Reduction of Thioxanthone Sulfoxide (1) with Sodium Borohydride.—Thioxanthone sulfoxide (0.100 g, 0.438 mmole) was allowed to react with 0.150 g (3.97 mmoles) of sodium borohydride in 15 ml of 95% ethanol. After stirring for 2 hr, the reaction mixture was worked up in the normal manner to afford 0.0763 g of a white solid, mp 203–217°. Thin layer chromatography of this solid indicated that it is mainly *cis*-thioxanthenol sulfoxide (**3α**) (lit.[3] mp 218–218.5°), contaminated with trace amounts of thioxanthone and thioxanthenol. The infrared spectrum (Nujol) of the crude reaction product was quite similar to the spectrum of **3α**.[20]

Reduction of Thioxanthone Sulfoxide (1) with Sodium Borohydride in the Presence of Base. A. Excess Sodium Borohydride.—Sodium borohydride (0.805 g, 21.3 mmoles) was added to a solution of **1** (0.305 g, 1.34 mmoles) and sodium hydroxide (0.0507 g, 1.27 mmoles) in 50 ml of 95% ethanol. The reaction mixture was stirred for 2 hr, diluted with 5 ml of water, and then warmed on a steam bath for several minutes. The resulting solution was diluted with 300 ml of ice–water, allowed to stand for 1 hr, and the resulting solid removed by filtration. The solid was dried (*in vacuo*, calcium chloride) to afford 0.226 g (1.06 mmoles, 79% yield) of thioxanthenol (**4**), mp 104–105° (lit.[21] mp 104–105°). The infrared spectrum of this material was identical with that of authentic thioxanthenol.

B. An Equivalent of Sodium Borohydride.—Sodium borohydride (0.0152 g, 0.4 mmole) was added to a solution of thioxanthone sulfoxide (0.3003 g, 1.32 mmoles) and sodium hydroxide (0.0489 g, 1.22 mmoles) in 50 ml of 95% ethanol.[22] After stirring for 2 hr, the reaction mixture was diluted with 5 ml of water, heated on a steam bath (5 min), and then diluted with ice–water (300 ml). After standing for 1 hr, the resulting solid was removed by filtration and dried (*in vacuo*, calcium chloride). Thus, there was obtained 0.273 g (1.29 mmoles, 98% yield) of thioxanthone (**2**), mp 214–216° (lit.[23] mp 209°). Thin layer chromatography showed the material to be homogeneous and its infrared spectrum (Nujol) was identical with that of authentic thioxanthone.

Reaction of Thioxanthenol Sulfoxide (3) with Base. A. Sodium hydroxide (0.0543 g, 1.36 mmoles) was added to a solution of thioxanthenol sulfoxide (**3**)[24] (0.309 g, 1.34 mmoles) in 50 ml of 95% ethanol.[22] After stirring for 2 hr, the reaction mixture was diluted with water (5 ml), heated on a steam bath (5 min), and then diluted with ice–water (300 ml). After standing for 1 hr, the resulting solid was removed by filtration and dried (*in vacuo*, calcium chloride) to afford 0.279 g (1.32 mmoles, 97% yield) of **2**, mp 214–215° (lit.[23] mp 209°). The infrared spectrum (Nujol) of this material was identical with that of authentic **2**. Thin layer chromatography indicated the presence of **2** contaminated with trace quantities (<5%) of **1**.

B. Morpholine.—In separate experiments, **3α** (0.0070 g, 0.030 mmole) and **3β** (0.0069 g, 0.030 mmole) were each dissolved in 0.5 ml of morpholine. These solutions were examined by thin layer chromatography after standing for 10 hr at room temperature. Each solution suffered extensive conversion to thioxanthone, reaction being greater for **3β** than for **3α**. No other products could be detected by tlc. The reaction mixture did not develop a color under these conditions.

(20) All of the bands that do not appear in the spectrum of authentic **3α** may be found in the spectra of **2** and **4**.

(21) H. F. Oehlschlaeger and I. R. MacGregor, *J. Am. Chem. Soc.*, **73**, 5332 (1950).

(22) The solvent was degassed under vacuum and the reaction was carried out in an inert (N_2) atmosphere.

(23) E. G. Davis and S. Smiles, *Trans. Chem. Soc.*, **97**, 1290 (1910).

(24) A mixture was prepared from 0.1426 g of **3β** and 0.1664 g of **3α**.

Condensation of a 1,3,5-Triketone with Primary Amines to Form Diketoenamines or Diketoimines. Cyclization to Form N-Aryl-4-pyridones[1]

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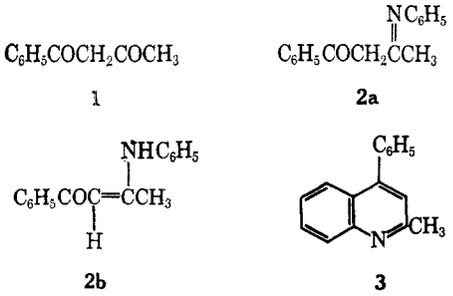
A 1,3,5-triketone was condensed with aniline and certain other primary amines in refluxing ethanol to form diketoenamines or the tautomeric diketoimines. The condensation involved the carbonyl group adjacent to the methyl group of the triketone. The diketoenamines obtained from the arylamines were cyclized by means of hot polyphosphoric acid to form N-aryl-2-methyl-6-phenyl-4-pyridones. The diketoenamine produced from *n*-butylamine failed to afford satisfactorily the N-alkyl-4-pyridone; instead the 4-pyrone was obtained. Mechanisms are suggested for these two courses of cyclizations.

The well-known condensation of a ketone with a primary amine to form an imine was long ago applied to benzoylacetone (**1**); either of the two carbonyl groups of this β-diketone might react with the amine. Actually, the carbonyl adjacent to the methyl group was shown to condense with aniline to give the ketoimine **2a**[2] or, more likely, the tautomeric ketoenamine **2b**.[3]



1

2a

2b

3

The ketoenamine was subsequently cyclized by means of sulfuric acid to afford quinoline **3** (see Experimental Section).[4]

In the present investigation, this type of carbon–nitrogen condensation was applied to triketone **4**, and the products were subjected to acid-catalyzed cyclization. Such a study promised to be of interest since not only might any of the three carbonyl groups of triketone **4** react with the amine, but the product from an aromatic amine might conceivably undergo two types of acid-catalyzed cyclizations. One of these cyclizations would be like that observed with **2a** (or **2b**) to afford a quinoline, and the other like that observed with triketone **4** and ethanolic ammonia which yields pyridone **5**.[5] In the latter cyclization, a diketoenamine was presumably an intermediate, but it was not isolated.[5]

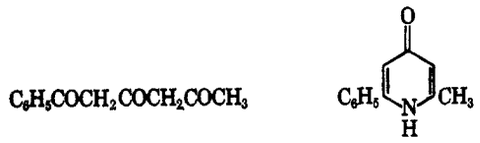
(1) This investigation was supported by U. S. Public Health Service Research Grant No. U. S. PHS CA 04455-08 and by the National Science Foundation Research Grant No. NSF GP 6486.

(2) C. Beyer, *Chem. Ber.*, **20**, 1770 (1887); R. H. Baker and A. H. Schlesinger, *J. Am. Chem. Soc.*, **68**, 2009 (1946).

(3) N. H. Cromwell, R. D. Babson, and C. E. Harris, *ibid.*, **65**, 312 (1943); N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank, and D. J. Wallace, *ibid.*, **71**, 3337 (1949).

(4) D. Fischer, G. Scheibe, P. Merkel, and R. Muller, *J. Prakt. Chem.*, **100**, 91 (1919).

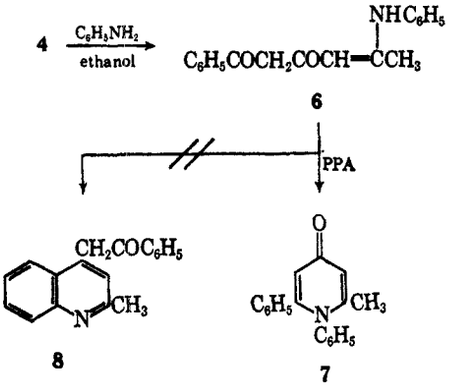
(5) R. J. Light and C. R. Hauser, *J. Org. Chem.*, **25**, 538 (1960).



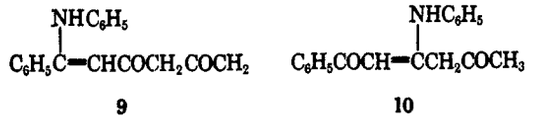
4 5

Actually, triketone **4** was found to react with aniline in refluxing ethanol to form diketoenamine **6** (or the diketoimine),[6] which underwent cyclization with hot polyphosphoric acid (PPA) to give the N-phenyl-4-pyridone **7**; none of the possible quinoline **8** was isolated (Scheme I).

SCHEME I

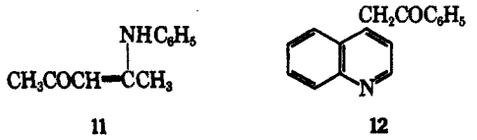


That the condensation of triketone **4** with aniline involved the carbonyl adjacent to the methyl group to form diketoenamine **6**, not the carbonyl adjacent to the phenyl group or the middle carbonyl to give **9** or **10**, respectively, was supported by certain observations. By analogy with the corresponding condensation of benzoylacetone with this amine,[7] **6** seemed more likely than **9**; **10** was eliminated by the fact that the product gave an enol test, since a diketoenamine analogous to **10** has recently been shown not to give this test.[8]



9 10

The structure of the condensation product was confirmed as **6** by independent synthesis involving benzoylation of ketoenamine **11** at the acetyl methyl position.[8] The product obtained from this benzoylation was not only the same as that from triketone **4** and aniline, but PPA cyclizations of the two samples afforded the same pyridone.

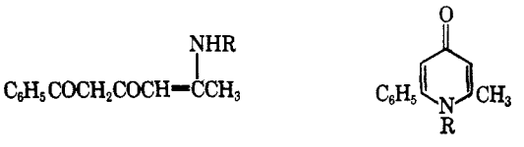


11 12

That the cyclization product from triketone **4** and aniline was pyridone **7**, not quinoline **8** (see Scheme I), was supported by its absorption spectra. Thus, not only did its infrared spectrum resemble those of other 4-pyridones,[9] but its ultraviolet and nuclear magnetic resonance (nmr) spectra clearly distinguished it from the possible quinoline **8** by comparison of these spectra with those of the closely related quinoline **12**, which was prepared by benzoylation of lepidine.[10]

The ultraviolet spectrum of the cyclic product from diketoenamine **6** showed maxima at 268 mμ (log ε 4.39), 241 (4.18), and 207 (4.40), whereas the spectrum of quinoline **12** exhibited maxima at 233 mμ (log ε 3.08) and 247 mμ (log ε 3.05). Even more significantly, the nmr spectrum of pyridone **7** showed singlets at 2.00 (3) and 6.40 ppm (2) representing the methyl and pyridone hydrogens, respectively. No methylene protons were present. On the other hand, the nmr spectrum of quinoline **12** clearly exhibited a methylene group at 4.70 ppm (singlet).

Similarly, triketone **4** was condensed with *o*-chloroaniline, *p*-chloroaniline, *p*-methoxyaniline, and *n*-butylamine in refluxing ethanol or benzene (acid catalyzed) to form diketoenamines **13a–d**, the first three of which were cyclized with hot PPA to give pyridones **14a–c**, respectively.

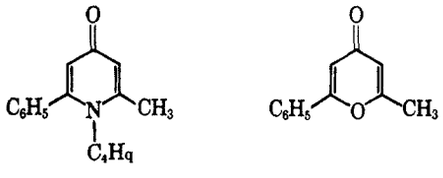


13a, R = C_6H_4Cl-*o*
b, R = C_6H_4Cl-*p*
c, R = $C_6H_4OCH_3$-*p*
d, R = C_4H_9-*n*

14a, R = C_6H_4Cl-*o*
b, R = C_6H_4Cl-*p*
c, R = $C_6H_4OCH_3$-*p*

The results for the diketoenamines **6** and **13a–d** are summarized in Table I and those for the pyridones **7** and **14a–c** in Table II. The general structures for these compounds were supported by analyses and infrared spectra (see Tables I and II). Since the specific structures of diketoenamine **6** (or the imine) and pyridone **7** were established as described above, those of the other compounds may be assumed also to be established.

Although the N-aryldiketoenamine **6** and **13a–c** were readily converted to corresponding N-arylpyridones by hot PPA, the N-*n*-butyldiketoenamine **13d** failed to afford satisfactorily the N-*n*-butylpyridone **15** under similar conditions; instead, the corresponding pyrone **16** was isolated (see Experimental Section).



15 16

The cyclization of diketoenamine **6** to form pyridone **7** was effected also with hot sulfuric acid, but the yield was only about half that obtained with PPA and an approximately equal amount of pyrone **16** was isolated. Although hot sulfuric acid converts ketoenamine **2b** to

(6) By analogy with the ketoenamine **2b**,[1] the present condensation product is assumed to have the diketoenamine structure.

(7) Evidently, benzoylacetone condenses with aniline more slowly than triketone **4**, since the β-diketone failed to afford an appreciable amount of ketoenamine **2a** in refluxing ethanol under the usual conditions; **2a** has been prepared by heating a mixture of benzoylacetone and aniline.[1] Acetylacetone, however, condensed with aniline in refluxing ethanol to form the corresponding ketoenamine in good yield.

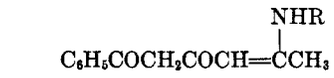
(8) S. Boatman and C. R. Hauser, *J. Org. Chem.*, **31**, 1785 (1966).

(9) See K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p 52.

(10) M. J. Weiss and C. R. Hauser, *J. Am. Chem. Soc.*, **71**, 2023 (1949).

TABLE I

N-SUBSTITUTED AMINO-1-PHENYLHEX-4-ENE-1,3-DIENES

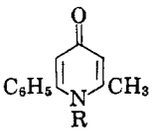


R	Compd	Mp, °C	Yield,[a] %	Infrared absorption bands (strong), μ	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
C_6H_5	**6**	98–99	75[b]	6.10, 6.20, 6.38, 6.72, 7.16	$C_{18}H_{17}NO_2$	77.40	6.12	5.01	77.22	6.18	5.16
C_6H_4Cl-*o*	**13a**	108–110	75[c]	6.20, 6.43, 6.72, 6.85, 7.14	$C_{18}H_{16}ClNO_2$	68.90	5.14	4.46	68.81	5.09	4.35
C_6H_4Cl-*p*	**13b**	139–140	58[c]		$C_{18}H_{16}ClNO_2$	68.90	5.14	4.46	68.77	5.09	4.36
$C_6H_4OCH_3$-*p*	**13c**	132–134	90[c]	6.10, 6.13, 6.20, 6.66, 6.72	$C_{19}H_{19}NO_3$	73.76	6.19	4.53	73.63	6.23	4.63
n-C_4H_9	**13d**	72–74	89[b]	6.22, 6.37, 6.73, 7.17, 7.95	$C_{16}H_{21}NO_2$	74.09	8.16	5.40	73.92	8.11	5.40

[a] The melting points of the products on which these yields were based were generally 3–5° lower than those recorded in this table [b] Recrystallized from hexane. [c] Recrystallized from ethanol–hexane.

TABLE II

N-SUBSTITUTED 2-PHENYL-6-METHYL-4(1H)-PYRIDONES

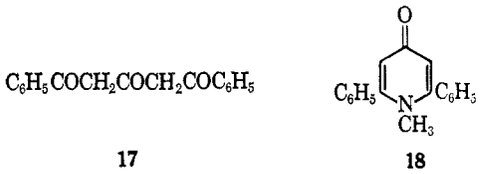


R	Compd	Mp, °C	Yield,[a] %	Infrared absorption bands (strong), μ	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
C_6H_5	**7**	242–243	95[b]	6.10, 6.40, 6.74, 6.94, 7.06	$C_{18}H_{15}NO$	82.73	5.79	5.36	82.67	5.87	5.45
C_6H_4Cl-*o*	**14a**	250–251	90[b]	6.12, 6.34, 6.76, 7.06	$C_{18}H_{14}ClNO$	73.10	4.77	4.74	72.70	4.86	4.72
C_6H_4Cl-*p*	**14b**	220–221	89[c]	6.22, 6.38, 6.73, 6.92, 7.17	$C_{18}H_{14}ClNO$	73.10[d]	4.77	4.74	72.80	4.84	4.77
$C_6H_4OCH_3$-*p*	**14c**	199–201	90[b]	6.11, 6.37, 6.72, 6.87, 7.02	$C_{19}H_{17}NO_2$	78.33	5.88	4.81	78.89	5.88	5.02

[a] The melting points of the products on which these yields were based were generally 3–5° lower than those recorded in this table. [b] Recrystallized from ethanol–water. [c] Recrystallized from methylene chloride–hexane. [d] Calcd for Cl: 11.99. Found for Cl: 11.69.

quinoline **3**,[11] none of quinoline **8** was obtained from diketoenamine **6**. Unsuccessful attempts were made to effect cyclization of diketoenamine **6** with cold, concentrated sulfuric acid (10 min), and to bring about thermal cyclizations of **6** and **13d** in refluxing toluene (4 hr); the starting compounds **6** and **13d** were largely recovered.

In contrast to triketone **4**, triketone **17** failed to condense appreciably with aniline or *n*-butylamine in refluxing ethanol to form diketoenamines under the usual conditions, and **17** was largely recovered. Such condensations might be effected under more appropriate conditions, however, since triketone **17** has been cyclized with methylamine to form pyridone **18** (42%),[5] the intermediate for which would presumably be the corresponding diketoenamine.



17

18

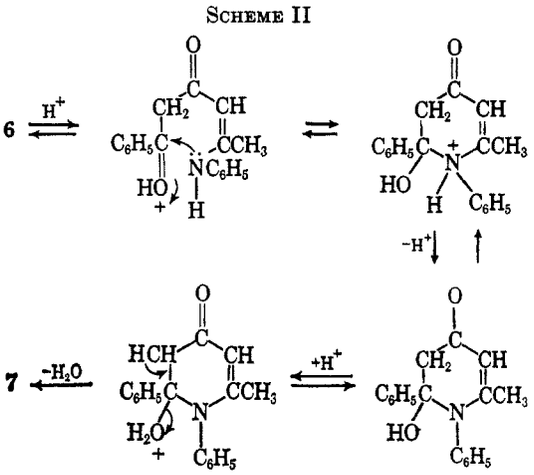
Discussion

Table I shows that the diketoenamines **6** and **13a–d** were obtained from triketone **4** and primary amines in yields of 58–89%. Apparently these are the first examples of such compounds that have been isolated and characterized.

Table II shows that the N-arylpyridones **7** and **14a–c** were obtained from the diketoenamine **6** and **13a–c** in yields of 89–95%. These N-arylpyridones are not only new but also appear to be the first examples of such compounds that have been prepared by direct cyclization of diketoenamines or diketoimines. However, certain other 2,6-disubstituted N-arylpyridones have previously been obtained (generally in low yield) from pyrones and aromatic amines.[12]

The mechanism of cyclization of the N-aryl diketoenamines to the N-arylpyridones, for example that of **6** to give **7**, is suggested to involve an acid-catalyzed, intramolecular addition reaction to form a cyclic hydroxyamine which undergoes an acid-catalyzed dehydration (Scheme II).

SCHEME II

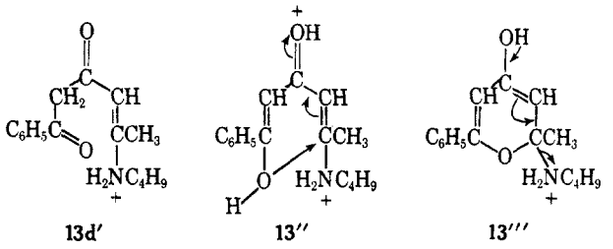


Although some protonation of the amino nitrogen of **6** by PPA may occur initially, it would presumably be sufficiently reversible for the mechanism indicated in Scheme II to operate. The failure of the *n*-butyl-

(11) Ketoenamine **2b** has previously been reported to afford quinoline **3** in 65% yield on treatment with concentrated sulfuric acid at steam bath temperature.[4] We have obtained **3** in slightly lower yield under similar conditions, and some benzoylacetone was also isolated. Under similar conditions PPA afforded only a small amount of **3** (indicated by tlc), and much of ketoenamine **2b** was recovered.

(12) (a) See M. Conrad and M. Gutzeit, *Ber.*, **20**, 154 (1887); (b) S. Hunig and G. Kobrich, *Ann.*, **617**, 181 (1958).

diketoenamine **13d** to afford satisfactorily the pyridone **15** under similar conditions (see above) may be ascribed to more extensive (less reversible) protonation of the amino nitrogen to form cation **13d'**, since this amino nitrogen is probably much more basic than that of an aryldiketoenamine such as **6**. The fact that diketoenamine **13d** afforded mainly pyrone **16** is suggested to involve further protonation of cation **13d'** and an intramolecular conjugate addition of the resulting dication **13d''** to form **13d'''** which eliminates *n*-butylamine.[13]

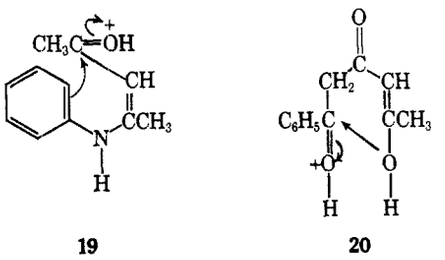


13d' **13''** **13'''**

An alternative course of reaction for the formation of pyrone **16** from diketoenamine **13d** would involve removal of the amino group from cation **13d'** to form triketone **4** which is known to undergo acid-catalyzed cyclization.[5] However, none of triketone **4** was detected in the crude product from **13d** and PPA, though an experiment with triketone **4** and PPA indicated that such detection should have been realized had **4** been an intermediate.[13]

The observation that even the aryldiketoenamine **6** is converted partly to pyrone **16** by hot sulfuric acid (see above) may be attributed to more extensive protonation of the amino nitrogen by this acid than by PPA which afforded exclusively the pyridone **7**. The pyrone **16** presumably arose by one or both of the courses indicated above for the *n*-butyl case.

Finally, the acid-catalyzed cyclization of a diketonenamine to form a pyridone rather than a quinoline, such as that of **6** to give **7** rather than **8** (see Scheme I), is interesting since the latter compound in which an aromatic ring would have been generated would presumably have been more stable thermodynamically. The preferential conversion of such a 1,3,5-trifunctional system to the pyridone is not surprising, however, because the activation energy required for this cyclization might be expected to be lower than that for production of the quinoline, in the transition state of which an aromatic ring would presumably have been disrupted as indicated in **19**. Actually, cyclization of 1,3,5-triketone **4** to form pyrone **16** occurs readily with sulfuric acid even at 0°; the mechanism should be similar to that represented in Scheme II, the first step being indicated in **20**.



19 **20**

(13) Treatment of triketone **4** with PPA for 1.5 hr on the steam bath afforded pyrone **16** (mp 85–86°) in 82% yield, though some of the starting **4** was indicated to be present in the crude reaction product by tlc.

Experimental Section[14]

Condensations of Triketone 4 with Primary Amines to Form Diketoenamines 6 and 13a–d. Method A.—A solution of 0.02 mole each of 1-phenylhexane-1,3,5-trione[15] (**4**) and the appropriate primary amine in 25–50 ml of absolute ethanol was refluxed for 6–12 hr. Most of the solvent was then removed on the steam bath, and the residue was triturated with hexane. After cooling, the solid was collected by filtration, washed with cold hexane, and recrystallized from an appropriate solvent to give yellow crystals (platelets) of the diketoenamines **6** and **13b–d** (see Tables I and II). Method B was found more satisfactory for the preparation of diketoenamine **13b** (see below).

All of the diketoenamines gave a deep green color with ethanolic ferric chloride.

An ethereal solution of diketoenamine **13d** was shaken with saturated, aqueous cupric acetate solution to form a gray precipitate, which was collected and recrystallized from chloroform–ethanol to give apparently the chelate, mp 197–200°.

Anal. Calcd for $C_{32}H_{40}N_2CuO_4$: C, 66.24; H, 6.95; N, 4.83. Found: C, 66.19; H, 7.04; N, 5.06.

Method B.—A mixture of 0.018 mole of triketone **4**, 0.023 mole of *o*-chloroaniline, and 0.05 g of *p*-toluenesulfonic acid monohydrate in 150 ml of benzene was refluxed while about 75 ml of the solvent together with an azeotrope of benzene and water (a by-product of the condensation) was distilled. More (100 ml) of benzene was added to the contents of the flask, and 100 ml more of the solvent and azeotrope was distilled. The remaining mixture was concentrated to about 25 ml, and sufficient petroleum ether (bp 30–60°) waa added to the warm solution to produce slight cloudiness; scratching initiated crystallization. The mixture was cooled and filtered, and the yellow solid was recrystallized to give diketoenamine **13b** (see Table I).

Cyclizations of Diketoenamines 6 and 13a–c to Form N-Arylpyridones 7 and 14a–c.—A suspension of 0.01 mole of the diketoenamine in ten times its weight of PPA was heated on the steam bath for 1.5 hr with occasional manual stirring. The mixture was cooled, and an amount of ice equal to ten times the weight of the PPA was added with stirring. The solution was neutralized with solid sodium bicarbonate or concentrated ammonia, and the resulting mixture was cooled and filtered. The solid was washed with cold water and recrystallized from an appropriate solvent to give white crystals of the N-arylpyridone (see Table II).

Also, a solution of 0.5 g of diketoenamine **6** in 5 g of concentrated sulfuric acid was heated on the steam bath for 1 hr, then poured over crushed ice. The mixture was shaken with ether, and the layers were separated. The acidic, aqueous layer was made basic with concentrated ammonia, and shaken with ether. The dried ethereal layer was evaporated, and the residue was chromatographed on silica gel to give pyridone **7** (mp 242–243°) in approximately 50% yield. Also, there was isolated from the ether extracts of the acid and basic aqueous solutions an approximately equal amount of pyrone **16** (mp 72–74) which appeared to be a mixture of the hydrated and anhydrous forms. One recrystallization from hexane raised the melting point to 84–86° (lit. mp 86–87°). That this was indeed the pyrone was further substantiated by thin layer chromatography (tlc) using a variety of solvents.

Treatment of Diketoenamine 13d with PPA.—A suspension of 1 g of **13d** in 8 g of PPA was heated on the steam bath for 1.5 hr, and the resulting solution was treated with ice essentially as described above for the other diketoenamines. Upon neutralization with sodium bicarbonate, the product separated as an oil and was extracted twice with ether. Removal of the solvent from the combined extracts gave 0.6 g of yellow solid. Two recrystallizations from hexane (Norit) gave a pale yellow solid, mp 85–86°. Tlc (20% methanol–benzene, silica gel) of this twice-recrystallized product showed two spots of about equal intensity (iodine). These corresponded to 2-methyl-6-phenylpyran-4-one (**16**) and starting material **13d**. Also, a third spot of slightly lower

(14) Melting points were taken on a Thomas–Hoover or Mel-Temp capillary melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 137 Infracord using potassium bromide pellets. Ultraviolet spectra were obtained with a Cary Model 14 recording spectrophotometer using 10^{-4} or 10^{-5} *M* solutions in 95% ethanol. Analyses were performed by Janssen Pharmaceutica, Beerse, Belgium, and by Triangle Chemical Laboratories, Chapel Hill, N. C.

(15) M. L. Miles, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **30**, 1007 (1965).

intensity was observed which may have been the desired 1-butyl-2-methyl-6-phenyl-4(1H)-pyridone (**15**). None of the triketone **4** was detected. Similarly, tlc of the crude reaction product showed three spots.

In two other experiments in which diketoenamine **13d** was treated with a much larger excess of PPA (ten times the amount used above), the pyrone **16** (once recrystallized) was isolated in yields of 50–60%. A further purified sample was analyzed.

Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.18; H, 5.49.

Registry No.—**4**, 1469-95-0; **6**, 7294-90-8; **7**, 7294-91-9; **13a**, 14337-92-9; **13b**, 14337-93-0; **13c**, 14337-94-1, **13d**, 14337-95-2; chelate of **13d**, 14481-59-5; **14a**, 14337-87-2; **14b**, 7143-75-1; **14c**, 14337-85-0; **16**, 1013-99-6.

A Kinetic Study of the Reduction of Di-*t*-butyl Ketone with *t*-Butylmagnesium Compounds[1]

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The rates of the reduction of di-*t*-butyl ketone with di-*t*-butylmagnesium and with the Grignard reagent from *t*-butyl chloride in tetrahydrofuran solvent have been studied and the reactions found to obey competitive consecutive second-order kinetics with $k_1 = 10k_2$ for the di-*t*-butylmagnesium reagent and $k_1' = 3.3k_2'$ for the Grignard reagent. The rates of the reductions by these two reagents under comparableconditions were very nearly the same. Mechanistic interpretations of these results, especially those from the Grignard reagent, are complicated by several factors which are discussed.

The recent publication by Ashby, Duke, and Neuman[3] on the kinetics of the Grignard *addition* reaction has prompted us to publish results on a kinetic study of the Grignard *reduction* reaction.

The products of the reaction of Grignard reagents or dialkylmagnesium compounds with ketones arise from either addition (eq 1), reduction (eq 2), or enolization (eq 3), or a combination of these reactions. Here

$$\text{"RMgX"} + R'_2C{=}O \longrightarrow RR'_2COMgX \quad (1)$$

$$\text{"}R_2CHCH_2MgX\text{"} + R'_2C{=}O \longrightarrow R'_2HCOMgX + CH_2{=}CR_2 \quad (2)$$

$$\text{"RMgX"} + R''(R'CH_2)C{=}O \longrightarrow R'CH{=}C(OMgX)R'' + RH \quad (3)$$

"RMgX" is used to represent the Grignard reagent from RX without purporting to suggest any specific structure and without designating the associated solvent. These equations can also be used to represent the reactions of dialkylmagnesium compounds if X is replaced by R. This second R group may (or may not) react further with another molecule of ketone. The *relative* rates of addition, reduction, and enolization have been studied[4,5,6] as well as the kinetics of the addition reaction alone.[3,7] We are unaware of any kinetic study aimed specifically at the reduction reaction of Grignard reagents and/or dialkylmagnesium compounds.

The system chosen for study was the reaction of di-*t*-butyl ketone (2,2,4,4-tetramethyl-3-pentanone) with a *t*-butyl Grignard reagent and with di-*t*-butylmagnesium. Hereafter in this paper R will be used exclusively to represent the *t*-butyl group.

$$(CH_3)_3CC(=O)C(CH_3)_3 + \text{"}(CH_3)_3CMgX\text{"} \longrightarrow (CH_3)_3CC(OMgX)(H)C(CH_3)_3 + CH_2{=}C(CH_3)_2 \quad (4)$$

The choice of di-*t*-butyl ketone precludes the enolization reaction (eq 3) and the use of the sterically hindered ketone and bulky Grignard reagent not only prevents the addition reaction[8] (eq 1) but also causes the reduction reaction to proceed at a conveniently slow rate.

Results

The rate of appearance of product was followed by quenching aliquots or individual samples of the reaction mixture at appropriate intervals with 1 *M* ammonium chloride solution and determining the relative amounts of starting material (di-*t*-butyl ketone) and product (di-*t*-butylcarbinol) by gas chromatography. The original experiments were in ether solvent but the gradual formation of a precipitate in the reaction mixture as it progressed forced a change to tetrahydrofuran (THF) solvent in which the reaction was completely homogeneous. The results of the kinetic investigations are summarized in Table I for the di-*t*-butylmagnesium reagent and in Table II for the Grignard reagent from *t*-butyl chloride. Figure 1 is representative of the second-order rate plots for the data from the Grignard reagent experiments. The plots for the di-*t*-butylmagnesium experiments were entirely analogous. In those experiments in which the *t*-butyl Grignard reagent or di-*t*-butylmagnesium reagent were in excess, the ketone was completely used and the rate followed second-order kinetics (as indicated in Figure 1)

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(2) Taken in part from the M. S. Thesis of M. S. Singer, Stanford University, Stanford, Calif., 1963. Complete presentation of the data on the *t*-butyl Grignard reductions can be found in this source.

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