[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Cyclization of β-Ketonitriles or β-Ketoamides with Ketones by Polyphosphoric Acid to Form Substituted 2-Pyridones[1]

BY CHARLES R. HAUSER AND CHARLES J. EBY

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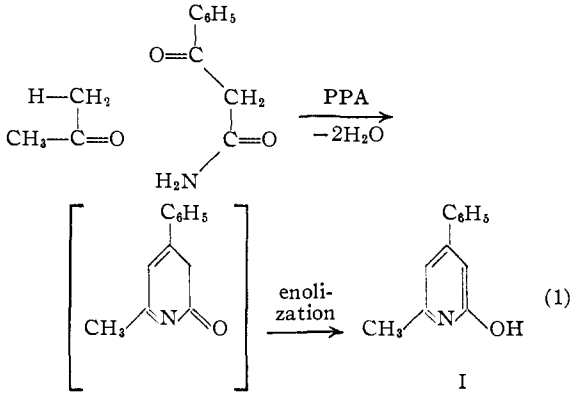
β-Ketonitriles or β-ketoamides were found to undergo an aromatic type of cyclization with ketones in the presence of polyphosphoric acid to form 2-pyridones. The structures of certain of these products were established by physical and chemical means. The product from benzoylacetonitrile and cyclohexanone was dehydrogenated to form a quinoline. The present method is especially suitable for the synthesis of highly substituted 2-pyridones.

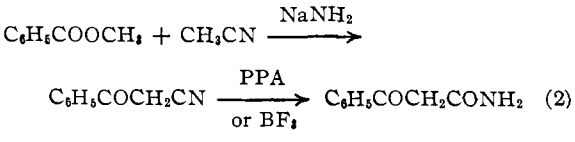
It is well known that the three conjugated double bonds in an aromatic system may arise from a cyclization involving appropriately situated carbonyl groups and active hydrogens through the loss of water or by subsequent enolization. An apparently new example of such an aromatic cyclization was realized in the present investigation from β-ketoamides and ketones by means of polyphosphoric acid (PPA). Thus, benzoylacetamide was cyclized with acetone to form 4-phenyl-6-methyl-2-pyridone (I) in 60% yield (equation 1).



(1)

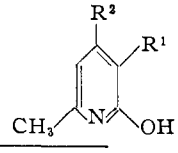
I

The β-ketoamide was prepared in 81% yield through the condensation of methyl benzoate with acetonitrile by means of sodium amide,[2] followed by treatment of the resulting β-ketonitrile with polyphosphoric acid or boron fluoride in acetic acid[3] (equation 2).



(2)

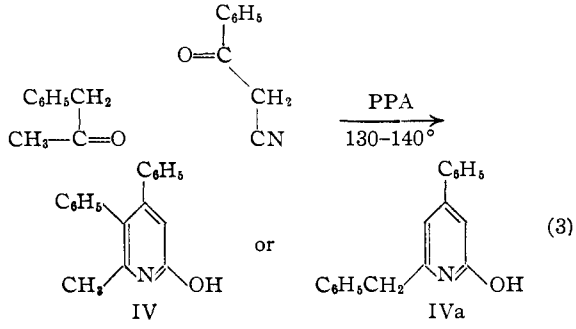
Similarly α-acetyl-α-toluamide and α-benzoylpropionamide, which were prepared by the method represented in equation 2, were cyclized with acetone to form 2-pyridones II and III in yields of 18 and 38%, respectively.



II, R^1 C_6H_5, R^2 = CH_3
III, R^1 = CH_3, R^2 = C_6H_5

Since polyphosphoric acid effects not only the cyclization of β-ketoamides with acetone but also the conversion of β-ketonitriles to the amides,[3] it seemed possible to realize the cyclization directly from the β-ketonitriles and ketone. This was verified. Thus, treatment of the appropriate β-ketonitriles and acetone with this acid at 130–140° produced 2-pyridones I, II and III in yields of 68, 29 and 43%, respectively. The fact that these yields are 5–11% better than those obtained starting with the β-ketoamides indicates that the β-ketonitrile is not first converted to the β-ketoamide but to an intermediate that cyclizes with the ketone. This intermediate, which presumably would produce the β-ketoamide on hydrolysis, appears to be more difficult to form starting with the β-ketoamide.

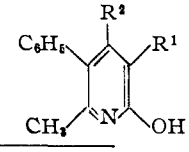
The β-ketonitriles were cyclized with several other ketones (Tables I and II). Thus, benzoylacetonitrile was cyclized with phenylacetone to form 2-pyridone IV or IVa in 63% yield. Structure IV is probable since its formation would involve the methylene hydrogens of the ketone which are known to be more reactive than the methyl hydrogens, especially in acidic medium[4] (equation 3).



(3)

IV IVa

Similarly α-acetyl-α-tolunitrile, α-benzoylpropionitrile and α-nicotinylpropionitrile were cyclized with phenylacetone to form presumably 2-pyridones V, VI and VII in yields of 58, 60 and 34%, respectively.



V, R^1 = C_6H_5, R^2 = CH_3
VI, R^1 = CH_3, R^2 = C_6H_5
VII, R^1 = CH_3, R^2 = C_5H_4N

(1) Supported by the Office of Ordnance Research, U. S. Army.

(2) Charles J. Eby and Charles R. Hauser, THIS JOURNAL, **79**, 723 (1957), first paper of present series.

(3) Charles R. Hauser and Charles J. Eby, *ibid.*, **79**, 725 (1957), second paper of present series.

(4) For example, the boron fluoride catalyzed acetylation of phenylacetone with acetic anhydride involves the methylene hydrogen; see C. R. Hauser, F. W. Swamer and J. T. Adams, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1954, Vol. VIII, Chapter 3, pp. 103, 186.

TABLE I

CYCLIZATION OF β-KETONITRILES OR β-KETOAMIDES WITH KETONES BY POLYPHOSPHORIC ACID TO FORM 2-PYRIDONES

β-Ketonitrile	Ketone	2-Pyridone	M.p., °C.	Yield, %
Benzoylaceto-	Acetone	4-Phenyl-6-methyl-2-pyridone (I)	198–202	68[a]
α-Acetyl-α-tolu-	Acetone	3-Phenyl-4,6-dimethyl-2-pyridone (II)	215–218	29[b,c]
α-Benzoylpropio-	Acetone	3,6-Dimethyl-4-phenyl-2-pyridone (III)	155–157	43[d]
Benzoylaceto-	Phenylacetone	4,5-Diphenyl-6-methyl-2-pyridone (IV)	264–266	63
α-Acetyl-α-tolu-	Phenylacetone	3,5-Diphenyl-4,6-dimethyl-2-pyridone (V)	295–297	58
α-Benzoylpropio-	Phenylacetone	4,5-Diphenyl-3,6-dimethyl-2-pyridone (VI)	299–302	60
α-Nicotinylpropio-	Phenylacetone	3,6-Dimethyl-4-nicotinyl-5-phenyl-2-pyridone (VII)	310–312	34
Benzoylaceto-	Cyclohexanone	2-Hydroxy-4-phenyl-5,6,7,8-tetrahydroquinoline (VIII)	283–285	53
Benzoylaceto-	Acetophenone	4,6-Diphenyl-2-pyridone (IX)	204.5–207.5[e]	5

[a] The yield of 2-pyridone I from benzoylacetamide and acetone was 60%. [b] Obtained on heating the reaction mixture 20 minutes on the steam-bath and 15 minutes at 125°. The yield under the usual conditions was only 14%. [c] The yield of 2-pyridone II from α-acetyl-α-toluamide and acetone was 18%. [d] The yield of 2-pyridone III from α-benzoylpropionamide and acetone was 38%. [e] Reported m.p. 207–208°; see note 12.

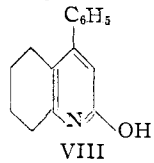
TABLE II

ANALYTICAL DATA FOR THE 2-PYRIDONES OBTAINED

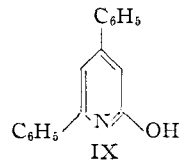
2-Pyridone	M.p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
I	202.5–204.5[a,b]	$C_{12}H_{11}ON$	77.81	5.99	7.56	78.05	5.91	7.52
II	218–220.5[a]	$C_{13}H_{13}ON$	78.36	6.58	7.03	78.27	6.58	6.97
III	159.5–161[a]	$C_{13}H_{13}ON$	78.36	6.58	7.03	78.51	6.33	7.16
IV	267–269[a]	$C_{18}H_{15}ON$	82.73	5.79	5.36	83.04	5.68	5.10
V	305–307[c]	$C_{19}H_{17}ON$	82.88	6.22	5.09	82.98	6.48	5.00
VI	305–307[a]	$C_{19}H_{17}ON$	82.88	6.22	5.09	82.62	6.13	5.08
VII	310–312[d]	$C_{18}H_{16}ON_2$	78.23	5.84	10.14	78.30	5.91	9.97
VIII	284.5–286[c]	$C_{15}H_{15}ON$	79.97	6.71	6.22	80.01	6.61	6.10

[a] Recrystallized from methanol. [b] Melting point on Kofler micro hot-stage 208°; reported m.p. (207°) (ref. 6). [c] Recrystallized from acetic acid–water. [d] Recrystallized from methanol–water and sublimed twice at 235° (2.5 mm.).

Also, benzoylacetonitrile was cyclized with cyclohexanone and with acetophenone to form 2-pyridones VIII and IX in yields of 53 and 5%, respectively.

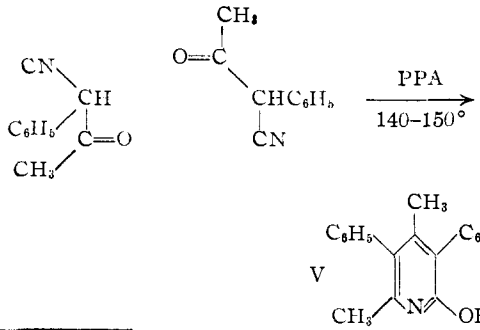


VIII



IX

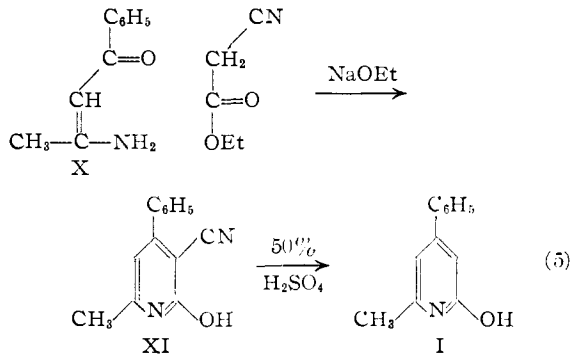
Apparently acetophenone is not sufficiently reactive to produce a satisfactory yield under the conditions employed. In an attempt to cyclize α-acetyl-α-tolunitrile with this ketone some self-condensation of the β-ketonitrile occurred to form 2-pyridone V (11%), in which one of the nitrile groups evidently was eliminated. The β-ketonitrile underwent self-condensation in much better yield (55%) by treating it alone with polyphosphoric acid at 140–150° (equation 4).[5]



(4)

(5) This reaction was carried out in this Laboratory by James G. Murray.

The structure of pyridone I was established by an independent synthesis by the method of Basu[6] which involves the cyclization of benzoylacetoneimine or its tautomer X with ethyl cyanoacetate followed by hydrolysis and decarboxylation of XI (equation 5).



X

XI

I

(5)

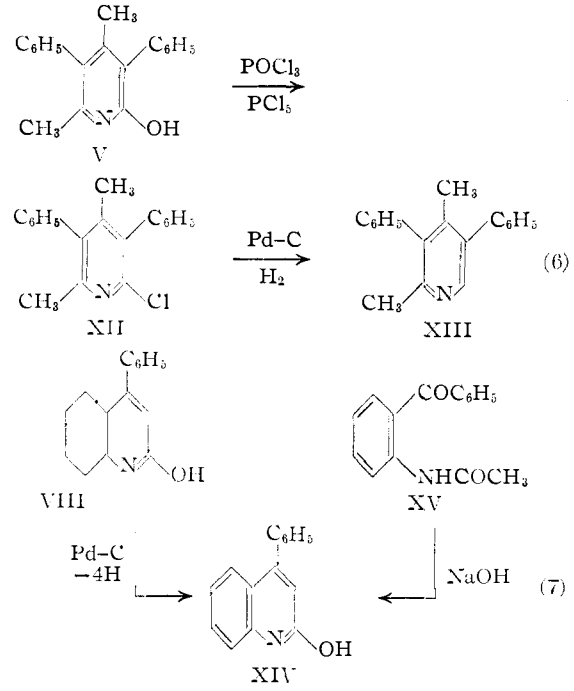
Pyridone V was converted to pyridine XIII through the intermediate chloro derivative XII. This reaction (equation 6) is characteristic of a 2- or 4-hydroxypyridine.[7]

The structure of pyridone VIII was established by dehydrogenation to form 2-hydroxy-4-phenylquinoline (XIV). The product was shown to be identical with a sample of XIV prepared by the method of Camps[8] involving the cyclization of 2-N-acetylaminobenzophenone (XV) (equation 7).

(6) U. Basu, *J. Indian Chem. Soc.*, **12**, 299 (1935).

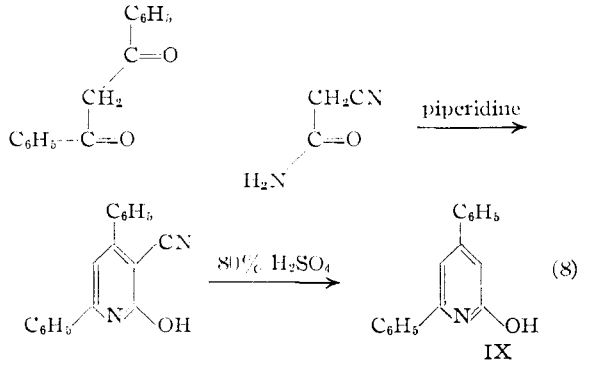
(7) H. S. Mosher, Chapter 8, "Heterocyclic Compounds," R. Elderfield (editor), John Wiley and Sons, Inc., New York, N. Y., Vol. I, 1950.

(8) R. Camps, *Arch. Pharm.*, **237**, 683 (1889).



In addition to these proofs of structure, all of the 2-pyridones prepared gave characteristic faint orange-red coloration with ferric chloride[9] and ultraviolet absorption spectra (Table III) similar to certain previously known 2-pyridones.[10,11]

The present method appears to be the best known for the synthesis of the highly substituted 2-pyridones I-VIII. In fact, only the first of these compounds, 2-pyridone I, seems to have been described previously. This compound, which was obtained in 68% yield by the present method, was produced in only 10% yield in Basu's method[6] which was employed in connection with the proof of structure (see equation 5). However, 2-pyridone IX, which was obtained in only 5% yield by our method, previously has been prepared in better yields by other methods, one of which may be represented by equation 8.[12]



Attempts to extend the present method employing benzoylacetonitrile or α-acetyl-α-tolunitrile with ethyl phenylacetate or phenylacetaldehyde were unsuccessful. Apparently the aldehyde underwent self-condensation and cyclization.[13]

Although boron fluoride in acetic acid converts β-ketonitriles to β-ketoamides at 110–120°,[3] this reagent failed to effect the cyclization of benzoylacetonitrile with phenylacetone to form IV at this temperature.

(9) See ref. 7, p. 442.
(10) H. Specker and H. Gawrosch, *Ber.*, **75B**, 1338 (1942).
(11) F. Ramirez and A. Paul, *J. Org. Chem.*, **19**, 183 (1954).
(12) U. Basu, *J. Indian Chem. Soc.*, **7**, 481 (1930).

TABLE III

SUMMARY OF ULTRAVIOLET ABSORPTION DATA

2-Pyridone	$\lambda_{max.}$ mμ	ε	$\lambda'_{max.}$, mμ	ε	$\lambda''_{max.}$, mμ	ε
I	319	5900	260	16700	233	>30000
II	309	10200	238	Shld.		
III	311	7200	230	>30000		
IV	318	7200	..			
V	314	11000	240	Shld.		
VI	314	8000	242	20000	230	30000
VII	317	8200	..			
VIII	317	6600	255	Shld.		

Experimental[14]

Cyclization of β-Ketonitriles or β-Ketoamides with Ketones to Form 2-Pyridones.—To 75–125 g. of polyphosphoric acid was added molecular equivalents (0.025–0.05 mole) of the β-ketonitrile[2] or β-ketoamide[3] and the ketone. The resulting mixture was stirred at room temperature for a few minutes, then on the steam-bath for 30 minutes and finally in a Woods metal-bath at 130–140° for 30 minutes.[15] Usually an additional equivalent of the ketone was added after the mixture was heated on the steam-bath.[16] The dark mixture was then added with stirring to 200–300 g. of crushed ice and 200 ml. of ether was added. The resulting mixture was stirred for 30 minutes and the two layers were separated. The aqueous layer was neutralized with solid sodium bicarbonate to precipitate the 2-pyridone. The solvent was removed from the ethereal layer and more 2-pyridone sometimes isolated from the residue. The 2-pyridones were recrystallized from appropriate solvents.

The yields and the melting points on which they are based are given in Table I. The melting points of further purified samples and the analytical data are given in Table II. Although the melting points had a slight range when taken in the usual manner, the products were essentially pure. One of the 2-pyridones (I), which melted at 202.5–204.5° employing the usual melting point bath, melted sharply at 208° on a Kofler micro hot-stage. The ultraviolet absorption spectra of these compounds are given in Table III.[17]

Self-condensation of α-Acetyl-α-tolunitrile to Form 2-Pyridone V.[5]—A mixture of 5 g. of α-acetyl-α-tolunitrile and 25 g. of polyphosphoric acid was stirred and heated at 140–150° for 30 minutes. After cooling, water was added. The solid was removed by filtration and recrystallized from water–acetic acid, yielding 1.80 g. (55%) of 3,5-diphenyl-4,6-dimethyl-2-pyridone (V) as a colorless solid, m.p. 300–306°. A sample recrystallized from acetic acid–water melted at 305–307°.

Benzoylacetoneimine (X).—This compound was prepared by a modification of the method of Knoevenagel,[18] who did not report the yield.

Through a solution of 40.5 g. (0.25 mole) of benzoylacetone[19] in 250 ml. of absolute ethanol was bubbled dry ammonia gas for 1.5 hours, and the resulting clear yellow solution allowed to stand overnight in a stoppered flask. The crystals that gradually precipitated were collected to

(13) T. Zincke and A. Breuer, *Ann.*, **226**, 23 (1884).
(14) Melting points are uncorrected. Microanalyses are by Galbraith Laboratories, Knoxville, Tenn.
(15) Preliminary experiments with benzoylacetonitrile and phenylacetone gave none of 2-pyridone IV on heating only on the steam-bath, and the yield was lowered from 63 to 42% when the metal-bath temperature was raised from 130–140° to 150° (for 30 minutes.)
(16) In the reaction with acetone, a reflux condenser was employed.
(17) Ultraviolet absorption spectra were taken in absolute methanol on a Warren Spectracord, model 3000.
(18) E. Knoevenagel, *Ber.*, **36**, 2187 (1903).
(19) R. M. Manyik, F. C. Frostick, J. J. Sanderson and C. R. Hauser, THIS JOURNAL, **75**, 5030 (1953).

give 32.35 g. (80%) of benzoylacetoneimine (X), m.p. 138.5–140.5°, reported[18] m.p. 143°.

Cyclization of X with Ethyl Cyanoacetate to Form XI and its Conversion to 2-Pyridone I.—This reaction was effected by a modification of the method of Basu[6] who reported no yield.

To a solution of sodium ethoxide (prepared from 2.72 g., 0.117 mole, of sodium) in 100 ml. of absolute ethanol, was added a solution of 13.4 g. (0.117 mole) of ethyl cyanoacetate in 50 ml. of absolute ethanol, followed immediately by 19.0 g. (0.117 mole) of benzoylacetoneimine (X) in 25 ml. of absolute ethanol. The mixture was refluxed for 6 hours, and allowed to stand overnight at room temperature. Water (200 ml.) and 10 ml. (0.12 mole) of concentrated hydrochloric acid were added, and the resulting precipitate collected and recrystallized from methanol to give 4.95 g. (20%) of 3-cyano-4-phenyl-6-methyl-2-pyridone (XI), m.p. 276–277°, reported[8] m.p. 277°.

A mixture of 0.53 g. (0.0025 mole) of XI and 25 ml. of 50% sulfuric acid was heated 2 hours on the steam-bath with no apparent change, and then refluxed 30 minutes over a bunsen burner. The resulting solution was chilled in ice-water to precipitate a white solid which was triturated with saturated sodium bicarbonate solution to give 0.20 g. (44%) of 2-pyridone I, m.p. 195–198.5°. One recrystallization from methanol raised the melting point to 201–203°, 208° (Kofler micro hot-stage); reported[6] m.p. 207°. A mixed melting point with 2-pyridone I prepared in the general procedure was undepressed.

Conversion of 2-Pyridone IV to Chloro Derivative XII.—A mixture of 11.4 g. (0.042 mole) of 3,5-diphenyl-4,6-dimethyl-2-pyridone (IV), 20 g. of phosphorus pentachloride and 25 ml. of phosphorus oxychloride was refluxed on the Woods metal-bath at 140° for 24 hours. The reaction mixture was decomposed with ice and the product taken up in ether. The ether solution was washed with sodium bicarbonate solution and dried over magnesium sulfate. The solvent was removed to give 6.35 g. of a dark solid, m.p. 193–208°. One recrystallization from benzene gave 3.2 g. (26%) of 2,4-dimethyl-3,5-diphenyl-6-chloropyridine (XII), m.p. 213–220°. Two additional recrystallizations from benzene gave white crystals, m.p. 223–225°.

Anal. Calcd. for $C_{19}H_{16}NCl$: C, 77.67; H, 5.49; N, 4.77; Cl, 12.07. Found: C, 77.58; H, 5.46; N, 4.83; Cl, 12.14.

Dechlorination of XII to Form XIII.—A stirred solution of 0.4 g. (0.013 mole) of 2,4-dimethyl-3,5-diphenyl-6-chloropyridine (XII) in a mixture of 50 ml. each of absolute ethanol and ethyl acetate was hydrogenated over palladium (0.2 g.)-on-charcoal at atmospheric pressure. The theoretical amount of hydrogen was taken up overnight. The catalyst was removed (suction filtration) and the solvents were evaporated (water-pump) leaving 0.4 g. of a white solid which was triturated with sodium bicarbonate solution and taken up in ether. After drying over magnesium sulfate, the solvent was removed and the residue (0.2 g.) recrystallized from 30–60° petroleum ether to give 0.15 g. (43%) of 2,4-dimethyl-3,5-diphenylpyridine (XIII), m.p. 99–100.5°.

Anal. Calcd. for $C_{19}H_{17}N$: C, 87.99; H, 6.61; N, 5.40. Found: C, 88.18; H, 6.73; N, 5.37.

Dehydrogenation of 2-Pyridone VIII to Form XIV.—In a sublimation apparatus was placed a thoroughly mixed sample of 0.22 g. (0.001 mole) of 2-hydroxy-4-phenyl-5,6,7,8-tetrahydroquinoline (VIII) with 0.11 g. of 5% palladium-on-charcoal. The apparatus was evacuated to 30 mm. pressure and placed in a Woods metal-bath at 200°. There was collected 0.15 g. (68%) of 2-hydroxy-4-phenylquinoline (XIV), m.p. 253–256°, reported[8] m.p. 259°. One additional sublimation raised the melting point to 260–261.5° (sealed tube) which was not depressed upon admixture with a sample of XIV obtained below.

2-N-Acetylaminobenzophenone (XV).—This compound was prepared by a modification of the method of Bischler and Barad,[20] who did not report the yield.

A mixture of 8.0 g. (0.04 mole) of *o*-aminobenzophenone and 10.8 g. (0.106 mole) of acetic anhydride was stirred and heated on the steam-bath for 1 hour. The resulting dark clear solution was stirred and heated with 25 ml. of water for 1 hour to decompose the excess acetic anhydride. After neutralizing the acidic solution with an excess of sodium bicarbonate, the aqueous layer was decanted and the residual dark heavy oil was dissolved in a minimum of methanol. The solution was clarified by filtration and cooled in a Dry Ice–acetone mixture to give an oil which solidified on scratching. The white solid was collected by suction filtration to give 7.8 g. (82%) of 2-N-acetylaminobenzophenone (XV), m.p. 78–82°, reported[20] m.p. 88.5–89°.

Cyclization of XV to Form XIV.—This reaction was effected by a modification of the procedure of Camps.[8]

To a warm mixture of 6.0 g. (0.025 mole) of 2-N-acetylaminobenzophenone (XV), 50 ml. of 95% ethanol and 150 ml. of water was added 1.5 g. (0.0375 mole) of sodium hydroxide in a minimum of water. The mixture was refluxed for 2 hours, cooled in ice and the solid collected by vacuum filtration. After refluxing with 100 ml. of 3 *N* hydrochloric acid for 6 hours (to hydrolyze any uncyclized amide), the solid was collected by vacuum filtration of the cooled mixture, and recrystallized from 95% ethanol to give 4.1 g. (74%) of 2-hydroxy-4-phenylquinoline (XIV), m.p. 254–257°; reported m.p. 259°.[8] Sublimation at 180–190° (2 mm.) raised the melting point to 260–261.5°. This melting point was undepressed upon admixture with a sample of XIV prepared above.

(20) A. Bischler and D. Barad, *Ber.*, **25**, 3080 (1892).

DURHAM, N. C.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Synthesis of β-Diketone Esters from Sodio Ketones and Mono Acid Chloride Esters of Succinic and Adipic Acids. Avoidance of Stobbe and Dieckmann Reactions

BY CHARLES R. HAUSER AND BRUCE O. LINN[1]

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Sodio ketones, prepared by means of sodium amide, were acylated with the mono acid chloride-ethyl esters of succinic and adipic acids to form the corresponding β-diketone-esters. This was accomplished satisfactorily by an adaptation of an earlier method involving the use of three equivalents of the sodio ketone to one of the acid chloride. The possible Stobbe and Dieckmann reactions, which occur in attempts to acylate sodio ketones with diethyl succinate and adipate, were avoided under the present conditions. An extension of the method is indicated. The β-diketone-ester from sodio cyclohexanone and the mono acid chloride ester of adipic acid was cleaved by alkali with ring opening to form a ketone dicarboxylic acid.

It was shown recently[2] that certain β-diketones that are not obtained satisfactorily by the common base-catalyzed acylation of ketones with esters[3]

(1) American Cyanamid Co. Fellow, 1954–1955.

(2) B. O. Linn and C. R. Hauser, THIS JOURNAL, **78**, 6066 (1956).

(3) See C. R. Hauser, F. W. Swamer and J. T. Adams, "Organic Reactions," Vol. VIII, John Wiley and Sons, Inc., New York, N. Y., 1954, Chapter 3.