone, S., *Boll Sci. Fac. chim. ind. Bologna*, **11**, 93 (1953); *Chem. Abstr.*, **49**, 6226g (1955).
(9) Aiello, T., and Giambrone, S., *Ric. sci.*, **23**, 2233 (1953); *Chem. Abstr.*, **48**, 10002d (1954).
(10) Aiello, T., and Giambrone, S., *Ric. Ac.*, **24**, 49 (1954); *Chem. Abstr.*, **49**, 3129c (1955).
(11) Aiello, T., and Pappalardo, G., *Gazz. chim. ital.*, **81**, 282 (1951).
(12) Aiello, T., and Spiro, V., *Gazz. chim. ital.*, **89**, 2526 (1959).
(13) Aiello, T., Spiro, V., and Madonia, P., *Gazz. chim. ital.*, **87**, 11 (1957).
(14) Aiello, T., Spiro, V., and Vaccaro, G., *Gazz. chim. ital.*, **89**, 2232 (1959).
(15) Albertson, N. F., and Filman, J. L., *J. Am. Chem. Soc.*, **71**, 2818 (1949).
(16) Alexander, E. R., and Baldwin, S., *J. Am. Chem. Soc.*, **73**, 356 (1951).
(17) Allen, C. F. H., and Vittum, P. W., U. S. Patent 2,735,764; *Chem. Abstr.*, **52**, 15317a (1958).
(18) Allen, G., Jr., and Webb, J. S., U. S. Patent 2,901,489; *Chem. Abstr.*, **54**, 2358g (1960).
(19) Anderlein, F., *Ber.*, **22**, 2512 (1889).
(20) Anderson, F. E., Duca, C. J., and Scudi, J. V., *J. Am. Chem. Soc.*, **73**, 4967 (1951).
(21) Anderson, H. J., *Can. J. Chem.*, **35**, 21 (1957).
(22) Anderson, H. J., *Can. J. Chem.*, **37**, 2053 (1959).
(23) Anderson, T., *Ann.*, **105**, 349 (1858).
(24) Andrisano, R., Pappalardo, G., and Bolognari, L., *Gazz. chim. ital.*, **85**, 1430 (1955).
(25) Angelico, F., *Atti accad. nazl. Lincei* (5), **14**, II, 167 (1905).
(26) Angelico, F., and Calvello, G., *Gazz. chim. ital.*, **31**, II, 4 (1901).
(27) Angelico, F., and Labisi, C., *Gazz. chim. ital.*, **40**, I, 411, 417 (1910).
(28) Anthony, W. C., *J. Org. Chem.*, **25**, 2049 (1960).
(29) Arbuzov, Y. A., *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* 547 (1952); *Chem. Abstr.*, **47**, 4875g (1953).
(30) Arsenault, G. P., and MacDonald, S. F., *Can. J. Chem.*, **39**, 2043 (1961).
(31) Astill, B. D., and Boekelheide, V., *J. Am. Chem. Soc.*, **77**, 4079 (1955).
(32) Bachman, G. B., and Hersey, L. Y., *J. Am. Chem. Soc.*, **68**, 2496 (1946).
(33) Bailey, J., U. S. Patent 2,843,486; *Chem. Abstr.*, **52**, 15317a (1958).
(34) Bak, B., *Acta Chem. Scand.*, **9**, 1355 (1955); *Chem. Abstr.*, **50**, 6917e (1956).
(35) Baker, B. R., Schaub, R. E., and Williams, J. H., *J. Org. Chem.*, **17**, 116 (1952).
(36) Baltazzi, E., *Compt. rend.*, **254**, 702 (1962).
(37) Baltazzi, E., unpublished results.
(38) Bamberger, E., and Djerdjian, G., *Ber.*, **33**, 536 (1900).
(39) Barton, D. H. R., and Morgan, L. R., Jr., *Proc. Chem. Soc.*, 206 (1961).
(40) Bayer, A., and Emmerling, H., *Ber.*, **3**, 517 (1870).
(41) Berthier, G., and Pullman, B., *Compt. rend.*, **231**, 744 (1950).
(42) Birkofer, L., Richter, P., and Ritter, A., *Ber.*, **93**, 2804 (1960).
(43) Blatt, A. H., *J. Org. Chem.*, **15**, 565 (1950).
(44) Bonino, G. B., *Pontif. Acad. Sci. Acta*, **9**, 65 (1945); *Chem. Abstr.*, **45**, 7445i (1951).
(45) Bonino, G. B., and Chiorboli, P., *Atti accad. nazl. Lincei*, **10**, 104 (1951).
(46) Bonino, G. B., and Marinangeli, A. M., *Atti accad. nazl. Lincei*, **19**, 222 (1955).
(47) Bonino, G. B., and Marinangeli, A. M., *Atti accad. nazl. Lincei*, **19**, 393 (1955).

(48) Bonino, G. B., and Mirone, P., *Atti accad. nazl. Lincei*, **17**, 167 (1954).
(49) Bonino, G. B., and Mirone, P., *Atti accad. nazl. Lincei*, **23**, 198 (1958).
(50) Booth, H., Johnson, A. W., Markham, E., and Price, R., *J. Chem. Soc.*, 1587 (1959).
(51) Bordner, C. A., U. S. Patent 2,600,289; *Chem. Abstr.*, **47**, 4373c (1953).
(52) Bortnick, N. M., and Fegley, M. F., U. S. Patent 2,770,628; *Chem. Abstr.*, **51**, 6701i (1957).
(53) Brewster, J. H., and Eliel, E. L., *Org. Reactions*, **7**, 99 (1953).
(54) Brooker, L. G. S., and Heseltine, D. W., U. S. Patent 2,646,430; *Chem. Abstr.*, **48**, 1188f (1954).
(55) Brooker, L. G. S., and White, F. L., *J. Am. Chem. Soc.*, **73**, 1094 (1951).
(56) Buchta, E., and Schamberger, H., *Ber.*, **92**, 1363 (1959).
(57) Buckingham, A. D., Harris, B., and LeFevre, R. J. W., *J. Chem. Soc.*, 1626 (1953).
(58) Buckley, G. D., and Elliott, T. J., *J. Chem. Soc.*, 1508 (1947).
(59) Bullerwell, R. A. F., Lawson, A., and Morley, J. V., *J. Chem. Soc.*, 3283 (1954).
(60) Burckhalter, J. H., and Short, J. H., *J. Org. Chem.*, **23**, 1278 (1958).
(61) Burke, W. J., and Hammer, G. N., *J. Am. Chem. Soc.*, **76**, 1294 (1954).
(62) Busse, W. F., and Lambert, J. M., U. S. Patent 2,618,200; *Chem. Abstr.*, **47**, 3040e (1953).
(63) Buu-Hoi, Ng. Ph., *J. Chem. Soc.*, 2882 (1949).
(64) Buu-Hoi, Ng. Ph., *Rec. trav. chim.*, **73**, 187 (1954).
(65) Buu-Hoi, Ng. Ph., Royer, R., and Hubert-Habart, M., *Rec. trav. chim.*, **73**, 188 (1954).
(66) Buu-Hoi, Ng. Ph., and Xuong, Ng. D., *J. Org. Chem.*, **20**, 850 (1955).
(67) Buu-Hoi, Ng. Ph., Xuong, Ng. D., and Gazave, J. M., *J. Org. Chem.*, **20**, 639 (1955).
(68) Caccia-Bava, A. M., and Chierici, L., *Boll. Chim. Farm.*, **89**, 397 (1950); *Chem. Abstr.*, **45**, 4236i (1951).
(69) Cantor, P. A., Lancaster, R., and VanderWerf, C. A., *J. Org. Chem.*, **21**, 918 (1956).
(70) Cantor, P. A., and VanderWerf, C. A., *J. Am. Chem. Soc.*, **80**, 970 (1958).
(71) Cappellina, F., and Drusiani, A., *Gazz. chim. ital.*, **84**, 939 (1954).
(72) Capuano, S., and Giammanco, L., *Gazz. chim. ital.*, **85**, 217 (1955).
(73) Capuano, S., and Giammanco, L., *Gazz. chim. ital.*, **86**, 119 (1956).
(74) Capuano, S., and Giammanco, L., *Gazz. chim. ital.*, **87**, 857 (1957).
(75) Castro, A. J., Corwin, A. H., Peck, J. F., and Wei, P. E., *J. Org. Chem.*, **24**, 1437 (1959).
(76) Chichibabin, A. E., and Seide, O. A., *J. Russ. Phys. Chem. Soc.*, **46**, 1216 (1914).
(77) Chierici, L., *Farm. sci. e tec.*, **7**, 618 (1952); *Chem. Abstr.*, **47**, 12344i (1953).
(78) Chierici, L., *Farmaco* (Pavio), *Ed. sci.*, **8**, 156 (1953); *Chem. Abstr.*, **48**, 2038b (1954).
(79) Chierici, L., and Cella, A., *Ann. chim.* (Rome), **43**, 141 (1953).
(80) Chierici, L., and Serventi, G., *Gazz. chim. ital.*, **86**, 1278 (1956).
(81) Chierici, L., and Serventi, G., *Gazz. chim. ital.*, **90**, 23 (1960).
(82) Chiorboli, P., *Atti accad. nazl. Lincei*, **12**, 588 (1952).
(83) Chiorboli, P., *Atti accad. nazl. Lincei*, **12**, 713 (1952).
(84) Chiorboli, P., and Manaresi, P., *Gazz. chim. ital.*, **83**, 114 (1953).
(85) Chiorboli, P., and Manaresi, P., *Gazz. chim. ital.*, **84**, 248 (1954).
(86) Chiorboli, P., and Morelli-Emiliani, A., *Gazz. chim. ital.*, **81**, 906 (1951).
(87) Chiorboli, P., and Morisi, G., *Gazz. chim. ital.*, **84**, 1066 (1954).
(88) Christensen, D., Hansen, L., and Andersen, J. R., *J. Chem. Phys.*, **24**, 720 (1956).
(89) Chu, E. J. H., and Chu, T. C., *J. Org. Chem.*, **19**, 266 (1954).
(90) Ciamician, G., *Ber.*, **34**, 3952 (1901).
(91) Ciamician, G., and Demnstedt, M., *Ber.*, **15**, 2582 (1882).
(92) Ciamician, G., and Demnstedt, M., *Ber.*, **16**, 1536 (1883).
(93) Ciamician, G., and Silber, P., *Ber.*, **19**, 3027 (1886).
(94) Cloke, J. B., *J. Am. Chem. Soc.*, **51**, 1174 (1929).
(95) Closs, G. L., and Schwartz, G. M., *J. Org. Chem.*, **26**, 2609 (1961).
(96) Coates, H., Cook, A. H., Heilbron, I. M., and Lewis, F. B., *J. Chem. Soc.*, 419 (1943).
(97) Cocolas, G. H., and Hartung, W. H., *J. Am. Chem. Soc.*, **79**, 5203 (1957).
(98) Coleman, G. H., Nichols, G., Martens, T. F., *Org. Syn.*, **25**, 14 (1945).
(99) Cook, A. H., and Mayer, J. R., *J. Chem. Soc.*, 482 (1944).
(100) Copes, J. P., Fuller, D. L., and McKinley, C., U. S. Patent 2,671,789; *Chem. Abstr.*, **49**, 4028c (1955).
(101) Cornforth, J. W., and Firth, M. E., *J. Chem. Soc.*, 1091 (1958).
(102) Corwin, A. H., Bailey, W., Jr., and Viohl, P., *J. Am. Chem. Soc.*, **64**, 1267 (1942).
(103) Corwin, A. H., and Ellingson, R. C., *J. Am. Chem. Soc.*, **66**, 1146 (1944).
(104) Corwin, A. H., and Kleinspehn, G. G., *J. Am. Chem. Soc.*, **75**, 2089 (1953).
(105) Corwin, A. H., and Kleinspehn, G. G., *J. Am. Chem. Soc.*, **76**, 5641 (1954).
(106) Corwin, A. H., and Quattlebaum, W. M., Jr., *J. Am. Chem. Soc.*, **58**, 1081 (1936).
(107) Corwin, A. H., and Quattlebaum, W. M., Jr., *J. Am. Chem. Soc.*, **58**, 1983 (1936).
(108) Corwin, A. H., and Straughn, J. L., *J. Am. Chem. Soc.*, **70**, 1416 (1948).
(109) Corwin, A. H., and Straughn, J. L., *J. Am. Chem. Soc.*, **70**, 2968 (1948).
(110) Corwin, A. H., and Viohl, P., *J. Am. Chem. Soc.*, **66**, 1137 (1944).
(111) Cosulich, D. B., U. S. Patent 2,805,227; *Chem. Abstr.*, **52**, 3866c (1958).
(112) Curry, T. H., *Dissertation Abstr.*, **18**, 1615 (1958).
(113) Cusmano, S., and Sprio, V., *Gazz. chim. ital.*, **82**, 567 (1952).
(114) Cymerman, J., and Gilbert, W. S., *J. Chem. Soc.*, 3529 (1952).
(115) Davoll, J., *J. Chem. Soc.*, 3902 (1953).
(116) De Cat, A., *Industrie chim. belge*, **17**, 652, 772, 838, 1027 (1952); *Chem. Abstr.*, **48**, 540i (1954).
(117) Dezelic, M., and Bobarevic, B., *Bull. soc. chimistes rep. populaire Bosnie Herzegovine*, **7**, 5 (1958); *Chem. Abstr.*, **54**, 14227g (1960).
(118) Dezelic, M., and Dolibic, G., *Bull. soc. chimistes rep. populaire Bosnie Herzegovine*, **6**, 11 (1957); *Chem. Abstr.*, **52**, 10054f (1958).
(119) Dimroth, K., and Pintschovius, U., *Ann.*, **639**, 102 (1961).
(120) Doak, K. W., and Corwin, A. H., *J. Am. Chem. Soc.*, **71**, 159 (1949).

(121) Doyle, F. P., Mekta, M. D., Sach, G. S., and Pearson, J. L., *J. Chem. Soc.*, 4458 (1958).
(122) Drewitt, J. G. N., and Lincoln, J., U. S. Patent 2,551,731; *Chem. Abstr.*, **45**, 8298h (1951).
(123) Dunlop, A. P., and Hurd, C. D., *J. Org. Chem.*, **15**, 1160 (1950).
(124) Dunlop, A. P., and Swadesk, S., U. S. Patent 2,655,512; *Chem. Abstr.*, **48**, 11495d (1954).
(125) Ehrhart, G., and Hennig, I., *Ber.*, **89**, 1568 (1956).
(126) Eisner, U., Lichtarowicz, A., and Linstead, R. P., *J. Chem. Soc.*, 733 (1957).
(127) Elderfield, R. C., and Hageman, H. A., *J. Org. Chem.*, **14**, 605 (1949).
(128) Elming, N., and Clauson-Kaas, N., *Acta Chem. Scand.*, **6**, 867 (1952).
(129) Erickson, J. G., and Keps, J. S., *J. Am. Chem. Soc.*, **77**, 485 (1955).
(130) Euler, H., and Hasselquist, H., *Hoppe-Seyler's Z. physiol. Chem.*, **306**, 49 (1956); *Chem. Abstr.*, **51**, 6601h (1957).
(131) Evans, G. L., Gray, H. W., and Jacobson, H. W., *J. Am. Chem. Soc.*, **72**, 2727 (1950).
(132) Farstorp, J., Raleigh, D., and Schniepp, L. E., *J. Am. Chem. Soc.*, **72**, 869 (1950).
(133) Fegley, M. F., Bortnick, N. M., and McKeever, L. H., *J. Am. Chem. Soc.*, **79**, 4144 (1957).
(134) Fessenden, R., and Crowe, D. F., *J. Org. Chem.*, **25**, 598 (1960).
(135) Fetizon, M., and Baranger, P., *Compt. rend.*, **236**, 1428 (1953).
(136) Fetizon, M., Fritel, H., Livisalles, J., and Baranger, P., *Compt. rend.*, **242**, 2014 (1956).
(137) Findlay, S. P., *J. Org. Chem.*, **21**, 644 (1956).
(138) Fischer, H., *Stezber, math. physik Klasse Akad. Wiss. Mundren*, 410 (1915).
(139) Fischer, H., *Ber.*, **55**, 2390 (1922).
(140) Fischer, H., *Ann.*, **452**, 283 (1927).
(141) Fischer, H., *Org. Syn.*, **21**, 67 (1941).
(142) Fischer, H., and Ammann, H., *Ber.*, **56**, 2320 (1923).
(143) Fischer, H., and Bartholemaus, E., *Ber.*, **45**, 466 (1912).
(144) Fischer, H., and Baumler, R., *Ann.*, **468**, 58 (1929).
(145) Fischer, H., and Ernst, P., *Ann.*, **477**, 147 (1926).
(146) Fischer, H., and Fink, E., *Hoppe-Seyler's Z. Physiol. Chem.*, **283**, 152 (1948); *Chem. Abstr.*, **45**, 5618a (1951).
(147) Fischer O., and Hepp, E., *Ber.*, **19**, 2251 (1886).
(148) Fischer, H., and Loewe, H., *Ann.*, **615**, 124 (1958).
(149) Fischer, H., and Rothweiler, F., *Ber.*, **56**, 512 (1923).
(150) Fischer, H., and Schubert, F., *Hoppe-Seyler's Z. physiol. Chem.*, **155**, 99 (1926).
(151) Fischer, H., and Zeile, K., *Ann.*, **483**, 251 (1930).
(152) Fischer, H., and Zerweck, W., *Ber.*, **55**, 1942 (1922).
(153) Fournari, P., Person, M., and Watelle-Marion, G., *Compt. rend.*, **253**, 1059 (1961).
(154) Frisch, K. C., and Kary, R. M., *J. Org. Chem.*, **21**, 931 (1956).
(155) Fuhlage, D. W., and VanderWerf, C. A., *J. Am. Chem. Soc.*, **80**, 6248 (1958).
(156) Fuson, N., and Josien, M. L., *J. Chem. Phys.*, **20**, 1043 (1952).
(157) Fuson, N., and Josien, M. L., *J. phys. Radium*, **15**, 652 (1954).
(158) Fuson, N., Josien, M. L., Powell, R. L., and Utterback, E. *J. Chem. Phys.*, **20**, 145 (1952).
(159) Gallagher, J. A., *Dissertation Abstr.*, **16**, 451 (1956).
(160) Gardner, T. S., *J. Org. Chem.*, **23**, 823 (1958).
(161) Gardner, T. S., Wenis, E., and Lee J., *J. Org. Chem.*, **23**, 823 (1958).
(162) Gardner, T. S., Wenis, E., and Lee, J., *J. Org. Chem.*, **24**, 570 (1959).
(163) Ghigi, E., and Drusiani, A., *Atti. accad. Sci. ist. Bologne, Class sci. fis.*, **11**, No. 3, 1 (1956); *Chem. Abstr.*, **51**, 6602e (1957).
(164) Ghigi, E., and Drusiani, A., *Atti accad. sci. ist. Bologne, Class sci. fis.*, **11**, No. 4, 14 (1957); *Chem. Abstr.*, **52**, 11818a (1958).
(165) Ghigi, E., and Drusiani, A., *Atti accad. Bologne Rend (XI)*, **5**, 56 (1960); *Chem. Abstr.*, **54**, 5613i (1960).
(166) Giambrone, S., and Fabra, J., *Ann. Chim.* (Rome), **50**, 237 (1960).
(167) Gilman, H., and Fullhart, L., *J. Am. Chem. Soc.*, **68**, 978 (1946).
(168) Gilman, H., and Garner, G. C., *J. Am. Chem. Soc.*, **69**, 1946 (1947).
(169) Gilman, H., Stucknisch, C. G., and Nobis, J. F., *J. Am. Chem. Soc.*, **68**, 326 (1946).
(170) Gonzalez, F. G., and de Castro Brzezicki, R., *Anales. real soc. espan. fis. quim.* (Madrid), **46B**, 68 (1950); *Chem. Abstr.*, **55**, 6183b (1961).
(171) Gonzalez, F. G., and Gonzalez, J. M. R., *Anales real soc. espan. fis. quim.* (Madrid), **47B**, 549 (1951); *Chem. Abstr.*, **46**, 10149 (1952).
(172) Gonzalez, F. G., Sanchez, A. G., and Gomez, J. G., *Anales real soc. espan. fis. quim.* (Madrid), **54B**, 519 (1958); *Chem. Abstr.*, **53**, 8116b (1959).
(173) Grobb, C. A., and Ankli, P., *Helv. Chim. Acta*, **32**, 2010 (1949).
(174) Grobb, C. A., and Camenisch, K., *Helv. Chim. Acta*, **36**, 49 (1953).
(175) Grobb, C. A., and Utzinger, H., *Helv. Chim. Acta*, **37**, 1256 (1954).
(176) Guryanova, E. N., Yanovskaya, L. A., and Terentev, A. P., *Zh. Fiz. Khim.*, **25**, 897 (1951); *Chem. Abstr.*, **46**, 2360b (1952).
(177) Gyoerffy, E., *Compt. rend.*, **232**, 515 (1951).
(178) Hai, P. V., Buu-Hoi, Ng. Ph., and Xuong, Ng. D., *J. Org. Chem.*, **23**, 39 (1958).
(179) Haley, C. A. C., and Maitland, P., *J. Chem. Soc.*, 3155 (1951).
(180) Harley-Mason, J., *J. Chem. Soc.*, 2433 (1952).
(181) Harvey, D. G., *J. Chem. Soc.*, 1638 (1950).
(182) Hauk, A. L., and Bock, L. H., U. S. Patent 2,243,630; *Chem. Abstr.*, **35**, 5720 (1941).
(183) Hayes, A., Kenner, G. W., and Williams, N. R., *J. Chem. Soc.*, 3779 (1958).
(184) Hein, F., and Beierlein, U., *Pharm. Zentralhalle*, **96**, 401 (1957); *Chem. Abstr.*, **52**, 14608e (1958).
(185) Hein, F., and Melichar, F., *Pharmazie*, **9**, 455 (1954); *Chem. Abstr.*, **49**, 10283 (1955).
(186) Helferich, B., O'Hein, R., Geist K., Junger, H., and Wiehle, D., *Ann.*, **646**, 45 (1961).
(187) Hellman, H., *Angew. Chem.*, **65**, 473 (1953).
(188) Helzig, L., and Zeisel, W., *Monatsh.*, **9**, 217, 882, 1045 (1888).
(189) Helzig, L., and Zeisel, W., *Monatsh.*, **10**, 144 (1889).
(190) Hendrickson, J. B., and Rees, R., *J. Am. Chem. Soc.*, **83**, 1250 (1961).
(191) Herz, W., *J. Am. Chem. Soc.*, **71**, 3982 (1949).
(192) Herz, W., *J. Am. Chem. Soc.*, **75**, 483 (1953).
(193) Herz, W., *J. Org. Chem.*, **22**, 1260 (1957).
(194) Herz, W., and Brasch, J., *J. Org. Chem.*, **23**, 711, 1513 (1958).
(195) Herz, W., and Courtney, C. F., *J. Am. Chem. Soc.*, **76**, 576 (1954).
(196) Herz, W., Dittmer, K., and Cristol, S. J., *J. Am. Chem. Soc.*, **69**, 1698 (1947).

(197) Herz, W., Raden, D. S., and Murty, D. R. K., *J. Org. Chem.*, **21**, 896 (1956).
(198) Herz, W., and Rodgers, J. L., *J. Am. Chem. Soc.*, **73**, 4921 (1951).
(199) Herz, W., and Settine, R. L., *J. Org. Chem.*, **24**, 201 (1959).
(200) Herz, W., and Tocker, S., *J. Am. Chem. Soc.*, **77**, 6355 (1955).
(201) Hobbs, C. F., *Dissertation Abstr.*, 1061 (1960).
(202) Holland, R. S., and Smyth, C. P., *J. Phys. Chem.*, **59**, 1088 (1955).
(203) Huisgen, R., and Laschtuvka, E., *Chem. Ber.*, **93**, 65 (1960).
(204) Huisgen, R., and Laschtuvka, E., German Patent 1,048,582; *Chem. Abstr.*, **55**, 4533e (1961).
(205) Hielscher, R., *Ber.*, **31**, 277 (1898).
(206) Huntress, E. H., Lesslie, T. E., and Hearon, W. M., *J. Am. Chem. Soc.*, **78**, 419 (1956).
(207) Hurd, D., and Buess, C. M., *J. Am. Chem. Soc.*, **78**, 5667 (1956).
(208) Icke, R. N., *Org. Syn.*, **3**, 723 (1955).
(209) Ipatieff, V. N., Germain, J. E., and Pines, H., *Bull. soc. chim. France*, 259 (1951).
(210) Issleib, K., and Brack, A., *Z. anorg. allgem. Chem.*, **292**, 245 (1957).
(211) Iwakura, Y., and Hayashi, K., *Yuki Gosei Kagaku Kyokai Shi*, **15**, 463 (1957); *Chem. Abstr.*, **51**, 17881e (1957).
(212) Iwakura, Y., and Hayashi, K., Japanese Patent 3787 (1960); *Chem. Abstr.*, **55**, 1655d (1961).
(213) Jeffreys, R. A., and Knott, E. B., *J. Chem. Soc.*, 1028 (1951).
(214) Jimenz, J. F., and Roncero, A. V.: *Anales real soc. espan. fis. quim.* (Madrid), **45B**, 1591 (1949); *Chem. Abstr.*, **46**, 7088 (1952).
(215) Johnson, A. W., Markham, E., Price, R., and Shaw, K. B., *J. Chem. Soc.*, 4254 (1958).
(216) Jones, J. I., *J. Chem. Soc.*, 1392 (1950).
(217) Jones, R. G., *J. Am. Chem. Soc.*, **77**, 4069 (1955).
(218) Jones, R. G., and Kornfeld, E. C., U. S. Patent 2,744,915; *Chem. Abstr.*, **51**, 2871g (1957).
(219) Josien, M. L., and Fuson, N., *Compt. rend.*, **232**, 833 (1951).
(220) Josien, M. L., and Fuson, N., *J. Chem. Phys.*, **22**, 1264 (1954).
(221) Josien, M. L., Paty, M., and Pineau, P., *Compt. rend.*, **241**, 199 (1955).
(222) Josien, M. L., Pineau, P., Paty, M., and Fuson, N., *J. Chem. Phys.*, **24**, 1261 (1956).
(223) Julia, M., and Ballarge, M., *Bull. soc. chim. France*, 931 (1957); *Chem. Abstr.*, **52**, 1126h (1958).
(224) Kildisheva, O. V., Linkova, M. G., and Knunyants, I. L. *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 719 (1957); *Chem. Abstr.*, **52**, 3776 (1958).
(225) King, S. M., Bauer, C. R., and Lutz, R. E., *J. Am. Chem. Soc.*, **73**, 2253 (1951).
(226) Klamerth, O., and Kutscher, W., *Ber.*, **85**, 444 (1952).
(227) Kleinspehn, G. G., *J. Am. Chem. Soc.*, **77**, 1546 (1955).
(228) Kleinspehn, G. G., and Corwin, A. H., *J. Am. Chem. Soc.*, **75**, 5295 (1953).
(229) Kleinspehn, G. G., and Corwin, A. H., *J. Org. Chem.*, **25**, 1048 (1960).
(230) Kloetzel, M. C., *J. Am. Chem. Soc.*, **69**, 2271 (1947).
(231) Knorr, L., and Rabe, P., *Ber.*, **34**, 2397 (1901).
(232) Knott E. B., *J. Chem. Soc.*, 186 (1948).
(233) Kojima, S., *J. Chem. Soc. Japan, Ind. Chem. Sect.*, **58**, 470 (1955); *Chem. Abstr.*, **50**, 4903a (1956).
(234) Kondo, H., and Ohno, S., *J. Pharm. Soc. Japan*, **71**, 693 (1951); *Chem. Abstr.*, **46**, 8086 (1952).
(235) Kreutzberger, A., and Kalter, P. A., *J. Org. Chem.*, **25**, 554 (1960).
(236) Kreutzberger, A., and Kalter, P. A., *J. Org. Chem.*, **26**, 3790 (1961).
(237) Kuhn, R., and Dury, K., *Ann.*, **571**, 44 (1951).
(238) Kuhn, R., and Kainer, H., *Ann.*, **578**, 227 (1952).
(239) Kuhn, R., and Kainer, H., *Biochim. Biophys. Acta*, **12**, 325 (1953); *Chem. Abstr.*, **48**, 11391a (1954).
(240) Kuhn, R., and Ostwald, G., *Ber.*, **89**, 1423 (1956).
(241) Kuhn, R., and Stein, O., *Ber.*, **70**, 567 (1937).
(242) Kursanov, D. N., and Parnes, Z. N., *Dokl. Akad. Nauk SSSR*, **109**, 315 (1956); *Chem. Abstr.*, **51**, 1944i (1957).
(243) Kutscher, W., and Klamerth, O., *Hoppe-Seyler's Z. physiol. Chem.*, **286**, 190 (1951).
(244) Kutscher, W., and Klamerth, O., *Hoppe-Seyler's Z. physiol. Chem.*, **289**, 229 (1952).
(245) Kutscher, W., and Klamerth, O., *Ber.*, **86**, 352 (1953).
(246) Kutscher, W., and Klamerth, O., German Patent 1,011,886; *Chem. Abstr.*, **54**, 14268 (1960).
(247) Lancaster, R. E., Jr., and VenderWerf, C. A., *J. Org. Chem.*, **23**, 1208 (1958).
(248) Landon, J., and Sjogren, B., Swedish Patent 134,543; *Chem. Abstr.*, **47**, 3344i (1953).
(249) Langheld, K., *Ber.*, **42**, 2973 (1909).
(250) Lapin, H., and Horeau, A., *Bull. soc. chim. France*, 1703 (1960).
(251) Larsen, E. M., and Terry, G. A., *J. Am. Chem. Soc.*, **73**, 500 (1951).
(252) Lebas, J. M., and Josien, M. L., *Bull. soc. chim. France*, 251 (1957).
(253) Leditschka, H., *Ber.*, **85**, 483 (1952).
(254) Lesher, G. Y., and Surrey, A. R., *J. Am. Chem. Soc.*, **77**, 636 (1955).
(255) Lespagnol, A., and Dumont, J. M., Mercier, J., and Etzensperger, Mme., *Bull. soc. pharm. Lille*, **No. 1**, 87 (1955); *Chem. Abstr.*, **50**, 3399a (1956).
(256) Letellier, G., and Bonthillier, L. P., *Can. J. Biochem. Physiol.*, **34**, 1123 (1956).
(257) Lipp, P., and Seeles, H., *Ber.*, **62**, 2456 (1929).
(258) Lore, E. V., and Brooker, L. G. S., U. S. Patent 2,515,912; *Chem. Abstr.*, **45**, 3567f (1951).
(259) Lukes, R., *Collection Czech. Chem. Commun.*, **12**, 641 (1947).
(260) Lukes, R., and Cersinka, O., *Chem. Listy*, **51**, 2144 (1957); *Chem. Abstr.*, **52**, 5378d (1958).
(261) Lukes, R., Clesek, J., and Trojanek, J., *Collection Czech. Chem. Commun.*, **24**, 1987 (1959); *Chem. Abstr.*, **53**, 20032 (1959).
(262) Lukes, R., and Pliml, J., *Chem. Listy*, **49**, 1821 (1955); *Chem. Abstr.*, **50**, 9379a (1956).
(263) Lung, K., Yu, S., and Li, S., *Chung Shan Ta Hsueh Hsueh Pao*, **2**, 45 (1957); *Chem. Abstr.*, **54**, 22563b (1960).
(264) MacDonald, S. F., *J. Chem. Soc.*, 4184 (1952).
(265) MacDonald, D. M., and MacDonald, S. F., *Can. J. Chem.*, **33**, 573 (1955).
(266) MacDonald, S. F., and Stedman, R. J., *Can. J. Chem.*, **33**, 458 (1955).
(267) Malachowski, R., and Jankiewica-Wasowska, J., *Roczniki Chem.*, **25**, 35 (1951); *Chem. Abstr.*, **47**, 2694b (1953).
(268) Malinovskii, M. S., and Baranov, S. N., *Zh. Obshch. Khim.*, **22**, 1970 (1952); *Chem. Abstr.*, **47**, 9282h (1953).
(269) Malinovskii, M. S., and Baranov, S. N., *Zh. Priklad. Khim.*, **25**, 410 (1952); *Chem. Abstr.*, **47**, 2694b (1953).
(270) Malinovskii, M. S., and Morgun, G. E., *J. Appl. Chem. USSR*, **25**, 367 (1952); *Chem. Abstr.*, **49**, 4624g (1955).
(271) Malinovskii, M. S., and Morgun, G. E., *Zh. Priklad. Khim.*, **26**, 185 (1953); *Chem. Abstr.*, **48**, 8785h (1954).

(272) Mandell, L., and Blanchard, W. A., *J. Am. Chem. Soc.*, **79**, 6198 (1957).
(273) Marinangeli, M., *Ann. chim.* (Rome), **44**, 211 (1954).
(274) Martel, J., *Compt. rend.*, **244**, 626 (1957).
(275) Marvel, C. S., Nowak, R. M., and Economy, J., *J. Am. Chem. Soc.*, **78**, 6171 (1956).
(276) Matteson, D. S., and Snyder, H. R., *J. Am. Chem. Soc.*, **79**, 3610 (1957).
(277) Matteson, D. S., and Snyder, H. R., *J. Org. Chem.*, **22**, 1500 (1957).
(278) Meszaros, L., and Bartok, M., *Acta Univ. Szegediensis, Acta Phys. Chem.*, **4**, 161 (1958); *Chem. Abstr.*, **53**, 15040g (1959).
(279) Meyazake, M., Nanishi, K., Kariuone, K., and Ota, S., Japanese Patent 2773 (1957); *Chem. Abstr.*, **52**, 4693c (1958).
(280) Micovic, V. M., and Mihailovic, M. L., *J. Org. Chem.*, **18**, 1190 (1953).
(281) Middleton, W. J., U. S. Patent 2,726,249; *Chem. Abstr.*, **50**, 10775f (1956).
(282) Middleton, W. J., U. S. Patent 2,779,766; *Chem. Abstr.*, **51**, 10586f (1957).
(283) Middleton, W. J., U. S. Patent 2,793,215; *Chem. Abstr.*, **52**, 1279a (1958).
(284) Middleton, W. J., U. S. Patent 2,940,977; *Chem. Abstr.*, **54**, 21129c (1960).
(285) Middleton, W. J., U. S. Patent 2,961,447; *Chem. Abstr.*, **55**, 8874c (1961).
(286) Milazzo, G., *Gazz. chim. ital.*, **81**, 710 (1951).
(287) Milazzo, G., *Experientia*, **8**, 259 (1952); *Chem. Abstr.*, **46**, 10853 (1952).
(288) Milazzo, G., *Gazz. chim. ital.*, **82**, 362 (1952).
(289) Milazzo, G., *Gazz. chim. ital.*, **82**, 808 (1952).
(290) Milazzo, G., *Naturwissenschaften*, **39**, 81 (1952); *Chem. Abstr.*, **47**, 401e (1953).
(291) Milazzo, G., *Gazz. chim. ital.*, **83**, 392 (1953).
(292) Minagawa, T., *Proc. Imp. Acad.* (Tokyo), **21**, 33 (1945); *Chem. Abstr.*, **47**, 151i (1953).
(293) Mirone, P., *Gazz. chim. ital.*, **86**, 165 (1956).
(294) Mirone, P., Dursiani, A. M., and Lorenzelli, V., *Ann. chim.* (Rome), **46**, 1217 (1956).
(295) Mirone, P., and Fabbri, G., *Gazz. chim. ital.*, **86**, 1079 (1956).
(296) Mirone, P., and Lorenzelli, V., *Ann. chim.* (Rome), **48**, 72 (1958).
(297) Mirone, P., and Lorenzelli, V., *Ann. chim.* (Rome), **48**, 881 (1958).
(298) Mirone, P., and Vampiri, M., *Atti accad. nazl. Lincei*, **12**, 405 (1952).
(299) Miyazaki, M., Mizuno, C., and Umio, S., Japanese Patent 3786; *Chem. Abstr.*, **55**, 1653i (1961).
(300) Moffett, R. B., *J. Org. Chem.*, **14**, 862 (1949).
(301) Morelli, G., and Stein, M. L., *J. Med. Pharm. Chem.*, **2**, 79 (1960); *Chem. Abstr.*, **54**, 18475i (1960).
(302) Muic, N., and Fles, D., *Arhiv. Kemi*, **22**, 182 (1950); *Chem. Abstr.*, **46**, 4527 (1952).
(303) Murakoski, I., *Yakugaku Zasshi*, **78**, 598 (1958); *Chem. Abstr.*, **52**, 18409i (1958).
(304) Murray, J. V., and Cloke, J. B., *J. Am. Chem. Soc.*, **68**, 126 (1946).
(305) Muzzari, G., and Borgo, A., *Gazz. chim. ital.*, **35**, I, 477; II, 19 (1905).
(306) Nagakuro, S., and Hosya, T., *Bull. Chem. Soc. Japan*, **25**, 179 (1952); *Chem. Abstr.*, **47**, 5189i (1953).
(307) Naqvi, N., and Fernando, Q., *J. Org. Chem.*, **25**, 551 (1960).
(308) National Office of Aerodynamic Studies and Research: British Patent 736,505; *Chem. Abstr.*, **52**, 16330e (1958).
(309) Nenitzescu, C. D., Necsoiu, I., and Zalman, M., *Comun. acad. rep. populare Romine*, **7**, 421(1957); *Chem. Abstr.*, **52**, 16330e (1958).
(310) Nicolaus, R., *Gazz. chim. ital.*, **83**, 239 (1953).
(311) Nicolaus, R., *Ric. sci.*, **23**, 1636 (1953); *Chem. Abstr.*, **48**, 12732f (1954).
(312) Nicolaus, R., *Gazz. chim. ital.*, **85**, 659 (1955).
(313) Nicolaus, R. A., and Mangoni, L., *Gazz. chim. ital.*, **85**, 1378 (1955).
(314) Nicolaus, R. A., and Mangoni, L., *Gazz. chim. ital.*, **86**, 358 (1956).
(315) Nicolaus, R. A., Mangoni, L., and Mitisi, D., *Ann. chim.* (Rome), **46**, 847 (1956).
(316) Nicolaus, R. A., and Nicoletti, R., *Ann. chim.* (Rome), **47**, 167 (1957).
(317) Nicolaus, R. A., and Oriente, G., *Gazz. chim. ital.*, **84**, 230 (1954).
(318) Nicolaus, R. A., Scarpati, R., and Fortino, C., *Rend. accad. sci. fis. mat.*, **26**, 51 (1959); *Chem. Abstr.*, **54**, 493i (1960).
(319) Noland, W. E., and Kuryla, W. C., *J. Org. Chem.*, **25**, 486 (1960).
(320) Novikov, S. S., and Belikov, V. M., *Izv. Akad. Nauk. SSSR, Otd. Khim. Nauk*, 1098 (1959); *Chem. Abstr.*, **54**, 1488 (1960).
(321) Novikov, S. S., Safonova, E. N., and Belikov, V. M., *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1053 (1960); *Chem. Abstr.*, **54**, 24641b (1960).
(322) Nystrom, R. F., Rainer, C., and Berger, A., *J. Am. Chem. Soc.*, **80**, 2896 (1958).
(323) Ochiai, E., and Karii, M., *J. Pharm. Soc. Japan*, **59**, 18 (1939).
(324) Osuge, K., *J. Pharm. Soc. Japan*, **75**, 1281 (1955); *Chem. Abstr.*, **50**, 8595h (1956).
(325) Overberger, C. G., Palmer, P. C., Macks, B. S., and Byrd, N. R., *J. Am. Chem. Soc.*, **77**, 4100 (1955).
(326) Patterson, J. M., and Dunchko, P., *J. Org. Chem.*, **24**, 878 (1959).
(327) Paytash, P. L., Sparrow, E., and Gathe, J. C., *J. Am. Chem. Soc.*, **72**, 1415 (1950).
(328) Perez, S. S., Herraez, M. A., Igea, F. J., and Esteve, J., *J. Anales real soc. espan. fis. quim.* (Madrid), **51B**, 91 (1955); *Chem. Abstr.*, **49**, 8642i (1955).
(329) Perveev, F. Ya., and Kuznetsiva, E. M., *Zh. Obshch. Khim.*, **28**, 2360 (1958); *Chem. Abstr.*, **53**, 3190e (1959).
(330) Perveev, F. Ya., and Martinson, E., *Zh. Obshch. Khim.*, **29**, 2922 (1959); *Chem. Abstr.*, **54**, 12105 (1960).
(331) Perveev, F. Ya., Vekshina, E. M., and Surenkova, L. N., *Zh. Obshch. Khim.*, **27**, 1526 (1957); *Chem. Abstr.*, **52**, 3767g (1958).
(332) Pike, R. M., U. S. Patent 2,881,184; *Chem. Abstr.*, **53**, 16152c (1959).
(333) Plieninger, H., and Buhler, W., *Angew. Chem.*, **71**, 163 (1959).
(334) Potts, H. A., and Smith, G. F., *J. Chem. Soc.*, 4018 (1957).
(335) Pratesi, P., and Castorina, G., *Gazz. chim. ital.*, **83**, 913 (1953).
(336) Preininger, V., Potesilova, H., and Santavy, F., *Chem. Listy*, **52**, 25 (1958); *Chem. Abstr.*, **52**, 13481g (1958).
(337) Prelog, V., *Helv. Chim. Acta*, **28**, 576 (1945).
(338) Raecke, B., *Angew. Chem.*, **70**, 1 (1958).
(339) Ramart-Lucas, P., Grumez, M., Hoch, J., Klein, J., Martynoff, M., and Roch, M., *Bull. soc. chim. France*, 1017 (1954).
(340) Ramart-Lucas, P., Hoch, J., and Klein, J., *Compt. rend.*, **232**, 336 (1951).
(341) Rapoport, H., Christian, C. G., and Spencer, G., *J. Org. Chem.*, **19**, 840 (1954).

(342) Rapoport, H., and Willson, C. D., *J. Org. Chem.*, **26**, 1102 (1961).
(343) Reed, K. J., British Patent 696,646; *Chem. Abstr.*, **48**, 4343c (1954).
(344) Reed, K. J., U. S. Patent 2,725,378; *Chem. Abstr.*, **51**, 909a (1957).
(345) Reed, K. J., U. S. Patent 2,739,148; *Chem. Abstr.*, **51**, 901c (1957).
(346) Reich, H. E., and Levine, R., *J. Am. Chem. Soc.*, **77**, 4913 (1955).
(347) Reitsema, R. H., *J. Am. Chem. Soc.*, **71**, 2041 (1949).
(348) Reppe, W., *Ann.*, **596**, 80 (1955).
(349) Reppe, W., *Ann.*, **601**, 128 (1956).
(350) Rips, R., and Buu-Hoi, Ng. Ph., *J. Org. Chem.*, **24**, 372 (1959).
(351) Rips, R., Derappe, Ch., and Buu-Hoi, Ng. Ph., *J. Org. Chem.*, **25**, 390 (1960).
(352) Risenberg, D. S., and Weil, E., U. S. Patent 2,951,081; *Chem. Abstr.*, **55**, 4532d (1961).
(353) Roberts, J. D., *J. Am. Chem. Soc.*, **78**, 4495 (1956).
(354) Rocek, J., *Chem. Listy*, **47**, 1781 (1953); *Chem. Abstr.*, **49**, 1055b (1955).
(355) Rogers, M. A. T., *J. Chem. Soc.*, 590 (1943).
(356) Rosenberg, D. S., and Weil, E., U. S. Patent 2,951,081.
(357) Runge, R., *Ann. Physik.*, **31**, 67 (1834).
(358) Rupe, H., and Gisiger, F., *Helv. Chim. Acta*, **8**, 338 (1925).
(359) Ryskiewicz, E. E., and Silverstein, R. M., *J. Am. Chem. Soc.*, **76**, 5802 (1954).
(360) Safonova, E. N., Belikov, V. M., and Novikov, S. S., *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1307 (1959); *Chem. Abstr.*, **54**, 1487 (1960).
(361) Sanchez, A. G., and Gomez, J. G., *Anales real soc. espan. fis. quim.* (Madrid), **54B**, 753 (1958).
(362) Santhamma, V., *Proc. Natl. Inst. Sci. India*, **22A**, 204 (1956); *Chem. Abstr.*, **51**, 14406i (1957).
(363) Sardina, M. T., and Bonino, C., *Boll. sci. fac. chim. ind. Bologna*, **12**, 155 (1954); *Chem. Abstr.*, **49**, 10709b (1955).
(364) Sargeson, A. M., and Sasse, W. F., *Proc. Chem. Soc.*, 150 (1958).
(365) Sarsen, S., and Bernstein, J., *J. Am. Chem. Soc.*, **72**, 4447 (1950).
(366) Sausen, G. N., Engelhardt, V. A., and Middleton, W. J., *J. Am. Chem. Soc.*, **80**, 2815 (1958).
(367) Sazonova, V. A., and Sorokina, L. P., *Dokl. Akad. Nauk SSSR*, **105**, 993 (1955); *Chem. Abstr.*, **50**, 11339g (1956).
(368) Scarpati, R., and Nicolaus, R., *Rend. accad. sci. fis. e mat. (Soc. nazl. sci. Napoli)*, **26**, 9 (1959); *Chem. Abstr.*, **54**, 493i (1960).
(369) Schick, J. W., and Hartough, H. D., U. S. Patent 2,625,550; *Chem. Abstr.*, **47**, 4653h (1953).
(370) Schulte, K. E., and Zinnert, F., *Arch. Pharm.*, **286**, 452 (1953); *Chem. Abstr.*, **51**, 13844c (1957).
(371) Schulte, K. E., and Zinnert, F., *Arch. Pharm.*, **288**, 60 (1955); *Chem. Abstr.*, **50**, 12024h (1956).
(372) Schutt, H., U. S. Patent 2,898,344; *Chem. Abstr.* **54**, 17418 (1960).
(373) Scott, F. L., and Scott, M. T., *J. Am. Chem. Soc.*, **79**, 6077 (1957).
(374) Scrocco, M., Caglioti, L., and Caglioti, V., *Atti acad. nazl. Lincei*, **24**, 316 (1958).
(375) Scrocco, M., and Nicolaus, R., *Atti accad. nazl. Lincei*, **20**, 795 (1956).
(376) Scrocco, M., and Nicolaus, R., *Atti accad. nazl. Lincei*, **21**, 103 (1956).
(377) Scrocco, M., and Nicolaus, R., *Atti accad. nazl. Lincei*, **22**, 311 (1957).
(378) Scrocco, M., and Nicolaus, R., *Atti accad. nazl. Lincei*, **22**, 500 (1957).
(379) Shirley, D. A., Gross, B. H., and Roussel, P. A., *J. Org. Chem.*, **20**, 225 (1955).
(380) Shuikin, N. I., and Tulupov, V. A., *Vestnik Moskov. Univ.*, **11**, No. 3, *Ser. Fiz. Mat. i Estestven. Nauk* No. 2, 73 (1956); *Chem. Abstr.*, **50**, 12445i (1956).
(381) Siegrist, A. E., and Duennenberger, M., U. S. Patent 2,901,480; *Chem. Abstr.*, **55**, 1658c (1961).
(382) Silverstein, R. M., Ryskiewicz, E. E., and Chaikin, S. W., *J. Am. Chem. Soc.*, **76**, 4485 (1954).
(383) Silverstein, R. M., Ryskiewicz, E. E., Willard, C., and Koehler, B. C., *J. Org. Chem.*, **20**, 668 (1955).
(384) Singer, W. E., *Dissertation Abstr.*, **18**, 1822 (1958).
(385) Skinner, G. S., and Perkins, J. F., Jr., *J. Am. Chem. Soc.*, **72**, 5569 (1950).
(386) Smissman, E. E., Graber, M. B., and Winzler, R. J., *J. Am. Pharm. Assoc.*, **45**, 509 (1956).
(387) Smith, G. F., *J. Chem. Soc.*, 3842 (1954).
(388) Snyder, H. R., and Smith, C. W., *J. Am. Chem. Soc.*, **66**, 350 (1944).
(389) Snyder, H. R., Smith, C. W., and Stewart, J. M., *J. Am. Chem. Soc.*, **66**, 200 (1944).
(390) Söderbäck, E., *Acta Chem. Scand.*, **8**, 1851 (1954); *Chem. Abstr.*, **50**, 297g (1956).
(391) Sonn, A., *Ber.*, **68**, 148 (1935).
(392) Southwick, P. L., and Crouch, R. T., *J. Am. Chem. Soc.*, **75**, 3413 (1953).
(393) Southwick, P. L., Sapper, D. I., and Pursglove, L. A., *J. Am. Chem. Soc.*, **72**, 4940 (1950).
(394) Southwick, P. L., and Seitard, L. L., *J. Am. Chem. Soc.*, **71**, 2532 (1949).
(395) Sprio, V., *Gazz. chim. ital.*, **85**, 569 (1955).
(396) Sprio, V., *Gazz. chim. ital.*, **86**, 96 (1956).
(397) Sprio, V., and Fabra, I., *Ann. chim.* (Rome), **46**, 263 (1956).
(398) Sprio, V., and Fabra, I., *Gazz. chim. ital.*, **86**, 1059 (1956).
(399) Sprio, V., and Fabra, I., *Ann. chim.* (Rome), **49**, 2053 (1959).
(400) Sprio, V., and Madonia, P., *Gazz. chim. ital.*, **85**, 965 (1955).
(401) Sprio, V., and Madonia, P., *Gazz. chim. ital.*, **86**, 101 (1956).
(402) Sprio, V., and Madonia, P., *Gazz. chim. ital.*, **87**, 171 (1957).
(403) Sprio, V., Madonia, P., and Caronia, R., *Ann. chim.* (Rome), **49**, 169 (1959).
(404) Sprio, V., and Vaccaro, G. C., *Ann. chim.* (Rome), **49**, 2075 (1950); *Chem. Abstr.*, **54**, 16483f (1960).
(405) Strell, M., and Kreis, F., *Ber.*, **87**, 1011 (1954).
(406) Sugasawa, S., and Ushioda, S., *Tetrahedron*, **5**, 48 (1959).
(407) Sugimoto, N., *J. Pharm. Soc. Japan*, **64**, 193 (1944); *Chem. Abstr.*, **45**, 2862c (1951).
(408) Sugisawa, H., and Aso, K., *Tohoku J. Agr. Res.*, **10**, 137 (1959); *Chem. Abstr.*, **54**, 11015b (1960).
(409) Süs, O., Glos, M., Möller, K., and Eberhardt, H. D., *Ann.*, **583**, 150 (1953).
(410) Süs, O., Möller, K., Dieterich, R., Eberhardt, H., Gles, M., Grundkötter, M., Hoffmann, H., and Schäfer, H., *Ann.*, **593**, 91 (1953).
(411) Swain, C. G., Kaiser, L. E., and Knee, T. E. C., *J. Am. Chem. Soc.*, **77**, 4681 (1955).
(412) Tatsuoka, S., Ueno, Y., Nawa, H., Matsuoka, T., Ueyanagi, J., Nakamori, R., Honjo, M., and Miyamoto, M., Japanese Patent 10579 (1957); *Chem. Abstr.*, **52**, 17288d (1958).
(413) Tatsuoka, S., Ueno, Y., Tanoka, K., Ueyanagi, T., Nawa, H., Morimoto, H., Sugwa, T., Nakamor, N., Mitsuno, Y., and Matsuoka, T., Japanese Patent 8280 (1958); *Chem. Abstr.*, **54**, 4618g (1960).

(414) Tedder, J. M., and Webster, B., *J. Chem. Soc.*, 3270 (1960).
(415) Terentev, A. P., and Domborvskii, A. V., *Zh. Obshch. Khim.*, **21**, 278 (1951); *Chem. Abstr.*, **45**, 7025 (1951).
(416) Terentev, A. P., and Makarova, A. N., *J. Gen. Chem. USSR*, **21**, 295 (1951).
(417) Terentev, A. P., and Makarova, A. N., *Zh. Obshch. Khim.*, **21**, 270 (1951).
(418) Terentev, A. P., Volodina, M. A., Podlesiva, N. L., and Golubeva, N. E., *Dokl. Akad. Nauk SSSR*, **114**, 1036 (1957); *Chem. Abstr.*, **52**, 3767e (1958).
(419) Terentev, A. P., and Yanovaskaya, L. A., *J. Gen. Chem. USSR*, **21**, 281 (1952); *Chem. Abstr.*, **46**, 2049b (1952).
(420) Terentev, A. P., Yanovskaya, L. A., and Terenteva, E. A., *Zh. Obshch. Khim.*, **22**, 859 (1952); *Chem. Abstr.*, **47**, 3294g (1953).
(421) Thiele, J., *Ann.*, **303**, 54 (1898).
(422) Thiele J. and Manchot, W., *Ann.*, **303**, 47 (1898).
(423) Timoschevskaya, N. M., *Tr. Karkov. Politekhn. Inst.*, **4**, 73 (1954); *Chem. Abstr.*, **52**, 7279a (1958).
(424) Timoshevskaya, N. M., *Zh. Obshch. Khim.*, **22**, 153 (1952); *Chem. Abstr.*, **46**, 11178a (1952).
(425) Treibs, A., *Ann.*, **602**, 153 (1957).
(426) Treibs, A., and Bader, H., *Ann.*, **627**, 182 (1958).
(427) Treibs, A., and Derra, R., *Ann.*, **589**, 76 (1954).
(428) Treibs, A., and Derra-Scherer, H., *Ann.*, **589**, 188 (1954).
(429) Treibs, A., and Derra-Scherer, H., *Ann.*, **589**, 196 (1954).
(430) Treibs, A., and Dieth, A., *Ber.*, **94**, 298 (1961).
(431) Treibs, A., and Dinelli, D., *Ann.*, **517**, 152 (1935).
(432) Treibs, A., and Fritz, G., *Angew. Chem.*, **66**, 562 (1954).
(433) Treibs, A., and Herrmann, E., *Ann.*, **592**, 1 (1955).
(434) Treibs, A., and Herrmann, E., *Hoppe-Seyler's Z. physiol. Chem.*, **299**, 168 (1955).
(435) Treibs, A., Herrmann, E., and Meissner, E., *Ann.*, **612**, 229 (1958).
(436) Treibs, A., and Hintermeier, K., *Ber.*, **87**, 1167 (1954).
(437) Treibs, A., and Hintermeier, K., *Ann.*, **592**, 11 (1958).
(438) Treibs, A., and Hintermeier, K., *Ann.*, **605**, 35 (1957).
(439) Treibs, A., and Hitzler, O., *Ber.*, **90**, 787 (1957).
(440) Treibs, A., and Kolm, H. G., *Ann.*, **614**, 176 (1958).
(441) Treibs, A., and Kolm, H. G., *Ann.*, to be published.
(442) Treibs, A., and Michl, K. H., *Ann.*, **577**, 115 (1952).
(443) Treibs, A., and Michl, K. H., *Ann.*, **577**, 129 (1952).
(444) Treibs, A., and Michl, K. H., *Ann.*, **577**, 134 (1952).
(445) Treibs, A., and Michl K. H. *Ann.* **589**, 163 (1954).
(446) Treibs A. and Michl, K. H., *Ann.*, **589**, 168 (1954).
(447) Treibs, A., and Newmayr, F., *Ber.*, **90**, 76 (1957).
(448) Treibs, A., and Ohorodnik, A., *Ann.*, **611**, 139 (1958).
(449) Treibs, A., and Ott, W., *Ann.*, **577**, 119 (1952).
(450) Treibs, A., and Reitsam, F., *Ber.*, **90**, 777 (1957).
(451) Treibs, A., and Reitsam, F., *Ann.*, **611**, 205 (1958).
(452) Treibs, A., and Scherer, H., *Ann.*, **577**, 139 (1952).
(453) Treibs, A., and Seifert, W., *Ann.*, **612**, 242 (1958).
(454) Treibs, A., and Zimmer-Galler, R., *Ber.*, **93**, 2539 (1960).
(455) Treibs, A., and Zimmer-Galler, R., *Ber.*, **93**, 2547 (1960).
(456) Treibs, A., and Zinsmeister, R., *Ber.*, **90**, 79 (1957).
(457) Treibs, A., and Zinsmeister, R., *Ber.*, **90**, 87 (1957).
(458) Tuomikoski, P., *J. phys. radium*, **15**, 318 (1954).
(459) Tuomikoski, P., *J. phys. radium*, **16**, 347 (1955).
(460) Ugryumov, P. S., *Zh. Obshch. Khim.*, **20**, 1848 (1950); *Chem. Abstr.*, **45**, 2469c (1951).
(461) Umio, S., *Yukagaku Zasshi*, **79**, 1048 (1959); *Chem. Abstr.*, **54**, 5611c (1960).
(462) Umio, S., and Mizuno, C., *Yakugaku Zasshi*, **77**, 418 (1957); *Chem. Abstr.*, **51**, 12068 (1957).
(463) Valentine, F. R., Jr., Canadian Patent 495,686; *Chem. Abstr.*, **49**, 16496i (1955).
(464) Vasquez, A., and Cruz, J. R., *Anales real soc. espan. fis. quim.* (Madrid), **49B**, 91 (1953); *Chem. Abstr.*, **48**, 2029b (1954).
(465) Vaughan, S. W. R., and Peters, H. R., *J. Org. Chem.*, **18**, 382 (1953).
(466) Vila, J. P., and Masso, B., *Anales real soc. espan. fis. quim.* (Madrid), **48B**, 155 (1952); *Chem. Abstr.*, **47**, 6871c (1953).
(467) Wahlstam, H., *Arkiv Kemi*, **11**, 251 (1957); *Chem. Abstr.*, **52**, 1141f (1958).
(468) Walker, R. A., and Sickels, J. P., U. S. Patent 2,527,165; *Chem. Abstr.*, **45**, 2984g (1951).
(469) Waller, C. W., Weiss, M. J., and Webb, J. S., U. S. Patent 2,785,181; *Chem. Abstr.*, **51**, 14820d (1957).
(470) Waller, C. W., Weiss, M. J., Webb, J. S., U. S. Patent 2,962,503; *Chem. Abstr.*, **55**, 10470e (1961).
(471) Waller, C. W., Wolf, C. F., Stein, W. J., and Hutchings, B. L., *J. Am. Chem. Soc.*, **79**, 1265 (1957).
(472) Walsh, E. O., *J. Chem. Soc.*, 726 (1942).
(473) Wasserman, H. H., and Brons, J. B., *J. Org. Chem.*, **19**, 515 (1954).
(474) Wasserman, H. H., and Liberles, A., *J. Am. Chem. Soc.*, **82**, 2086 (1960).
(475) Webb, I. D., and Borcherdt, G. T., *J. Am. Chem. Soc.*, **73**, 752 (1951).
(476) Webb, I. D., and Borcherdt, G. T., U. S. Patent 2,640,057; *Chem. Abstr.*, **48**, 4595c (1954).
(477) Weiss, M. J., U. S. Patent 2,797,228; *Chem. Abstr.*, **52**, 1264c (1958).
(478) Weiss, M. J., Webb, J. S., and Smith, J. M., Jr., *J. Am. Chem. Soc.*, **79**, 1266 (1957).
(479) White, F. L., and Brooker, L. G. S., U. S. Patent 2,518,737; *Chem. Abstr.*, **45**, 968c (1951).
(480) Wilson, W., *J. Chem. Soc.*, 3524 (1952).
(481) Woodbridge, R. G., and Dougherty, G., *J. Am. Chem. Soc.*, **72**, 4320 (1950).
(482) Xuong, Ng. D., Thu-Cuc, N. T., and Buu-Hoi, Ng. Ph., *Bull. soc. chim. France*, 221 (1958).
(483) Yamamoto, K., Japanese Patent 9467 (1958); *Chem. Abstr.*, **54**, 5696f (1960).
(484) Yamamoto, K., Japanese Patent 1983 (1959); *Chem. Abstr.*, **54**, 9957h (1960).
(485) Yamamoto, K., Hattori, T., and Kariyone, K., *J. Pharm. Soc. Japan*, **75**, 1219 (1955); *Chem. Abstr.*, **50**, 8597e (1956).
(486) Yamamoto, K., and Kimura, H., *J. Pharm. Soc. Japan*, **76**, 482 (1956); *Chem. Abstr.*, **51**, 365f (1957).
(487) Yurev, Yu. K., *J. Gen. Chem. USSR*, **10**, 1839 (1940); *Chem. Abstr.*, **35**, 4377 (1941).
(488) Yurev, Yu. K., *Tr. Vses. Soveshch. Riga*, 405 (1955); *Chem. Abstr.*, **53**, 14078 (1959).
(489) Yurev, Yu. K., and Elyakov, G. B., *Zh. Obshch. Khim.*, **26**, 2350 (1956); *Chem. Abstr.*, **51**, 5042h (1957).
(490) Yurev, Yu. K., Kondrateva, G. Ya., and Kartaskevskii, A. I., *Zh. Obshch. Khim.*, **22**, 513 (1952); *Chem. Abstr.*, **47**, 2748b (1953).
(491) Yurev, Yu. K., Korobitsyna, I. K., Ben-Yakir, R. D., Savina, L. A., and Akishim, P. A., *Vestnik Moskov. Univ.* **6**, No. 2, *Ser. Fiz. Mat. i Estestven Nauk* No. 1, 37 (1951); *Chem. Abstr.*, **47**, 124b (1953).
(492) Yurev, Yu. K., Korobitsyna, I. K., and Kuznetsova, M. L., *Zh. Obshch. Khim.*, **20**, 1493 (1954); *Chem. Abstr.*, **45**, 5680b (1951).
(493) Yurev, Yu. K., and Levi, I. S., *Vestnik Moskov. Univ. Ser. Mat., Mekhan., Astron., Fiz. i Khim.*, **11**, No. 2, 153 (1956); *Chem. Abstr.*, **52**, 355a (1958).
(494) Yurev, Yu. K., and Makarov, N. V., *Zh. Obsch. Khim.*, **28**, 885 (1958); *Chem. Abstr.*, **52**, 17233b (1958).

(495) Yurev, Yu, K., and Tronowa, W. A., *J. Gen. Chem. USSR*, **11**, 244, (1941); *Chem. Abstr.*, **35**, 5893 (1941).
(496) Yurev, Yu. K., and Vendelshtein, E. G., *Zh. Obshch. Khim.*, **21**, 259 (1951); *Chem. Abstr.*, **45**, 7564a (1951).
(497) Yurev, Yu. K., and Vendelshtein, E. G., *Zh. Obshch. Khim.*, **23**, 2053 (1953); *Chem. Abstr.*, **49**, 3120b (1955).
(498) Zalay, E., *Vegyipari Kutato Intezetek Kozlemenyei*, **4**, 101 (1954); *Chem. Abstr.*, **52**, 16273b (1958).