[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

The Attempted Condensation of Aromatic Aldehydes with β-Picoline Methiodide

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β-Picoline methiodide has been made from highly purified β-picoline. Contrary to several recent reports in the literature β-picoline methiodide does not condense with *p*-dimethylaminobenzaldehyde in alcohol solution in the presence of piperidine catalyst.

While the reactivity for condensation reactions of methyl groups in the α- or γ-positions of pyridines or quinolines has been well established[1] it has also been shown that a methyl in the β-position of these heterocyclic compounds is unreactive in such reactions.[2] Furthermore, it has been reported that the reactivity of the activated methyls is markedly accentuated by conversion of the tertiary bases to their quaternary alkiodides.[3] But even the alkiodides of compounds of the 3-methylisoquinoline type are unreactive in condensations.[4]

According to modern theory applied to condensation reactions, both from the point of view of activation of the methyl compound[5] and also of resonance stabilization in the product,[6a,6b] α- and γ-picoline and their methiodides (and their analogs) should be capable of reaction while β-picoline derivatives should be incapable. A number of contradictory reports have accumulated with regard to the reactivity of β-methylpyridine and -quinoline, and related compounds, producing some question as to the true status of the problem.

Recent papers[7,8] reporting the condensation of aromatic aldehydes with 3-methylisoquinoline and its methiodide to give 3-styrylisoquinoline derivatives appear to be in direct contradiction to the earlier work of Mills and Smith.[4] The reactivity of the 3-methylisoquinoline derivatives is understandable when the molecule is viewed as a benzo-α-picoline.

Two papers[9,10] by widely separated groups report that the condensation of β-picoline methiodide (as well as of the α- and γ-picoline methiodides) with *p*-dimethylaminobenzaldehyde under the usual conditions[6] gave high yields (75–85%) of the styrylpyridine methiodide. Neither group specified the source of its β-picoline, and neither characterized either the base or its methiodide. Although the work of Brown and Murphey[11] on the alkylation of the α-, β- and γ-picolines with methyl chloride in liquid ammonia in the presence of sodium amide indicates that the β-methyl group is reactive under certain conditions, these results reported[9,10] for β-picoline methiodide should be subject to considerable doubt as being contradictory to earlier experience and theory.[1–6] However, the authors offered neither proof for nor comment on the novelty of their findings.

Reilly 98% β-picoline was purified chemically[2a,12,13] to remove the more reactive impurities. This purified β-picoline was transformed into the crystalline methiodide which under the usual condensation conditions[6] with *p*-dimethylaminobenzaldehyde gave no trace of red color nor any isolatable condensation product of any sort. The recovery of the aldehyde and of β-picoline methiodide was 97–100%. The results presented are based upon many repetitions of the condensation procedure with numerous variations as of time of reaction, solvent, etc., and under no circumstances was any β-styryl compound isolated.

Although under more drastic conditions condensations of aldehydes with β-picoline methiodide might possibly be attained the results of Crippa and Verdi[9] and of Doja and Prasad,[10] which are summarized in Table I, cannot be clarified at this time.

Experimental

β-Picoline (Reilly Tar and Chemical Co., "98% pure") was purified (a) by fractionation and (b) by refluxing with phthalic and acetic anhydrides[12]; b.p. 144–145° at 760 mm.

β-Picoline Methiodide.—A mixture of 10 cc. (9.6 g.) of β-picoline, 20 cc. of methanol and 10 cc. of methyl iodide was refluxed for two hours on a steam-bath. Upon evaporation of solvent and excess methyl iodide 24 g. (100%) of oily residue was obtained. When this was cooled and washed repeatedly by stirring with ether and decanting the ether there was eventually obtained a white crystalline solid which melted at steam-bath temperature but resolidified on cooling; m.p. 98–99°. After purification by filtration in methanol, evaporation, washing, and crystallizing, the product still melted at 98–99°.

Anal. Calcd. for $C_7H_{10}NI$: C, 35.7; H, 4.3. Found: C, 35.6; H, 4.2.

Attempted Condensation of β-Picoline Methiodide with *p*-Dimethylaminobenzaldehyde.—A mixture of 4.7 g. (0.02 mole) of β-methylpyridine methiodide and 3.0 g. (0.02 mole) of *p*-dimethylaminobenzaldehyde was dissolved in 30 cc. of methanol, 10 drops of piperidine was added and the solution was refluxed for five hours on the steam-bath. When the methiodide of the chemically[12] purified β-picoline was used no color developed and *no* crystals separated on cooling. After evaporating to dryness unchanged aldehyde was extracted with ether. After evaporation of the ether extracts 3 g. (100%) of recovered *p*-dimethylaminobenzaldehyde remained as an oil at 100° and crystallized on cooling; m.p. 71–73°. This recovered aldehyde, 3 g., plus 3 g. of

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[1] (a) E. Jacobsen and C. L. Reimer, *Ber.*, **16**, 1086, 2602 (1883); (b) O. Doebner and W. von Miller, *ibid.*, **18**, 1640 (1885); (c) H. Baurath, *ibid.*, **20**, 2719 (1887); (d) C. Friedländer, *ibid.*, **38**, 159 (1905); (e) E. Düring, *ibid.*, **38**, 164 (1905); (f) G. Gasda, *ibid.*, **38**, 3699 (1905).

[2] (a) P. Schwarz, *ibid.*, **24**, 1676 (1891); (b) W. Koenigs and E. Bischkopf, *ibid.*, **34**, 4327 (1901).

[3] A. Kaufmann and L. G. Vallette, *ibid.*, **45**, 1736 (1912).

[4] W. H. Mills and J. L. B. Smith, *J. Chem. Soc.*, **121**, 2724 (1922).

[5] A. P. Phillips, *J. Org. Chem.*, **13**, 622 (1948).

[6] (a) A. P. Phillips, *ibid.*, **12**, 333 (1947); (b) *ibid.*, **14**, 302 (1949).

[7] H. Erlenmeyer, H. Baumann and E. Sorkin, *Helv. Chim. Acta*, **31**, 1978 (1948).

[8] F. L. White and L. G. S. Brooker, U. S. Patent 2,466,523.

[9] G. B. Crippa and T. Verdi, *Ann. chim. applicata*, **26**, 418 (1936); see *C. A.*, **31**, 2214 (1937).

[10] M. Q. Doja and K. B. Prasad, *J. Indian Chem. Soc.*, **24**, 301 (1947); see *C. A.*, **42**, 6362 (1948).

[11] H. C. Brown and W. A. Murphey, THIS JOURNAL, **73**, 3308 (1951).

[12] (a) G. Reithof and S. G. Richards, S. A. Savitt and D. F. Othmer, *Ind. Eng. Chem., Anal. Ed.*, **18**, 458 (1946); (b) G. Reithof, U. S. Patent 2,443,479.

[13] G. Reithof, U. S. Patent. 2,388,499.

TABLE I

COMPARISON OF CONDENSATION PRODUCTS OF α-, β- AND γ-PICOLINE METHIODIDES WITH *p*-DIMETHYLAMINO- AND *p*-DIETHYLAMINOBENZALDEHYDE

		Phillips[8]		Doja and Prasad[10]		Crippa and Verdi[9]	
Isomer	Para substituent	M.p., °C.	Yield, %	M.p., °C.	Yield, %	M.p., °C.	Yield, %
α	$(CH_3)_2N$	273–274	98–100	265	83		
	$(C_2H_5)_2N$	246–247	98–100	240	78		
β	$(CH_3)_2N$	.....	None obtained	247	82	247	Not stated
	$(C_2H_5)_2N$	.....	...	222	84		
γ	$(CH_3)_2N$	258–259	100	262	76		
	$(C_2H_5)_2N$	221–222	100	232	86		

phenylhydrazine gave 4.8 g. (100%) of yellow crystals of the phenylhydrazone; m.p. 150–151°.

Pure unchanged β-picoline methiodide, 4.7 g. (100%), m.p. 98–99°, was recovered from the ether-insoluble fraction by solution in methanol, treatment with Darco, filtration, evaporation and crystallization.

When the original Reilly 98% β-picoline, purified only by distillation, was used to make the methiodide the condensation reaction with *p*-dimethylaminobenzaldehyde had a different result. The reaction solution became deep claret colored; after evaporation of the reaction mixture to 10 cc. and cooling, 0.1–0.2 g. (2%) of deep red crystals was obtained. Recrystallized from methanol, these melted at 258–259° and were shown by melting point, analysis and ultraviolet absorption spectrum to be identical with the γ-(*p*′-dimethylaminostyryl)-pyridine methiodide described earlier.[6b] Careful working up of the filtrates from these crystals resulted in a 97% recovery of both aldehyde and β-picoline methiodide as described above. This process can be used to obtained the pure β-picoline methiodide from the less pure material.

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The Action of N-Bromosuccinimide on Lignin Sulfonates

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Lignin sulfonates with essentially one aromatic bromine per aromatic ring have been obtained with the use of N-bromosuccinimide. These derivatives result in good yield and have undergone small methoxyl loss and little other change. The brominated products appear useful for degradative and structural studies because of demonstrable increase in stability of otherwise sensitive aromatic rings.

Introduction

As an approach to elucidation of the structure of lignin sulfonic acid, it seemed desirable to investigate new ways of brominating the material. Stabilization of the aromatic ring and labeling positions for degradative studies are among the results sought in such an approach. One of the methods developed in this study for controlled bromination without significant degradation has been with the use of N-bromosuccinimide.

Much of the reported work on halogenation of lignin derivatives has been carried out under intentionally drastic conditions in order to obtain simple degradation products rather than as a step in controlled degradation.[2] The breakdown of halogenated lignins has usually resulted in low yields or a variety of products by routes that make speculation about the structure of the original lignin preparation hazardous. Lautsch and Piazolo[3] found that a brominated lignin, upon oxidation with cobaltic hydroxide, yielded 8% of 6-bromovanillin. They also obtained 10% of 5-iodovanillin by degradation of spruce iodolignin (prepared from acetomercurilignin). In each case the position of the major part of the substituted halogen atom is not certain. In a survey of bromination of lignin sulfonic acid and some model substances, Kratzl and Bleckmann[4] reported loss of about 50% of the sulfur in the lignin derivative, considerable degradation, and evidence of some dibrominated aromatic rings.

Procedure

Buu-Hoï[5] has shown that various alkyl phenyl ethers react with NBS to give good yields of compounds brominated in the nucleus. It was thought, therefore, that aromatic bromination of lignin sulfonic acid might occur. Possible reactions of oxidation (involving carbinol groups or dehydrogenation of neighboring carbon atoms) were not considered. Yields of brominated lignin sulfonates were 10–15% less than quantitative (after dialysis), and the products had suffered a small reduction in methoxyl value and sulfur content and there was evidence of some oxidation (infrared spectra). However, the bromination reaction appears quite straightforward and of significant interest with respect to stabilization and amount of bromine introduced.

Attempts to brominate insoluble lignin preparations in chloroform with NBS gave ambiguous results and an incomplete reaction. Further efforts were therefore concentrated on the limited selection of lignin sulfonate derivatives soluble in chloroform or other suitable organic solvents. Among the former are the salts of lignin sulfonic acid and methylated lignin sulfonic acid with dimethyloctadecylamine.[6] These salts in chloroform, upon treatment with NBS at 22–25° for 48 hours, gave a non-homogeneous product with not more than 0.4 atom of bromine per C_9 unit. Another chloroform-soluble derivative giving more interest-

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(1) Department of Surgery, School of Medicine, University of Washington, Seattle 5, Washington.

(2) L. E. Wise, "Wood Chemistry," Reinhold Publishing Corp., New York, N. Y., 1946, pp. 308–311, contains a summary of many of the reactions of lignins with halogens.

(3) W. Lautsch and G. Piazolo, *Ber.*, **73** (1), 317 (1940).

(4) K. Kratzl and Ch. Bleckmann, *Monatsh.*, **76**, 185 (1947).

(5) Ng. Ph. Buu-Hoï, *Ann.*, **556**, 1 (1944).

(6) From studies by Dr. A. E. Markham and Dr. J. L. McCarthy of the Pulp Mills Project, University of Washington.