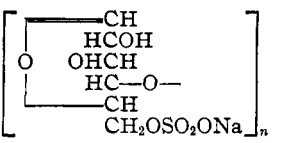
3. No sulfur was removed by dialysis.

4. The physical properties of this acid were different from those of the original substance. It had the appearance of an amorphous granular powder in contrast with the fibrous structure of the original substance.



5. A 1% solution of the acid had a P_H of 3.6.

6. The tentative structural formula shown is proposed for the substance in which n is unknown.

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The Synthesis and Reactions of Certain Nitrogen Ring Compounds over Nickel

BY CHARLES F. WINANS AND HOMER ADKINS

In this group of three papers we are surveying the application of nickel as a catalyst for reactions which result in the formation of amines.[1] These reactions are of four general types. In the first type are those in which an amine reacts with an alcohol or amine with the elimination of water or ammonia

$$ROH + RNH_2 \longrightarrow R_2NH + H_2O \quad (I)$$
$$RNH_2 + RNH_2 \longrightarrow R_2NH + NH_3 \quad (II)$$

In the second group a cyano, oximino, nitro or nitroso group is hydrogenated successively to an imine and an amine

$$RC{\equiv}N \xrightarrow{H_2} RCH{=}NH \quad (III)$$
$$R_2C{=}NOH \xrightarrow{H_2} R_2C{=}NH + H_2O \quad (IV)$$
$$RCH{=}NH \xrightarrow{H_2} RCH_2NH_2 \quad (V)$$

In the third group a nitrogen to nitrogen or nitrogen to carbon bond undergoes hydrogenolysis with the formation of amines

$$RCH(N{=}CHR)_2 \xrightarrow{H_2} RCH_2NH_2 + (RCH_2)_2NH \quad (VI)$$
$$RNHNHR \xrightarrow{H_2} 2RNH_2 \quad (VII)$$

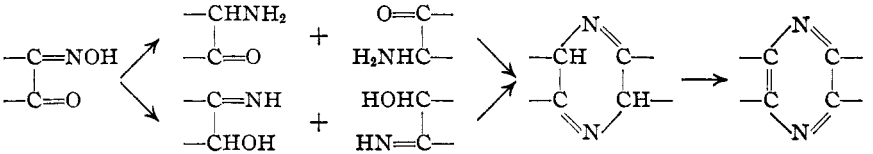
In the fourth group an imine, aldehyde or ketone adds an amine, followed in most cases by hydrogenolysis with the elimination of ammonia or water

$$RCH{=}NH + R'NH_2 \longrightarrow RCH(NH_2)NHR \xrightarrow{H_2} RCH(R)NH + NH_3 \quad (VIII)$$
$$RCH{=}O + R'NH_2 \longrightarrow RCH(OH)NHR \xrightarrow{H_2} RCH(R)NH + H_2O \quad (IX)$$

(1) Winans and Adkins, THIS JOURNAL, (a) **54**, 306 (1932); (b) **55**, 2051 (1933).

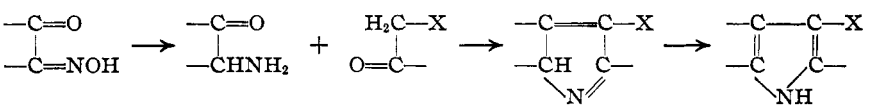
The present paper is concerned primarily with the application of these reactions in the synthesis and transformation of nitrogen ring compounds. A summary of the experimental results obtained in the synthesis of certain pyrrolidones, pyrazines and pyrroles is given in Table I, while in Table II is found a summary of the results in the hydrogenation and hydrogenolysis of certain α-amino nitriles, glyoxalones and pyrazolones.

Pyrazines.—The tendency toward the formation of pyrazines at the expense of open chain amines when α-oximino ketones or alcohols are subjected to hydrogenation over nickel has been noted previously in connection with the hydrogenation of benzil dioxime and benzoin oxime over nickel.[1b] Braun and Meyer[2] first observed this reaction in the reduction of oximes with sodium amalgam. The monoxime of benzil over nickel gave more tetraphenylpyrazine than of the open chain amino alcohol, while the oximino-acetoacetic ester, -acetophenone, and -hydrindone, gave only the corresponding pyrazines. The reaction (*cf.* IX) may be formulated as involving either the reaction of an amino with a carbonyl group or an imino with a hydroxyl group. In either case, the resulting dihydro pyrazine would be oxidized by air, according to Braun and Meyer, to the pyrazine



The second hypothesis must be assumed to explain the formation of a pyrazine from benzoin oxime, but since the yield of the pyrazine was much lower from benzoin oxime than from benzil oxime, reaction probably also proceeds according to the first hypothesis.

Pyrrroles.—Knorr's[3] well-known and generally applicable synthesis of pyrroles involves the reduction with zinc and acetic acid of an α-oximino (isonitroso) ketone in the presence of a ketone having an active methylene group adjacent to the carbonyl. The type synthesis according to Knorr is as follows where X is acyl or carbalkoxy



The synthesis, in addition to the reduction, involves two types of reaction, one a Knoevenagel condensation of a ketone with an active methylene in the presence of an amine, and the other the reaction of an amine with a carbonyl.

(2) Braun and Meyer, *Ber.*, **21**, 19 (1888).

(3) Knorr, *ibid.*, **17**, 1638 (1884); *Ann.*, **236**, 317 (1886); *cf.* Hollins, "Synthesis of Nitrogen Ring Compounds," D. Van Nostrand and Company, New York, 1924.

The application of catalytic hydrogenation at 100-200 atmospheres over nickel to the Knorr synthesis has been quite successful. The reactions proceeded to completion at temperatures of 50 to 90° within less than one hour. Success in the use of catalytic hydrogenation in this synthesis depends upon attaining conditions under which the oximino group is hydrogenated without the carbonyl group being affected. Eight variously substituted pyrroles as indicated in Table I have been prepared and isolated in yields of from 23 to 74%, the average being over 50%. The yields are, in the case of the five pyrroles previously reported, higher than those obtained by Knorr's original method. Knorr and Lange[4] obtained better yields (based upon the amino ketone) through the isolation and reaction of the latter with the β-diketone or β-keto ester.

TABLE I

SYNTHESIS OF PYRROLIDONES, PYRAZINES AND PYRROLES

Name and moles of hydrogen acceptors	Yield of products
Ethyl β-phenyl-β-cyanopyruvate (0.09)	26% 4-Phenyl-3-keto-pyrrolidone (m. p. 288–289°)
Ethyl β-phenyl-β-cyanopropionate (0.15)	89% 4-Phenylpyrrolidone (m. p. 76–77°)
Ethyl β-cyanopropionate (0.15)	38% Pyrrolidone (m. p. 23–26°)
Ethyl γ-oximinovalerate (0.10)	63% 5-Methylpyrrolidone (m. p. 33–35°)
Dimethylglyoxime (0.26)	18% 2,3-Diaminobutane (b. p. 145–155°)
	76% Tetramethylpyrazine hydrate (m. p. 76–77°)
Benzil monoxime (0.09)	42% Tetraphenylpyrazine (m. p. 242–243°)
	36% α,β-Diphenylethanolamine (m. p. 160–161°)
Oximinoacetoacetic ester (0.16)	43% 2,5 - Dimethyl - 3,6 - dicarbethoxy - pyrazine (m. p. 87–88°)
Oximinoacetophenone (0.10)	54% 2,5-Diphenylpyrazine (m. p. 193–194°)
Oximinohydrindone (0.03)	78% 2,3,5,6-Di-indenopyrazine (m. p. 270–271°)
Oximinoacetoacetic ester (0.11); diacetylmethane (0.11)	63% 2,4 - Dimethyl - 3 - acetyl - 5 - carbethoxypyrrole (m. p. 143–144°)
Oximinoacetoacetic ester (0.10); acetoacetic ester (0.10)	67% 2,4-Dimethyl - 3,5 - dicarbethoxypyrrole (m. p. 135–136°)
Oximinoacetophenone (0.10); acetoacetic ester (0.10)	35% 2 - Methyl - 3 - carbethoxy - 4 - phenylpyrrole (m. p. 107°)
Oximinodiacetylmethane (0.10); acetoacetic ester (0.10)	74% 2,4 - Dimethyl - 5 - acetyl - 3 - carbethoxypyrrole (m. p. 140–141°)
Oximinodibenzoylmethane (0.025); acetoacetic ester (0.025)	51% 2 - Benzoyl - 3 - phenyl - 4 - carbethoxy - 5-methylpyrrole (m. p. 156–157°)
Oximinohydrindone (0.03); acetoacetic ester (0.03)	44% 2 - Methyl - 3 - carbethoxy - 4,5 - indenopyrrole (m. p. 199–200°)
	39% Ethyl β - amino - (1 - hydroxy - N - 2-hydrineno)-butyrate (m. p. 95–96°)
Oximinobenzoylacetylmethane (0.03); acetoacetic ester (0.03)	56% 2,4 - Dimethyl - 3 - carbethoxy - 5 - benzoylpyrrole (m. p. 110–111°)
Oximinoacetoacetic ester (0.05); benzoyl acetonitrile (0.05)	23% 2 - Phenyl - 3 - cyano - 4 - methyl - 5-carbethoxypyrrole (m. p. 85–86°)

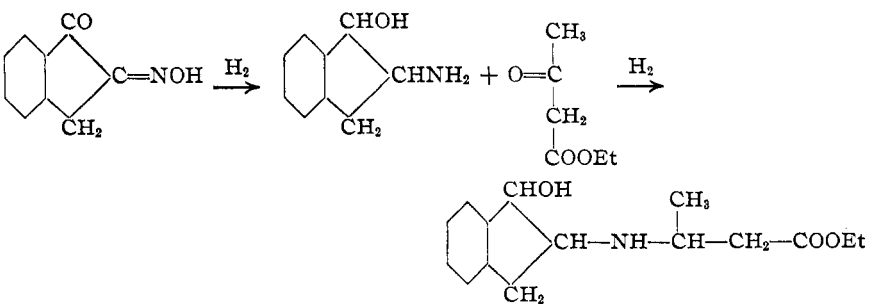
(4) Knorr and Lange, *Ber.*, **35**, 2998 (1902).

TABLE II

HYDROGENATION OF α-AMINO NITRILES, GLYOXALONES AND PYRAZOLONES

Name and moles of hydrogen acceptor	Yield of products
Methyleneaminoacetonitrile (0.59)	66% N-Methylethylenediamine 109–111°
	18% Di(β-N-methylaminoethyl)-amine 95–100° (25 mm.)
Diethylaminoacetonitrile (0.36)	37% N,N-Diethylethylenediamine 140–150°
	23% Di(β-diethylamino-ethyl)-amine130–135° (26 mm.)
Piperidinoacetonitrile (0.36)	50% β-Piperidino-ethylamine 80–85° (22 mm.)
	24% Di-(β-piperidinoethyl)-amine 160–170° (22 mm.)
Piperidinoisobutyronitrile (0.24)	78% Piperidine 100–110° (740 mm.)
Piperidinocaprylonitrile (0.17)	79% Piperidine 100–110°
	22% n-Octylamine 85–87° (14 mm.)
Piperidinophenylacetonitrile (0.20)	82% Piperidine 100–110°
	50% β-Phenethylamine 75–80° (8 mm.)
	24% Di-β-phenethylamine 170–175° (8 mm.)
4,5-Diphenylglyoxalone (0.08)	82% 4,5 - Dicyclohexyl - dihydroglyoxalone, m. p. 237–239°
4,5-Dicyclohexylglyoxalone (0.04)	77% 4,5 - Dicyclohexyl - dihydroglyoxalone, m. p. 237–239°
4,5-Diethylglyoxalone (0.03)	76% 4,5-Diethyldihydroglyoxalone, m. p. 192–193°
1 - Phenyl - 3 - methylpyrazolone - 5 (0.11)	68% Butyranilide, m. p. 90–91°
1,3-Diphenylpyrazolone-5 (0.04)	95% β-Phenylpropionanilide, m. p. 89–90°
1 - Phenyl - 3 - methyl - 4 - benzal-pyrazolone-5 (0.02)	80% α-Benzyl-β-aminobutyranilide (as hydrochloride)

The reaction of oximinohydrindone with acetoacetic ester gave a considerable yield of a product in addition to the pyrrole. Apparently to some extent the hydrogenation of the carbonyl group of oximinohydrindone preceded or accompanied the hydrogenation of the oximino group thus limiting the Knorr synthesis, for a yield of 39% of ethyl β-amino-(1 hydroxy N-2 hydrindeno)-butyrate was obtained, *i. e.*



Knorr and Lange observed a similar reaction in attempting to prepare a pyrrole from oximinoacetone and methyl ethyl ketone.

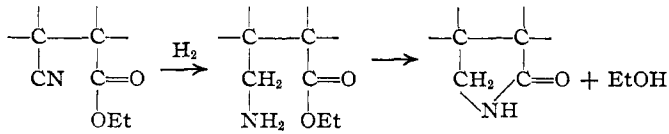
It should be pointed out that isomeric pyrroles were formed from oximino-

acetoacetic ester and diacetylmethane, and from oximinodiacetylmethane and acetoacetic ester. From this result it would seem reasonable to expect that such pairs of isomers could be prepared by switching the oximino group from one to the other of a pair of suitable compounds. However, such is not the case for from oximinoacetoacetic ester and dibenzoylmethane none of the expected pyrrole was obtained, but only a trace of 2,5-dimethyl-3,6-dicarbethoxypyrazine and large amounts of dibenzoylmethane. While oximinobenzoylacetylmethane plus acetoacetic ester was readily converted into a pyrrole, changing the oximino group from the diketone to the ester (oximinoacetoacetic ester and acetylbenzoylmethane) gave anomalous results. A compound of m. p. 128° was obtained in 89% yield (calculated as the pyrrole), but four rather than two molecular equivalents of hydrogen was absorbed in the process. The analysis for carbon showed 65.7 instead of 70.8 as calculated for the pyrrole, and the hydrogen was 7.13 instead of 6.27. The carbon content agreed with that for an amino alcohol in which one carbonyl group had been hydrogenated (thus making impossible the Knoevenagel condensation necessary for a Knorr pyrrole synthesis) but the hydrogen analysis was too low for this compound (7.85). The analysis for nitrogen gave values (5.03) between those for the pyrrole (5.16) and the amino alcohol (4.78). Similarly a product, m. p. 95–96°, analyzing low in carbon and high in hydrogen for a pyrrole, was obtained from the hydrogenation of a mixture of oximinopropiophenone and acetoacetic ester. Obviously, these data do not establish the nature of these two products but they do indicate that the course of the reaction is modified by the position of the oximino group.

The formation of a cyanopyrrole from oximinoacetoacetic ester and benzoyl acetonitrile is a new development of the pyrrole synthesis, and depends on the fact that over nickel a cyano group is less readily reduced than an oximino group. Under carefully controlled conditions the pyrrole synthesis was carried out without hydrogenation of the cyanide, giving rise to 2-phenyl-3-cyano-4-methyl-5-carbethoxypyrrole.

A crystalline product could not be isolated from the reaction mixture of oximinoacetoacetic ester and diethyl keto succinate.

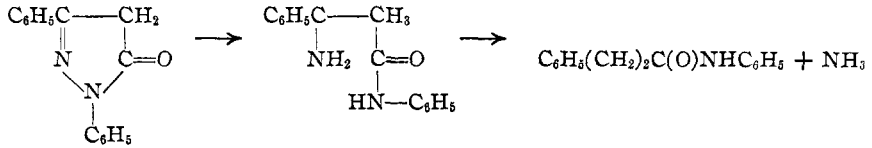
Pyrrolidones.—Pyrrolidone itself and two derivatives, *i. e.*, 4-phenyl, and 4-phenyl-3-keto, were obtained by the hydrogenation at 50–90° of three β-cyano esters, the type reaction being as indicated



The amine produced by the hydrogenation of an oximino ester, γ-oximinovalerate, lost alcohol and 5-methylpyrrolidone was formed. The yields

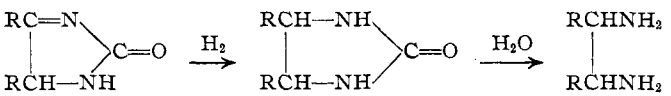
in all cases were greater than those previously reported for the preparation of these compounds.

Pyrazolones.—The nitrogen to nitrogen bond in pyrazolones is apparently readily cleaved by hydrogen over nickel at 120–150° (*cf.* VII). Two pyrazolones which had no substituent in position 4 (*i. e.*, derived from β-keto esters having no α-substituent) underwent cleavage of the cycle with the subsequent elimination of ammonia to give a substituted amide. This reaction took place almost quantitatively with 1,3-diphenylpyrazolone-5 and to the extent of 68% with the 1-phenyl-3-methylpyrazolone.



Pyrazolones having an ethyl, benzyl, benzal or β-phenylethyl radical in the 4 position apparently underwent a similar cleavage without the occurrence of the second step involving the elimination of ammonia. The hydrogen absorption was correct for this reaction and no ammonia was eliminated. The resulting β-amino anilides could not be purified satisfactorily. However, in the case of the 4-benzyl (or benzal) substituted pyrazolone an excellent yield (80%) of the hydrochloride of the α-benzyl-β-aminobutyranilide was isolated. The failure to obtain a similar product from the ethyl and β-phenylethyl substituted pyrazolones was apparently due to lack of material.

Glyoxalones.—Either 4,5-diphenyl- or dicyclohexyl-glyoxalone was hydrogenated at 200° in good yield (77–82%) to 4,5-dicyclohexyl dihydroglyoxalone. Similarly 4,5-diethylglyoxalone was converted into the corresponding dihydro compound. The relative ease of hydrogenation of the double bond in these two glyoxalones is to be contrasted with the complete resistance to hydrogenation of the similar double bond in the imidazole or glyoxaline series.[1b] The hydrogenation of the double bond in the glyoxalones renders available a method for the preparation of 1-2 diamines from the corresponding acyloins.



α-Aminonitriles.—The hydrogenation of six α-aminonitriles did not result in the development of a generally satisfactory method for the preparation of 1,2-diamines. Methyleneaminoacetonitrile was readily hydrogenated at 80–100° and a fair yield (66%) of N-methylethylenediamine was obtained. Diethyl aminoacetonitrile gave only a 37% yield of the desired amine, while four different α-piperidinonitriles underwent a rapid hydrogenolysis at the piperidino linkage and none of the desired β-piperidino-

amine was obtained. This is a further example of the type of reaction listed as VIII above.

$$C_5H_{10}NCH(R)CN \longrightarrow C_5H_{10}NH + RCH_2CH_2NH_2$$

Experimental Part

The synthesis of the heterocyclic compounds listed in Table I was effected with approximately 4 g. of a Raney nickel catalyst.[5,6] The pyrrolidones were prepared in ether solution at 70–90°, absorption of hydrogen being complete in 0.75–1.0 hour. The pyrroles and pyrazines were formed in alcoholic solution at 70–90° in 0.75–1.0 hour. At this temperature hydrogenation of the oximino group was effected readily, and the resulting amino ketone condensed to give a pyrazine or pyrrole before the carbonyl group was reduced. The hydrogenations were, in general, carried out at the lowest temperature consistent with reasonable speed in an attempt to avoid side reactions. This hydrogenation temperature was found experimentally by observing the so-called "inflection point," the temperature above which the drop in pressure of hydrogen due to absorption was greater than the rise in pressure due to the heating of the bomb and contents. The "inflection temperature" is determined in part by the void in the bomb, which in this case was such that the drop in pressure per mole of hydrogen absorbed was about 2300 pounds per sq. inch.

In the synthesis of 4-phenyl-2,3-diketopyrrolidine, tetraphenylpyrazine, 2-methyl-3-carbethoxy-4,5-indenopyrrole, 2,4-dimethyl-3-acetyl-5-carbethoxypyrrole, 2,4-dimethyl-5-acetyl-3-carbethoxypyrrole and 2,4-dimethyl-3,5-dicarbethoxypyrrole crystals of the reaction product had separated from the mixture in the bomb. These were redissolved in the reaction solvent, filtered from the used catalyst and recrystallized. In the other cases where no crystals had separated the reaction mixtures were filtered from the catalyst, allowed to evaporate in air for two to three days and then if necessary in a vacuum desiccator over sulfuric acid in order to effect crystallization. By this process a thick sirup was obtained in the preparation of 2-phenyl-3-cyano-4-methyl-5-carbethoxypyrrole. The sirup was extracted with hot methylcyclohexane from which were deposited long needles of the cyanopyrrole on evaporation of the solvent. This product was then easily recrystallized from methylcyclohexane.

Oximinohydrindone and acetoacetic ester gave a crystalline product from the reaction mixture which was difficultly soluble in 95% alcohol. This was the 2-methyl-3-carbethoxy-4,5-indenopyrrole referred to above. After removal of these crystals the addition of water to the mother liquor gave a precipitate of fine white crystals which after recrystallization from methylcyclohexane gave the correct analysis for ethyl β-amino-(1-hydroxy-N-2-hydrindeno)-butyrate.

Most of the heterocyclic compounds were recrystallized from 70% alcohol. Glacial acetic acid was used for tetraphenylpyrazine, and methylcyclohexane for 4-phenylpyrrolidone and 2-phenyl-3-cyano-4-methyl-5-carbethoxypyrrole. Pyrrolidone, 5-methylpyrrolidone and tetramethylpyrazine were isolated by distillation.

The hydrogenations of the α-aminonitriles listed in Table II were effected in ether or ethanol solution with approximately 8 g. of Raney nickel in half an hour at 80–100°. The products of the reaction were separated by distillation under reduced pressure through a small Widmer column.

The glyoxalones were hydrogenated at 200° with a kieselguhr supported nickel catalyst[7] in ethanol solution in three to five hours. The crystalline hydrogenation product had separated from the reaction mixture when the bomb was opened.

The pyrazolones were hydrogenated in ethanol at 150° with approximately 5 g. of

(5) M. Raney, U. S. Patent 1,628,190 (May 19, 1927).
(6) Covert and Adkins, THIS JOURNAL, **54**, 4116 (1932).
(7) Covert, Connor and Adkins, *ibid.*, **54**, 1651 (1932).

Raney nickel in three hours. Evaporation of the reaction mixture in air deposited crystals of the anilides. The hydrochloride of the anilide of α-benzyl-β-aminobutyrate was formed in ether and had a m. p. of 155–156° after recrystallization from ethanol.

Anal. Calcd. $C_{17}H_{21}ON_2Cl$: Cl, 11.62. Found: Cl, 11.55.

The 4,5-dicyclohexylglyoxalone was prepared by refluxing 40 g. of duodecahydrobenzoin and 22 g. of urea in 150 ml. of glacial acetic acid for six hours. On cooling to room temperature crystals of the product separated. The reaction mixture was poured into 500 ml. of water, and the filtered product was washed with water to remove excess urea and acetic acid, and with ether to remove unchanged acyloin. After drying in air the product weighed 37 g. (82%), m. p. 287–289°.

The 4,5-diethylglyoxalone was prepared by refluxing 40 g. of propionin $C_2H_5C(O)CH(OH)C_2H_5$ and 35 g. of urea in 100 ml. of glacial acetic acid for six hours. The cooled solution from which some crystals had separated was poured into 400 ml. of water. The precipitated product was filtered, washed with water and recrystallized from 95% ethyl alcohol. After drying in air the product weighed 23 g. (44%) m. p. 293–294°.

The following compounds were prepared as previously described: ethyl β-phenyl-β-cyanopyruvate,[8] ethyl β-phenyl-β-cyanopropionate,[9] ethyl β-cyanopropionate,[10] oximinoacetoacetic ester,[11] oximino acetophenone,[12] oximinohydrindone,[13] oximinodiacetylmethane,[14] oximinodibenzoylmethane,[15] oximinobenzoyl acetone,[16] methyleneaminoacetonitrile,[17] diethylaminoacetonitrile,[18] piperidinoacetonitrile,[19] piperidinophenylacetonitrile,[19] 1-phenyl-3-methyl-pyrazolone-5,[20] 1,3-diphenylpyrazolone-5,[21] and 4,5-diphenylglyoxalone.[22]

The properties of the following list of compounds prepared in this investigation have been compared with those previously described by others: pyrrolidone,[23] 5-methylpyrrolidine,[24] 2,3-diaminobutane,[25] tetramethylpyrazine,[26] α,β-diphenylethanolamine,[27] tetraphenylpyrazine,[28] 2,5-dimethyl-3,6-dicarbethoxypyrazine,[29] 2,5-diphenylpyrazine,[30] 2,4-dimethyl-3-acetyl-5-carbethoxypyrrole,[31] 2,4-dimethyl-3-ethyl-5-carbethoxypyrrole,[32] 2,4-dimethyl-3,5-dicarbethoxypyrrole,[33] 2-methyl-3-carbethoxy-4-phenylpyrrole,[34] 2,4-dimethyl-5-acetyl-3-carbethoxypyrrole,[35] 2,4-dimethyl-3-carbeth-

(8) Erlenmeyer, *Ann.*, **271**, 173 (1892).
(9) Bredt and Kallen, *ibid.*, **293**, 344 (1896).
(10) Drusher, *Am. J. Sci.*, **187**, 544 (1914).
(11) Wahl and Beauveault, *Bull. soc. chim.*, [3] **33**, 554 (1905).
(12) Claisen and Manasse, *Ber.*, **20**, 2194 (1887).
(13) Gabriel and Stelzner, *ibid.*, **29**, 2604 (1896).
(14) Wolff, *Ann.*, **325**, 139 (1902).
(15) Neufville and Pechmann, *Ber.*, **23**, 3378 (1890).
(16) Wolff, *Ann.*, **325**, 136 (1902).
(17) "Organic Syntheses," Collective volume, 1932, p. 347.
(18) Klages and Margolinsky, *Ber.*, **36**, 4189 (1903).
(19) Knoevenagel, *ibid.*, **37**, 4023 (1904).
(20) Knorr, *Ann.*, **238**, 104 (1887).
(21) Knorr and Koltz, *Ber.*, **20**, 2846 (1887).
(22) "Organic Syntheses," Vol. XII, 1932, p. 34.
(23) Gabriel, *Ber.*, **22**, 3338 (1889).
(24) Tafel, *ibid.*, **22**, 1863 (1889).
(25) Morgan and Hickenbottom, *J. Soc. Chem. Ind.*, **43**, 307 (1924).
(26) Brandes and Stoehr, *J. prakt. Chem.*, [2] **53**, 501 (1896).
(27) Goldschmidt, *Ber.*, **20**, 493 (1887).
(28) Feist and Arnstein, *ibid.*, **28**, 3168 (1895).
(29) Wleügel, *ibid.*, **15**, 1050 (1882).
(30) Braun and Meyer, *ibid.*, **21**, 19 (1888).
(31) Zanetti and Levi, *Gazz. chim. ital.*, **54**, 547 (1894).
(32) Fischer and Wallach, *Ber.*, **58**, 2818 (1925).
(33) Knorr, *Ann.*, **236**, 317 (1886).
(34) Knorr and Lange, *Ber.*, **35**, 3002 (1902).
(35) Mognanini, *ibid.*, **21**, 2866 (1888).

oxy-5-benzoylpyrrole,[36] N-methylethylenediamine,[37] N,N-diethylethylenediamine,[38] β-piperidinoethylamine,[39] butyranilide,[40] β-phenylpropionanilide.[41]

Di-(β-methylaminoethyl)-amine (I), di(β-diethylaminoethyl)-amine (II), and di(β-piperidinoethyl)-amine (III) were isolated and characterized as picrates. There are given below in order for each of these derivatives the formula, m. p., neutral equivalent (calcd. and found), and analysis for picric acid (calcd. and found).

(I) $C_6H_{17}N_3 \cdot 3C_6H_3O_7N_3$; 172–173°; 43.6, 41; 83.9%, 83.6%
(II) $C_{12}H_{29}N_3 \cdot 3C_6H_3O_7N_3$; 165–166°; 71.6, 70; 76.1%, 76.2%
(III) $C_{14}H_{29}N_3 \cdot 3C_6H_3O_7N_3$; 210–211°; 79.6, 81; 74.0%, 73.6%

Picric acid was determined as nitron (diphenylenedoanilinohydrotriazole) picrate according to the method of Utz.[42]

In Table III are listed the names, melting points and analyses of compounds isolated and described herewith for the first time.

TABLE III

MELTING POINTS AND ANALYSES

Name	M. p., °C.	Formula	Calcd. C, %	Calcd. H, %	Found C, %	Found H, %
4-Phenyl-2,3-diketopyrrolidine	288–289	$C_{10}H_9O_2N$	68.5	5.18	68.6	5.25
2,3,5,6-Di-indenopyrazine	270–271	$C_{18}H_{12}N_2$	84.4	4.79	84.4	4.90
2-Benzoyl-3-phenyl-4-carbethoxy-5-methylpyrrole	156–157	$C_{21}H_{19}O_3N$	75.6	5.70	75.1	5.63
2-Methyl-3-carbethoxy-4,5-indenopyrrole	199–200	$C_{15}H_{15}O_2N$	74.7	6.22	74.8	6.28
Ethyl β-amino(1-hydroxy-N-2 hydrindeno)-butyrate	95–96	$C_{15}H_{21}O_3N$	68.5	7.98	68.7	7.86
2-Phenyl-3-cyano-4-methyl-5-carbethoxypyrrole	85–86	$C_{15}H_{15}O_2N_2$	70.9	5.51	71.2	5.62
4,5-Diethyldihydroglyoxalone	192–193	$C_7H_{14}ON_2$	59.1	9.93	58.9	9.80
4,5-Diethylglyoxalone	293–294	$C_7H_{12}ON_2$	59.9	8.67	59.7	8.71
4,5-Dicyclohexylglyoxalone	287–290	$C_{15}H_{24}ON_2$	72.6	9.68	72.5	9.78
4,5-Dicyclohexyldihydroglyoxalone	237–239	$C_{15}H_{26}ON_2$	72.1	10.45	71.9	10.44

Summary

Catalytic hydrogenation over nickel has been applied successfully to the Knorr synthesis of a number of pyrroles. Pyrrolidones have been prepared from cyano or oximino esters which upon hydrogenation yielded γ-amino esters. A number of pyrazines have been prepared from α-dioximes and α-oximino ketones, or alcohols. The double bond in glyoxalone in contrast to that in glyoxaline rings may be hydrogenated over nickel, thus making it possible to prepare 1,2-diamines from acyloins. The nitrogen to nitrogen bond in pyrazolones has been shown to be subject to hydrogenolysis. Deamination resulted in the case of certain pyrazolones but β-amino acid

(36) Fischer, Schneller and Zerweck, *Ber.*, **55**, 2390 (1922).
(37) Johnson and Bailey, THIS JOURNAL, **38**, 2141 (1916).
(38) Ristenpart, *Ber.*, **29**, 2526 (1896).
(39) Gabriel, *ibid.*, **53**, 1991 (1920).
(40) Gerhardt, *Ann.*, **187**, 166 (1877).
(41) Hughes, *Ber.*, **25**, 747 (1892).
(42) Utz, *Z. anal. Chem.*, **47**, 140 (1908).

anilides from the pyrazolones substituted in the 4 position were stable, thus permitting the preparation of certain β-amino acids. The hydrogenation of α-aminonitriles to substituted 1,2-diamines has not been generally successful due in part to the ease of hydrogenolysis of compounds of this type.

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The Reaction between Aliphatic Orthoformates and Acetone

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Ethyl orthoformate reacts with acetone in absolute ethyl alcohol solution to yield a compound known as a ketone acetal or ketal

$$CH_3COCH_3 + HC(OC_2H_5)_3 \longrightarrow HCOOC_2H_5 + (CH_3)_2C(OC_2H_5)_2 \qquad (1)$$

a drop or two of concentrated sulfuric acid or equally effective ammonium chloride, hydrochloric acid or pyridine hydrochloride acting as catalyst.[1]

It would seem at first glance that Equation 1 is not needed inasmuch as the ketone could be conceived as reacting with the alcohol, splitting off water which then would react with the ortho ester. Moreover, if it is the orthoformate which reacts, why is the alcohol necessary? To answer these questions and if possible to obtain information as to optimum conditions for the reaction, several runs were made using various solvents and catalysts, in most cases ethyl compounds.

The reagents, acetone, alcohol and orthoformate, were mixed in equimolecular amounts and allowed to stand at the temperature of the room (which was quite constant around 25°) for five to seven days. Where sulfuric acid was used as a catalyst the color of the solution darkened and the temperature rose as much as 10° during the first twenty-four hours. The products were isolated according to Claisen's method.[1]

Using the following amounts of reagents with various catalysts the following yields of ketals were obtained: 0.143 mole + 1 drop H_2SO_4, 13%; 0.286 mole + 1.3 g. NH_4Cl, 26%; 0.19 mole + 0.75 g. NH_4Cl, 30%; 0.68 mole + 1 drop HCl, 27%. Omission of the solvent or of the orthoformate gave zero yields. Using equimolecular amounts of isoamyl alcohol as a solvent also gave zero yields. Replacement of the ethyl alcohol by ethyl ether using 1 drop of sulfuric acid as catalyst gave an unchanged yield (13%).

A series of runs was then carried out to determine the applicability of this reaction to the preparation of higher homologs of diethyl ketal.

Equimolecular amounts of acetone, the alcohol and the corresponding orthoformate were used. In each case 0.15 g. of ammonium chloride was used as a catalyst for every

(1) Claisen, *Ber.*, **29**, 1007 (1896); *ibid.*, **47**, 3171 (1914); Arbusow, *ibid.*, **40**, 3303 (1907); Tschitschibabin and Jelgasin, *ibid.*, **47**, 48 and 1851 (1914).