of IX prepared by the thermal elimination of methyl mercaptan from 1-benzoyl-3-methyl-3-thioisosemicarbazide (X).[8] The compounds were identical with respect to melting point, mixed melting point and infrared spectrum.

Thus it now is clear that the reaction of phenylglyoxylic acid semicarbazone (VI) with iodine and base actually yields 2-amino-5-phenyl-1,3,4-oxadiazole (IX). The reaction of IX with hot sodium hydroxide solution to yield IV (whose properties in solution may of course resemble I, II, and III) can be pictured as the base-catalyzed ring cleavage of IX and subsequent ring closure on the nitrogen. It is interesting that the intermediate in this reaction is probably the same as in the reaction of 1-benzoylsemicarbazide (VIII) with base.

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N,N-Disubstituted Carboxamides as Agents for the Acylation of Pyrroles[1]

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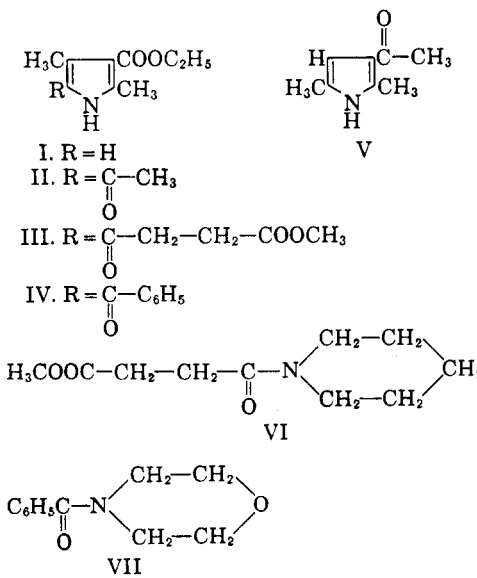
Several pyrrolecarboxaldehydes and other acylpyrroles were prepared in this laboratory as intermediates for the synthesis of potential anticancer agents[1a] and for the prosecution of certain synthetic studies[1b] in the porphyrin area.

The use of *N,N*-dimethylformamide and phosphoryl chloride for the formylation of pyrroles has been reported by a number of investigators.[4-11] The utility and convenience of this formylation method prompted us to examine *N,N*-disubstituted carboxamides of homologous carboxylic acids as potential agents for the introduction of other acyl groups into pyrroles under relatively mild conditions.

Vilsmeier and Haack[12] were the first to demonstrate the utility of *N,N*-disubstituted formamides for the formylation of aromatic systems. The formation of a quinaldine derivative from *N*-methylacetanilide and phosphoryl chloride had been observed earlier by Fischer, Müller, and Vilsmeier,[13] and it was suggested[12] that this condensation might have proceeded *via* the *o*-acetylation of the anilide. Despite this observation, the use of *N,N*-disubstituted carboxamides and phosphoryl chloride by subsequent investigators for the acylation of aromatic nuclei appears to have been limited[13a] to formylation with formamide derivatives.

In an effort to extend the scope of the acylation method, we first attempted acetylation of the pyrrole ring with *N,N*-dimethylacetamide. This reagent with phosphoryl chloride was found to convert ethyl 2,4-dimethyl-3-pyrrolecarboxylate (I) to its 5-acetyl derivative (II). Similarly 2,5-dimethylpyrrole afforded 3-acetyl-2,5-dimethylpyrrole (V). In order to test further the generality of the reaction, acylation with the more complex carboxamide, *N*-(β-carbomethoxypropionyl)piperidine (VI),[14] was attempted. Amide VI, prepared from methyl β-(chloroformyl)propionate and piperidine,



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(4) E. J.-H. Chu and T. C. Chu, *J. Org. Chem.*, 19, 266 (1954).

(5) G. F. Smith, *J. Chem. Soc.*, 3842 (1954).

(6) R. M. Silverstein, E. E. Ryskiewicz, and S. W. Chaikin, *J. Am. Chem. Soc.*, 76, 4485 (1954).

(7) E. E. Ryskiewicz and R. M. Silverstein, *J. Am. Chem. Soc.*, 76, 5802 (1954).

(8) R. A. Nicolaus and L. Mangoni, *Ann. chim. (Rome)*, 46, 865 (1956); *Chem. Abstr.*, 51, 6600i (1957).

(9) E. Ghigi and A. Drusiani, *Atti accad. sci. ist. Bologna, Classe sci. fis.*, 11, No. 3, 1 (1956); *Chem. Abstr.*, 51, 6602d (1957).

(10) E. Ghigi and A. Drusiani, *Atti accad. sci. ist. Bologna, Classe sci. fis.*, 11, No. 4, 14 (1957); *Chem. Abstr.*, 52, 11818a (1958).

(11) R. Rips and N. P. Buu-Hoï, *J. Org. Chem.*, 24, 372 (1959).

(12) A. Vilsmeier and A. Haack, *Ber.*, 60, 119 (1927).

(13) O. Fischer, A. Müller, and A. Vilsmeier, *J. prakt. Chem.*, 109, 69 (1925).

(13a) NOTE ADDED IN PROOF. Following the completion of this work and its acceptance for publication, the acylation of certain indoles and of pyrrole using various *N,N*-disubstituted carboxamides and phosphoryl chloride was recently reported. See W. C. Anthony, *J. Org. Chem.*, 25, 2049 (1960).

(14) M. Semonský and A. Černý, *Chem. Listy*, 47, 281 (1953); *Chem. Abstr.*, 49, 233a (1955).

TABLE I

ACYLPYRROLES PREPARED BY ACYLATION WITH *N,N*-DISUBSTITUTED CARBOXAMIDES

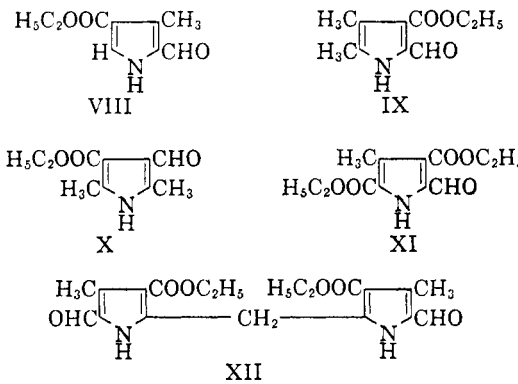
Acyl-pyrrole	Pro-cedure	Reaction[a] Time, Min.	Reaction Temp.	Yield,[b] %	Observed[c] M.P.	Lit. M.P.
II	A	15	80–85[d]	67[e]	140–141[f]	142[g]
III	A	15	80–85[d]	40[h]	149–150.5[i]	—
IV	B	15	85–95	62[e]	109–110.5[j]	108[g]
V	A	15	80–85[d]	40[k]	94.5–95[l]	94.5[m]
VIII	B	15	50–60	72[e]	126–127[n]	127.5–128.5[o]
IX	B	90	85–90	75[e]	128–132	131.5–132[p]
X	B	90	85–90	93[e]	152–153.5	151–151.5[q]
XI	B	50	120–135[r]	59[e]	122–124[s]	124–125[t]
XII	B	15	60	89[e]	191–192.5[u]	188[v]

[a] Length of time during which the reaction mixture was held at the indicated reaction temperature. [b] Figures represent yields of recrystallized product. [c] Melting points were determined on a hot stage apparatus (Nalge-Axelrod or Fisher-Johns). [d] Reaction was carried out by refluxing an ethylene dichloride solution of the reactants. [e] Crystallized from ethanol and/or aqueous ethanol. [f] Mixed m.p. with authentic II prepared according to the method of Fischer and Schneller showed no depression. See H. Fischer and K. Schneller, *Z. physiol. Chem.*, **128**, 248 (1923). [g] H. Fischer, K. Schneller, and W. Zerweck, *Ber.*, **55**, 2390 (1922). [h] Crystallized from methanol and/or aqueous methanol. [i] *Anal.* Calcd. for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98. Found: C, 59.73; H, 6.64; N, 4.84. [j] Saponified, then decarboxylated to 2-benzoyl-3,5-dimethylpyrrole, m.p. 117.5–119°; reported m.p. 118–119° according to G. K. Almström, *Ann.*, **409**, 291 (1915). [k] Crystallized from benzene. [l] *Anal.* Calcd. for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.14; H, 8.13; N, 10.74. [m] G. Magnanini, *Gazz. chim. ital.*, **19**, 283 (1889). [n] Oxime, m.p. 175–177°. *Anal.* Calcd. for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.16; H, 6.19; N, 14.34. Reported m.p. 167° according to H. Fischer and O. Wiedemann, *Z. physiol. Chem.*, **155**, 52 (1926). [o] A. H. Corwin and G. G. Kleinspehn, *J. Am. Chem. Soc.*, **75**, 2089 (1953). [p] G. G. Kleinspehn and A. H. Corwin, *J. Am. Chem. Soc.*, **76**, 5641 (1954). [q] H. Fischer and W. Zerweck, *Ber.*, **55**, 1947 (1922). [r] Oil bath temperature. [s] *Anal.* Calcd. for $C_{12}H_{15}NO_6$: C, 56.91; H, 5.97. Found: C, 56.72; H, 6.09. Mixed m.p. with authentic XI prepared according to the method of Corwin, *et al.* (*cf.* ref. [t]) showed no depression. [t] A. H. Corwin, W. A. Bailey, Jr., and P. Viohl, *J. Am. Chem. Soc.*, **64**, 1267 (1942). [u] Dioxime, m.p. 218–219°. *Anal.* Calcd. for $C_{19}H_{24}N_4O_6$: C, 56.43; H, 5.98; N, 13.86. Found: C, 56.28; H, 5.94; N, 14.07. Reported m.p. 221° with discoloration at 215°; *cf.* ref. [v]. [v] H. Fischer and P. Halbig, *Ann.*, **447**, 123 (1926).

was not isolated but was employed directly in solution for the acylation of I. In this instance the anticipated keto ester III resulted. Aroylation of I with *N*-benzoylmorpholine[15] (VII) was next attempted, and the benzoylpyrrole IV was obtained.

It appears that this acylation method may be of quite general applicability. The recent observation by Bredereck and co-workers[16] that phosphoryl chloride can promote the self-condensation of *N,N*-dialkylcarboxamides to β-oxocarboxamides suggests, however, that this latter condensation may occur in preference to the desired acylation in cases where the aromatic nucleophile is insufficiently reactive.

The formylation of several monopyrroles and of a dipyrrylmethane was carried out in the course of the present work. In each case formylation was accomplished with *N,N*-dimethylformamide and phosphoryl chloride. The five aldehydes VIII–XII had previously been prepared only by other methods. Of particular interest is the successful formylation of diethyl 3-methyl-2,4-pyrroledicarboxylate, a rather weak nucleophile, to give the corresponding 5-formyl derivative (XI). Nicolaus and Mangoni have reported[8] the formylation of each of two slightly more reactive isomers of XI at boiling water bath temperature using these same reagents. In the present instance we have been able to obtain XI by carrying out formylation at oil bath temperatures exceeding 120°.



The experimental results of these acylation studies are summarized in Table I.

EXPERIMENTAL

The data of Table I represent the results of experiments in which the amount of the pyrrole acylated ranged from 1.5 to 350 mmoles. Except for those experiments in which the *N,N*-disubstituted carboxamide was employed as a solvent for the reaction, the amount of phosphoryl chloride and of *N,N*-disubstituted carboxamide ranged from 1.10 to 1.33 moles for each mole of the pyrrole.

Acylation procedure A. The procedure employed was essentially that described by Silverstein and co-workers[17] for the formylation of pyrrole using *N,N*-dimethylformamide.

(15) L. Knorr, *Ann.*, **301**, 7 (1898).

(16) H. Bredereck, R. Gompper, and K. Klemm, *Chem. Ber.*, **92**, 1456 (1959).

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

In the preparation of acetylpyrrole V, the crude product was distilled *in vacuo* prior to subsequent purification by recrystallization.

The *N*-(β-carbomethoxypropionyl)piperidine (VI) required for the synthesis of pyrrole III was prepared by the addition of methyl β-(chloroformyl)propionate (1 mole) to an ethylene dichloride solution of piperidine (2 moles). After removal of the piperidine hydrochloride by filtration, the filtrate was treated with phosphoryl chloride with cooling, and the pyrrole I was then introduced. Following the reflux period, the mixture was cooled to room temperature, then shaken well with aqueous sodium acetate solution. The ethylene dichloride phase was evaporated to dryness, and the residue was purified by recrystallization.

In the preparation of pyrrole II, solid pyrrole I and then ethylene dichloride were added to the *N*,*N*-dimethylacetamide–phosphoryl chloride mixture. Following the reflux period, the product was worked up as described in the case of pyrrole III.

Acylation procedure B. The procedure employed is based upon that described by Campaigne and Archer[18] for the preparation of *p*-dimethylaminobenzaldehyde.

In the cases of aldehydes VIII and XII *N*,*N*-dimethylformamide was present in considerable excess. A solution of the starting pyrrole in the latter was added to the *N*,*N*-dimethylformamide–phosphoryl chloride mixture. In the preparation of acylpyrroles IV, IX, X, and XI the solid pyrrole to be acylated was added to the appropriate *N*,*N*-disubstituted amide–phosphoryl chloride mixture.

The reaction mixture in the preparation of benzoylpyrrole IV proved to be largely immiscible with aqueous sodium acetate solution. Homogeneity was achieved by addition of ethanol and by heating for a few minutes. The product crystallized upon standing. The *N*-benzoylmorpholine[14] required for this acylation experiment was prepared and isolated prior to use.

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(18) E. Campaigne and W. L. Archer, *Org. Syntheses*, **33**, 27 (1953).

Condensation of 3-Aminoquinones with *o*-Phenylenediamine[1]

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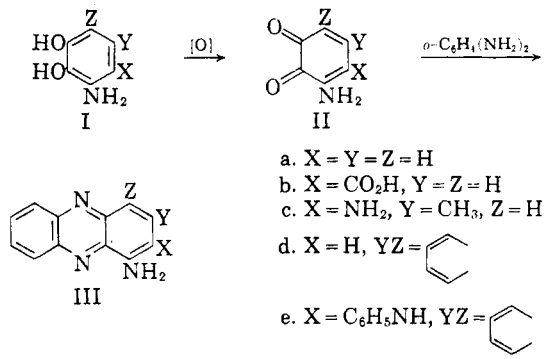
To investigate their conversion to pyridine compounds,[3] five unisolated 3-amino-1,2-quinones (II) have been prepared from corresponding aminocatechols (I) by oxidation with silver oxide or lead dioxide. Each aminoquinone and 3-nitro-4-anilinonaphthoquinone-1,2 is transformed to the corresponding derivative of 1-amino-(III) and 1-nitrophenazine by condensation with *o*-phenylenediamine in an inert solvent.[4]



EXPERIMENTAL[5]

Preparation of aminocatechols (I). *3-Aminocatechol* (Ia). According to Vermeulen[6] 3-nitrocatechol, m.p. 86°, was obtained in 15% yield on nitration of catechol with red fuming nitric acid in ether, and was reduced in 68% yield with tin in hydrochloric acid,[6] in 31% yield by aluminum amalgam in ether, or in 75% yield by hydrogen over palladium on charcoal to unstable 3-aminocatechol, m.p. 142–145°, isolated as its hydrochloride salt, m.p. 198–202.5° dec.[6]

3,4-Dihydroxyanthranilic acid (Ib). To 50.0 g. (0.33 mole) of vanillin and 60 ml. of pyridine in a round bottom flask equipped with a condenser and drying tube and externally cooled to 10°, 50 ml. of acetyl chloride was slowly added with shaking while the temperature did not rise appreciably. The mixture was heated about 1 hr. on a steam bath until the contents became an amber syrup. On addition of 100 g. of ice with stirring the syrup solidified. A pale yellow precipitate of *3-methoxy-4-acetoxybenzaldehyde* recrystallized from ethanol as colorless fluffy needles, 52.1 g. (81.7%), m.p. 76°.[7] It was nitrated[8] in 77.4% yield to *2-nitro-3-methoxy-4-acetoxybenzaldehyde*, m.p. 85.5° by red fuming nitric acid in carbon tetrachloride at 5°.

To 13.0 g. (0.054 mole) of this aldehyde in 84 ml. of glacial acetic acid, 120 ml. of 30% hydrogen peroxide was added at room temperature. After 3 hr. 30 ml. of 30% hydrogen peroxide was added. After 24 hr. evaporation of the solvent in an air stream left a yellow solid, *2-nitro-3-methoxy-4-acetoxybenzoic acid*, which recrystallized from ethanol as yellow plates, 12.5 g. (91.2%) m.p. 265–267°. On treatment with 160 ml. of 10% aqueous sodium hydroxide with warming to 45°, followed by neutralization with 10% hydrochloric acid, 12.5 g. (0.049 mole) of the acid was hydrolyzed to pale yellow amorphous *2-nitrovanillic acid* which recrystallized

(1) Financial support from National Institutes of Health Grants Nos. H-2295 and CY-2895 is gratefully acknowledged.

(2) This investigation was carried out during the tenure of a Predoctoral Fellowship from the National Heart Institute, United States Public Health Service, 1959–1960.

(3) J. H. Boyer and L. R. Morgan, Jr., *J. Am. Chem. Soc.*, **82**, 4748 (1960).

(4) Previously a preferred method for the preparation of 1-aminophenazine (III) consisted in heating 1-amino-6-nitrodiphenylamine with ferrous oxalate dihydrate and lead at 250–260°. (D. L. Vivian, *J. Org. Chem.*, **21**, 565 (1956)). The yield is more than doubled in the present procedure. Derivatives of 1-aminophenazine have been obtained in unspecified poor yield from condensation in acetic acid at 40° of *o*-phenylenediamine as its hydrochloride and corresponding derivatives of 3-aminobenzoquinone-1,2. The unisolated aminoquinones were obtained from corresponding aminocatechols by atmospheric oxidation in an ammoniacal solution. (F. Kehrmann and P. Prunier, *Helv. Chim. Acta*, **7**, 984 (1924). F. Kehrmann and N. Poehl, *Helv. Chim. Acta*, **9**, 485 (1926)).

(5) Semimicro analyses by Alfred Bernhardt, Max Planck Institut Microanalytisches Laboratorium, Mülheim (Ruhr), Germany. Melting points are uncorrected.

(6) M. H. Vermeulen, *Rec. trav. chim.*, **25**, 12 (1905).

(7) F. Tiemann and N. Nagai, *Ber.*, **11**, 646 (1878).

(8) A. Butenandt and H. G. Schlossberger, *Chem. Ber.*, **85**, 565 (1952).