

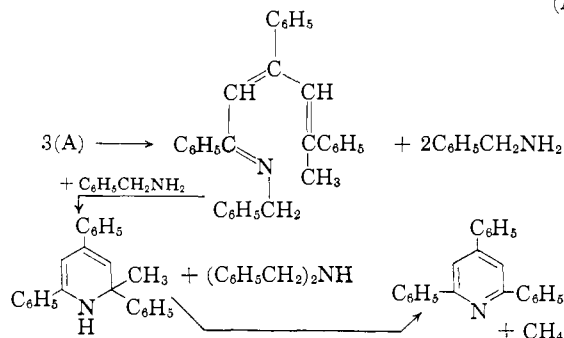
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CARNEGIE INSTITUTE OF TECHNOLOGY]

The Reddelien Synthesis of 2,4,6-Triarylpyridines and its Mechanism¹BY LUIS AMOROS-MARIN² AND ROBERT B. CARLIN

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Acetophenone and benzylamine, heated together in the presence of a trace of hydrobromic acid, gave 2,4,6-triphenylpyridine, in accordance with Reddelien's observations. Other substances isolated from the reaction mixture and characterized were ammonia, benzaldehyde, benzyl- α -phenylethylamine and dihydroprynone. No sensible amount of methane, required by the reaction sequence postulated by Reddelien, was formed, and the amine isolated by Reddelien and considered by him to have been dibenzylamine almost certainly was benzyl- α -phenylethylamine instead. Acetophenone and *p*-chlorobenzylamine, heated with a trace of hydrobromic acid, afforded 2,6-diphenyl-4-*p*-chlorophenylpyridine, and similarly *p*-chloroacetophenone and benzylamine yielded 2,6-di-*p*-chlorophenyl-4-phenylpyridine. The structures of these two triarylpyridines were established by independent syntheses. These observations suggested a mechanism for the Reddelien synthesis of 2,4,6-triarylpyridines, an essential feature of which is the dehydrogenation of benzylamine by acetophenone benzylimine, a reaction similar to that proposed by Angyal to account for the Sommelet reaction. Syntheses of 2-phenyl-4,6-di-*p*-chlorophenylpyridine and of 2-*p*-chlorophenyl-4,6-diphenylpyridine from the corresponding pyrylium salts were carried out by the method of Dilthey.

In connection with the identification of a by-product derived from the Fischer indole reaction of *p*-chloroacetophenone 2,6-dichlorophenylhydrazone in the presence of stannous chloride at 260°, a synthesis of 2,4,6-tri-*p*-chlorophenylpyridine (I) was required.³ A promising approach to this synthesis appeared to be that reported by Reddelien,⁴ who prepared 2,4,6-triphenylpyridine by heating acetophenone and benzylamine with small amounts of hydrobromic acid. He also observed that when acetophenone benzylimine was heated with a little benzylamine hydrochloride, 2,4,6-triphenylpyridine was again formed; and in addition the mixture contained an amine whose benzoyl derivative had the same m.p. as that reported for the N-benzoyl derivative of dibenzylamine. Reddelien offered the following sequence of reactions to account

$$\text{C}_6\text{H}_5\text{COCH}_3 + \text{C}_6\text{H}_5\text{CH}_2\text{NH}_2 \xrightarrow{\text{HBr}} \text{C}_6\text{H}_5\text{C}(\text{CH}_3)=\text{NCH}_2\text{C}_6\text{H}_5 \quad (\text{A})$$


for his observations. Although Reddelien did not establish whether methane was evolved from his reaction mixture, Riehm⁵ had shown that methane was produced when acetone reacted with ammonium chloride at 265° to yield 2,4,6-trimethylpyridine.

When the synthesis of 2,4,6-tri-*p*-chlorophenylpyridine (I) was attempted by heating *p*-chloroacetophenone with benzylamine in the presence of hydrobromic acid, the crystalline product was not I but 2,6-di-*p*-chlorophenyl-4-phenylpyridine (II).

(1) Submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the Carnegie Institute of Technology.

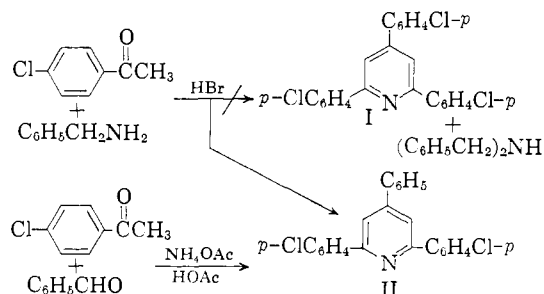
(2) American Viscose Corp. Fellow, 1954-1955.

(3) R. B. Carlin and L. Amoros-Marin, *THIS JOURNAL*, **81**, 720 (1959).

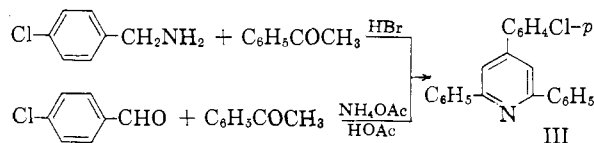
(4) G. Reddelien, *Ber.*, **53**, 334 (1920).

(5) P. Riehm, *Ann.*, **230**, 16 (1887).

The structure of II was established by its independent synthesis from benzaldehyde, *p*-chloroacetophenone and ammonium acetate in glacial acetic acid solution, a method developed and thoroughly studied by Weiss.⁶ The tri-*p*-chlorophenylpyridine I was also synthesized by Weiss' method; *p*-chlorobenzaldehyde, *p*-chloroacetophenone and ammonium acetate gave I in 41% yield.



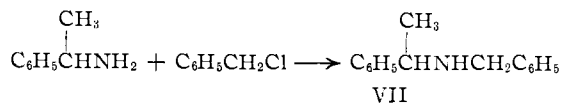
The isolation of II and not I from the interaction of benzylamine and *p*-chloroacetophenone by Reddelien's method indicates that the aryl group that ultimately occupies the 4-position of the pyridine system is derived from the benzylamine and not from the acetophenone. This conclusion was confirmed by heating acetophenone with *p*-chlorobenzylamine and a little hydrobromic acid. The only crystalline product isolated was identical with the product from acetophenone, *p*-chlorobenzaldehyde and ammonium acetate and was therefore 2,6-diphenyl-4-*p*-chlorophenylpyridine (III).



A detailed search of the reaction mixture from acetophenone, benzylamine and a trace of hydrobromic acid was now undertaken in an effort to gather additional evidence bearing on the mechanism of the reaction. Provision was made to collect gases and any volatile liquids that might be evolved from the mixture during the course of the reaction. Ammonia was indeed evolved; it was collected in dilute hydrochloric acid and weighed as

(6) M. Weiss, *THIS JOURNAL*, **74**, 200 (1952).

ammonium chloride. No water-insoluble gas (*e.g.*, methane) could be detected. The volatile liquid was chiefly water; a small quantity of a liquid, b.p. about 190°, probably acetophenone, was also identified, but no toluene could be detected. The contents of the reaction vessel were treated with ethanol, which caused the separation of crystalline 2,4,6-triphenylpyridine. The ethanol-soluble mother liquors were divided into a neutral and a basic fraction. The latter yielded on distillation under reduced pressure a major fraction which proved to be benzyl- α -phenylethylamine (VII). Its identity was established by comparison of its infrared spectrum with that of a sample synthesized from



α -phenylethylamine and benzyl chloride. Crystalline phenylthiourea derivatives of the two amine samples were also prepared. The mixed melting point was undepressed and again the infrared spectra were essentially identical. Curiously, the N-benzoyl derivative of VII melts at 109–111°, which is also the m.p. of N-benzoyldibenzylamine. It is therefore most probable that the amine isolated by Reddelien actually was VII and not dibenzylamine.

A third, high-boiling amine fraction was a viscous yellow oil, insoluble in hydrochloric acid, which could not be induced to crystallize. Attempts to prepare crystalline derivatives were also unsuccessful.

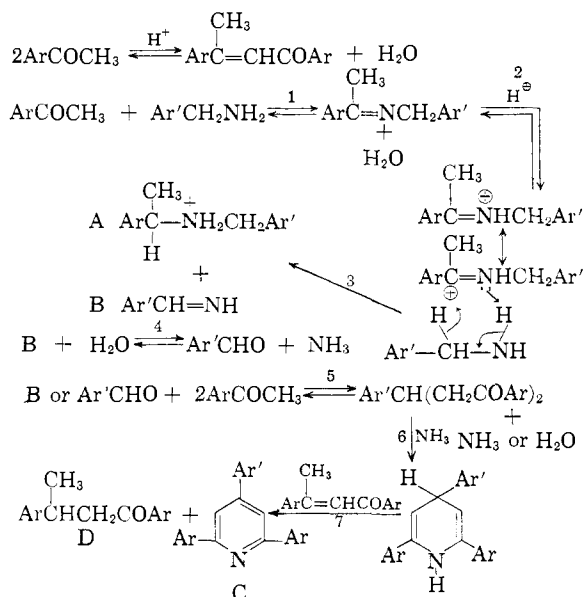
The neutral fraction from the Reddelien reaction mixture yielded benzaldehyde as its bisulfite derivative. The aldehyde was regenerated from this derivative by treatment with base and identified as its phenylhydrazone. Distillation of the residual neutral fraction yielded a clear yellow oil which crystallized from ethanol. The crystalline material melted at 70–72° and was at first believed to be benzylacetophenone. However, a mixture of a

sample with authentic benzylacetophenone showed a 20° melting point depression. Instead the neutral compound proved to be 1,3-diphenyl-1-butanone (dihydrodypnone, $\text{C}_6\text{H}_5\text{CH}(\text{CH}_3)\text{CH}_2\text{COC}_6\text{H}_5$, (VIII)), identified with an authentic sample prepared by hydrogenation of dypnone by mixed melting point determination and by the essential identity of the infrared spectra. A higher-boiling neutral fraction contained some 2,4,6-triphenylpyridine, but no other crystalline material could be isolated, nor could crystalline derivatives be prepared.

The isolation of ammonia, benzaldehyde, dihydrodypnone (VIII) and benzyl- α -phenylethylamine (VII) and the failure to observe methane or toluene evolution from the Reddelien reaction of benzylamine with acetophenone suggested a mechanism that appears to account satisfactorily for all of the observations on this reaction now on record.

Steps 1–3 in this mechanism are derived from the work of Angyal and his collaborators and their proposed mechanism for the Sommelet reaction.⁷ In step 3 we have combined the hydride ion shift, which forms an essential part of Angyal's mechanism and which Snyder and Demuth⁸ have accepted after their investigation of the Sommelet reaction, with the concept of a six-ring transition state to account for the formation of both benzaldehyde (step 4) and benzyl- α -phenylethylamine (VII, from A). Steps 5–7 are those proposed by Weiss⁶ to account for his observations. In step 5 the familiar aldol and Michael-type reactions are combined; the reversibility of these reactions under the imposed conditions has been demonstrated by Frank and Seven.⁹ Step 6 is the well-known dihydropyridine formation from a 1,5-diketone and ammonia, and step 7, the dehydrogenation of the dihydropyridine by dypnone, accounts for the formation of both the 2,4,6-triarylpyridine and the dihydrodypnone (D, VIII when $\text{Ar} = \text{C}_6\text{H}_5$). A reaction directly analogous to step 7 was observed by Weiss,⁶ who isolated and characterized 25% of the theoretical amount of benzylacetophenone (in addition to 2,4,6-triphenylpyridine) from the mixture formed by treating benzaldehyde and acetophenone with ammonium acetate in acetic acid. Weiss also called attention to other analogous reactions.⁶ It is perhaps curious that only dihydrodypnone (VIII) and no benzylacetophenone was isolated in the present investigation. The explanation may be that, as Weiss pointed out,⁶ benzylacetophenone can be lost by condensation with benzaldehyde. Dihydrodypnone would be expected to condense with benzaldehyde much less readily.

Numerous simple variations on this mechanism are possible and cannot at this time be excluded. For example, one might equally well write imino or benzylimino groups in place of carbonyl groups in steps 5 and 7. Since water, ammonia and benzylamine all are known to be present in the reaction mixture, the carbonyl group and both possible



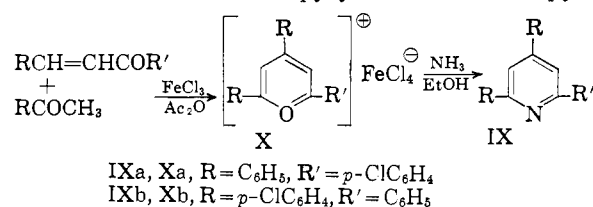
(7) S. J. Angyal and R. C. Rassack, *J. Chem. Soc.*, 2700 (1949); *Nature*, **161**, 723 (1948); S. J. Angyal, D. R. Penman and G. P. Warwick, *J. Chem. Soc.*, 1742 (1953); S. J. Angyal, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., Vol. VIII, 1954, p. 197.

(8) H. R. Snyder and J. R. Demuth, *THIS JOURNAL*, **78**, 1981 (1956).

(9) R. L. Frank and R. P. Seven, *ibid.*, **71**, 2029 (1949).

kinds of its nitrogen derivatives are undoubtedly present, and it is not now possible to indicate whether one of these forms predominates in steps 5 and 7 or whether all three take part.

To complete the series of 2,4,6-triarylpyridines in which the aryl groups were phenyl and *p*-chlorophenyl in all permutations, the syntheses of 2-phenyl-4,6-di-*p*-chlorophenylpyridine (IXa) and of 2-*p*-chlorophenyl-4,6-diphenylpyridine (IXb) were required. Owing to the reversibility of the aldol and Michael-type reactions,⁹ the Weiss procedure starting either with *p*-chlorobenzal-*p*-chloroacetophenone and acetophenone or with *p*-chlorobenzalacetophenone and *p*-chloroacetophenone led to mixtures of 2,4,6-triarylpyridines whose separations into their components were not attempted. The method of Dilthey,¹⁰ however, was successfully adapted to the syntheses of the two triarylpyridines IX. In this method a chalcone is treated with an acetophenone in the presence of ferric chloride in acetic anhydride solution. The benzo-pyrylium-ferric chloride double salt (X) separates from solution and is converted to the corresponding pyridine by treatment with ammonia in ethanol. Inasmuch as mixtures of pyrylium salts and of pyri-



dines were not produced when the preparations of X and IX were carried out, it appears that in these instances at least, the method of Dilthey, unlike that of Weiss, does not permit appreciable reverse aldol and Michael-type reactions to occur.

2,4-Di-*p*-chlorophenyl-6-phenylpyrylium ferrichloride (Xb) was also prepared by two methods reported by Le Fevre.¹¹ *p*-Chloroacetophenone and either benzoic anhydride or benzoyl chloride, in the presence of ferric chloride, gave the same crystalline product formed when *p*-chlorobenzalacetophenone was condensed with *p*-chloroacetophenone by Dilthey's procedure. This observation afforded additional confirmation of the irreversibility of the condensation reactions employed by Dilthey.

Experimental¹²

Preparation of 2,4,6-Triarylpyridines by Reddelien's Procedure.—A mixture of 17 g. of acetophenone, 15 g. of benzylamine and 4 drops of 48% hydrobromic acid was heated while water collected in the azeotrope separator provided for that purpose; then the mixture was heated at 190° for an additional half-hour. The cooled mixture was poured into aqueous ethanol, and the 3 g. (12%) of white crystalline 2,4,6-triphenylpyridine that separated was collected. Recrystallization from ethanol gave small, white needles, m.p. 137–138°; Reddelien⁴ reported m.p. 135–136°.

A mixture of 21 g. of *p*-chloroacetophenone, 15 g. of benzylamine and 4 drops of 48% hydrobromic acid, subjected to the same procedure, gave 2,6-di-*p*-chlorophenyl-4-phenylpyridine (II) in 12% yield. The product was isolated by pouring the reaction mixture into ethanol and purified by

recrystallization from the same solvent. It formed white needles, m.p. 183–184°.

Anal. Calcd. for C₂₃H₁₆NCl₂: C, 73.41; H, 4.02; N, 3.72; Cl, 18.85. Found: C, 73.60; H, 4.01; N, 3.80; Cl, 19.31.

A mixture of 33 g. of *p*-chlorobenzylamine,¹³ 28 g. of acetophenone and 0.5 ml. of 48% hydrobromic acid similarly gave 2,6-diphenyl-4-*p*-chlorophenylpyridine in 7% yield, white needles, m.p. 128–130° (as reported⁹) after recrystallization from ethanol.

Preparation of 2,4,6-Triarylpyridines by Weiss' Procedure.—A solution of 4.2 g. of *p*-chlorobenzaldehyde, 9.3 g. of *p*-chloroacetophenone and 30 g. of ammonium acetate in 75 ml. of glacial acetic acid was boiled for an hour. The separated oil gradually crystallized as the mixture cooled. Recrystallization from acetone gave 5 g. (41%) of white needles, m.p. 269–270°, of 2,4,6-tri-*p*-chlorophenylpyridine (I), undepressed by admixture with a sample obtained as a by-product derived from the Fischer indole reaction of *p*-chloroacetophenone 2,6-dichlorophenylhydrazine.³ Infrared spectra of the two samples were essentially identical.

Application of the same procedure to 3.2 g. of benzaldehyde, 9.3 g. of *p*-chloroacetophenone, 30 g. of ammonium acetate and 75 ml. of glacial acetic acid produced 1.4 g. (25%) of 2,6-di-*p*-chlorophenyl-4-phenylpyridine (II), white needles, m.p. 184–185°, after recrystallization from ethanol. A mixture of this substance with a sample prepared by Reddelien's procedure showed no m.p. depression, and the infrared absorption spectra were essentially identical.

Likewise, 4.2 g. of *p*-chlorobenzaldehyde, 7.2 g. of acetophenone, 30 g. of ammonium acetate and 75 ml. of glacial acetic acid, boiled for 3 hours, gave 3.4 g. (66%) of 2,6-diphenyl-4-*p*-chlorophenylpyridine (III), m.p. 128–130° (as reported⁹) after recrystallization from ethanol. A mixture of this substance with a sample prepared by Reddelien's method showed no m.p. depression, and the infrared spectra were essentially identical.

Isolation of Products from the Reaction of Acetophenone and Benzylamine.—A mixture of 102 g. of acetophenone, 90 g. of benzylamine and 1 ml. of 48% hydrobromic acid was heated in a flask fitted with an azeotrope separator, a thermometer and a condenser. Escaping gases were bubbled into dilute hydrochloric acid after passing through the condenser. No detectable amount of gas passed through the hydrochloric acid during the course of the reaction. The mixture was heated for 1.5 hours at 110° before any condensate was allowed to collect in the azeotrope separator; then heating was continued at 180–240° for two hours. Evaporation to dryness of the hydrochloric acid solution used to trap the escaped ammonia afforded 13 g. (0.25 mole) of ammonium chloride. The azeotrope separator contained 22 ml. of liquid, chiefly water. The liquid was acidified and extracted with ether. Removal of the ether left a residue that was subjected to distillation in a micro-still. A few drops of material boiling at about 190° was collected, but nothing having the b.p. of toluene was observed.

The mixture in the flask was poured into aqueous ethanol, and 16 g. of white, crystalline 2,4,6-triphenylpyridine, m.p. 137–138°, was collected by filtration. The filtrate was diluted with excess water, and the oil that separated was extracted into ether. The ether solution was extracted with 10% aqueous hydrochloric acid, the aqueous layer was made basic, and the precipitated oil was extracted into ether. Evaporation of the ether left a residue that was distilled under diminished pressure. The first clean-cut fraction was 9.5 g. of a clear, yellow oil, b.p. 147–150° (4 mm.). Its infrared spectrum was essentially indistinguishable from that of authentic benzyl- α -phenylethylamine (VII, preparation, see below), and the phenylthiourea derivatives, both m.p. 155–156°, showed no m.p. depression when mixed. Infrared spectra of the phenylthiourea derivatives were also essentially identical. The infrared spectrum of diphenylamine differed from that of VII. and the infrared spectrum of the phenylthiourea derivative of diphenylamine, m.p. 144–145°, also differed from that from benzyl- α -phenylethylamine (VII).

Anal. Calcd. for C₂₂H₂₂N₂S: C, 76.26; H, 6.40. Found: C, 76.41; H, 6.31.

Continued distillation gave a second basic fraction, 20 g. of a transparent, yellow, viscous oil, b.p. 200–240° (4 mm.), which was insoluble in 10% hydrochloric acid. No crystal-

(10) W. Dilthey, *J. prakt. Chem.*, [2] **102**, 209 (1921).

(11) R. J. W. Le Fevre and J. Pearson, *J. Chem. Soc.*, 1197 (1933);

P. P. Hopf and R. J. W. Le Fevre, *ibid.*, 1989 (1938).

(12) Melting points are corrected.

(13) J. Graymore and D. R. Davies, *J. Chem. Soc.*, 293 (1945).

line material could be isolated from this fraction, nor could any crystalline derivative be obtained.

The ether solution that remained after hydrochloric acid extraction was shaken with saturated aqueous sodium bisulfite, and the 10 g. of white crystalline precipitate that formed was collected by filtration. A 1-g. sample of this material was treated with aqueous sodium hydroxide and the mixture extracted with ether. After treatment of this ether solution with 1.5 ml. of phenylhydrazine and 1 ml. of glacial acetic acid, the ether was removed and the residual solid recrystallized from ethanol. The crystalline benzaldehyde phenylhydrazone melted at 154–156°, alone or when mixed with an authentic sample.

The ether solution that remained after the bisulfite treatment was subjected to distillation. An 8-g. fraction, b.p. 190° (4 mm.), consisted of a viscous oil that crystallized on cooling. Recrystallization from ethanol afforded white needles, m.p. 71–73°, depressed 20° when mixed with benzylacetophenone, m.p. 70–72°, prepared by hydrogenation of benzalacetophenone over platinum oxide.¹⁴ The oxime of the isolated ketone melted at 92–93°, in close agreement with the m.p. 93.5–94° reported¹⁵ for the oxime of 1,3-diphenyl-1-butanone (VIII). Accordingly, a sample of VIII was prepared by hydrogenation of dypnone¹⁶ over platinum oxide, and a mixture of this sample and one of the substance obtained from the Reddelein reaction mixture showed no m.p. depression. The infrared spectra of the two samples were also essentially indistinguishable.

A second neutral fraction from the Reddelein reaction mixture, b.p. 190–280° (4 mm.), was a clear, yellow oil from whose ethanol solution an additional 5.1 g. of 2,4,6-triphenylpyridine crystallized. No other crystalline material could be isolated from this oil, nor could any crystalline derivative be prepared.

Benzyl- α -phenylethylamine (VII) was prepared from benzyl chloride and α -phenylethylamine,¹⁷ b.p. 148–150° (2 mm.). The N-benzoyl derivative, apparently previously unreported in the literature, had the m.p. 109–111°.

Anal. Calcd. for C₂₂H₂₁NO: C, 83.77; H, 6.71; N, 4.44. Found: C, 83.41; H, 6.47; N, 4.26.

No m.p. depression was observed when this derivative was mixed with one prepared from the corresponding base isolated (above) from the Reddelein reaction mixture, but the latter had its m.p. depressed 20° when it was mixed with the N-benzoyl derivative from dibenzylamino, m.p. 109–111°, as reported.¹⁸

2,4-Diphenyl-6-*p*-chlorophenylpyridine (IXa) and 2,4-Di-*p*-chlorophenyl-6-phenylpyridine (IXb) by the General Procedure of Dilthey.¹⁰—The former was prepared by treating a solution of 4 g. of benzalacetophenone and 3 g. of *p*-chloroacetophenone in 20 ml. of acetic anhydride gradually with 5 g. of anhydrous ferric chloride and heating the mixture for

an hour on the steam-bath. When the mixture cooled, 3.5 g. (34%) of yellow-green crystalline pyrylium ferrichloride (Xa) separated. Washing with acetic acid and with ether gave a specimen of m.p. 279°. A suspension of 2.5 g. of this salt in ethanol was treated with ammonia until no more hydrated ferric oxide precipitated. The mixture was heated and filtered, and the clear solution when cooled deposited a white solid. Recrystallization of this material from ethanol afforded a 75% yield of white needles, m.p. 138–139°, reported¹⁹ 137–138°. The infrared spectrum of this compound showed the same general characteristics as had those of the other 2,4,6-triarylpyridines.

Application of the same procedure to 4.8 g. of *p*-chloro-benzalacetophenone, 3.0 g. of *p*-chloroacetophenone, 6 g. of ferric chloride and 25 ml. of acetic anhydride gave 3.7 g. (34%) of a yellow-green pyrylium ferrichloride (Xb), m.p. 265°, from which 1.7 g. (65%) of crude IXb was obtained, m.p. 142–144°. Washing with hot concentrated hydrochloric acid and recrystallization from petroleum ether (b.p. 60–110°) gave white needles, m.p. 145–146°.

Anal. Calcd. for C₂₃H₁₈NCl₂: C, 73.41; H, 4.02; N, 3.72. Found: C, 74.05; H, 4.04; N, 3.60.

Picrate, yellow needles from ethanol, m.p. 232–233°.

Anal. Calcd. for C₂₉H₁₈N₄Cl₂O₇: C, 57.53; H, 2.99; N, 9.26. Found: C, 57.62; H, 3.01; N, 9.41.

The infrared spectrum of IXb was also similar in its general characteristics to those of the other 2,4,6-triarylpyridines.

2,4-Di-*p*-chlorophenyl-6-phenylpyrylium ferrichloride (Xb) by the Methods of Le Fevre.¹¹—A mixture of 6.0 g. of *p*-chloroacetophenone, 10 g. of benzoic anhydride and 6 g. of anhydrous ferric chloride was heated for a half-hour on the steam-bath, boiled with ethanol and the solid collected by filtration and washed with acetic acid and with ether. The yellow-green substance (0.9 g., 8%) melted at 263–265° after recrystallization from acetone-benzene. A mixture with the substance prepared by Dilthey's method (above) gave no m.p. depression.

The same pyrylium salt was also prepared by gradually adding 4 g. of anhydrous ferric chloride to an ice-cooled mixture of 6 g. of *p*-chloroacetophenone and 7 g. of benzoyl chloride. The dark-colored solid present after the mixture was kept overnight at room temperature was boiled with ethanol, and the insoluble solid was collected by filtration and washed with acetic acid and with ether. The m.p. of this substance (1 g., 10%) was 260–262°, undepressed when mixed with a sample prepared by Dilthey's procedure.

Infrared absorption spectra were measured by means of a Perkin-Elmer model 21 double beam spectrophotometer equipped with sodium chloride optics. The spectra of dibenzylamine and of benzyl- α -phenylethylamine were measured on the pure liquids; the spectrum of 1,3-diphenyl-1-butanone (VIII) was measured in carbon disulfide solution; and all other spectra were measured in chloroform solutions. Concentrations of all of these solutions were about 20 mg./ml.

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(14) R. Adams, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 167.

(15) M. A. Spielman and C. W. Mortenson, *THIS JOURNAL*, **61**, 666 (1939).

(16) A. Müller and G. Spinoza, *Österr. Chem. Ztg.*, **49**, 130 (1948).

(17) K. Parck, *J. prakt. Chem.*, [2] **86**, 284 (1912).

(18) H. Franzen, *Ber.*, **42**, 2465 (1909).

(19) C. Gastaldi, *Gazz. chim. ital.*, **51** II, 289 (1921).