inhomogeneity present, determined as previously described,[10] amounts to about 5% for each isomer.

A 53-plate distribution was run on a mixture of 10 mg. each of 2,4-, 2,5- and 3,5-xylenol in the system cyclohexane–phosphate buffer of *p*H 11.08. Optical densities were measured at wave lengths of 275, 281 and 285 mμ. From these measurements, three simultaneous equations were derived for the determination of the quantity of each isomer in each tube.[11]

The calculated amounts are plotted in Fig. 4 (curves 1, 2 and 3). As can be seen, 3,5-xylenol separates readily from 2,4- and 2,5-xylenol. From the shape and appearance of each curve, it is evident that each compound distributes itself essentially independently of the others in accordance with the distribution law. Since the ratios of the partition coefficients of the un-ionized forms of these isomers are similar,[7] their separation in this distribution results mainly from their different acid strengths.

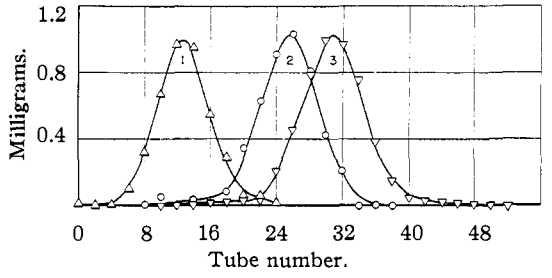

Fig. 4.—Separation of xylenols by 53-plate distribution: Δ, curve 1, 3,5-xylenol; O, curve 2, 2,5-xylenol; ∇, curve 3, 2,4-xylenol.

An experiment using similar quantities and solvent pair was conducted with a mixture of *o*-, *m*- and *p*-ethylphenols. For determination of each compound, optical densities were measured at wave lengths of 272, 279 and 285 mμ.[11]

A plot of these calculated amounts is given in Fig. 5. It may be observed that the *o*-ethylphenol separates easily from the *meta* and *para* isomer. This is so because the ortho compound has a higher partition coefficient and greater *pK* than the other isomers.[7]

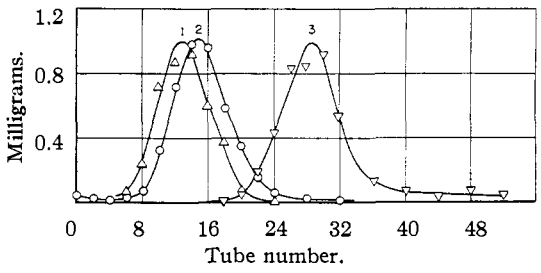

Fig. 5.—Separation of ethylphenols by 53-plate distribution: Δ, curve 1, *m*-ethylphenol; O, curve 2, *p*-ethylphenol; ∇, curve 3, *o*-ethylphenol.

For both xylenols and ethylphenols, the isomers separate in order of decreasing acid strength. When dealing with a material suspected of containing a mixture of isomeric phenols, important clues concerning molecular orientation could be obtained from the countercurrent distribution curves by identifying one component and then applying previously observed correlations between molecular structure on the one hand and partition coefficients and ionization constants on the other.

Acknowledgment.—The author is indebted to George Goldbach for technical assistance.

Summary

Application of the method of countercurrent distribution to the separation of isomeric phenols is described. The method was also used successfully for establishing purity of phenols.

CENTRAL EXPERIMENT STATION
DEPARTMENT OF INTERIOR
U. S. BUREAU OF MINES
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Pyridines. IV. A Study of the Chichibabin Synthesis[1]

BY ROBERT L. FRANK AND RAYMOND P. SEVEN

The condensation of aldehydes, ketones, α,β-unsaturated carbonyl compounds or various derivatives of such compounds with ammonia or its derivatives to form substituted pyridines is one of the oldest of organic reactions.[2] The transformations involved, as studied extensively by Chichibabin and his co-workers,[3] can be regarded as aldol condensations, generally in conjunction with Michael-type reactions, and ring closures involving ammonia.

Because of the formation of mixtures of pyridines and various by-products, the method has had a poor reputation for synthetic purposes.[4] Indeed, in all of Chichibabin's reports, there are but two instances[3a,b] of yields of single products higher than 20%. Some notable exceptions,[5,6]

(1) For the previous communication on pyridine chemistry, see Frank and Weatherbee, THIS JOURNAL, **70**, 3482 (1948).

(2) Hübner and Geuther, *Ann.*, **114**, 45 (1860).

(3) (a) Chichibabin, *Bull. soc. chim.*, [5] **4**, 1826 (1937); (b) Chichibabin, *J. Russ. Phys.-Chem. Soc.*, **37**, 1229 (1905); *Chem. Centr.*, **77**, I, 1438 (1906); (c) Chichibabin and co-workers, *J. prakt. Chem.*, **107**, 109, 122, 129, 132, 138, 145, 154 (1924).

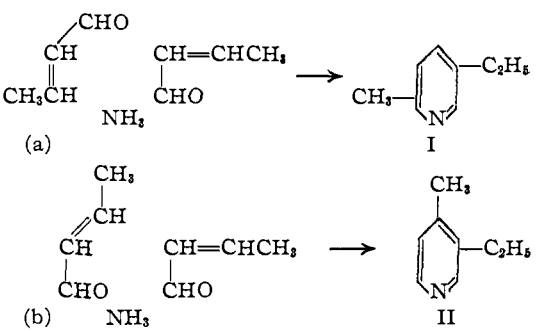
(4) See Sidgwick, "Organic Chemistry of Nitrogen," Oxford University Press, 1937, p. 518.

(5) (a) Farbenwerke vorm. Meister Lucius u. Brüning, British Pat. 146,869 (July 5, 1920); (b) Frank, Blegen, Dearborn, Myers and Woodward, THIS JOURNAL, **68**, 1368 (1946).

(6) Stitz, *Oesterr. Chem. Z.*, **45**, 159 (1942); *C. A.*, **38**, 2040 (1944).

however, especially the reaction of paraldehyde with ammonia to form aldehyde-collidine (I) in yields as high as 70%[5b] have prompted further study of the scope and course of this interesting condensation.

A. Influences on the Course of Reaction and Yields of Products.—The experimental conditions affect both structures and amounts of the products. Chichibabin[3c] used two general methods, heating a carbonyl compound with an aldehyde–ammonia in a sealed tube, and passing ammonia and the carbonyl compound(s) in the vapor phase over a catalyst such as alumina. The reactions have been represented in part by equations a and b in the case of crotonaldehyde and ammonia.

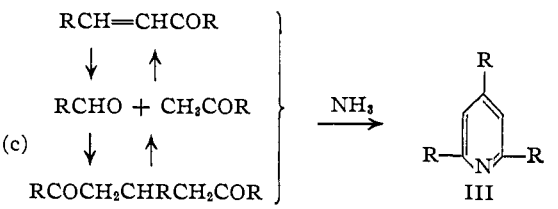


The ratio of the occurrence of reaction a to that of reaction b was found to be greater in Chichibabin's sealed-tube method than in the vapor phase, but both methods gave complex mixtures.[3c] The best yield of the vapor phase reaction appears to have been reported by Stitz, who obtained a 56% yield of β-picoline from acrolein and ammonia.[6]

A third method, used in all the experiments of this paper, involves heating the carbonyl compounds or derivatives with 28% aqueous ammonia in the presence of ammonium acetate. This use of aqueous ammonia has a surprising (and unexplained) effect in that the mixtures are less complex and the yields of single products consequently higher. For example, reaction according to equation a is almost completely favored over that of equation b,[5b,7] as illustrated by the formation of aldehyde-collidine in runs 19–24 and also by the formation of 2,3,4-collidine rather than 2,3,6-collidine from methyl vinyl ketone and its derivatives (runs 28 and 29).

Other factors of temperature, catalyst, time, etc., are of importance, as brought out in the Experimental Part. It has been previously demonstrated that the use of a large excess of ammonia increases the yields of pyridines.[5b]

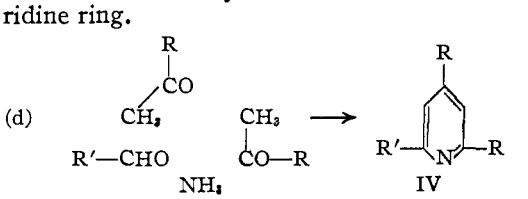
The fact that acetaldehyde, acetal, paraldehyde and crotonaldehyde or its ethoxyl derivatives all give aldehyde-collidine (I) as the principal product (runs 19–24) suggests that crotonaldehyde may be represented as an intermediate in the reaction (equation a). The condensation of benzalacetophenone with ammonia would thus be expected to yield 3-benzyl-2,4,6-triphenylpyridine. We were surprised to obtain instead 2,4,6-triphenylpyridine (run 1). This result indicates that during the reaction a reverse aldol condensation can occur with the formation of an equilibrium mixture (scheme c). The pyridine formation is thus different from reactions a and b in that the condensation occurs between one molecule of the α,β-unsaturated carbonyl compound (or its equivalent) and one of the methyl ketone.



Further evidence for the establishment of an equilibrium mixture is that one obtains the same product from a mixture of benzaldehyde and acetophenone (run 2), a mixture of benzalacetophenone and acetophenone (run 3), or from benzaldiacetophenone (run 4) (see also runs 5–7).[8]

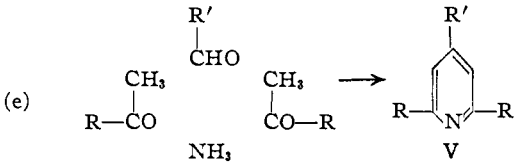
The reversible nature of the aldol condensation under the conditions necessary for pyridine formation constitutes one of the chief limitations of the Chichibabin synthesis, and explains the formation of mixtures in many instances. For example, if one uses an α,β-unsaturated carbonyl compound which can undergo a reverse aldol reaction, and the products recondense to give a new α,β-unsaturated carbonyl compound, then of course there will occur a mixture of products. If the fragments can recombine only to give the original α,β-unsaturated carbonyl compound, however, then a single product predominates. This is illustrated by the isolation of single products in runs 1–7 and the formation of oily mixtures by similar reactions of ammonia with ethylideneacetone (run 8), with cinnamaldehyde, with a mixture of benzalacetone and acetophenone (run 9), and with a mixture of benzalacetophenone and acetone (run 10).

If scheme c represents the interaction of two molecules of a methyl (or methylene) ketone with one of an aldehyde (or their equivalent condensation products), the reactants can then be oriented in either of two ways for the formation of the pyridine ring.



(7) In the careful work of Graf, Langer and Haumeder (*J. prakt. Chem.*, **150**, 153 (1938)) there was isolated in the form of its picrate from the use of 2700 g. of paraldehyde only 0.38 g. of β-collidine (II), along with 671 g. of aldehyde-collidine (I).

(8) Additional evidence is the isolation of benzylacetophenone as a reduction product in run 9. This must have arisen from the series: benzalacetone + acetophenone → benzalacetophenone + acetone → benzylacetophenone.



In the formation of 2,4,6-triphenylpyridine and of pentaphenylpyridine the product is the same according to either scheme (d and e; R = R′), but we were interested in determining which of the reactions prevailed, and to test the point we prepared some pyridines using substituted benzaldehydes (d and e, R ≠ R′).

Condensations using *p*-chlorobenzaldehyde and acetophenone (run 11), *p*-chlorobenzalacetophenone and acetophenone (run 12) and *p*-chlorobenzaldiacetophenone (run 13) (d and e, R = C_6H_5, R′ = *p*-ClC_6H_4) all gave the same *p*-chlorophenyldiphenylpyridine. There was an indication in the results of these runs that the product was 4-(*p*-chlorophenyl)-2,6-diphenylpyridine (V, R = C_6H_5, R′ = *p*-ClC_6H_4) rather than 2-(*p*-chlorophenyl)-4,6-diphenylpyridine (IV, R = C_6H_5, R′ = *p*-ClC_6H_4), because run 13, starting with the diketone *p*-chlorobenzaldiacetophenone, gave a higher yield than run 11 or run 12. The diketone is a direct precursor for the formation of 4-(*p*-chlorophenyl)-2,6-diphenylpyridine but not for the 2-*p*-chlorophenyl isomer.

More conclusive evidence that the pyridine was the 4-*p*-chlorophenyl derivative was obtained by direct synthesis of the latter from *p*-chlorobenzaldiacetophenone and hydroxylamine hydrochloride under conditions milder than those for the Chichibabin reaction. The product was identical with the compound obtained in runs 11–13.

Similar results were obtained in reactions with anisaldehyde and acetophenone (run 14) with anisalacetophenone and acetophenone (run 15) and with anisaldiacetophenone (run 16) (d and e, R = C_6H_5, R′ = *p*-$CH_3OC_6H_4$). Here again the highest yield of product was formed from the diketone (run 16), and the structure was shown by direct synthesis with hydroxylamine hydrochloride to be 4-anisyl-2,6-diphenylpyridine (V, R = C_6H_5, R′ = *p*-$CH_3OC_6H_4$). Thus reaction e predominates in this series.

It is probably nevertheless true that reactions d and e are competitive in many cases. An example is run 17, in which the condensation of benzalacetone and acetone with ammonia yielded small amounts of the two dimethylphenylpyridines, isolated as their picrates, corresponding to structures IV and V (R = CH_3, R′ = C_6H_5).[9] Of incidental interest in run 17 is the isolation of a third picrate corresponding in analysis to that of a methylphenylstyrylpyridine. It is probably the formation of condensation by-products of this type which accounts for the lower yields of single pyridines obtained from methyl ketones than from phenyl ketones (compare also runs 1 and 8).

Other condensations of this type (c, d and e) were tried using a mixture of veratralacetophenone and acetophenone, veratraldiacetophenone, a mixture of 2,3-dimethoxybenzaldehyde and acetophenone, a mixture of benzaldehyde and pinacolone, and acrylophenone (as ω-dimethylaminopropiophenone hydrochloride and also as ω-ethoxypropiophenone). All gave only heavy dark oils. A mixture of *m*-methoxybenzalacetophenone and acetophenone formed an 18% yield of 2,6-diphenyl-4-(*m*-methoxyphenyl)-pyridine (run 18).

It will be noted that formation of a pyridine in equations d and e must involve the loss of two hydrogen atoms. This apparently occurs readily, as we found no dihydropyridines among our products. In two cases, however, runs 9 and 10, there was isolated benzylacetophenone, the reduction product of benzalacetophenone (see footnote 8).

B. Use of Derivatives of Aldehydes, Ketones or α,β-Unsaturated Carbonyl Compounds.—In the formation of aldehyde-collidine in the Chichibabin reaction, the fact that paraldehyde gives much higher yields than acetaldehyde, and also that a large excess of ammonia results in increased yields, indicates that formation of higher-molecular-weight by-products may result partly from linear polymerization of the simple aldehydes or α,β-unsaturated carbonyl compounds. Thus higher yields might be expected if the carbonyl compound in the reaction mixture is made available slowly by the gradual decomposition of a derivative.

To try out this possibility a number of simple acetals and ethanol-addition compounds of α,β-unsaturated aldehydes and ketones were prepared and the yields of pyridines from them compared with those from the unprotected aldehydes and ketones.

The results, summarized in Table II, show that protection of the carbonyl and ethylenic functions does increase the yields, but that of the cases tried none showed the marked improvement achieved by the use of paraldehyde or acetal in place of acetaldehyde (runs 19–21). Nevertheless, for some compounds this scheme is probably the best means of preparation: *viz.*, the formation of 2,3,4-collidine from 1,3,3-triethoxybutane (run 29).

Experimental

Chichibabin Syntheses.—The reactions were carried out in an electrically heated 600-ml. steel autoclave of the type used for high-pressure hydrogenations.[10] A copper gasket was used, but was changed frequently due to erosion by ammonia. In most cases the autoclave was held horizontally in the heating jacket and rocked through a 30°

(9) These were characterized by analysis of their picrates. 2,6-Dimethyl-4-phenylpyridine is known (see Table I); the other was therefore assumed to be 2,4-dimethyl-6-phenylpyridine.

(10) Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, Wis., 1937, p. 29.

angle thirty-six times per minute. In a few runs (runs 19, 22 and 28) in which the starting mixture was homogeneous, the vessel was heated in an upright position without agitation.

The materials were for the most part simply mixed in the autoclave. With crotonaldehyde (run 22) and with methyl vinyl ketone (run 28) the compounds were first mixed in an ice-cooled flask because of the initial exothermic reaction; with acrolein (run 25) this initial reaction was violent and led to immediate polymer formation so that the autoclave reaction could not be run at all. The ammonia was added as a 28% aqueous solution; the amounts used were ten times the theoretical amount, based on a quantitative yield of the principal product. The effect of lesser amounts of ammonia, known to diminish the yields,[5b] was further demonstrated by some comparative runs in the present series. When runs 21 and 27 were repeated with three-tenths the amount of ammonium hydroxide, the yields dropped to 39 and 6%, respectively.

Pressures generated varied with the materials and the temperature, ranging in the runs of Table I from 1050 to 1375 pounds per square inch, and of Table II from 660 to 1450 pounds per square inch except as noted.

The temperature of the experiments, unless otherwise noted, was 250°, although reaction evidently begins at about 200°. The reactions are exothermic; this is not usually noticeable in small autoclaves, but spontaneous temperature rises to 310° have been observed, especially in reactors of more than a few liters capacity. Experiments using temperatures as high as 300° had no adverse effect on the yields.

Reaction times ranged from one to four hours; most runs were heated for three. Some comparative studies made in the preparation of aldehyde-collidine from acetal and paraldehyde indicated that the reaction is probably completed in a matter of minutes at 250°.

The use of ammonium acetate improves the yields but is not necessary for reaction to occur. For example, when runs 20 and 21 were repeated using no ammonium acetate, the yields of aldehyde-collidine were 37 and 34%, respectively. Ammonium chloride showed the same effect as ammonium acetate, but tended to corrode the reactor.

No single procedure sufficed for the isolation of the products in all the runs; they are therefore grouped as follows, the information given supplementing that in Tables I and II:

Runs 1–4: The oily layer, separated from the reaction mixture, was taken up in methanol–benzene and the product (2,4,6-triphenylpyridine) crystallized therefrom.

Runs 5, 6, 7, 11, 12, 13, 16: The oily layer from the crude reaction mixture was dissolved in hot ethanol, cooled, and the crystals collected and recrystallized.

Run 8: The reaction mixture was extracted with five 20-ml. portions of chloroform, the extract dried over anhydrous potassium carbonate, and the solution fractionally distilled through a ten-inch helix-packed column to give 3.83 g., b. p. 51–60° (30 mm.); $n^{20}D$ 1.4479, of an unknown base, the picrate of which melted at 172.5–174° (not identical with the picrate of 2,4-lutidine), and 9.76 g. of 2,4,6-collidine.

Runs 9 and 10: The oily layer from the reaction mixture was fractionally distilled, with no clean-cut fraction predominating, and a fraction of b. p. 143–180° (9 mm.) (200–230° (30 mm.)) allowed to stand. A few crystals formed; these were recrystallized once from ethanol and twice from methanol and proved to be benzylacetophenone (see Table I).

Run 14: The oily layer from the reaction mixture was dissolved in hot ethanol–benzene (95:5) and filtered to remove a few crystals. The filtrate, combined with a chloroform extract of the aqueous layer of the reaction mixture, was steam distilled until the distillate was clear. The residue was dissolved in chloroform, and methanol added nearly to the point of formation of an oil. More crystals formed; these, combined with those already obtained, weighed 0.38 g. Recrystallization from benzene, methanol–chloroform (60:40), and ethanol–benzene (80:20) gave colorless needles, m. p. 229–230°.

Anal.[11] C, 80.62, 80.31; H, 6.65, 6.64. This by-product was not further investigated.

The chloroform–methanol solution was evaporated, the residue dissolved in hot ethanol, and the solution cooled to yield crystalline 4-anisyl-2,6-diphenylpyridine.

Runs 15 and 18: These were worked up in the same manner as runs 5, 6, 7, 11, 12, 13 and 16, except that the reaction mixtures were first steam distilled to remove volatile impurities.

Run 17: The oily layer from the reaction mixture was distilled to form two fractions, b. p. 60–175° (4 mm.) and 175–260° (4 mm.). From the lower-boiling cut were obtained the two picrates of the dimethylphenylpyridines described in Table I. From the higher-boiling fraction was obtained 0.5 g. of the third picrate described under run 17 in Table I.

Runs 19–30: The products in all these runs, except run 25, which formed a polymer before it could be placed in the autoclave, were obtained by saturation of the reaction mixtures with potassium carbonate, thorough extraction with chloroform, and fractional distillation of the extracts.

Benzaldiacetophenone.—To a solution of 83.2 g. (0.399 mole) of benzalacetophenone and 60 g. (0.400 mole) of acetophenone in 500 ml. of ethanol was added a hot solution of 40 g. of sodium hydroxide in 60 ml. of water. The mixture was heated on a steam-cone for ten minutes, allowed to stand for four hours, and poured into water. The oily insoluble precipitate crystallized on trituration under 150 ml. of 50% aqueous ethanol. Recrystallization from 220 ml. of acetic acid–ethanol (65:35) gave 12.5 g. of colorless crystals, m. p. 189–193°, probably dibenzaltriacetophenone.[12] The mother liquors on standing overnight deposited crystalline benzaldiacetophenone, which after two recrystallizations from acetic acid–ethanol (50:50) weighed 39.3 g. (38%) and melted at 82–84° (lit.,[13] 85°).

Benzaldesoxybenzoin and Benzaldidesoxybenzoin (Benzamaron).—A mixture of 50 g. (0.255 mole) of desoxybenzoin and 250 g. (2.36 moles) of freshly-distilled benzaldehyde in 250 ml. of ethanol and 20 g. of potassium hydroxide in 100 ml. of 50% aqueous ethanol, which turned light orange and cloudy, was allowed to stand for fifty-three hours at room temperature. The crystals (18.1 g.) which precipitated were collected on a filter, washed with 50 ml. of 60% aqueous ethanol and 50 ml. of water, triturated under 35 ml. of boiling ethanol, and the mixture filtered while hot. The crystals on the filter were 13.3 g. (22%) of benzaldidesoxybenzoin, m. p. 215–219° (lit.,[13] 218–219°). When 50 ml. of water was added to the combined filtrates and washings, and the solution allowed to stand for thirty-six hours, 16.0 g. (22%) of colorless needles of benzaldesoxybenzoin formed, m. p. 98–100° (lit.,[14] 100°).

Ethylideneacetone.—The procedure of Grignard and Fluchaire,[15] using a total of 717 g. (905 ml., 12.32 moles) of acetone, 424 ml. of ether, 200 ml. of 12% aqueous sodium hydroxide, and 320 g. (7.27 moles) of acetaldehyde gave as the final product (after dehydration by means of 15 g. of oxalic acid dihydrate) 143 g. (23.5%) of ethylideneacetone, b. p. 119–124° (740 mm.); $n^{20}D$ 1.4359; sp. gr. $^{20}_4$ 0.855; *MR* calcd., 24.9; *MR* found, 25.7.

***p*-Chlorobenzalacetophenone.**—To a solution of 28.1 g. (0.20 mole) of *p*-chlorobenzaldehyde and 24.0 g. (0.20 mole) of acetophenone in 175 ml. of ethanol was added 15 ml. of 10% aqueous sodium hydroxide. After fifteen minutes the crystalline product was collected on a filter and recrystallized from ethanol to yield 38.0 g. (78%) of

(11) Microanalyses were carried out by Miss Emily Davis, Mrs. Jane Wood, and the Clark Microanalytical Laboratory.

(12) Kostanecki and Rossbach, *Ber.*, **29**, 1488 (1896).

(13) Knoevenagel and Weissgerber, *ibid.*, **26**, 436 (1893).

(14) Knoevenagel and Weissgerber, *ibid.*, **26**, 441 (1893).

(15) Grignard and Fluchaire, *Ann. chim.*, [10] **9**, 10 (1928).

TABLE I

PYRIDINE SYNTHESES BY THE CHICHIBABIN REACTION

Temperature 250°; time three hours; 28% ammonium hydroxide used is ten times theoretical amount

Run	Starting materials	Moles	Moles NH_4OAc	Products isolated	Yield, %
1	Benzalacetophenone	0.40	0.052	2,4,6-Triphenylpyridine[a]	42
2	Benzaldehyde	0.25	.065	2,4,6-Triphenylpyridine[a]	36
	Acetophenone	1.00			
3	Benzaldiacetophenone	0.25	.065	2,4,6-Triphenylpyridine[a]	39
	Acetophenone	0.325			
4	Benzaldiacetophenone	.12	.031	2,4,6-Triphenylpyridine[a]	42
5	Benzaldehyde	.075	.019	Pentaphenylpyridine[b]	20
	Desoxybenzoin	.16			
6	Benzaldesoxybenzoin	.03	.0078	Pentaphenylpyridine[b]	8
	Desoxybenzoin	.03			
7	Benzaldidesoxybenzoin	.025	.0065	Pentaphenylpyridine[b]	18
8	Ethylideneacetone	.80	.0096	2,4,6-Collidine[c]	20
9	Benzalacetone	.25	.065	Benzylacetophenone (0.04 g.)[d]	..
	Acetophenone	1.00			
10	Benzalacetophenone	0.25	.065	Benzylacetophenone (2.8 g.)[e]	..
	Acetone	.325			
11	*p*-Chlorobenzaldehyde	.075	.019	4-(*p*-Chlorophenyl)-2,6-diphenylpyridine	18
	Acetophenone	.225			
12	*p*-Chlorobenzalacetophenone	.075	.039	4-(*p*-Chlorophenyl)-2,6-diphenylpyridine	32
	Acetophenone	.112			
13	*p*-Chlorobenzaldiacetophenone	.075	.039	4-(*p*-Chlorophenyl)-2,6-diphenylpyridine	51
14	Anisaldehyde	.13	.034	4-Anisyl-2,6-diphenylpyridine[f]	16
	Acetophenone	.27			
15	Anisalacetophenone	.10	.026	4-Anisyl-2,6-diphenylpyridine[f]	11
	Acetophenone	.11			
16	Anisaldiacetophenone	.10	.026	4-Anisyl-2,6-diphenylpyridine[f]	38
17	Benzalacetone	.25	.065	2,6-Dimethyl-4-phenylpyridine[g]	3.7[h]
	Acetone	1.00		2,4-Dimethyl-6-phenylpyridine[i]	4.9[h]
				A methylphenylstyrylpyridine[j]	0.8[h]
18	*m*-Methoxybenzalacetophenone	0.13	.034	2,6-Diphenyl-4-(*m*-methoxyphenyl)-pyridine[k]	18
	Acetophenone	.135			

[a] Needles from ethanol, m. p. 137–138°. *Anal.* Calcd. for $C_{23}H_{17}N$: C, 89.87; H, 5.57; N, 4.56. Found: C, 90.26, 90.27; H, 5.70, 5.98; N, 4.64. Picrate, m. p. 193–194° (Ectors, *Bull. Acad. roy. Belgique, Classe des Sciences*, [5] **9**, 501 (1923); *Chem. Zentr.*, **95**, I, 913 (1924) reported m. p.'s 138 and 192°, respectively). [b] Blades from glacial acetic acid, m. p. 245–247° (lit., reference 13, 239–240°). [c] B. p. 74° (28 mm.); $n^{20}D$ 1.4957; picrate, m. p. 154.5–155.5°. [d] M. p. 63–68°; mixed m. p. with authentic sample 67–70°. [e] M. p. 70.5–71.5°; *Anal.* Calcd. for $C_{15}H_{14}O$: C, 85.68; H 6.71. Found: C, 85.63; H, 6.90. Oxime, m. p. 81.5–83.5° (Perkin and Stenhouse (*J. Chem. Soc.*, 59, 996 (1891)) reported m. p. 82°). [f] Crystalline by-product also formed (see Experimental). [g] B. p. 60–175° (4 mm.); picrate, m. p. 236–238°. (Baeyer and Piccard (*Ann.*, **384**, 208 (1911)) reported m. p. *ca.* 230°). *Anal.* Calcd. for $C_{19}H_{16}N_4O_7$: C, 55.34; H, 3.91; N, 13.59. Found: C, 55.32; H, 4.07; N, 13.77. [h] Pyridine isolated only as picrate; yield calculated from picrate. [i] B. p. 60–175° (4 mm.); picrate, m. p. 186–187°. *Anal.* Calcd. for $C_{19}H_{16}N_4O_7$: C, 55.34; H, 3.91; N, 13.59. Found: C, 55.60; H, 4.10; N, 13.73. [j] B. p., 175–260° (4 mm.); picrate, m. p. 234–234.5°. *Anal.* Calcd. for $C_{26}H_{20}N_4O_7$: C, 62.40; H, 4.03; N, 11.19. Found: C, 62.56; H, 4.31; N, 11.23. [k] Colorless needles from ethanol–benzene (80:20); m. p. 123.5–124°. *Anal.* Calcd. for $C_{23}H_{16}N(OCH_3)$: C, 85.43; H, 5.68; N, 4.15; OCH_3, 9.20. Found: C, 85.29; H, 5.79; N, 4.11; OCH_3, 9.79, 9.68.

light yellow flat blades, m. p. 112–114° (lit.,[16] 115–116°).

***p*-Chlorobenzaldiacetophenone.**—Forty-five grams (0.32 mole) of *p*-chlorobenzaldehyde, 115.6 g. (0.96 mole) of acetophenone and 700 ml. of ethanol were placed in a 1-l. erlenmeyer flask. To this was added a hot solution of 80 g. of sodium hydroxide in 80 ml. of water. After an initial exothermic reaction, the mixture was allowed to stand for twelve hours with occasional swirling, then warmed and poured into 10 l. of water. The insoluble oil was separated, crystallized in ethanol, and recrystallized twice from ethanol to give 47.5 g. (41%) of colorless blades, m. p. 108–110°. An analytical sample, further recrystallized from ethanol, melted at 109.5–110.5°.

Anal. Calcd. for $C_{23}H_{19}O_2Cl$: C, 76.13; H, 5.28. Found: C, 76.34; H, 5.36.

4-(*p*-Chlorophenyl)-2,6-diphenylpyridine (by Means of Hydroxylamine).—A solution of 1.8 g. (0.005 mole) of *p*-chlorobenzaldiacetophenone and 0.7 g. (0.01 mole) of hydroxylamine hydrochloride in 20 ml. of ethanol in a 30-ml. test-tube was placed in the bottom of a 600-ml. steel autoclave with the thermocouple well in the tube when the autoclave was sealed (30 ml. of ethanol was also placed in the autoclave to equalize evaporation in the test-tube during heating). The autoclave was heated at 160° for six hours. Crystals formed in the test-tube on cooling; recrystallization from ethanol gave 0.75 g. (44%) of colorless needles, m. p. 128.5–130°.

Anal. Calcd. for $C_{23}H_{16}NCl$: C, 80.81; H, 4.72; N, 4.10. Found: C, 80.66; H, 4.77; N, 4.31.

(16) Dilthey, Neuhaus, Reis and Schommer, *J. prakt. Chem.*, **124**, 81 (1930).

TABLE II

PYRIDINE SYNTHESES BY THE CHICHIBABIN REACTION

Temperature 250°; time 1.5–3.3 hours; 28% ammonium hydroxide used is ten times theoretical amount

Run	Starting material	Moles	Mole NH_4OAc	Product	Yield, %
19	Acetaldehyde	1.6	0.026	Aldehyde-collidine (I)[a]	34
20	Acetal[b]	1.27	.032	Aldehyde-collidine (I)[a]	57.5
21	Paraldehyde[b]	0.67	.026	Aldehyde-collidine (I)[a]	59.5
22	Crotonaldehyde	.10	.013	Aldehyde-collidine (I)[a]	18
23	Crotonaldehyde diethyl acetal	.33	.0091	Aldehyde-collidine (I)[a]	19
24	1,1,3-Triethoxybutane[c]	.53	.013	Aldehyde-collidine (I)[a]	46
25	Acrolein	1.00	....	Polymer	
26	Acrolein diethyl acetal	0.76	.019	Tar	
27	1,1,3-Triethoxypropane	.40	.052	β-Picoline[d]	20
28	Methyl vinyl ketone	.20	.026	2,3,4-Collidine[e]	12
29	1,3,3-Triethoxybutane	.40	.052	2,3,4-Collidine[e]	20

[a] B. p. 68–73° (22 mm.); $n^{20}D$ 1.4959–1.4971; m. p. picrate 167–168° (lit. (see reference 5b), b. p. 68° (18 mm.)) $n^{20}D$ 1.4971; m. p. picrate 164°. [b] Pressures in runs 20 and 21 reached 4000 and 2950 pounds per square inch, respectively. [c] Temperature of this run 220–228°. [d] B. p. 141–148° (740 mm.); $n^{20}D$ 1.5023; m. p. picrate 149–150° (Ladenburg (*Ann.*, **247**, 10 (1888)) reported m. p. 149–150°). [e] B. p. 78–81° (25 mm.); $n^{20}D$ 1.5118 in run 28; b. p. 83–93° (28 mm.); $n^{20}D$ 1.5097 in run 29; m. p. picrate 163–164°; m. p. picrolonate 240–241° (dec.) (Prelog, Komzak and Moor (*Helv. Chim. Acta*, **25**, 1654 (1942)) reported m. p. picrate 164°; m. p. picrolonate 239°).

Mixed m. p.'s with the products of runs 11–13 showed no depression.

Anisalacetophenone.—This was prepared by the method of Pond, Maxwell and Norman[17] from 25.0 g. (0.183 mole) of anisaldehyde, 22.0 g. (0.183 mole) of acetophenone, 180 ml. of ethanol and 20 ml. of 10% aqueous sodium hydroxide. The light yellow blades weighed 25.5 g. (58%), m. p. 74–76° (lit.,[17] 77–78°).

Anisaldiacetophenone.—A mixture of 2.7 g. (0.02 mole) of anisaldehyde, 7.2 g. (0.06 mole) of acetophenone, 50 ml. of ethanol and a solution of 5 g. of sodium hydroxide in 5 ml. of hot water was shaken for five minutes and allowed to stand for three days. The solid product was collected and twice recrystallized from ethanol to give 5.67 g. (79%) of colorless blades, m. p. 92–95°. An analytical sample, recrystallized twice from ethanol and twice from butanol, also melted at 92–95°.

Anal.[18] Calcd. for $C_{23}H_{18}O_2(OCH_3)$: C, 80.42; H, 6.19; OCH_3, 8.66. Found: C, 80.33; H, 6.28; OCH_3, 9.07.

4-Anisyl-2,6-diphenylpyridine (by Means of Hydroxylamine).—This compound was made in the same manner as was 4-(*p*-chlorophenyl)-2,6-diphenylpyridine, using the same amounts (g. and moles) of materials. The product, crystallized from ethanol-acetone (95:5) was 1.04 g. (62%) of diamond-shaped plates, m. p. 96.5–100.5°. An analytical sample, recrystallized several times from ethanol, melted at 99.5–101°.

Anal. Calcd. for $C_{23}H_{16}N(OCH_3)$: C, 85.43; H, 5.68; N, 4.15; OCH_3, 9.20. Found: C, 85.54; H, 5.81; N, 4.04; OCH_3, 9.42. Mixed m. p.'s with the products of runs 14–16 showed no depression.

Veratralacetophenone.—The procedure of Dickinson, Heilbron and Irving[19] using 35.0 g. (0.21 mole) of veratraldehyde, 24.0 g. (0.20 mole) of acetophenone, 160 ml. of ethanol and 90 ml. of 10% aqueous sodium hydroxide gave 21.9 g. (41%) of yellow blades, m. p. 87–88° (lit.,[19] 88°).

Veratraldiacetophenone.—To a solution of 36.3 g. (0.219 mole) of veratraldehyde and 55.0 g. (0.458 mole) of acetophenone in 264 ml. of ethanol was added 66 g. of sodium hydroxide dissolved in 66 ml. of hot water, and the mixture heated on a steam-cone for one hour, then allowed to stand for two days. When this was poured into 7 l. of water, a sticky paste formed. A sample dissolved in ethanol crystallized in a refrigerator. This was used to seed the main portion. Recrystallization twice from ethanol gave 30 g. (35.5%) of colorless flakes, m. p. 103–106°. An analytical sample, further crystallized from ethanol, melted at 106–107°.

Anal. Calcd. for $C_{25}H_{24}O_4$: C, 77.30; H, 6.23. Found: C, 77.34; H, 6.27.

ω-Dimethylaminopropiophenone Hydrochloride and ω-Ethoxypropiophenone.—ω-Dimethylaminopropiophenone, a Mannich base from acetophenone,[20] was available as its hydrochloride. From 50.0 g. (0.234 mole) was obtained 17.4 g. of crude acrylophenone ($n^{20}D$ 1.5602) by steam distillation of its water solution for six hours, extraction of the distillate with chloroform, and evaporation of the chloroform. The crude acrylophenone, dissolved in 40 ml. of dry ethanol containing five drops of concentrated hydrochloric acid, refluxed for ten minutes, and allowed to stand for three hours, yielded on distillation 18.4 g. (44% based on the Mannich salt) of ω-ethoxypropiophenone, b. p. 120–122° (8 mm.); $n^{20}D$ 1.5168.

Crotonaldehyde Diethyl Acetal and 1,1,3-Triethoxybutane.—These were prepared by the method of Pingert[21] for the analogous compounds from acrolein, using 118.4 g. (1.69 moles) of crotonaldehyde and the corresponding amounts of the other reagents. Final fractional distillation gave 10.9 g. (4.5%) of crotonaldehyde acetal, b. p. 44–48° (19 mm.), $n^{20}D$ 1.4097, and 122 g. (38%) of 1,1,3-triethoxybutane, b. p. 83–84° (19 mm.); $n^{20}D$ 1.4074.

In preparations in which only the unsaturated acetal is desired rather than both compounds the method of Schmidt[22] using crotonaldehyde, ethyl orthoformate and zinc chloride is recommended for yields of 50–60%.

Acrolein Diethyl Acetal and 1,1,3-Triethoxypropane.—These were prepared exactly as described by Pingert[21] to give 31.3 g. (8.5%) of acrolein acetal, b. p. 45–50° (23 mm.); $n^{20}D$ 1.3955, and 76.7 g. (15.5%) of 1,1,3-triethoxypropane, b. p. 84–87° (22 mm.); $n^{20}D$ 1.4077 (see remarks in preceding preparation on method of Schmidt[22]).

Methyl Vinyl Ketone and 1,3,3-Triethoxybutane.—Methyl vinyl ketone was obtained by drying and distilling the commercial azeotrope supplied by the Organic Chemicals Department of E. I. du Pont de Nemours and Co.,

(17) Pond, Maxwell and Norman, THIS JOURNAL, **21**, 955 (1899).

(18) Methoxyl determinations were kindly carried out by Mr. Robert Anderson, Miss Virginia Menikheim and Mr. Charles Strickler.

(19) Dickinson, Heilbron and Irving, *J. Chem. Soc.*, 1888 (1927).

(20) Mannich and Heilner, *Ber.*, **55**, 356 (1922).

(21) Pingert, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Vol. 25, 1945, p. 1.

(22) Schmidt (Schering-Kahlbaum A.G.), German patent 553,177 (June 22, 1932); *Chem. Zentr.*, **103**, II, 2108 (1932).

b. p. 80–82°. For the triethoxy compound, 77 g. (1.1 moles of methyl vinyl ketone containing a trace of hydroquinone, 148 g. (1.00 mole) of ethyl orthoformate, 115 g. (2.50 moles) of absolute ethanol, and 0.1 g. of hydrogen chloride dissolved in 8 ml. of absolute ethanol were mixed in a 500-ml. erlenmeyer flask and allowed to stand, tightly stoppered, for seven days. After heating under reflux for fifteen minutes, the mixture was neutralized with 28% aqueous ammonia, dried over anhydrous magnesium sulfate, and fractionally distilled through a ten-inch helix-packed column to yield 137.5 g. (66% based on methyl vinyl ketone) of 1,3,3-triethoxybutane, b. p. 79–82° (15 mm.); $n^{20}D$ 1.4137 (lit.,[23] 1.4148).

Summary

1. The use of excess aqueous ammonia in the Chichibabin synthesis of pyridines gives better yields of single products than does the use of aldehyde–ammonias or vapor-phase condensation.

2. An important limitation of the Chichibabin synthesis of pyridines from methyl or methylene ketones and aldehydes or α,β-unsaturated carbonyl compounds is the reversible nature of the aldol condensation under the conditions of the reaction. Proper choice of substituents is necessary for formation of single products in satisfactory yields.

3. The condensation of two molecules of a methyl aryl ketone with a substituted aryl aldehyde and aqueous ammonia occurs so as to form a pyridine with the substituted aromatic nucleus on the γ-position of the pyridine.

4. Protection of simple aldehydes or α,β-unsaturated carbonyl compounds by formation of their acetals or similar derivatives gives increased yields of pyridines in the Chichibabin synthesis.

(23) Dykstra, THIS JOURNAL, **57**, 2255 (1935).

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[CONTRIBUTION FROM THE WM. H. CHANDLER CHEMISTRY LABORATORY, LEHIGH UNIVERSITY]

Studies in the Diphenylacetic Acid Series. I. Nitro and Amino Acids[1]

BY I. MOYER HUNSBERGER[2] AND E. D. AMSTUTZ

In view of the reported[3] high anti-tubercular activity of 1,1,1-trichloro-2-bis-*p*-aminophenylethane, it was felt that an examination of the preparation, properties and anti-bacterial effectiveness of 4,4′-diaminodiphenylacetic acid (XII) and its derivatives might bring to light new substances of value in the treatment of tuberculosis.

The only recorded synthesis of 4,4′-diaminodiphenylacetic acid[4] (XII) employs the condensation of aniline with dichloroacetic acid (or glyoxylic acid diacetate) with subsequent rearrangement of the dianilinoacetic acid which is presumably formed as an intermediate. Since this method formed the subject of considerable controversy and the structure of the product was never conclusively proved, it appeared that such a proof of structure must necessarily precede any use of the method for preparative purposes. The present paper reports the synthesis of the above diamino acid by an unambiguous route (see Reaction Sequence) and substantiates the work of Heller, at least in those respects pertinent to our interest.

It appeared at the outset that the best approach would be through the unknown 4,4′-dinitrodiphenylacetic acid (IX). Symons and Zincke[5] obtained mainly resinous acidic material from the nitration of diphenylacetic acid (I) using nitric acid (sp. gr. 1.5). However, they also isolated a small amount of unidentified neutral material melting at 180°, which was believed to be a nitrated benzophenone. The literature since 1874 is devoid of any further reference to the nitration of I. By nitrating ethyl diphenylacetate with red fuming nitric acid at −18° Werner[6] produced ethyl bis-(2,4-dinitrophenyl)-acetate in good yield.

In the present investigation diphenylacetic acid (I) was nitrated with white fuming nitric acid at 30° almost exactly according to the method recently used for nitrating the similarly constituted 1,1,1-trichloro-2,2-diphenylethane.[3] The crude resinous product undoubtedly consisted of a mixture of nitro compounds, but two recrystallizations from glacial acetic acid yielded *ca.* 7% of pure 3,4′-dinitrodiphenylacetic acid (II) as a white crystalline powder, m. p. 180.5–183.5°. The configuration of II was established by decarboxylation to 3,4′-dinitrodiphenylmethane (III) and by oxidation to 3,4′-dinitrobenzophenone (IV). The latter was reduced to 3,4′-diaminobenzophenone (V), acetylation of which produced 3,4′diacetamidobenzophenone (VI). Esterification of II with methanol and hydrogen chloride afforded methyl 3,4′-dinitrodiphenylacetate.

The formation of the 3,4′-dinitro acid (II) is somewhat unexpected since nitration of 1,1,1-trichloro-2,2-diphenylethane affords 1,1,1-trichloro-2,2-bis-(*p*-nitrophenyl)-ethane[3,7] in good yield. Although it is possible that II is not the main product formed, no other pure substance has been isolated thus far.

(1) Abstracted, in part, from a thesis presented by I. Moyer Hunsberger to the Graduate Faculty of Lehigh University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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(3) Kirkwood and Phillips, THIS JOURNAL, **69**, 934 (1947).

(4) Heller, *Ann.*, **333**, 247 (1904); **358**, 349 (1908); **375**, 261 (1910); *Ber.*, **41**, 4264 (1908); compare Ostromisslensky *ibid.*, **41**, 3019, 3029 (1908).

(5) Symons and Zincke, *Ann.*, **171**, 117 (1874).

(6) Werner, *Ber.*, **39**, 1278 (1906).

(7) Haskelberg and Lavie, *ibid.*, **69**, 2267 (1947).