The dioxophosphate XIX was insoluble in benzene and methylene chloride, sparingly soluble in acetone and acetonitrile, and somewhat soluble in DMF and DMSO. The P^{31} nmr in DMSO had *two* septets centered at -1.3 ppm due to the coupling of the P nucleus with the six protons of the two CH_3O groups and with the single proton on the carbon. The H^1 nmr spectrum in deuterated DMSO had a 2 H^1 signal at τ -1.41 due to the acidic ureide NH protons, a 1 H^1 doublet, J_{HP} = 17 cps, at 4.18 due to the lone proton on carbon, coupled to phosphorus, and a 6 H^1 doublet, J_{HP} = 11.5 cps, at 6.20 due to the two equivalent methoxy groups on phosphorus. The infrared spectrum (Nujol mull) had broad absorption in the HX region at 3.7–4.0, a strong band at 5.78 (ureide CO), and strong bands at 6.00 and 6.18 μ, probably due to H-bonded lactam CO; there were bands at 8.00 and at 9.50 μ, attributed to the phosphate ester.

Formation of the Triethylammonium Salt of 5-Hydroxybarbituric Acid 5-Dimethyl Phosphate (XIX) and Reaction of the Salt with Diazomethane.—A suspension of the dioxophosphate XIX (2.2 g, 9 mm) in methylene chloride (30 ml) was treated, dropwise with triethylamine. A clear, red solution was obtained upon addition of *ca.* 1 mole equiv of the amine (1.4 ml). The solvent was removed at 20° (25 mm) and the red residue was dried at 90° (0.5 mm). This salt had $\delta_{P^{31}}$ = 0.0 ppm (*vs.* H_3PO_4). The H^1 nmr spectrum in $CDCl_3$ had a broad signal at τ -0.7, a 6 H^1 doublet, J_{HP} = 11.2 cps, at 6.15, and the quartet J_{HH} = 7 cps, at 6.80, and the triplet at 8.72, expected from the triethylamine. The infrared spectrum (CH_2Cl_2) had very strong bands at 6.00 and 6.20 μ.

A clear solution of the salt in methanol (15 ml) was treated with ethereal diazomethane. After 48 hr at 10°, the solution was treated with drops of acetic acid, and distilled. The residue (1.9 g) had an infrared spectrum (in CH_2Cl_2) which was identical with that of the crude product from the reaction of 5-hydroxy-6-methoxyuracil 5-dimethyl phosphate (XIII) with diazomethane.

The crude product (1.9 g) of the methylation was sublimed at 110° (0.1 mm), yielding 750 mg of colorless crystals mp 65–67°. Crystallization from hexane gave **5-hydroxy-2,4,6-trimethoxypyrimidine 5-dimethyl phosphate** (XIV, mp 67–71°) identified by its infrared and H^1 nmr spectra (see above).

Reaction of Anhydrous Alloxan with Dimethyl Phosphite in the Absence of Solvent.—Dimethyl phosphite (9.3 g, 3 mole equiv) was added to anhydrous alloxan (4.0 g) under N_2. The exothermic reaction led initially to a clear solution, which then deposited crystals. After 12 hr at 20°, the mixture was diluted with benzene (25 ml), stirred for 30 min, and filtered. The solid was washed with benzene (25 ml) and the benzene fractions were combined (*vide infra*).

The colorless solid obtained above (4.1 g, 58%) proved to be 5-hydroxybarbituric acid 5-dimethyl phosphate (XIX), $\delta_{P^{31}}$ = -1.3 ppm (in DMSO). The identification was confirmed by infrared and H^1 nmr spectra.

N,N′-Dimethylparabanic Acid.—It was prepared from N,N′-dimethylurea and oxalyl chloride, as described.[9] It was recrystallized from water and dried at 100° (0.1 mm, mp 154–155°; infrared bands were at 5.70 and 5.78 μ (CH_2Cl_2); a H^1 nmr singlet was at τ 6.80 ($CDCl_3$).

Reaction of N,N′-Dimethylparabanic Acid (XI) with Triethyl Phosphite. Formation of N-Tetramethylbiparabanyl (XXV).—A suspension of XI (4.42 g) in triethyl phosphite (20.6, 4 mole equiv) was kept for 2 hr at 20°, without any evidence of reaction. The mixture was then kept for 4 hr at reflux temperature, and the yellow solution was distilled to remove all liquids boiling below 45° (35 mm). The residue was treated with cold ethanol (140 ml) and filtered. The **N-tetramethylbiparabanyl** (XXV, 3.8 g, 91%, mp *ca.* 200°) was recrystallized twice from ethanol, affording yellow needles, mp 216–217°.

Anal. Calcd for $C_{10}H_{12}N_4O_4$: C, 47.6; H, 4.8; N, 22.2; mol wt, 252. Found: C, 47.4; H, 4.8; N, 22.0; mol wt, 246 (isothermal distillation in CH_2Br_2).

The H^1 nmr spectrum ($CDCl_3$) had two singlets of equal intensities at τ 6.66 and 6.90; these are attributed, respectively, to the six equivalent protons of the two methyl groups attached to the imide nitrogens, and to the six equivalent protons of the two methyl groups attached to the amide nitrogens. The infrared spectrum (in CH_2Cl_2) had two carbonyl bands of nearly equal intensities; at 5.73 (ureide CO) and at 5.88 μ (unsaturated lactam).

Catalytic Hydrogenation of N-Tetramethylbiparabanyl (XXV).—A suspension of the yellow biparabanyl (1.0 g) in ethanol (100 ml) was hydrogenated in the presence of PtO_2 catalyst (150 mg) at 40 psi, at 20°. The colorless product was filtered while hot. On cooling, the crude, colorless dihydrobiparabanyl XXVI or XXVII (0.82 g, mp 165–175°) separated. One recrystallization from ethanol gave the analytical sample, mp 185–186°.

Anal. Calcd for $C_{10}H_{14}N_4O_4$: C, 47.2; H, 5.5; N, 22.0. Found: C, 47.1; H, 5.7; N, 21.7.

The H^1 nmr spectrum ($CDCl_3$) had one strong and one weak set of three singlets each. The singlets of the major set were at τ 5.65 (methine H^1) and at 7.00 and 7.02 (CH_3N); the integrated ratio of the first signal to the other two was as 1:6. The methine H^1 of the weak set was shifted 4.5 cps to low field relative to that of the strong set. One CH_3N signal of the weak set was shifted 2 cps to low field, the other 11 cps to high field of the corresponding signals of the major set. The infrared spectrum (CH_2Cl_2) had one strong carbonyl band at 5.80 and a weak carbonyl band at 5.65 μ (proportion *ca.* 4:1). It was assumed that the crystalline material in solution consisted of a major and a minor diastereomer, possibly easily interconverted.

Attempted Reaction of Parabanic Acid with Trimethyl Phosphite.—No identifiable product could be isolated when the reagents were kept for 15 days at 20° or for 16 hr at 100° (1:3 mole ratio).

Attempted Reaction of Parabanic Acid with Dimethyl Phosphite.—The following conditions failed to cause a reaction between these substances: (1) 48 hr at 20°; (2) 24 hr in boiling xylene; (3) 1 hr at 20°; 10 hr at 125°, in the presence of a few drops of triethylamine.

Acid-Catalyzed Condensation of a Reissert Compound with Acrylonitrile

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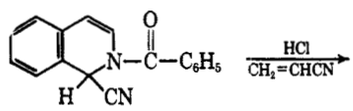
The acid-catalyzed condensation of 2-benzoyl-1,2-dihydroisoquinaldonitrile (I) with acrylonitrile afforded a pale yellow solid product to which the structure 2-(1-isoquinolyl)-3-cyano-5-phenylpyrrole (III) has been assigned. This compound was hydrolyzed to the corresponding carboxylic acid, which, in turn, was decarboxylated to give 2-(1-isoquinolyl)-5-phenylpyrrole (VII). The latter compound, in turn, was synthesized independently in a completely unambiguous manner. Other reactions of the initial condensation product are described, and a mechanism for its formation is suggested.

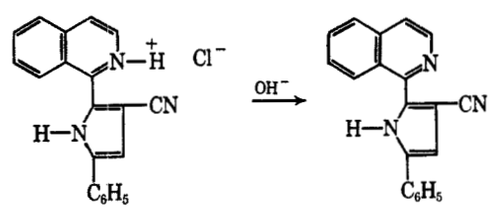
In a previous communication,[1] a description was given of the acid-catalyzed condensation of 2-benzoyl-1,2-dihydroisoquinaldonitrile (I) with 1,1-diphenylethylene to produce 2-(1-isoquinolyl)-3,3,5-triphenylpyrrolenine. A similar reaction has now been carried out between I and acrylonitrile, with hydrochloric acid as catalyst, and the hydrochloride (II) of 2-(1-isoquinolyl)-3-cyano-5-phenylpyrrole (III) was obtained. Treatment of II with sodium hydroxide solution afforded III, which showed the characteristic in-

(1) T. T. Yee, W. E. McEwen, and A. P. Wolf, *Tetrahedron Letters*, 3115 (1965).

frared absorption peaks for the N–H and cyano groups at 2.9 and 4.5 μ, respectively. The elucidation of the structure of III is the major consideration of the remainder of this manuscript.

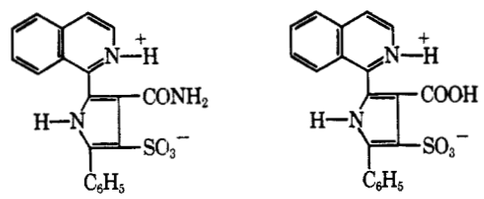


I



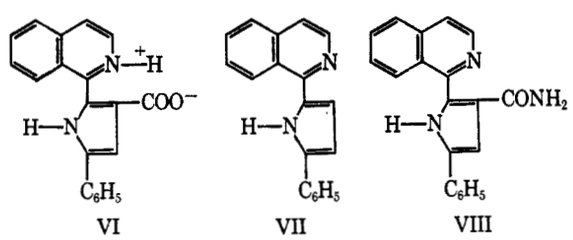
II III

Brief treatment of III with hot 80% sulfuric acid resulted in simultaneous sulfonation and hydrolysis of the compound, as indicated by the infrared spectrum and the elemental analysis of the product. The resulting 2-(1-isoquinolyl)-3-carboxamido-5-phenyl-4-pyrrolesulfonic acid (IV) was isolated in the form of its sodium salt. This acid, by further treatment with dilute sulfuric acid, was converted to the diacid V, which was isolated in the form of the disodium salt.



IV V

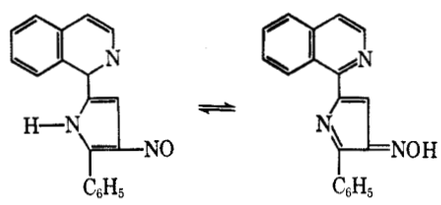
For the stepwise hydrolysis of 2-(1-isoquinolyl)-3-cyano-5-phenylpyrrole (III), polyphosphoric acid was used successfully. The yield of 2-(1-isoquinolyl)-3-carboxamido-5-phenylpyrrole (VIII) was almost quantitative. When a 48% solution of hydrogen bromide in glacial acetic acid was used in the place of polyphosphoric acid, the formation of the amide VIII was bypassed, and the corresponding acid VI was obtained directly, together with a small amount of the decarboxylated product, 2-(1-isoquinolyl)-5-phenylpyrrole (VII). A much better yield of VII was obtained when VI was maintained at its melting point until evolution of carbon dioxide ceased.



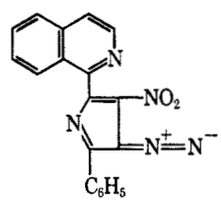
VI VII VIII

In the expectation of the occurrence of ring opening or possibly of degradative cleavage of 2-(1-isoquinolyl)-5-phenylpyrrole (VII), this compound was treated with sodium nitrite in glacial acetic acid. Two products were obtained from this reaction, one of which was a yellow solid of molecular formula $C_{19}H_{11}N_5O_2$, sensitive to heat and light, and the other one, a bright green solid of molecular formular $C_{19}H_{13}N_3O$. The yellow solid showed in its infrared spectrum a strong absorption peak at 4.6 μ, which is a characteristic peak for 3-diazopyrroles,[2] and another absorption band at 8.3 μ, which was attributed to the presence of a nitro group. Thus, it seemed that this product was an isoquinolylnitrodiazophenylpyrrole and that the reaction was similar to the known nitrosation reaction of 2,5-diphenylpyrrole.[3]

The green product of this reaction showed in its infrared spectrum strong absorption bands between 7 and 8 μ, which were attributed to the presence of a nitroso group. Furthermore, it was found that, by a change of the reaction conditions and a reduction of the amount of sodium nitrite used, the yield of the green, presumably nitroso, derivative was favored over that of the yellow solid. Thus, it was reasoned that, in the reaction of 2-(1-isoquinolyl)-5-phenylpyrrole with nitrous acid, an isoquinolylnitrosophenylpyrrole is formed first and that further reaction of this compound with nitrous acid results in the formation of the isoquinolyldiazonitrophenylpyrrole. From a hydrolysis reaction of the green compound, described below, there was obtained evidence that the nitroso group is adjacent to the phenyl group on the pyrrole ring. On the basis of this information, structures IX and X were tentatively assigned to the green and yellow compounds, respectively.



IX



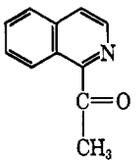
X

In relation to the structure of compound IX, it is noteworthy that, in the nmr spectrum, the characteristic band for the proton of the pyrrole nitrogen, falling usually at δ = 10–12 ppm, had disappeared, and instead a sharp singlet appeared at 6.6 ppm. This was interpreted as being due to tautomerization of the nitrosopyrrole to an isonitrosopyrrole structure.

Four products were obtained by the acid-catalyzed hydrolysis of compound IX, namely benzoic acid, carbon dioxide, 1-isoquinolyl methyl ketone (XI), and a white solid, mp 153–154°, of molecular formula $C_{19}H_{12}N_2O$. In the infrared spectrum of this last compound, a strong carbonyl absorption peak was observed at 6.0 μ, and the N–H absorption at 2.9 μ, characteristic of pyrroles, was absent. Furthermore, this solid formed an oxime when treated with hydroxylamine. The compound was found to be resistant to acid-

(2) E. Baltazzi and L. I. Krimen, *Chem. Rev.*, **63**, 511 (1963).
(3) J. M. Tedder and B. Webster, *J. Chem. Soc.*, 3270 (1960).

catalyzed hydrolysis, but it gave isoquinaldic acid and benzoic acid on alkaline hydrolysis. Further work will have to be carried out before the structure of this compound can be assigned in a definitive manner.



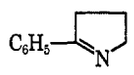
XI

With respect to the structures of 2-(1-isoquinolyl)-5-phenylpyrrole (VII) and its nitroso derivative (IX) two things were established with reasonable certainty from the information obtained through the experiment cited above: first, that the isoquinolyl group had to be at position 2 of the pyrrole ring, and second, that position 3 of the pyrrole did not bear any substituent. It would be hard to visualize a reasonable mechanism through which the isoquinolyl methyl ketone (XI) could arise if the isoquinolyl group were bonded to any other but position 2 of the pyrrole, and, for the same reasons, the adjacent position 3 could not bear either the phenyl or the nitroso substituent.

The degradation of 2,5-diphenylpyrrole by the action of hydrogen peroxide to give acetophenone and benzoic acid as products is a known reaction.[4] It was therefore thought that confirming evidence about the structure of 2-(1-isoquinolyl)-5-phenylpyrrole (VII) would be obtained if the degradation of this compound with hydrogen peroxide were to give products analogous to those obtained from the degradation of 2,5-diphenylpyrrole. In accord with this expectation, benzoic acid and isoquinolyl methyl ketone (XI) were obtained when compound VII was treated with hydrogen peroxide in glacial acetic acid.

The approach to the total synthesis of compound VII which proved to be successful consisted in starting from the pyrrole moiety of the molecule, with subsequent gradual construction of the isoquinoline part of the molecule.

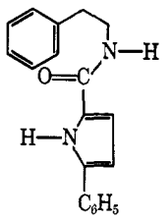
A new method was developed for the preparation of 2-phenylpyrrole. β-Benzoylpropionitrile might undergo a reductive cyclization in a fashion similar to that which 2-phenyl-3-benzoylpropionitrile undergoes,[5,6] and the resulting 2-phenyl-Δ^1-pyrroline (XII) could subsequently be dehydrogenated to 2-phenylpyrrole. In fact, β-benzoylpropionitrile was subjected to reductive cyclization in the presence of Raney nickel, and the crude pyrroline XII so obtained was dehydrogenated by being heated with selenium. 2-Phenylpyrrole was eventually obtained, but the over-all yield was very poor.



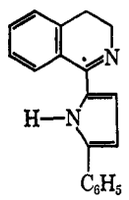
XII

As an alternative method for the synthesis of 2-phenylpyrrole, the decarboxylation of 2-phenyl-3-pyrrolecarboxylic acid was attempted. 2-Phenyl-3-carbethoxypyrrole was prepared by a Hantzsch synthesis from 1,2-dichloroethyl ethyl ether, ethyl benzoylacetate, and ammonia.[7,8] The reaction presumably involves first conversion of 1,2-dichloroethyl ethyl ether to chloroacetaldehyde, which subsequently reacts with ammonia and ethyl benzoylacetate to form 2-phenyl-3-carbethoxypyrrole. The ester was hydrolyzed to the corresponding acid, and this, in turn, was decarboxylated to give 2-phenylpyrrole. The yield of 2-phenylpyrrole obtained through this synthetic method was also poor, because, as is usual in Hantzsch pyrrole syntheses, a furan derivative was formed together with the desired product.

2-Phenylpyrrole was subsequently converted to 2-phenyl-5-carbethoxypyrrole by the preparation of 5-phenylpyrrylmagnesium bromide and subsequent reaction with ethyl chloroformate according to a known method.[9] The next step in the synthetic sequence involved the introduction of the β-phenethylamido group to the already synthesized pyrrole moiety. This was effected by heating β-phenethylamine with 2-phenyl-5-carbethoxypyrrole at a high temperature. The resulting N-(2-phenethyl)-5-phenyl-2-pyrrolecarboxamide (XIII) was subjected to the Bischler–Napieralski ring closure by being heated with phosphorus pentoxide in xylene. The yield of 2-(3,4-dihydro-1-isoquinolyl)-5-phenylpyrrole (XIV) was very poor, but this was expected since Bischler–Napieralski reactions of β-phenethylamides having no electron-donating substituents on the phenyl group are known to occur only with great difficulty. The dehydrogenation of 2-(3,4-dihydro-1-isoquinolyl)-5-phenylpyrrole (XIV) was effected by the action of palladium-on-charcoal catalyst at an elevated temperature. The yield of the product was almost quantitative. The independently synthesized 2-(1-isoquinolyl)-5-phenylpyrrole was identical with the product obtained by the decarboxylation of 2-(1-isoquinolyl)-5-phenyl-3-pyrrolecarboxylic acid (VI).



XIII



XIV

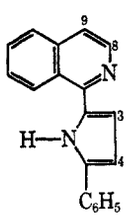
The position of the isoquinolyl and phenyl groups having been established through the evidence presented thus far, it remained for the exact position of the cyano group to be determined in order to complete the structure proof of compound III. For that purpose the nmr spectra of several pyrrole derivatives were carefully examined.

It is generally accepted that aromatic protons adjacent to a heteroatom absorb in the nmr region of the spectrum at lower frequencies than those at other positions. This phenomenon, which is attributed to electrostatic effects, is most marked when the heteroatom is either oxygen or nitrogen.[10] For example,

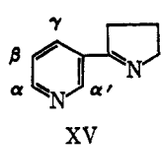
(4) A. Pieroni and P. Veremeenco, *Gazz. Chim. Ital.*, **56**, 455 (1926).
(5) M. T. Rogers, *J. Chem. Soc.*, 590 (1943).
(6) C. F. H. Allen and C. V. Wilson, *Org. Syn.*, **27**, 33 (1947).
(7) A. Fujita, *J. Pharm. Soc. Japan*, **519**, 450 (1925).
(8) I. H. Kondo and H. Suzuki, *ibid.*, **544**, 501 (1927).
(9) F. F. Blicke, R. J. Warzynski, J. A. Faust, and J. Gearin, *J. Am. Chem. Soc.*, **66**, 1675 (1944).
(10) L. M. Jackman, "Applications of Nuclear Magnetic Resonance

the α hydrogen of pyrrole itself appears at δ = 6.6 ppm, while the β hydrogen appears at 6.1 ppm.[10] In 2-(1-isoquinolyl)-5-phenylpyrrole (VII), the two protons at the 3 and 4 positions of the pyrrole ring, although they are structurally equivalent with respect to the nitrogen of the pyrrole, are not equivalent with respect to the nitrogen of the isoquinoline ring. The proton of the pyrrole ring adjacent to the isoquinoline group is by one position closer to the nitrogen of the latter group. Furthermore, there is spatial proximity between the isoquinolyl nitrogen and the hydrogen at position 3 which would be expected to enhance any electrostatic interactions between the two atoms. The orientation of the hydrogen at position 4 is such that a similar interaction should be either impossible or minimal for this hydrogen. It can therefore be predicted that the two pyrrole hydrogens will have distinctly different chemical shifts and that the hydrogen at position 3 will absorb at a lower field than the hydrogen at position 4.

That such a type of effect is indeed operative can be demonstrated by consideration of the nmr spectrum of myosmine (XV),[11] a compound which, for the purpose of this argument, can be considered as a model compound. The α and α' hydrogens of this compound are equally spaced from the nitrogen of pyridine and, in that respect, they should be equivalent in their nmr absorptions. However, the α' hydrogen occupies a position which makes it more exposed to electrostatic interaction with the nitrogen of the pyrroline ring than the α hydrogen.



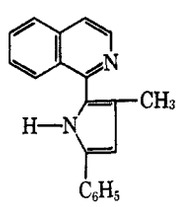
VII



XV

The four low-field signals in the nmr spectrum of myosmine (XV) were attributed to the four pyridine protons, and they were found to be, in order, a doublet, a quartet, an octet, and a quartet. The assignment which Pople, Schneider, and Bernstein made for these absorptions is as follows. The doublet at the lowest field with the least number of spin-coupling components was assigned to $H_{\alpha'}$. The quartet immediately to the right of this signal was assigned, by analogy with pyridine, to H_{α}. The octet was assigned to H_{γ}, and the last quartet was assigned to H_{β}. The fact that $H_{\alpha'}$ appears at a lower field than H_{α}, although both hydrogens are equivalent with respect to the pyridine–nitrogen, is a demonstration of the proximity effect which is due to the nitrogen of the pyrroline.

The nmr spectrum of 2-(1-isoquinolyl)-5-phenylpyrrole (VII) showed a broad multiplet at δ = 11.0, a multiplet at 8.6, a doublet at 8.2, a multiplet centered at 7.4, a multiplet at 6.9, and a triplet at 6.6 ppm. The relative intensities of these absorptions were, respectively, 1:1:1:9:1:1. The broad multiplet at the lowest field was assigned, by analogy with pyrrole, to the N–H group, the multiplet at 8.8 ppm to H_8, the doublet at 8.2 ppm with the least multiplicity to H_9, and the complicated multiplet at 7.4 ppm to the remaining aromatic protons of the isoquinolyl group and the phenyl protons. Finally, from the remaining two absorptions, the one at the lower field of 6.9 ppm was assigned on the basis of the argument presented above to H_3 and the one at 6.6 ppm to H_4. The assumption that these two high-field bands correspond to the two hydrogens of the pyrrole seems a reasonable one, since, from all the types of hydrogens of compound VII, the pyrrole hydrogens are those expected to appear at the higher field. This is confirmed also by intensity considerations. If the frequency assignments for H_3 and H_4 are correct ones, then it can be expected that the lower field band will not appear in the nmr spectrum of a 3-substituted 2-(1-isoquinolyl)-5-phenylpyrrole. For that purpose, 2-(1-isoquinolyl)-3-methyl-5-phenylpyrrole (XVI) was prepared by reduction of 2-(1-isoquinolyl)-3-carbethoxy-5-phenylpyrrole with lithium aluminum hydride, and the nmr spectrum of this compound was examined. Four major bands were obtained at δ = 11.0, 8.0, 6.4, and 2.2 ppm in the relative intensity ratio 1:11:1:3. No band corresponding to the absorption exhibited by compound VII at 6.9 ppm was obtained. The assignment of the absorptions seems to be uncomplicated, the additional sharp singlet at 2.2 ppm being attributed to the methyl protons, and the intensity ratios agree perfectly with the predicted numbers of different hydrogens.



XVI

Thus, if the assumption with respect to the relative absorption frequencies of H_3 and H_4 in compound VII is a valid one, it can be concluded that the methyl group in 2-(1-isoquinolyl)-3-methyl-5-phenylpyrrole (XVI) indeed occupies position 3 of the pyrrole ring. The methyl group in compound XVI marks the position that the cyano group occupies in compound III, and consequently the product of the reaction between the isoquinoline Reissert compound and acrylonitrile possesses the originally assigned structure of 2-(1-isoquinolyl)-3-cyano-5-phenylpyrrole (III).

Confirming evidence was obtained from a deuteration experiment. 2-(1-Isoquinolyl)-5-phenyl-3-pyrrolecarboxylic acid (VI) was converted to the sodium salt, and this, in turn, was dissolved in deuterium oxide and neutralized with dideuteriosulfuric acid. The oxygen-deuterated 2-(1-isoquinolyl)-5-phenyl-3-pyrrolecarboxylic acid was decarboxylated, and 2-(1-isoquinolyl)-5-phenyl-3-deuteropyrrole was thus obtained. If the deuterium is to indicate the position of the carboxyl group in 2-(1-isoquinolyl)-5-phenyl-3-pyrrolecarboxylic acid (VI), the band at δ = 6.9 ppm should be missing from the nmr spectrum of the deuterated 2-(1-isoquinolyl)-5-phenylpyrrole. Actu-

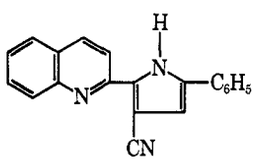
Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959, p 64.

(11) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 281.

ally, this band did not disappear completely, but its intensity was diminished to such an extent that it could not be measured through integration of the spectrum. In addition, the intensities of the bands corresponding to N–H and H_4 were also decreased. The relative intensities for the bands at δ = 11.0, 8.6, 8.2, 7.4, and 6.6 ppm were found to be, respectively, 0.7:1:1:9:0.4.

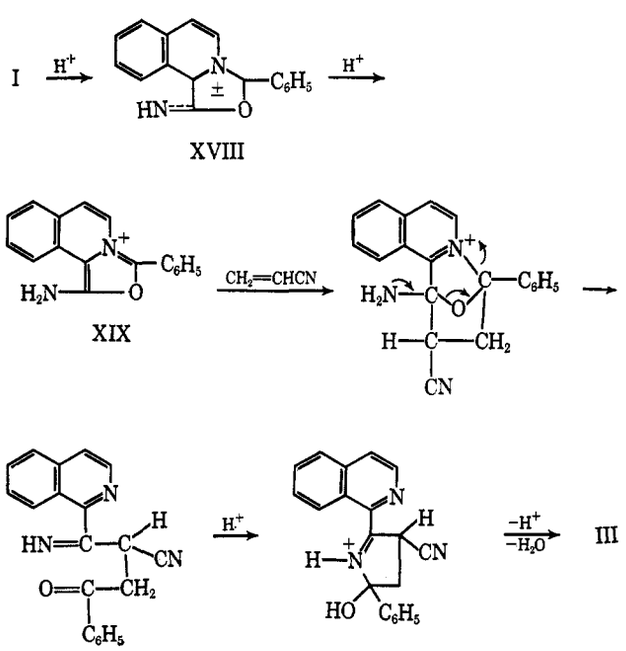
The data indicate that, in addition to the deuteration of position 3, partial deuterium exchange has occurred also at position 4 and at the N–H group. In addition to the evidence relating to the position of the carboxyl group, these data can also be considered to offer independent evidence about the nmr assignment of H_4, because this proton, together with the nitrogen proton, is the only hydrogen which would be expected to undergo deuterium exchange under the given, mildly acidic reaction conditions.

Another argument for the assignment of the cyano group to the 3 position of the pyrrole ring in structure III is based on analogy. Glover[12] obtained 2-(2-quinolyl)-3-cyano-5-phenylpyrrole (XVII) by the acid-catalyzed condensation of 1-benzoyl-1,2-dihydroquinaldonitrile with acrylonitrile. The corresponding carboxylic acid was obtained by hydrolysis of XVII. A total synthesis by an unambiquous route confirmed the structure of the acid.



XVII

Although no detailed study of the mechanism of the condensation reaction has been carried out, we suggest that one of the steps consists of a 1,3-dipolar addition reaction between acrylonitrile and the conjugate acid XIX of the mesoionic compound XVIII, which has been postulated to be formed as an intermediate in other acid-catalyzed reactions of Reissert compounds.[13,14]



XVIII

XIX

(12) D. C. Glover, Ph.D. Dissertation, University of Massachusetts, 1966.

Experimental Section[15]

2-Benzoyl-1,2-dihydroisoquinaldonitrile (I).—This compound was prepared according to the method of Weinstock and Boekelheide,[16] mp 126–127° (lit.[16] mp 125–126°).

Reaction of Acrylonitrile with 2-Benzoyl-1,2-dihydroisoquinaldonitrile (I).—To an ice-cold solution of 26.0 g (0.10 mole) of 2-benzoyl-1,2-dihydroisoquinaldonitrile (I) and 52 g (0.10 mole) of acrylonitrile in 250 ml of freshly distilled dioxane, 100 ml of concentrated hydrochloric acid solution (36.5%) was added dropwise, with vigorous stirring, over a period of 1 hr. The resulting dark red solution was stirred for 20 additional hr at room temperature. The yellow precipitate which separated was collected by filtration and washed, first with a dilute hydrochloric acid solution and then with water. There was obtained 16.5 g of a bright yellow solid, mp 275–276° dec after several recrystallizations from 1-butanol. On the basis of degradation and synthetic experiments described below, the structure of 2-(1-isoquinolyl)-3-cyano-5-phenylpyrrole hydrochloride (II) was assigned to this product. The filtrate, remaining after removal of the yellow solid, was evaporated to a small volume under a stream of air at room temperature. To the dark residue, 500 ml of water was added, and the solid which precipitated was collected by filtration; 7.5 g of an amorphous, dark red solid was obtained, mp 120–170°, which could not be further purified or characterized.

The yellow hydrochloride salt II was ground with a concentrated aqueous solution of sodium hydroxide in a mortar, and the thick paste which formed was diluted with an excess of water. To the resulting basic mixture a dilute solution of hydrochloric acid was added dropwise until the mixture was neutral, and the yellowish solid which precipitated was collected by filtration and thoroughly washed with water. A 10.0-g quantity of pale yellow 2-(1-isoquinolyl)-3-cyano-5-phenylpyrrole (III) was obtained which, after decolorization with charcoal and recrystallization from ethanol, had mp 221.5–222.0° dec. The infrared spectrum of this substance showed two characteristic bands at 2.9 and 4.5 μ which were assigned to the N–H and C≡N absorptions, respectively. The nmr spectrum showed four bands, a broad multiplet at δ = 13.3, a quartet at 8.5, a multiplet centered at 7.6, and a singlet at 6.4 ppm, in the relative intensity ratio 1:1:10:1, respectively. No isoquinaldamide or isoquinaldic acid could be obtained from the aqueous mother liquid or the reaction mixture.

Anal. Calcd for $C_{20}H_{14}ClN_3$ [hydrochloride salt of 2-(1-isoquinolyl)-3-cyano-5-phenylpyrrole]: C, 72.40; H, 4.25; Cl, 10.68; N, 12.66. Found: C, 72.86; H, 4.39; N, 12.25; Cl, 10.46. Calcd for $C_{20}H_{13}N_3$ [2-(1-isoquinolyl)-3-cyano-5-phenylpyrrole (III)]: C, 81.33; H, 4.44; N, 14.23. Found: C, 81.40; H, 4.54; N, 13.79.

Reaction of 2-(1-Isoquinolyl)-3-cyano-5-phenylpyrrole (III) with 80% Sulfuric Acid.—To 15.0 g of 2-(1-isoquinolyl)-3-cyano-5-phenylpyrrole (III), 100 ml of an 80% sulfuric acid solution was added, and the resulting mixture was slowly heated until a homogeneous solution was obtained and fumes of sulfur trioxide started to be evolved. The yellow solution was poured into 1000 ml of ice-cold water, and the solid which precipitated was collected by filtration and washed with water. A 15.0-g quantity of a bright yellow solid, mp 303–305° dec, was obtained to which the structure of 2-(1-isoquinolyl)-3-carboxamido-5-phenyl-4-pyrrolesulfonic acid (IV) was tentatively assigned on the basis of the infrared spectrum, the chemical and physical properties, and the method of preparation of this substance. Because it was impossible to recrystallize and purify this compound in the acid form, it was converted to the sodium salt in the following manner. The yellow solid was suspended in a small volume of 95% ethanol, and a dilute sodium hydroxide solution was added to the mixture dropwise until the solvent was slightly basic to litmus. The resulting mixture was warmed, and the clear solu-

(13) T. K. Liao and W. E. McEwen, *J. Org. Chem.*, **27**, 5257 (1961).

(14) R. L. Cobb and W. E. McEwen, *J. Am. Chem. Soc.*, **77**, 5042 (1955).

(15) Melting points are uncorrected. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. The infrared spectra were taken on either a Perkin-Elmer 137 Infracord or a Beckman IR-5 infrared spectrophotometer. The nmr spectra were taken on an A-60 nmr spectrometer at a sweep width of 1000 cps.

(16) J. Weinstock and V. Boekelheide, *Org. Syn.*, **38**, 58 (1958).

tion which resulted was subjected to slow crystallization. The solid which separated was collected by filtration and washed with cold 50% ethanol; 8.0 g of sodium 2-(1-isoquinolyl)-3-carboxamido-5-phenyl-4-pyrrolesulfonate was obtained and was recrystallized from 50% ethanol. The compound melts with decomposition at 260° and is very soluble in water.

Anal. Calcd for $C_{20}H_{18}N_3NaO_6S$ (the dihydrate of the sodium salt): C, 53.21; H, 4.02; N, 9.31; S, 7.10. Found: C, 53.19; H, 4.53; N, 8.77; S, 7.04.

Hydrolysis of 2-(1-Isoquinolyl)-3-carboxamido-5-phenyl-4-pyrrolesulfonic Acid (IV) with Sulfuric Acid.—A mixture of 15.0 g of 2-(1-isoquinolyl)-3-cyano-5-phenylpyrrole (III) and 100 ml of 80% sulfuric acid solution was slowly heated until a homogeneous solution was obtained, as in the previous reaction. The resulting yellow solution was poured into 1000 ml of ice-cold water, and the solid which precipitated was collected by filtration. A mixture consisting of this solid, 20 ml of concentrated sulfuric acid, and 180 ml of water was refluxed for 14 days. The reaction mixture was filtered while hot to give 12.5 g of yellow solid and an aqueous, acidic filtrate. The solid was suspended in 100 ml of ethanol, and the mixture was allowed to stand overnight. After filtration, 11.7 g of yellow solid, not melting at a temperature as high as 360°, was obtained. The solid was suspended again in a small volume of ethanol, and, to the mixture, a dilute solution of sodium hydroxide was added dropwise until the solvent was slightly basic to wet litmus paper. The mixture was heated, and the resulting clear solution was subjected to slow crystallization. After filtration, 8.5 g of the pale yellow disodium salt of 2-(1-isoquinolyl)-3-carboxy-5-phenyl-4-pyrrolesulfonic acid was obtained. This substance did not melt at a temperature as high as 360°. It could be recrystallized from 50% ethanol.

The alcoholic filtrate remaining after separation of the dibasic acid, V, was evaporated to a minimal volume, and the residue was chromatographed on grade III alumina.[17] When the column was eluted with absolute ethanol a yellow band passed into the filtrate, evaporation of which gave 0.5 g of yellow, crystalline 2-(1-isoquinolyl)-5-phenylpyrrole (VII), mp 140–141° after recrystallization from absolute ethanol. The structure of this product was proved by an independent synthesis described below. The nmr spectrum showed six major bands at δ = 11.0, 8.6, 8.2, 7.4, 6.9, and 6.6 ppm in the relative intensity ratio 1:1:1:9:-1:1, respectively.

When the original acidic aqueous filtrate from the reaction mixture was cooled, a small amount of a semisolid material was obtained which was collected, dissolved in a minimal volume of absolute ethanol, and chromatographed on grade III alumina. By prolonged elution with Skelly B solvent and subsequent evaporation of the solvent, a small additional amount of 2-(1-isoquinolyl)-5-phenylpyrrole (VII) was obtained, mp 140–141° after recrystallization from absolute ethanol.

Anal. Calcd for $C_{20}H_{14}N_2Na_2O_6S$ [disodium salt of 2-(1-isoquinolyl)-3-carboxy-5-phenyl-4-pyrrolesulfonic acid (monohydrate)]: C, 52.63; H, 3.09; N, 6.14; Na, 10.07; S, 7.03. Found: C, 52.73; H, 3.29; N, 6.09; Na, 9.27; S, 6.88. Calcd for $C_{19}H_{14}N_2$ [2-(1-isoquinolyl)-5-phenylpyrrole (VII)]: C, 84.42; H, 5.22; N, 10.36. Found: C, 84.50; H, 5.33; N, 10.08.

Alkali Fusion of 2-(1-Isoquinolyl)-3-cyano-5-phenylpyrrole (III).—A 2.0-g sample of 2-(1-isoquinolyl)-3-cyano-5-phenylpyrrole (III) was added to a molten mixture of 20 g of potassium hydroxide and 10 drops of water contained in a nickel crucible, and the mixture was fused at 280° for 5 min, with occasional stirring. The cooled mixture was added to 200 ml of water. The solid which was obtained was suspended in 50 ml of absolute ethanol. The mixture was filtered, and a dark grey solid was obtained plus an alcoholic filtrate. The filtrate was concentrated to a minimal volume and chromatographed on grade III alumina. By prolonged elution with Skelly B solvent, an orange-yellow band passed slowly through the column. After evaporation of the solvent and crystallization of the residue from ethanol–Skelly B, 0.4 g of yellow 2-(1-isoquinolyl)-5-phenylpyrrole (VII) was obtained, as identified by a mixture melting point test and by infrared spectral comparison with an authentic sample. By elution of the column with absolute ethanol and subsequent evaporation of the solvent, a red, oily material was obtained which was not identified.

The dark grey solid which was insoluble in cold ethanol was dissolved in boiling absolute ethanol, and the solution was decolorized with charcoal and subjected to crystallization. After filtration, 0.5 g of a white solid was obtained which had mp 283–284° after several recrystallizations from ethanol. To this product the structure of 2-(1-isoquinolyl)-5-phenylpyrrole-3-carboxamide (VIII) was assigned on the basis of the infrared spectrum and elemental analysis.

Anal. Calcd for $C_{20}H_{15}N_3O$: C, 76.66; H, 4.82; N, 13.41. Found: C, 76.61; H, 4.80; N, 13.52.

Hydrolysis of 2-(1-Isoquinolyl)-5-phenylpyrrole-3-carboxamide (VIII) with Sulfuric Acid.—A mixture of 4.5 g of 2-(1-isoquinolyl)-5-phenylpyrrole-3-carboxamide (VIII), 6 ml of concentrated sulfuric acid, and 50 ml of water was refluxed with stirring for 98 hr. The orange precipitate which had formed was collected by filtration of the hot reaction mixture, and 4.4 g of orange solid, mp 259–261° dec, was thus obtained. The solid was suspended in water, and the mixture was carefully neutralized by dropwise addition of a dilute solution of sodium hydroxide. After the resulting mixture has been allowed to stand for a few hours, the solid was collected by filtration and thoroughly washed with water; 4.0 g of white 2-(1-isoquinolyl)-5-phenyl-3-pyrrolecarboxylic acid (VI) was obtained, mp 264–265° dec after recrystallization from absolute ethanol. Compound VI was found to be relatively insoluble in common organic solvents. A convenient recrystallization method for this substance is that commonly used for purification of amino acids,[18] carried out as follows. Compound VI was dissolved in a 0.5 *N* sodium hydroxide solution and the insoluble impurities were removed by filtration. To the filtrate, ethanol was added, and the solution was heated to the boiling point. The hot solution was gradually neutralized, with stirring, by dropwise addition of a 5 *N* hydrochloric acid solution. When the solution was cooled, compound VI separated as a yellowish, crystalline solid.

When the hot, acidic, aqueous filtrate, obtained after separation of the orange solid from the original reaction mixture, was cooled, a red, semisolid material precipitated and was collected by removal of the aqueous layer by decantation. The solid was subsequently dissolved in a minimal volume of absolute ethanol and chromatographed on grade III alumina. By prolonged elution with Skelly B solvent, evaporation of the solvent from the filtrate and crystallization of the residue from ethanol–Skelly B, 0.2 g of 2-(1-isoquinolyl)-5-phenylpyrrole (VII), mp 137–139°, was obtained, as identified by an infrared spectral comparison with authentic material.

Anal. Calcd for $C_{20}H_{14}N_2O_2$ [2-(1-isoquinolyl)-5-phenyl-3-pyrrolecarboxylic acid (VI)]: C, 76.42; H, 4.49; N, 8.91. Found: C, 76.50; H, 4.77; N, 8.34.

Hydrolysis of 2-(1-Isoquinolyl)-3-cyano-5-phenylpyrrole (III) with Polyphosphoric Acid.—A mixture of 5.0 g of 2-(1-isoquinolyl)-3-cyano-5-phenylpyrrole (III) and 20 g of polyphosphoric acid was heated with stirring at 115° for 1.5 hr. To the resulting green-brown, viscous solution, 500 ml of water was added, and the mixture was allowed to stand at room temperature overnight. The yellow solid which had precipitated was collected by filtration and washed with water. The solid was suspended in 300 ml of water, and the mixture was neutralized by dropwise addition of a sodium hydroxide solution. A white solid precipitated and was collected by filtration and thoroughly washed with water; 5.0 g of 2-(1-isoquinolyl)-5-phenylpyrrole-3-carboxamide (VIII) was obtained, mp 280–283° after recrystallization from ethanol. A mixture melting point test with a sample of compound VIII obtained by the alkali fusion of compound III showed no depression in the melting point.

Although ethanol was found to be a good recrystallization medium for small quantities of 2-(1-isoquinolyl)-5-phenylpyrrole-3-carboxamide (VIII), it is not a satisfactory solvent for purification of large quantities of this compound because of its relative insolubility. In such cases nitrobenzene was found to be a more convenient solvent.

Hydrolysis of 2-(1-Isoquinolyl)-5-phenylpyrrole-3-carboxamide (VIII) with Hydrobromic Acid.—A mixture of 5.0 g of 2-(1-isoquinolyl)-5-phenylpyrrole-3-carboxamide (VIII), 50 ml of glacial acetic acid, and 50 ml of 48% hydrobromic acid was refluxed for 4 hr. When the resulting orange-red solution was cooled, a slow crystallization took place. The yellow, crystalline solid which formed was collected by filtration and washed

(17) H. Brockmann and H. Schodder, *Ber.*, **74**, 73 (1941).

(18) R. E. Steiger, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 84.

with water. It was subsequently ground in a mortar with a concentrated solution of sodium hydroxide, and the resulting thick paste was diluted with excess of water, whereupon most of the solid material dissolved in the basic, aqueous solution. The small amount of insoluble substance was removed by filtration, and the basic filtrate was carefully neutralized with a solution of hydrochloric acid. A few more drops of hydrochloric acid solution was added to make the aqueous layer slightly acidic, and the resulting mixture was allowed to stand at room temperature for several hours. By this treatment the original yellowish precipitate became gradually white, and the aqueous, slightly acidic layer became colorless. The white solid was collected by filtration and thoroughly washed with water; 4.5 g of 2-(1-isoquinolyl)-5-phenyl-3-pyrrolecarboxylic acid (VI), mp 258–261° dec, was thus obtained, as identified by infrared spectral comparison with the sample cited previously. When longer refluxing periods were used in this reaction, together with the carboxylic acid VI, some 2-(1-isoquinolyl)-5-phenylpyrrole (VII) was obtained which separated as the component of the reaction product which was insoluble in sodium hydroxide solution.

Decarboxylation of 2-(1-Isoquinolyl)-5-phenyl-3-pyrrolecarboxylic Acid (VI).—A 0.3-g portion of 2-(1-isoquinolyl)-5-phenyl-3-pyrrolecarboxylic acid (VI) was fused for 5 min at 280° in a small test tube. During the fusion, evolution of carbon dioxide was observed. The fused product was cooled and then boiled with a small volume of 95% ethanol. Collection of the crystals which eventually appeared in the alcohol solution afforded 0.2 g of 2-(1-isoquinolyl)-5-phenylpyrrole (VII), mp 135–138°, as identified by infrared spectral comparison and by a mixture melting point test with an authentic sample.

Esterification of 2-(1-Isoquinolyl)-5-phenyl-3-pyrrolecarboxylic Acid (VI).—A mixture consisting of 3.0 g of 2-(1-isoquinolyl)-5-phenyl-3-pyrrolecarboxylic acid (VI), 10 g of absolute ethanol, and 10 g of concentrated sulfuric acid was refluxed for 10 hr. The resulting solution was poured onto cracked ice, and the mixture was neutralized with concentrated ammonia solution. The yellow solid which formed was collected by filtration and recrystallized from absolute ethanol; 3.0 g of pale yellow 2-(1-isoquinolyl)-3-carbethoxy-5-phenylpyrrole, mp 149–150°, was obtained. It has not been possible to obtain good results in the elemental analysis of this compound because of its tendency to form an alcoholate on recrystallization from ethanol. However, the identity of this product was established by a hydrolysis experiment with alcoholic sodium hydroxide which regenerated the original acid VI, as identified through infrared spectral comparison.

When 2-(1-isoquinolyl)-5-phenylpyrrole-3-carboxamide (VIII) or 2-(1-isoquinolyl)-3-cyano-5-phenylpyrrole (III) was subjected to treatment with concentrated sulfuric acid and absolute ethanol, under the same conditions as described above, solvolysis took place, and the same ester was obtained, as identified by mixture melting point tests and by a comparison of the infrared spectra of the products with the authentic compound.

Cleavage of 2-(1-Isoquinolyl)-5-phenylpyrrole (VII) with Hydrogen Peroxide.—A modification of the procedure used by Pieroni and Veremeenco[4] for the cleavage of 2,5-diphenylpyrrole was used in this reaction.

To a solution of 10.0 g of 2-(1-isoquinolyl)-5-phenylpyrrole in 75 ml of glacial acetic acid, 25 g of 30% hydrogen peroxide was added all at once. The solution was warmed on the steam bath at 80–90° for 5 hr. The excess of acetic acid was removed by evaporation under a stream of air, the residue was taken up in 80 ml of 10% sodium hydroxide solution, and the solution was extracted with ether. The organic layer was washed twice with water and dried over anhydrous sodium sulfate. The ether was evaporated, and the residue was distilled *in vacuo*. The fraction distilling at 95° (0.35 mm) was collected. A very small amount of yellow liquid was obtained which was identified as 1-isoquinolyl methyl ketone (XI) by a comparison of the infrared spectrum of this substance with the spectrum of an authentic sample synthesized according to the method of Padbury and Lindwall.[19]

The basic aqueous layer, remaining after extraction with ether was neutralized by gradual addition of dilute sulfuric acid solution, and the dark semisolid material which formed was removed by filtration. This substance could not be further purified and identified. The neutral, aqueous filtrate was made acidic by addition of a sulfuric acid solution. A brown solid separated, and this was collected by filtration and redissolved in boiling water, and the solution was decolorized with charcoal. The almost colorless solution was cooled and the solid which crystallized was collected by filtration; 0.4 g of benzoic acid, mp 119–121°, was obtained, identified by a mixture melting point test with an authentic sample and by infrared spectral comparison.

Reaction of 2-(1-Isoquinolyl)-5-phenylpyrrole (VII) with Nitrous Acid.—To a vigorously stirred solution of 20 g of 2-(1-isoquinolyl)-5-phenylpyrrole in 180 ml of glacial acetic acid, a solution of 5 g of sodium nitrite in 12 ml of water was added dropwise, at the rate of 1 drop/min. Considerable evolution of heat was noticed during the reaction. After the addition had been completed the reaction was allowed to continue for an additional 0.5 hr with stirring. The resulting reaction mixture was filtered and the green precipitate was washed with a small amount of cold glacial acetic acid. Recrystallization of the solid from ethanol afforded 9.0 g of 2-(1-isoquinolyl)-4-nitroso-5-phenylpyrrole (IX) as green needles, mp 169–170° dec. The structure of this product was proved by the degradation experiments described below. The nmr spectrum showed a multiplet centered at δ 8.0 and a sharp singlet at 6.6 in the relative intensity ratio 12:1, respectively.

When the acetic acid filtrate, obtained after collection of the green solid, was cooled, a yellow-orange material separated and was collected by filtration; 4.5 g of light-sensitive, crystalline solid was obtained which was recrystallized from a 1:1 ratio of methanol–acetone. This compound was found to decompose without melting at 161°. The structure of 2-(1-isoquinolyl)-3-nitro-4-diazo-5-phenylpyrrole (X) was tentatively assigned to this product on the basis of infrared spectroscopic evidence.

Anal. Calcd for $C_{19}H_{15}N_3O_2$ [2-(1-isoquinolyl)-4-nitroso-5-phenylpyrrole (monohydrate)]: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.75; H, 4.59; N, 13.50. Calcd for $C_{19}H_{13}N_5O_3$ [2-(1-isoquinolyl)-3-nitro-4-diazo-5-phenylpyrrole (monohydrate)]: C, 63.50; H, 3.65; N, 19.49. Found: C, 63.69; H, 3.58; N, 18.56.

Hydrolysis of 2-(1-Isoquinolyl)-4-nitroso-5-phenylpyrrole (IX) with Sulfuric Acid.—A mixture of 8.0 g of 2-(1-isoquinolyl)-4-nitroso-5-phenylpyrrole (IX), 240 ml of water, and 80 ml of concentrated sulfuric acid was refluxed for 1 hr. During the reaction, evolution of a gas was observed, and this was determined to be carbon dioxide by passing it through a barium hydroxide solution. The original brown reaction solution was allowed to cool slowly at room temperature. During this process a semisolid, dark brown material and a lightly colored, crystalline solid deposited on the walls of the flask. These two substances were separately collected by mechanical means; 0.3 g of lightly colored crystals was thus obtained, mp 118–120°. This product was dissolved in boiling water and decolorized with charcoal. By slow crystallization of the solution and filtration, a white solid, mp 121–122°, was obtained, identified as benzoic acid by a mixture melting point test with an authentic sample and by infrared spectral comparison. The aqueous, acidic filtrate was partially neutralized with a sodium hydroxide solution, and the dark semisolid material which precipitated was collected by filtration. This substance was combined with the previously obtained brown semisolid material, and the whole was dissolved in a small volume of boiling absolute ethanol. By crystallization and filtration, 0.8 g of brown solid was obtained, mp 150–155°. This solid, after several decolorizations with charcoal and recrystallizations from 95% ethanol, afforded a white, crystalline compound, mp 153–154°. The oxime derivative of this substance was prepared following a standard procedure and was found to have mp 200–201° dec.

The still acidic, aqueous layer, obtained after removal of the semisolid material, was neutralized by gradual addition of a sodium hydroxide solution and extracted with chloroform. The chloroform layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The pleasant-smelling, oily residue was distilled *in vacuo*. A yellowish liquid distilling at 95° (0.35 mm) was collected, and 0.5 g of 1-isoquinolyl methyl ketone (XI) was thus obtained. This was identified by a comparison of the infrared spectrum with that of an authentic sample synthesized according to the method of Padbury and Lindwall.[19] The semicarbazone derivative of this compound was prepared according to a standard procedure, and it was found to possess mp 211–212° (lit.[19] mp 208°).

Anal. Calcd for $C_{12}H_{12}N_4O$ (semicarbazone of 1-isoquinolyl methyl ketone): C, 63.14; H, 5.30; N, 24.55. Found: C, 63.32; H, 5.60; N, 24.25. Calcd for $C_{19}H_{14}N_2O_2$ (unknown compound, mp 153–154°): C, 75.48; H, 4.67; N, 9.27. Found:

(19) J. J. Padbury and H. G. Lindwall, *J. Am. Chem. Soc.*, **67**, 1268 (1945).

C, 75.33; H, 4.45; N, 9.50. Calcd for $C_{19}H_{15}N_3O_2$ (oxime of the unknown compound): C, 71.92; H, 4.76; N, 13.24. Found: C, 72.12; H, 4.40; N, 12.81.

Reduction of 2-(1-Isoquinolyl)-3-carbethoxy-5-phenylpyrrole with Lithium Aluminum Hydride.—To an ice-cooled slurry of 4.0 g of lithium aluminum hydride in 100 ml of anhydrous ether, a solution of 12.0 g of 2-(1-isoquinolyl)-3-carbethoxy-5-phenylpyrrole in 800 ml of anhydrous ether was added dropwise and with vigorous stirring. After the addition was completed, the reaction was allowed to continue for 10 additional hr at room temperature, with vigorous stirring. The reaction mixture was cooled in an ice bath, and the excess lithium aluminum hydride was subsequently decomposed by gradual addition of water. The organic layer was separated from the aqueous layer and dried over anhydrous magnesium sulfate. After evaporation of the excess of the solvent, crystallization of the residue and filtration, 4.0 g of yellow 2-(1-isoquinolyl)-3-methyl-5-phenylpyrrole (XVI), mp 190–193°, was obtained, as identified by infrared and nmr spectroscopic analysis. The infrared spectrum of the compound showed no OH absorption, and the nmr spectrum showed four major types of hydrogens at δ = 11.0, 8.0, 6.4, and 2.2 ppm, in the relative ratio 1:11:1:3, respectively.

Deuteration of 2-(1-Isoquinolyl)-5-phenylpyrrole (VII).—The sodium salt of 2-(1-isoquinolyl)-5-phenyl-3-pyrrolecarboxylic acid was prepared by dissolving the acid VI in as small as possible an amount of hot, dilute sodium hydroxide solution, and then by allowing the resulting solution to undergo slow crystallization. The sodium salt was collected by filtration and recrystallized twice from water. It was subsequently dried *in vacuo* over P_2O_5 for 24 hr at 80°. The completely dry, reddish sodium salt of 2-(1-isoquinolyl)-5-phenyl-3-pyrrolecarboxylic acid was dissolved in deuterium oxide, and the solution was neutralized by dropwise addition of a 25% solution of dideuteriosulfuric acid in deuterium oxide. The deuterium 2-(1-isoquinolyl)-5-phenyl-3-pyrrolecarboxylate which precipitated was collected by filtration and dried *in vacuo* over P_2O_5. The deuterated acid was subsequently decarboxylated by being heated at 280°. The residue was dissolved in a small amount of chloroform and crystallized by addition of Skelly B solvent and cooling. The 2-(1-isoquinolyl)-5-phenyl-3-deuteriopyrrole which separated as a yellow, crystalline solid was collected by filtration and washed with a small amount of Skelly B solvent. The nmr spectrum of this compound showed five major types of protons at δ = 11.0, 8.7, 8.3, 7.2, and 6.5 ppm in the relative ratio 0.7:1:1:9:0.4, respectively.

Synthesis of 2-(1-Isoquinolyl)-5-phenylpyrrole (VII). 1. 2-Phenylpyrrole.—β-Bromopropiophenone was prepared according to the method of Halle and Britton[20] from β-bromopropionic acid. It was subsequently converted to β-benzoylpropionitrile according to the procedure of Allen, Gilbert, and Young,[21] and the nitrile was subjected to reductive cyclization by use of a modification of the procedure described for the preparation of 2,4-diphenylpyrrole.[6] To a suspension of 15.9 g of β-benzoylpropionitrile (0.1 mole) in 100 ml of methanol, 4 ml of settled Raney nickel catalyst was added. The reaction mixture was shaken in a Parr hydrogenation apparatus at room temperature under a hydrogen pressure of 50 psi for 9 hr. The hydrogenation was stopped when approximately 4 equiv of hydrogen had been absorbed. The catalyst was allowed to settle, and the methanolic solution was decanted from the solid. After complete removal of the solvent by heating at 100° under reduced pressure, approximately 14 g of crude 2-phenyl-Δ^1-pyrroline (XII) was obtained as a dark green, viscous oil. To the crude 2-phenyl-Δ^1-pyrroline, 3.0 g of selenium was added, and the mixture was heated at 250–260°, under a slow stream of nitrogen, for 3 hr. The reaction mixture was extracted with 50 ml of boiling benzene, and the catalyst was removed by filtration. The benzene was evaporated from the solution under reduced pressure, and the residue was steam distilled. By filtration of the steam distillate, 3.3 g of 2-phenylpyrrole, mp 120–125°, was obtained (reported in Beilstein, mp 120–125°); over-all yield based on β-benzoylpropionitrile was 12%.

An alternative method for the synthesis of 2-phenylpyrrole which gives a slightly better yield of the product, makes use of 1,2-dichloroethyl ethyl ether and ethyl benzoylacetate as starting materials.[7,8] To an ice-cooled mixture of 43.5 g of 1,2-dichloroethyl ethyl ether (0.42 mole), and 58.0 g of ethyl benzoylacetate (0.30 mole), 300 ml of a 25% aqueous solution of ammonia was added in small portions with stirring. The reaction was allowed to continue at room temperature with stirring for 18 hr. The aqueous layer was removed, and a small amount of ether was added to the dark brown organic layer. The ether solution was thoroughly washed with water until the aqueous extracts were neutral to litmus. The ether solution was subsequently dried over anhydrous sodium sulfate, and the volatile materials were removed by heating under reduced pressure. The dark, viscous residue was subjected to fractional distillation. The fraction distilling at 190° (1 mm was collected, and 15.0 g of the ethyl ester of 2-phenyl-3-pyrrolecarboxylic acid was obtained as a yellow, viscous liquid. The ester was subsequently saponified by refluxing with a solution of 4.0 g of sodium hydroxide in 20 ml of water and 20 ml of ethanol. The reaction solution was poured into ice-cold water, and the impurities which precipitated were removed by filtration. The basic, aqueous solution was neutralized by gradual addition of a dilute solution of hydrochloric acid, and the resulting solid was collected by filtration; 10.5 g of white 2-phenyl-3-pyrrolecarboxylic acid, mp 185–190° dec, was obtained (lit.[7] mp 192–193° dec). The acid was subsequently decarboxylated by being heated at 180–200° until evolution of carbon dioxide ceased. The dark, oily material which resulted was extracted with 500 ml of hot Skelly B solvent, and the solution was decolorized with charcoal. By crystallization of the solution and filtration, 6.0 g of slightly colored 2-phenylpyrrole, mp 127–129°, was obtained; over-all yield, based on ethyl benzoylacetate was 12.5%.

2. 2-Phenyl-5-carbethoxypyrrole.—The method employed was a modification of the procedure used for the preparation of 2,4-dimethyl-5-carbethoxypyrrole.[9] To 1.3 g of magnesium turnings, a few drops of a solution of 6.0 g (0.055 mole) of ethyl bromide in 5 ml of absolute ether was added, with vigorous stirring. When the bromide started reacting, 2 ml of absolute ether was added, and then the remaining part of the ethyl bromide was added as fast as refluxing allowed. After the mixture had been stirred for 15 additional min, a solution of 6.0 g of 2-phenylpyrrole (0.042 mole) in 30 ml of absolute ether was added dropwise over a period of 20 min, and the reaction mixture was refluxed for 0.5 hr on the steam bath. The reaction mixture was cooled to room temperature, and a solution of 5.8 g of ethyl chloroformate (0.053 mole) in 10 ml of absolute ether was added dropwise in the course of 0.5 hr. The mixture was heated on the steam bath for 1.5 hr, and then it was allowed to stand overnight at room temperature. The reaction mixture was cooled and then decomposed by gradual addition of 30 ml of a saturated aqueous solution of ammonium chloride, followed by 10 ml of water. The aqueous layer was removed, and sufficient ether was added to the organic layer to dissolve the yellow precipitate which resulted. The ether layer was washed twice with 20-ml portions of water and dried over anhydrous sodium sulfate. By evaporation of the excess of ether and cooling of the concentrated solution, crystallization took place. The solid was collected by filtration and washed with a small volume of cold ethanol. After one recrystallization from ethanol, 3.1 g of 2-phenyl-5-carbethoxypyrrole, mp 121–122°, was obtained in the form of yellow needles. The over-all yield was 35%, based on 2-phenylpyrrole.

3. N-(2-Phenethyl)-5-phenyl-2-pyrrolecarboxamide (XIII).—A mixture of 1.5 g of 2-phenyl-5-carbethoxypyrrole (0.007 mole) and 1.2 g of β-phenethylamine (0.01 mole) was heated at 240–250°, under reflux, for 4 hr. The red reaction solution was induced to deposit crystals by addition of a small volume of ether and Skelly B solvent. The white solid which formed was collected by filtration and washed with ether; 0.5 g of N-(2-phenethyl)-5-phenyl-2-pyrrolecarboxamide (XIII), mp 157–160°, was obtained, as identified by its infrared spectrum. After one recrystallization from ethanol the melting point of this substance was 160–162°.

4. Reaction of N-(2-Phenethyl)-5-phenyl-2-pyrrolecarboxamide (XIII) with Phosphorus Pentoxide.—A mixture of 1.0 g of N-(2-phenethyl)-5-phenyl-2-pyrrolecarboxamide, 10.0 g of phosphorus pentoxide, and 25 ml of anhydrous *p*-xylene was refluxed for 2 hr. The dark reaction mixture was poured into an excess of ice-cold water, and the precipitate which formed was collected by filtration. The dark brown solid was suspended in a small volume of a concentrated solution of sodium hydroxide, and the mixture was first diluted with water and then neutralized with a solution of sulfuric acid. The mixture was extracted with benzene, and the organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated by

(20) W. J. Halle and E. C. Britton, *J. Am. Chem. Soc.*, **41**, 845 (1919).
(21) C. F. H. Allen, M. R. Gilbert, and D. M. Young, *J. Org. Chem.*, **2**, 227 (1937).

heating it under reduced pressure, and the residue was chromatographed on grade IV alumina. Prolonged elution of the column with Skelly B solvent caused the development of a yellow band, which slowly passed into the filtrate. The excess of the solvent was evaporated from the filtrate, and an orange-yellow, oily substance separated. This slowly crystallized when the solution was allowed to stand for a few hours at room temperature. After filtration, 0.2 g of yellow 2-(3,4-dihydro-1-isoquinolyl)-5-phenylpyrrole (XIV), mp 113–114°, was obtained, as identified by its infrared spectrum.

5. **Dehydrogenation of 2-(3,4-Dihydro-1-isoquinolyl)-5-phenylpyrrole (XIV).**—A mixture of 0.3 g of 2-(3,4-dihydro-1-isoquinolyl)-5-phenylpyrrole and 0.05 g of 10% palladium-on-charcoal catalyst was heated at 180–200° under a slow stream of nitrogen for 45 min. The reaction mixture was taken up in 10 ml of boiling benzene, and the catalyst was removed by filtration. The excess of benzene was evaporated, and hot Skelly B solvent was added to the residue. By slow cooling, crystallization took place. After filtration, a yellow, crystalline solid was obtained which was recrystallized once from Skelly B solvent to give 0.2 g of 2-(1-isoquinolyl)-5-phenylpyrrole (VII), mp 140–141°. A mixture melting point test of this compound with a sample of the 2-(1-isoquinolyl)-5-phenylpyrrole obtained by the condensation of acrylonitrile with 1-cyano-2-benzoyl-1,2-dihydroisoquinaldonitrile (I) and the subsequent steps described previously showed no depression. The infrared spectra of the two compounds were identical also.

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The Nuclear Magnetic Resonance Spectra of the Enol Acetates and Ethers of Methylcyclopentanetriones and -diones. Homoallylic Spin Coupling

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The observation of homoallylic coupling (CH_3—C=C—CHR) through five bonds provides a convenient diagnostic method for elucidating the structures of enol ethers and acetates derived from 3-methyl-1,2-cyclopentanedione, 2-methyl-1,3-cyclopentanedione, 2-methyl-1,3,4-cyclopentanetrione, and related derivatives.

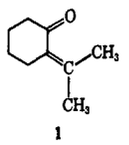
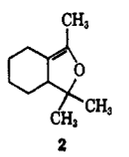
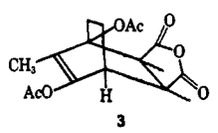
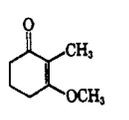
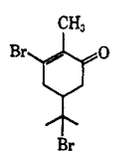
During the course of another investigation the problem arose of differentiating between isomeric enol acetates and enol ethers derived from unsymmetrically substituted 2-methyl-1,3-cyclopentanediones. The report following describes the successful application of nmr spectroscopy to this problem.

The term "homoallylic coupling" embraces those spin–spin interactions which occur between protons symmetrically disposed about a carbon–carbon double bond (CH—C=CCH).[1-3] The magnitude of this coupling lies in the range of 0–5 cps and is remarkably large in view of the five bonds which are involved. The geometry about the double bond, the conformation(s) adopted by the proton(s) with respect to the double bond, and the electron density at the double bond influence the magnitude of the homoallylic coupling constant.

trans, five-bond interactions are somewhat larger (*ca.* 0.5 cps) than *cis*, five-bond interactions.[4] This difference is clearly seen in the spectrum of 2-isopropylidenecyclohexanone (**1**)[5] (see Table I) where one of the vinyl methyl groups appears as a sharp triplet due to coupling with the *trans*-methylene group, while the other appears as a broad singlet due to smaller coupling with the same, but in this instance, *cis*-homoallylic methylene group. The appearance of a doublet vinyl methyl signal for vinyl ether **2** can also be attributed to spin coupling with the *trans*-homoallylic methine proton. Strong coupling with the *cis*-homoallylic methylene group would have produced a triplet or a complex multiplet.

TABLE I

MISCELLANEOUS COMPOUNDS SHOWING HOMOALLYLIC COUPLING

	CH_3 C=C (J, cps)
 **1**	1.77, broad singlet 1.92 t (~1.0)
 **2**	1.62 d (broadened) (~1.3)
 **3**	1.68 s
	1.71 t (~1.0)
	1.87 t (~1.0)

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