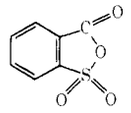
References and Notes

(1) Y. H. Chiang, J. S. Luloff, and E. Schippes, *J. Org. Chem.*, **34**, 2397 (1969).
(2) M. Kobayashi, *Bull. Chem. Soc. Jpn.*, **39**, 967 (1966).
(3) I. B. Douglass and B. S. Farah, *J. Org. Chem.*, **24**, 973 (1959), and (b) L. Field and P. M. Giles, *ibid.*, **36**, 309 (1971).
(4) W. B. Dickinson, U.S. Patent 3 328 452 (1967); *Chem. Abstr.*, **67**, 99652 (1967).
(5) For example, the carbonyl absorptions in succinic anhydride are reported at 1786 and 1850 and we found the carbonyl absorption of



to be at 1820 while the carbonyl absorption of 3,3′-dithiodipropionic acid is reported at 1690. Reported spectra are found in "Aldrich Library of Infrared Spectra", 2nd ed, 1974.
(6) W. E. Savige and M. A. Maclaren in "The Chemistry of Organic Sulfur Compounds", Vol 2, N. Karasch and C. Y. Meyers, Ed., Pargammon Press, Oxford, 1966, p 374, Chapter 15.
(7) "Aldrich Catalog/Handbook of Organic and Biochemicals", No. 18, Aldrich Chemical Co., Milwaukee, Wis., 1977, p 343.
(8) Melting points are uncorrected and no attempt was made to maximize yields. Infrared spectra were obtained using a Perkin-Elmer 727B spectrophotometer and nuclear magnetic resonance spectra were obtained using a Varian XL-100 spectrometer.

Reaction of Phenylglyoxal with Aniline under Acidic Conditions

John Correia

Department of Chemistry, Saint Mary's College
Moraga, California 94575

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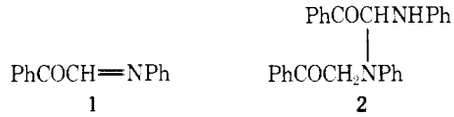
The reaction of phenylglyoxal with aniline in an acid medium has been investigated previously by two different groups.[1,2] Yates reported the isolation of only one product which he thought was phenylglyoxal anil (1). Proctor and co-workers made a more detailed investigation of this reaction in which they proposed structure **2** for Yates' product and isolated two new compounds: the major product (32%), which was not assigned a structure, and a minor product (10.5%). The minor product was reported to be the trans isomer of **1**.

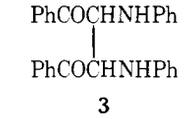


1 **2**

In this work, Proctor also described the synthesis of the two stereoisomers of 1 by a different reaction. Treatment of *N*-(*p*-toluenesulfonyl)phenacylaniline with base resulted in the formation of *cis*-**1** and this, in turn, was isomerized to the trans isomer by reaction with a palladium catalyst.

It was of interest to us to repeat some of the above work to confirm the reported structures and to identify Proctor's major product of undetermined structure. We have reinvestigated the reaction of phenylglyoxal with aniline and have isolated compounds **3, 4,** and **5** in pure form. Despite several attempts, we have failed to recover **1** from the reaction mixture or to detect its presence; however, *cis*- and *trans*-**1** were prepared from *N*-(*p*-toluenesulfonyl)phenacylaniline and these structures were confirmed by reduction to **6.**

Compound **3** (0.3% yield)[3] is the product originally found by Yates. In support of its structure, it can be synthesized by the alkaline oxidation of phenacylaniline; presumably via initial oxidation to **1** followed by an aldol type condensation of phenacylaniline with **1.** Compound **3** also undergoes a retro-aldol reaction with concentrated HCl to give phenacylaniline back again.



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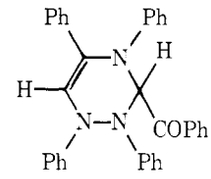

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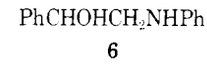
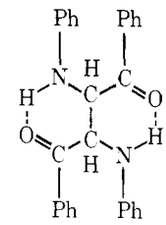


6

The IR and NMR spectra of **3** provide conclusive evidence for its structure and show, furthermore, that it exists as the intramolecularly hydrogen bonded configuration **7.**



7

The ^1H NMR spectrum in anhydrous dimethyl-d_6 sulfoxide shows broad peaks at δ 5.65, 5.74 (2 H), and 6.11. The combined areas of the peaks at δ 5.65 and 6.11 correspond to 2 H but their area ratio is 1.8 to 1. Addition of D_2O to the sample showed that the δ 5.65 and 6.11 peaks were due to NH.

The signal at δ 5.65 is very nearly the same as the corresponding NH absorption of phenacylaniline (δ 5.70) in the same solvent. Therefore, the δ 5.65 peak is due undoubtedly to hydrogen bonding of **3** to solvent while the δ 6.11 peak represents the intramolecular hydrogen bonds in **7.**

The IR spectrum can be explained similarly. Compound **3** has absorption at 1665 cm^{-1} in the solid state. It is insoluble in most solvents but partially soluble in a few such as pyridine. An IR spectrum taken in pyridine has a shoulder at approximately 1695 cm^{-1} on one of the pyridine absorption bands. This is an indication that some of the intramolecular hydrogen bonding in **7** is broken and the normal carbonyl frequency is observed.

The mechanism by which **3** is formed from phenylglyoxal and aniline is purely a matter of speculation due to its low yield. No analogy appears to exist for what amounts to a reductive coupling of **1** under acidic conditions. A low yield of **3** was obtained when *cis*-**1** was treated with acid but little can be inferred from this experiment.

Compound **4** (9% yield) proved to be a very unstable material as its structure would indicate. On standing or heating, it liberated aniline to give a mixture of products containing predominantly **5.** A good analysis could not be obtained for this substance due to its instability and difficulty in drying but its structure could be deduced from the following information.

The IR and NMR spectra indicate the presence of two NH groups, an aromatic ketone, and a one-proton singlet (>CH). The UV spectrum was similar to that of phenacylaniline but did have an increased intensity of absorption. The mass spectrum of **4** was unusual but particularly informative.

High resolution mass measurements show an apparent molecular ion at *m/e* 197 with an elemental composition of $C_{13}H_{13}N_2$. This cannot be a true molecular ion because of the inconsistency of the even number of nitrogens with an odd number molecular weight. If one infers the presence of a benzoyl group from the IR then a likely molecular formula would be $C_{20}H_{18}N_2O$. Thus there would have to exist in the

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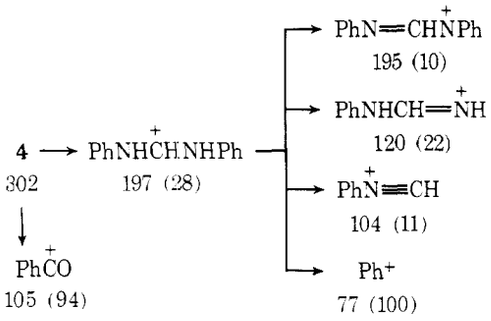
Scheme I

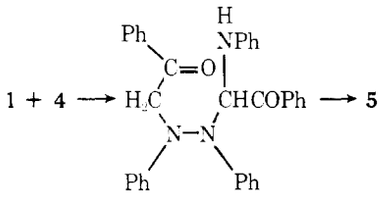


compound a structural feature which allows facile elimination of the benzoyl group to give a stable positive ion fragment. Structure **4** would give a positive ion that would be stabilized by dispersal of the charge onto the two adjacent nitrogens. It should be noted that **3** is reported to yield a molecular ion.

The observed fragmentation pattern of **4** (see Scheme I) provides excellent support for its structure, particularly the appearance of fragments at *m/e* 105 and 120.

Compound **4** is formed undoubtedly by the addition of aniline to phenylglyoxal anil. Such reactions of primary amines with imines are well known, although the adduct is usually not sufficiently stable to isolate.[4]

The compound described by Proctor as being the major product of the reaction was shown to be a mixture (see the Experimental Section) containing **5**. Compound **5** was isolated in 13% yield. We propose that it is formed by an unusual Michael condensation of **4** with **1** to give a ketone which eventually undergoes ring closure to yield the final product. This type of condensation shows the strong tendency of **1** to behave as an α,β-unsaturated ketone as well as an α-diketone.



Compound **5** has IR and NMR spectra consistent with its structure. The aromatic ketone and enamine structure are indicated by absorption at 1695 and 1660 cm^{-1}. The ^1H NMR spectrum exhibits two one-proton singlets in the appropriate region.

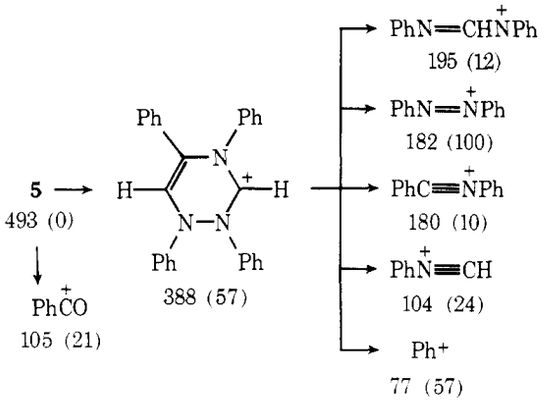
Analysis of **5** gave a molecular formula of $C_{34}H_{27}N_3O$, but again a true molecular ion could not be observed in the mass spectrum. High resolution measurements show an apparent molecular ion at *m/e* 388 with an elemental composition of $C_{27}H_{22}N_3$. For the reasons cited previously, it is evident that the molecule readily loses a benzoyl group to yield the stable *m/e* 388 positive ion.

The fragmentation pattern observed for **5** is explained well by its structure (see Scheme II). The appearance of the ion at *m/e* 182 (shown by high resolution measurements to be $C_{12}H_{10}N_2$) is an excellent indication of the presence of the hydrazobenzene portion within the compound.

When **5** was treated with hydrogen over a palladium catalyst until 1 mol was absorbed, there was formed a mixture of products which could not be characterized. Presumably, hydrogenation yields a benzylamine which undergoes further hydrogenolysis.

It is clear that the reaction of phenylglyoxal with aniline in an acid medium is a very complicated one. Most of the products obtained in either the pure state or as oils and mixtures undergo changes in their properties on standing and appear to be quite unstable. Only **3** and **5**, both of unexpected structure, can be considered to be stable products from the reaction.

Scheme II



Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were run on Perkin-Elmer Model 137 and Model 21 spectrophotometers. Ultraviolet spectra were run on a Hitachi Perkin-Elmer Model 139 UV–visible spectrophotometer, and the NMR spectra were obtained on a Varian Associates Model A-60 instrument. Mass spectral data were obtained at an ionizing voltage of 70 eV on a Varian MAT CH-7 mass spectrometer. Carbon and hydrogen analyses were performed by Galbraith Analytical Laboratories, Knoxville, Tenn.

Phenacylaniline. To a solution of 13.84 g (69.5 mmol) of phenacyl bromide[5] in 70 mL of 95% ethanol was added 13.70 mL (150 mmol) of aniline and the solution was allowed to stand at room temperature overnight. The solid which separated was filtered and recrystallized from 95% ethanol to give 9.96 g of yellow needles: mp 96–98 °C (lit.[2] mp 98 °C); UV λ_{max} (EtOH) 246 (ϵ 15 800), 286 nm (ϵ 2020); NMR ($CDCl_3$) δ 4.08 (s, 1 H), 4.60 (s, 2 H), 6.6–8.1 (m, 10 H); NMR (Me_2SO-d_6) δ 4.65 (d, J = 6.5 Hz, 2 H), 5.70 (t, J = 6.5 Hz, 1 H), 6.6–8.1 (m, 10 H). The broad singlet at δ 4.08 in $CDCl_3$ and the peak at δ 5.70 in Me_2SO-d_6 disappear when D_2O is added, and the one at δ 4.64 collapses to a sharp singlet.

Reduction of Phenacylaniline. A mixture of 498 mg (2.36 mmol) of phenacylaniline and 91 mg (2.41 mmol) of $NaBH_4$ in 7.0 mL of 95% ethanol was heated on a steam bath for 5 min. After cooling to room temperature, the mixture was poured onto 10 g of crushed ice whereupon a yellow oil was deposited. The oil was extracted into ether which was then dried over anhydrous $MgSO_4$ and evaporated to dryness under reduced pressure. All efforts to induce the resulting oil to crystallize failed so the hydrochloride was prepared.[6]

Dry hydrogen chloride was passed over the surface of a solution containing 475 mg of the oil dissolved in 10 mL of dry ether at 0 °C until no more solid was formed. The mixture was then filtered to give a white solid which was recrystallized from ethanol–ether. In this way was obtained 331 mg (56% from phenacylaniline) of 2-anilino-1-phenylethanol hydrochloride: mp 142.5–144 °C; IR (Nujol) 3320, 2600 (broad), 1590, 1060 cm^{-1}.

Anal. Calcd for $C_{14}H_{16}NOCl$: Cl, 14.20. Found: Cl, 14.42 (gravimetric).

Oxidation of Phenacylaniline. A mixture of 1.18 g (5.59 mmol) of phenacylaniline, 17 mL of 95% ethanol, and 0.05 mL of piperidine was heated under reflux on the steam bath for 4 h. After standing overnight open to the air, the solid which separated was filtered and recrystallized from ethyl acetate to give 0.35 g (30%) of **3**: mp 184–185 °C (lit.[2] mp 187 °C); NMR (Me_2SO-d_6) δ 5.65 (broad, 0.7 H), 5.74 (broad, 2 H), 6.11 (broad, 1.3 H), 6.5–8.0 (m, 20 H). Addition of D_2O caused the disappearance of the signals at δ 5.65 and 6.11 and that at δ 5.74 narrowed to a singlet.

When the reaction was run under a nitrogen atmosphere no **3** was formed and phenacylaniline was recovered in 70% yield.

Hydrolysis of 3. A mixture containing 100 mg (0.24 mmol) of **3** and 5 mL of concentrated HCl was heated at 100 °C for 5 min and then filtered quickly. An equal volume of water was added to the filtrate which was then made alkaline with dilute NaOH. The solid which separated was filtered to give 14 mg of a product melting at 90–95 °C whose IR spectrum proved to be identical with that of phenacylaniline.

The residue from the initial heating weighed 30 mg and the IR spectrum showed that it was essentially recovered **3**. Therefore, the

yield of phenacylaniline in the above reaction is 40% based on unrecovered **3**.

Preparation and Reduction of *cis*- and *trans*-1. The cis and trans anils were prepared as described previously and observed to have the reported spectral characteristics.[2] Each of the anils was reduced with $NaBH_4$ in the manner indicated for reduction of phenacylaniline. The hydrochlorides (34% from *cis*-**1** and 46% from *trans*-**1**) were compared to each other and to the hydrochloride of **6**. All three compounds proved to be the same by virtue of melting point, mixture melting point, and identity of IR spectra.

The cis anil was reacted with aniline in the manner described by Yates for reaction of phenylglyoxal with aniline.[1] A 4.5% yield of impure **3** was obtained; mp 169–173 °C.

Reaction of Phenylglyoxal with Aniline. Phenylglyoxal hydrate[7] was reacted with freshly distilled aniline using the procedure described by Proctor.[2] In a typical run, 7.70 g (50.6 mmol) of phenylglyoxal hydrate, 4.17 g (50.6 mmol) of aniline, and 10 mL of acetic acid in 50 mL of 95% ethanol were heated on a steam bath for 30 min to give 10.80 g of an orange oil. TLC showed that a minimum of seven compounds were present in the oil which was chromatographed on 100 g of Florisil.[8] Elution with 2:1 hexane–benzene gave, after crystallization from acetone, 34 mg (0.3%) of impure **3**, mp 165–168 °C. The IR spectrum of this material was identical to that of pure **3** obtained in other ways and it also did not depress the melting point of pure **3**.

The majority of the product was eluted with benzene in several fractions. Crystallization of the early benzene fractions yielded 2.54 g of yellow crystals, mp 68–76 °C. Recrystallization of the material from heptane failed to change the melting point significantly. The substance had the spectral properties described by Proctor for his major product but its mass spectrum was very complex. All of the ions observed for **5** were also observed for this material; in addition, ions were seen at *m/e* (rel intensity) 518 (23), 354 (5), 313 (11), 222 (5), 122 (5), and 120 (6). The compound of mass 518 is unstable. After standing for 1 month, no ion above *m/e* 389 was observed. Instead, an intense peak at *m/e* 93 was detected, probably due to aniline released in the decomposition.

When the mother liquors from the crystallization of the above product were allowed to evaporate slowly, rounded domes of yellow crystals were formed. Crystallization of these from 95% ethanol yielded 1.07 g (13%) of **5**: mp 173–175 °C. The anlytical sample melted at 175.5–176.5 °C: IR (Nujol) 1695, 1660, 1590, 1205 cm^{-1}; UV λ_{max} (EtOH) 243 (ϵ 34 400), 285 nm (ϵ 12 900); NMR ($CDCl_3$) δ 5.85 (s, 1 H), 6.47 (s, 1 H), 6.6–8.0 (m, 25 H); MS *m/e* (rel intensity)388 (57), 195 (12), 182 (100), 180 (10), 105 (21), 104 (24), 77 (57), 51 (8). High resolution mass measurements gave *m/e* 388.1824 ($C_{27}H_{22}N_3$ requires 388.1815) and *m/e* 182.0869 ($C_{12}H_{10}N_2$ requires *m/e* 182.0844).

Anal. Calcd for $C_{34}H_{27}N_3O$: C, 82.72; H, 5.52; N, 8.51. Found: C, 83.06; H, 5.61; N, 8.39.

Compound **5** underwent reaction when boiled in ethanol containing 10% concentrated HCl and also absorbed H_2 at atmospheric pressure in the presence of a Pd on charcoal catalyst. Apparent mixtures of products were formed.

The final homogeneous fraction was eluted from the column with 1:1 $CHCl_3$–MeOH. Low-temperature (−80 °C) crystallization from ethanol gave 0.68 g (9%) of **4**, mp 125–128 °C. The melting point is not indicative of the purity of the compound since an odor of aniline begins to emanate from the solid well below the melting temperature. TLC of the sample on silica gel gave one well defined spot while older, decomposed samples gave at least four spots. The substance had: IR (Nujol) 3410, 1695, 1590, 1215 cm^{-1}; UV λ_{max} (EtOH) 246 (ϵ 24 100), 286 nm (ϵ 3650); NMR ($CDCl_3$) δ 4.56 (broad, 2 H), 6.39 (s, 1 H), 6.6–8.1 (m, 15 H). Addition of D_2O caused the signal at δ 4.56 to disappear. MS *m/e* (rel intensity) 197 (28), 195 (10), 122 (24), 120 (22), 105 (94), 104 (11), 77 (100), 51 (24). High resolution measurements gave *m/e* 197.1076 ($C_{13}H_{13}N_2$ requires 197.1080). Compound **4** could not be dried adequately without decomposition so the mass spectrum had a water peak at *m/e* 18.

The other fractions obtained from the chromatography were solids or oils which could not be characterized.

Acknowledgment. The author is grateful to Mr. Kenneth Brown for experimental assistance and to the Department of Chemistry of Indiana University, Bloomington, Indiana for the determination of the mass spectra.

Registry No.—*cis*-**1**, 66749-85-7; *trans*-**1**, 66749-86-8; **3**, 66749-87-9; **4**, 66749-88-0; **5**, 66749-89-1; **6**, 31121-09-2; **6**·HCl, 3099-27-2; phenacylaniline, 5883-81-8; phenacyl bromide, 70-11-1; aniline, 62-53-3; phenylglyoxal, 1074-12-0.

References and Notes

(1) P. Yates, *J. Am. Chem. Soc.*, **74**, 5376 (1952).
(2) E. Fraser, W. Paterson, and G. R. Proctor, *J. Chem. Soc.*, 5107 (1963).
(3) The yield of this material varies depending on the procedure used to prepare it. Yates' procedure gives about 3% yield and simply heating phenylglyoxal hydrate and aniline together in ethanol in the absence of an acid catalyst for several hours also gives about a 3% yield.
(4) R. W. Layer, *Chem. Rev.*, **63**, 489 (1963).
(5) R. M. Cowper and L. H. Davidson, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 480.
(6) A referee has pointed out that this compound has been prepared from aniline and styrene oxide: R. Mathis, M. Maurette, and C. Lattes, *Bull. Soc. Chim. Fr.*, 3047 (1970); F. Baldwin, U.S. Patent 2 662 097; *Chem. Abstr.*, **49**, 11704c (1955). It is reported to be a high boiling liquid.
(7) H. A. Riley and A. R. Gray, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 509.
(8) The adsorbent was 60–200 mesh supplied by Matheson, Coleman and Bell.

Palladium-Catalyzed Reaction of 3-Bromopyridine with Allylic Alcohols: A Convenient Synthesis of 3-Alkylpyridines

Yoshinao Tamaru, Yoshimi Yamada, and Zen-ichi Yoshida*

Department of Synthetic Chemistry, Kyoto University, Yoshida, Kyoto 606, Japan

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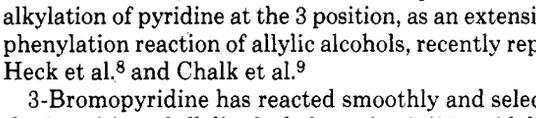
Compared with a wide variety of convenient methods for 2- and 4-alkylpyridines, the synthesis of 3-alkylpyridines is less common and rather laborious.[1] 3-Alkylpyridines have usually been prepared either by the alkylation of 3-pyridyllithium[2] or 3-picolyllithium[3] or by elaboration of nicotinic acid.[4] Therefore, and because of their particular pertinence to the alkaloids[5] and use in synthesis[6] (e.g., as a precursor of 1,5-diketones), a convenient preparative method for 3-alkylpyridines would be desirable.

In this context, we have examined the palladium-catalyzed alkylation of pyridine at the 3 position, as an extension to the phenylation reaction of allylic alcohols, recently reported by Heck et al.[8] and Chalk et al.[9]

3-Bromopyridine has reacted smoothly and selectively at the 3 position of allylic alcohols to give 3-(3′-pyridyl) ketones or aldehydes in the presence of 1 mol % of $Pd(OAc)_2$ (based on 3-bromopyridine, eq 1). In some cases, depending on the



(1)

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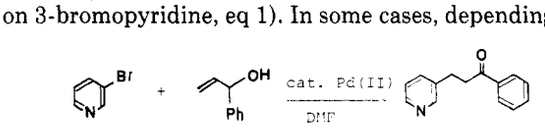

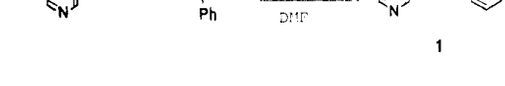

(2)

2 3 4

structure of the allylic alcohols and the reaction conditions, the positional isomer [2-(3′-pyridyl) ketone or aldehyde, **5**] and unsaturated alcohol **6** were also obtained as minor prod-

5 6

ucts. In Table I are summarized the reaction conditions and product distribution obtained with five kinds of allylic alcohols. Alcohols examined were allyl alcohol, α-, β-methallyl

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