[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF SOUTH CAROLINA]

Metallation of 2,4-Lutidine and 2,4,6-Collidine with Phenyllithium

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Received November 12, 1959

2,4-Lutidine and 2,4,6-collidine reacted with phenyllithium to give lithium derivatives at the 2 position. These were identified by reaction with benzaldehyde to form the corresponding phenylcarbinols. No evidence of reaction at the 4 position could be detected.

Since its discovery by Ziegler and Zeiser[1] α-picolyllithium has become a very widely used reagent. It is conveniently prepared by the hydrogen-metal exchange reaction of α-picoline with phenyllithium at room temperature. Initial attempts to prepare γ-picolyllithium by a similar process were unsuccessful.[2] Gilman and Broadbent[3] added γ-picoline to a solution of n-butyllithium and found that at $-80°$ no reaction took place. However, at $-10°$ they found that addition across the C=N bond occurred producing, after heating, 2-n-butyl-4-methylpyridine. Erlenmeyer and coworkers[4] found that when phenyllithium was treated with γ-picoline and subsequently carbonated and hydrolyzed, the product was 2-phenylhomoisonicotinic acid. This involved both addition across the C=N bond and metallation of the methyl group. Wibaut and Hey[5,6] reversed the procedure and added the phenyllithium solution to the γ-picoline on the assumption that if the metallation reaction is the more rapid of the two, the γ-picolyllithium should be formed in good yield. The γ-picolyllithium formed in this manner was treated with alkyl bromides and yields of up to 60% of the alkyl pyridine compounds were obtained. The reactions were carried out at room temperature.

2,4-Lutidine has been treated with phenyllithium.[7,8] The products obtained correspond to those expected if metallation occurs only on the α-methyl groups. The authors did not report any careful study to detect the formation of any of the γ- isomers.

Condensations with aldehydes also indicate that the α-methyl group is more reactive than that in the γ-position. Thus 2,4-lutidine condenses with benzaldehyde in the presence of acetic anhydride[9] or zinc chloride[10] to yield 2-styryl-4-methylpyridine as the only monostyryl derivative along with some 2,4-distyrylpyridine. 2,4,6-Collidine also reacts with aldehydes to give condensation at the 2-position. Dubke[11] reported the preparation of 4,6-dimethyl-2-picolylphenylcarbinol and 4,6-dimethyl-2-stilbazole by condensation of benzaldehyde with collidine but he did not prove the structure of his products. Koenigs and Bentheim[12] obtained 4,6-dimethyl-2-stilbazole by the same reaction and identified the product by oxidation to 4,6-dimethylpicolinic acid. Several other condensations with aldehydes at the 2-position have also been reported.[13-16]

This work was undertaken to determine the relative reactivities toward metallation on the 2- and 4- positions of 2,4-lutidine and of 2,4,6-collidine. This was done by treating the pyridine homologs with phenyllithium. The resulting pyridinelithium compounds were identified by reaction with benzaldehyde and isolation of the resulting phenylcarbinols. In order for the ratio of the final yields of the isomers to be equivalent to the ratio of the lithium derivatives it must be assumed that the rate of addition of each isomer to the benzaldehyde is equal. This assumption seems reasonable since addition of organolithium compounds to benzaldehyde is a very rapid reaction.

DISCUSSION

The phenyllithium solution was added to the 2,4-lutidine to minimize addition across the azomethylene linkage. In the case of 2,4,6-collidine the normal addition of the base to the phenyllithium was followed. After addition of the benzaldehyde, the phenylcarbinols were purified by crystallization of the hydrochloride–mercuric chlo-

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TABLE I

METALLATION OF 2,4-LUTIDINE AND 2,4,6-COLLIDINE

	Base Added, G.	Base Recovered, G.	Reaction Product, G.	Phenyl-2-carbinol, G.	Unident. Product, G.	Reaction Prod., %		Yield of 2-Carbinol, %[a]
						2-Carbinol	Unident. product	
2,4-Lutidine	25.0	14.5	18.1	17.9	0.2	99	1	85.8
2,4,6-Collidine	25.8	4.54	27.7	>26.3	<1.4	>95	<5	>64

[a] Based on pyridine homolog consumed in the reaction.

ride double salts. The results are summarized in Table I.

The 4-methyl-2-picolylphenylcarbinol was identified by dehydration to 4-methyl-2-stilbazole. The structure of the stilbazole had been proved previously[9] by oxidation to 4-methyl-2-picolinic acid and decarboxylation of this acid to 4-picoline.

The reaction product from the 2,4,6-collidine, after treatment with hydrochloric acid and mercuric chloride, was separated into three fractions. The major fraction yielded pure 4,6-dimethyl-2-picolylphenylcarbinol and amounted to 92.25% of the total product recovered. The second fraction was an oily mercuric chloride double salt which could not be crystallized. The base from this salt amounted to 5.25% of the total product. Its infrared spectrum was essentially the same as that of the main fraction except for an extra peak appearing between 8.2 and 8.4 μ. Dehydration of this material produced 4,6-dimethyl-2-stilbazole, identified by mixed melting points of several derivatives. It was estimated that this fraction consisted of over 50% 4,6-dimethyl-2-picolylphenylcarbinol. The third fraction of mercuric chloride double salt yielded only 2.5% of the total basic products and was not identified.

The major reaction product, 4,6-dimethyl-2-picolylphenylcarbinol, had been prepared by Dubke in 1894 along with the corresponding stilbazole but no attempt had been made to prove the structure. Koenigs and Bentheim[12] prepared the stilbazole and proved its structure by oxidation to 4,6-dimethylpicolinic acid. The melting points of the derivatives of our carbinol agreed with those of Dubke but those of our stilbazole did not completely agree with either set of authors, ours being higher in all cases. Final proof of structure was made by oxidation of our compound to 4,6-dimethylpicolinic acid. This acid has been prepared[17] and its structure proved by decarboxylation to 2,4-lutidine.

These results show that metallation of 2,4-lutidine and 2,4,6-collidine occurs at the 2- position. No evidence could be obtained of metallation at the 4- position.

EXPERIMENTAL

Reaction of 2,4-lutidine. Phenyllithium was prepared from 135.6 g. (0.8 mole) of bromobenzene and 14 g. (2.02 g.-atoms) of lithium in 750 ml. of absolute ether. The concentration of phenyllithium was found by titration with standard acid to be $0.98M$. This was subsequently checked by reaction with benzaldehyde to form benzhydrol and a value of $0.96M$ was obtained. Two hundred milliliters of this solution containing 0.196 mole of phenyllithium was added slowly to 25 g. of 2,4-lutidine (0.6 mole, a 30% excess) in 200 ml. of absolute ether under an atmosphere of nitrogen. The addition required 15 min. and the mixture was stirred an additional 15 min. An excess of benzaldehyde was then distilled directly into the reaction mixture. The product was decomposed and worked up in the usual manner. The basic constituents were obtained as a semisolid residue weighing 34.1 g. 2,4-Lutidine (14.5 g.) was separated by steam distillation and recovered, leaving 18.6 g. of nonvolatile material.

The residue was dissolved in dilute hydrochloric acid and precipitated with an excess of hot aqueous mercuric chloride. The mercuric chloride double salt separated initially as an oil. The liquid was decanted from this oil and the rest of the double salt separated as white crystals. By repeated extraction of the oily material the product was finally separated into a white solid as the major fraction and 1.2 g. of a dark brown residue. The mercury was precipitated from the mercuric chloride double salts with hydrogen sulfide and the free bases were recovered. The major fraction weighed 17.9 g. and melted at 92.1–92.3° and was shown to be 4-methyl-2-picolylphenylcarbinol.

Anal. Calcd. for $C_{14}H_{15}ON$: C, 78.84; H, 7.09. Found: C, 78.92; H, 7.04.

The amorphous material was not identified. Since it amounted to only 1% of the product, this represents the upper limit of condensation which could have occurred in the gamma position.

Preparation of 2-styryl-4-methylpyridine. A sample of the 4-methyl-2-picolylphenylcarbinol was refluxed 1 hr. with acetic anhydride. The mixture was poured into dilute sodium hydroxide solution, the product was taken up in hexane and recrystallized several times from hexane: m.p., 71.8–72.3°; picrate, m.p., 259–260°. Mixed melting points with an authentic sample prepared by the method of Clemo and Gourlay[9] gave no depression.

Reaction of 2,4,6-collidine. The procedure was essentially the same as that used for the 2,4-lutidine except that the collidine was added to the phenyllithium since there was no likelihood of addition across the azomethylene linkage. 2,4,6-Collidine (25.8 g., 0.213 mole) in 100 ml. of absolute ether was added to 0.194 mole of phenyllithium in 200 ml. of ether. After decomposition of the reaction mixture with water and acid and after removal of the ether layer, the mixture was made alkaline and the basic constituents extracted with chloroform. Removal of the chloroform under vacuum in a rotary evaporator gave 37.7 g. of residue. This was dissolved in hydrochloric acid and treated with mercuric chloride. Working up the products as above gave 75 g. of a white crystalline product, 4.5 g. of a brown oil, and 2.8 g. of a brown amorphous solid, completely insoluble in water. The major fraction of the mercuric chloride double salt yielded 25.6 g. of 2-(4,6-dimethylpicolyl)phenylcarbinol. The brown oil, on precipitation of the mercury, gave 1.5 g, of an oil which was shown to be largely the same material. and the other fraction gave 0.7 g. of an unidentified base.

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Finally, 4.5 g. of 2,4,6-collidine was recovered from the aqueous mother liquor.

Anal. of the carbinol. Calcd. for $C_{15}H_{17}ON$: C, 79.26; H, 7.54. Found: C, 78.62; H, 7.63.

Mercuric chloride–hydrochloride salt, m.p. 98–99° (reported[11] m.p. 99–100°); platinum tetrachloride–hydrochloride salt, m.p. 126–129°(reported[11] m.p. 125–130°); hydrochloride, m.p., 208–209° (reported[11] m.p. 209–211°).

Preparation of 2-styryl-4,6-dimethylpyridine. The collidylphenylcarbinol was dehydrated to the corresponding stilbazole by refluxing with an excess of acetic anhydride for 1 hr. The product was not purified but several derivatives were made. Mercuric chloride–hydrochloride salt, m.p. 231–232° (reported, m.p. 218–219°,[11] 220–222°[17]); picrate, m.p. 256° (reported, m.p. 240–241°,[11] 240–242°[17]); auric chloride-hydrochloride salt, m.p. 188–189° (reported, m.p. 189–191°,[11] 192–193°[17]).

The crude stilbazole was oxidized with potassium permanganate in acetone to 4,6-dimethylpicolinic acid. The product was purified by precipitation of the copper salt from aqueous solution and removal of the copper with hydrogen sulfide. After recrystallization from alcohol the acid melted at 157–158° (reported,[17] m.p. 155–156°); hydrazide, m.p. 74–75° (reported,[17] m.p. 77°).

The second fraction from the mercuric chloride purification was dehydrated with acetic anhydride. Several derivatives were made and their melting points and mixed melting points with the corresponding derivative of the 2-stilbazole are as follows: mercuric chloride-hydrochloride salt, m.p. 220–222° and 224–225°; platinum tetrachloride-hydrochloride salt, m.p. 241–242° and 242–243°; picrate, m.p. 242–244° and 249–250°.

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Aromatic and Pseudoaromatic Nonbenzenoid Systems. II. Studies Directed toward the 1,2-Diaza-3,5,7-cyclooctatriene System[1,2]

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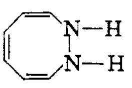
Received February 15, 1960

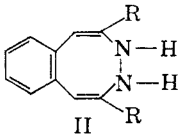
Molecular orbital calculations indicate a resonance energy of 2.99 β for 1,2-diaza-3,5,7-cyclooctatriene (I), and 4.76 β for the 5,6-benzo derivative (IIc). Compounds of structure IIIa and IIIb, which differ from derivatives of II only by the positions of double bonds, were synthesized. The failure of these derivatives of III to rearrange to the corresponding derivatives of II in the presence of a hydrogenation catalyst was noted. The calculated resonance energy of I, although large, is interpreted as being consistent with a lack of aromatic character in a ring system such as I.

According to the simple molecular orbital theory,[4,5] if cyclooctatetraene were planar it would have a significantly lower resonance energy than benzene (1.66 β *vs.* 2.00 β). In its simplest form the theory also predicts that a planar cyclooctatetraene would have a triplet ground state. Energy would be required to enlarge the interior natural angles of the tub form of cyclooctatetraene to force it into a planar configuration, and the resonance that could be gained is insufficient to bring this about. The molecule consequently exists in the tub form,[6,7] and has very little resonance energy.

From the molecular orbital point of view, 1,2-diaza-3,5,7-cyclooctatriene (I) is essentially a cyclooctatetraene containing 10 electrons. It therefore satisfies Hückel's rule ($4n+2$ π electrons)[8] and might be expected to be aromatic. It therefore seemed that the synthesis of such a system might be carried out, and more detailed molecular orbital calculations might be made and compared with experiment.

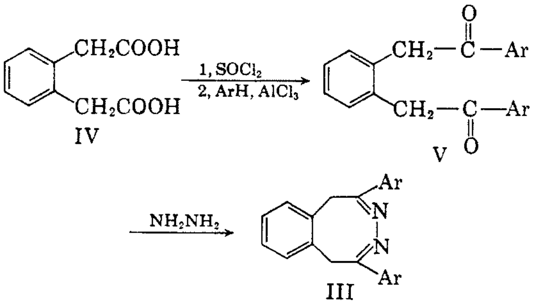


I



II

a. R = phenyl
b. R = 2,4-xylyl
c. R = H



a. Ar = phenyl
b. Ar = 2,4-xylyl
c. Ar = H

The molecular orbital calculations were carried out for I with the usual assumptions[4,5]: (a) a planar system with exchange integrals all equal to β for adjacent atoms and zero otherwise, (b)

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