[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

N- and *C*-Benzoylation of *p*-Aminoacetophenone with Methyl Benzoate by Sodium Amide. Synthesis of β-Diketones Having *p*-Acylamino and *p*-Hydroxy Groups[1]

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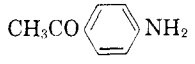
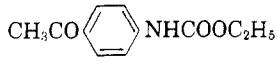
p-Aminoacetophenone underwent *N*-benzoylation with sodium amide and methyl benzoate to form *p*-benzoylaminoacetophenone which then underwent *C*-benzoylation with these reagents to give the corresponding β-diketone amide. This β-diketone was cyclized with hydrazine and urea to produce a pyrazole and pyrimidol, respectively. Other acylations of ketone amides and the benzoylation of *p*-hydroxyacetophenone were effected to form the corresponding β-diketones. These condensations furnish a significant extension of the Claisen method of synthesis of β-diketones. The mechanism is considered to involve intermediate dianions.

Broadbent and Chu[2] have observed that *p*-aminoacetophenone (I) undergoes *N*-carbethoxylation on treatment with sodium amide followed by ethyl carbonate to form II which, however, fails to undergo further carbethoxylation in the presence of excess of these reagents. These workers had hoped to effect the *C*-carbethoxylation of I or II to produce the corresponding β-keto ester.

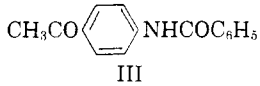


I

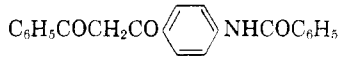


II

We have found that ketone amine I undergoes *N*-benzoylation with sodium amide and methyl benzoate to form ketone amide III which, in addition, undergoes *C*-benzoylation in the presence of excess of these reagents to give β-diketone amide IV. The reaction was carried out by adding I to sodium amide in liquid ammonia followed by the ester in ether.



III



IV

In Table I are summarized the yields of III and IV obtained from I with various equivalent amounts of sodium amide and methyl benzoate. It can be seen from this table that only III was obtained with equivalents of the base and ester but that IV was also produced with excesses of these reagents. Moreover the ratio of IV to III increased as the excess of reagents was increased. These two products were separated by converting the β-diketone amide (IV) to its copper chelate which was relatively insoluble in methanol. The β-diketone amide was regenerated by treatment of the chelate with acid. The yields of III and IV given in Table I are based on essentially pure compounds.

TABLE I

YIELDS OF III AND IV FROM I WITH VARIOUS EQUIVALENTS OF REAGENTS

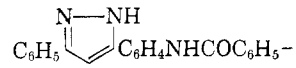
Reagents[a]		Products	
Sodium amide, equiv.	Methyl benzoate, equiv.	III, yield %	IV, yield %
1	1	89[b]	0
3	2	46	32
4	3	21	54

[a] One equivalent of ketone amine I was used in each experiment. [b] Some (10%) of ketone amine I was recovered.

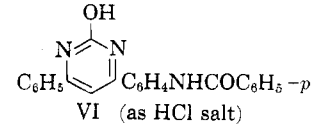
The monobenzoylated product was shown to be *p*-benzoylaminoacetophenone (III) by a mixed melting point with an authentic sample of this compound prepared from I and benzoyl chloride by the usual Schotten-Baumann reaction.

The structure of the dibenzoylated product was established as IV by a positive ferric chloride enol test and by the formation of a copper chelate, both of which are characteristic of β-diketones. The presence of the —CONH— group in IV was indicated[3] by an infrared absorption band at 3330 cm.$^{-1}$

The β-diketone structure of IV was confirmed by characteristic cyclizations with hydrazine[4] and urea[5] to form pyrazole V (96%) and pyrimidol VI (58%), respectively. The latter product was isolated as its monohydrochloride salt. An unstable



V



VI (as HCl salt)

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

(2) H. Broadbent and C. Chu, *J. Am. Chem. Soc.*, **75**, 226 (1953).

(3) See R. Richards and H. Thompson, *J. Chem. Soc.*, 1248 (1947).

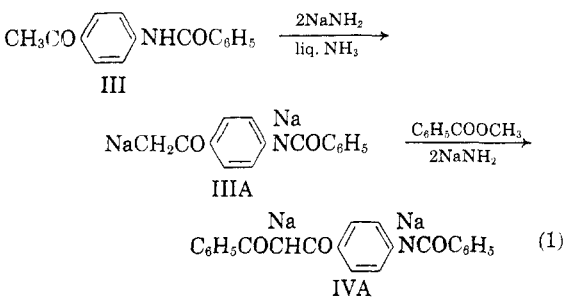
(4) See E. Royals, *Advanced Organic Chemistry*, Prentice-Hall, Inc., New York, N. Y., 1954, p. 658.

(5) See C. Hauser and R. Manyik, *J. Org. Chem.*, **18**, 588 (1953).

dihydrochloride salt also appeared to form (see Experimental).

β-Diketone amide IV was prepared not only by treating ketone amine I with excess sodium amide and methyl benzoate (Table I) but also by the action of these reagents on ketone amide III the disodium salt of which is presumably an intermediate under the former conditions. Indeed the yield of IV from ketone amide III in the presence of three equivalents of sodium amide and two of methyl benzoate was approximately the same (52%) as that (54%) obtained from ketone amine I employing four equivalents of the base and three of the ester. This was anticipitated on the basis that one equivalent each of the base and ester was required to convert the amine group of I to the amide group of III (see Table I).

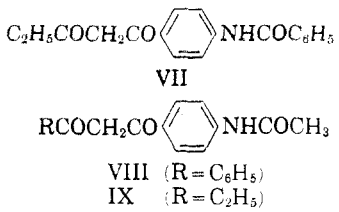
The mechanism of formation of IV from III evidently involves the *C*-benzoylation of the dianion of disodium salt IIIA which is presumably first formed from III in the presence of two or more equivalents of sodium amide (Equation 1). The α-hydrogen of the resulting β-diketone[6] would be ionized to form disodium salt IVA from which β-diketone amide IV was subsequently liberated by acidification of the reaction mixture.



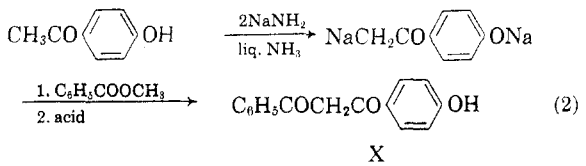
It is not surprising that disodium salt IIIA did not exhibit *N*-benzoylation to form *p*-dibenzoylaminoacetophenone since sodio benzanilide (prepared by means of sodium amide)[7] failed to undergo *N*-benzoylation with methyl benzoate under similar conditions to give dibenzanilide.

Similarly *p*-benzoylaminoacetophenone (III) was propionylated to form β-diketone-amide VII (20%), and the corresponding *p*-acetylaminoacetophenone was benzoylated and propionylated to give β-diketone amides VIII (20%) and IX (13%), respectively. The yields of these β-diketones could probably be improved. The possible acyl exchange was not observed under the conditions employed.

Also, *p*-hydroxyacetophenone was benzoylated to form β-diketone phenol X (37%). This product was isolated through its copper chelate. Similar to the acylations of the dianions of ketone-amides



such as IIIA (Equation 1), the formation of X evidently involves the *C*-acylation of the intermediate dianion (equation 2).



These condensations of ketones having hydrogens more acidic than their α-hydrogens furnish a significant extension of the well known Claisen method of acylation of ketones to form β-diketones.[6] Actually, relatively few such acylations of ketones involving intermediate dianions appear to have been realized previously.[6] A number of acylations of *o*-hydroxyacetophenone and its derivatives have been accomplished but at least certain of these might have involved the preferential *O*-acylation, of the intermediate dianion followed by intramolecular *C*-acylation.[8] Such a cyclic mechanism would not be possible for the present acylations of the dianions of *para*-substituted ketones. These reactions might have involved preferential *O*- or *N*-acylation followed by intermolecular *C*-acylation but this seems unlikely in view of the failure of sodio benzanilide to undergo acylation under similar conditions (see above).

An attempt to employ the present method for the acylation of diacetone alcohol resulted in the formation of benzoylacetone. Apparently this β-hydroxy ketone[9] underwent a reversed aldol condensation to form sodio acetone which then was benzoylated, or the reversed aldol condensation might have occurred after benzoylation.

It should be mentioned that sodio acetophenone failed to undergo acylation with methyl *p*-benzoylaminobenzoate or *p*-hydroxybenzoate in the presence of excess sodium amide under the conditions employed with ketone amide III. Apparently the active hydrogens in these esters was ionized by the sodium amide, thereby deactivating the carbonyl groups of the esters.

EXPERIMENTAL[10]

N- and C-benzoylation of p-aminoacetophenone (I) *to form*

(6) See C. Hauser, F. Swamer, and J. Adams, *Org. Reactions*, VIII, Chapter 3 (1954).

(7) That sodium amide converts amides of the type $RCONHC_6H_5$ to their sodium salts is shown by their alkylation with alkyl halides by means of this base: V. Wolf, *Ann.*, **576**, 35 (1952).

(8) See ref. 6, p. 91.

(9) The α-hydroxyketone, butyroin, has evidently been acylated with ethyl acetate by means of sodium ethoxide; see ref. 6, pp. 72–73, and R. Woodward and E. Blout, *J. Am. Chem. Soc.*, **65**, 562 (1943).

(10) Melting points are uncorrected. Microanalyses are by Galbraith Laboratories, Knoxville, Tenn.

III *and* IV. *Table I.* To a stirred suspension of 0.10, 0.30, or 0.40 mole of sodium amide in 350 ml. of liquid ammonia[11] was added 13.5 g. (0.10 mole) of *p*-aminoacetophenone, followed after 30 min. by 0.10, 0.20, or 0.30 mole of methyl benzoate in an equal volume of dry ether during about 5 min. After stirring for 1.5 hr. more, the liquid ammonia was removed on the steam bath while dry ether was being added to maintain constant volume. The resulting ether suspension was stirred overnight.

In the experiment with equivalent amounts of the three reactants, the reaction mixture was filtered, and the solid triturated with 6*N* hydrochloric acid and dried to give 21.15 g. (89%) of *p*-benzoylaminoacetophenone (III), m.p. 199–201° (204–206° on Kofler Micro Hot Stage); reported m.p. 205°.[12] The melting point of this product was not depressed upon admixture with an authentic sample of III prepared from *p*-aminoacetophenone and benzoyl chloride by the Schotten-Baumann procedure.[12] From the hydrochloric acid wash there was recovered 1.4 g. (10%) of *p*-aminoacetophenone, m.p. 104–105°; reported m.p. 105°.[13]

In the experiments with excesses of sodium amide and methyl benzoate, the reaction mixture was filtered, and the solid washed with ether. The solid then was added to ice water, and the mixture acidified with acetic acid. The crude product was dissolved in 2 l. of hot methanol and an excess of a saturated aqueous solution of copper acetate was added.[11] The resulting precipitate was collected on a funnel and washed thoroughly with hot methanol to give the copper chelate of β-diketone IV, m.p. 362° (dec.). The copper salt was dissolved in concentrated sulfuric acid and the solution poured onto excess ice. The liberated β-diketone was taken up in chloroform, and the solution washed with saturated sodium bicarbonate solution and dried over magnesium sulfate. Removal of the solvent (water aspirator) gave 1-*p*-*N*-benzoylaminophenyl-3-phenylpropane-1,3-dione (IV), m.p. 181–183°. One recrystallization from 95% ethanol gave light yellow needles, m.p. 184.5–186°.

Anal. Calcd. for $C_{22}H_{17}O_3N$: C, 76.95; H, 4.99; N, 4.08. Found: C, 77.01; H, 4.71; N, 3.85.

The product (IV) gave a red enol test with ferric chloride.

Evaporation of the methanol mother liquor from the copper chelate precipitation gave a solid which, after being washed with water, yielded *p*-*N*-benzoylaminoacetophenone (III), m.p. and mixed m.p. 199–201° (204–206° on Kofler Micro Hot Stage). The yields of products are summarized in Table I.

Benzoylation of p-benzoylaminoacetophenone (III) *to form β-diketone* IV. To a stirred suspension of 0.15 mole of sodium amide in 350 ml. of liquid ammonia was added through a powder funnel 12 g. (0.05 mole) of *p*-benzoylaminoacetophenone (III), followed after 15 min. by 13.6 g. (0.10 mole) of methyl benzoate in an equal volume of dry ether during 20 min. After stirring for one hour more, the liquid ammonia was replaced by dry ether, and the resulting ether suspension was stirred at room temperature for 24 hr. The reaction mixture was added to ice water, and acidified with iced 6*N* hydrochloric acid. The precipitate (pink) was collected on a funnel, and dissolved in ethanol. To the ethanolic solution was added an aqueous solution of sufficient copper acetate to precipitate completely the copper chelate of the β-diketone.[11] The copper chelate was collected on a funnel, washed with hot ethanol, and decomposed with 10% sulfuric acid.[11] The liberated β-diketone was taken up in chloroform, washed with saturated sodium bicarbonate solution and dried over magnesium sulfate. The solvent was removed to give 8.9 g. (52%) of β-diketone IV, m.p. 179–182° and 184.5–186° after recrystallization from 95% ethanol.

Cyclization of β-diketone IV *with hydrazine to form pyrazole* V. To a solution of 1.7 g. (0.005 mole) of β-diketone IV in 250 ml. of methyl alcohol was added dropwise with swirling and heating on the steam bath 4.8 g. (0.15 mole) of 95% hydrazine. The heating was continued for 30 min. To the clear yellow solution was added gradually with swirling 100 ml. of water. The solution was then cooled in a dry ice–acetone bath to precipitate a white solid which was collected on a funnel and washed with water. There was obtained 1.5 g. (89%) of 3-*p*-*N*-benzoylaminophenyl-5-phenylpyrazole (V), m.p. 253–254.5°, and 0.1 g. of this product, m.p. 247–250°; total yield 96%.

Anal. Calcd. for $C_{22}H_{17}ON_3$: C, 77.85; H, 5.05; N, 12.38. Found: C, 77.60; H, 4.91; N, 12.10.

As expected, the product (V) gave a negative enol test with ferric chloride.

Cyclization of β-diketone IV *with urea to form pyrimidol* VI. To a mixture of 3.43 g. (0.01 mole) of β-diketone IV, 70 ml. of absolute ethanol, and 0.96 g. (0.016 mole) of urea was added 11 ml. of an absolute ethanol solution of 2.1*N* (0.024 mole) hydrogen chloride. The mixture was refluxed 8 days (protected from moisture by a drying tube). A clear orange solution resulted after 1 day, and an orange solid was present after the 8-day refluxing period. The mixture was cooled and filtered. The orange-yellow solid was washed with ether to give 1.15 g. of the monohydrochloride salt of 4-*p*-benzoylamino-6-phenylpyrimidol (VI), m.p. 283–293°. Addition of dry ether to the filtrate and washings precipitated more orange solid (apparently the dihydrochloride of VI) which started to decompose (turned red). This solid was immediately washed with saturated sodium bicarbonate solution to produce more (1.2 g.) of yellow salt VI, m.p. 260–280°. A mixed melting point of this sample with that melting at 283–293° was 268–276°. The total yield of the crude monohydrochloride of VI was 58%. Two recrystallizations from methanol raised the melting point to 297–299°.

Anal. Calcd. for $C_{23}H_{18}O_2N_3Cl$: C, 68.40; H, 4.49; N, 10.40. Found: C, 68.62; H, 4.51; N, 10.33.

1-p-N-Benzoylaminophenylpentane-1,3-dione (VII). This β-diketone was prepared essentially as described for IV employing 0.15 mole of sodium amide in 350 ml. of liquid ammonia, 11.9 g. (0.05 mole) of ketone III, and 10.2 g. (0.10 mole) of methyl propionate in 50 ml. of dry ether. After adding the solution of the ester during 20 min., the ammonia was immediately replaced by ether, and the resulting ether suspension stirred at room temperature for 24 hr. The reaction mixture was added to ice water and filtered. The solid consisted of 9.35 g. (79%) of recovered ketone III. Acidification of the filtrate precipitated 2.9 g. (20%) of 1-*p*-*N*-benzoylaminophenylpentane-1,3-dione (VII), m.p. 164–170°. One recrystallization from 95% ethanol raised the melting point (white needles) to 170.5–172°.

Anal. Calcd. for $C_{18}H_{17}O_3N$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.28; H, 5.98; N, 4.89.

1-p-N-Acetylaminophenyl-3-phenylpropane-1,3-dione (VIII). To a stirred suspension of 0.15 mole of sodium amide in 350 ml. of liquid ammonia was added 8.85 g. (0.05 mole) of *p*-*N*-acetylaminoacetophenone[14] followed 35 min. later by 13.6 g. (0.10 mole) of methyl benzoate in 50 ml. of dry ether over a period of 20 min. After replacing the ammonia by ether and refluxing the ether suspension for 24 hr., the reaction mixture was added to ice water, the ether layer separated and the water layer acidified. The β-diketone was collected in chloroform and isolated through its copper chelate (m.p. 313° dec.). There was obtained 2.85 g. (20%) of β-diketone VIII, m.p. 157–162°. One recrystallization from benzene raised the melting point (yellow needles) to 162–164°.

Anal. Calcd. for $C_{17}H_{15}O_3N$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.58; H, 5.58; N, 5.03.

1-p-N-Acetylaminophenylpentane-1,3-dione (IX). This β-diketone was prepared essentially as described for VIII

(11) See ref. 6, p. 122.

(12) F. Chattaway, *J. Chem. Soc.*, **85**, 390 (1904).

(13) V. Drewsen, *Ann.*, **212**, 162 (1882).

(14) See L. Fieser, *Experiments in Organic Chemistry*, Second Edition, D. C. Heath and Co., New York, N. Y., 1941, p. 165; and C. Derick and J. Bornmann, *J. Am. Chem. Soc.*, **35**, 1281 (1913).

employing methyl propionate instead of methyl benzoate. The copper chelate (m.p. 292° dec.) was acidified to give after recrystallization from benzene, 1.5 g. (13%) of β-diketone IX, m.p. 132–134°. One more recrystallization raised the melting point of IX to 135–136.5°.

Anal. Calcd. for $C_{13}H_{15}O_3N$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.76; H, 6.36; N, 5.92.

Benzoylation of p-hydroxyacetophenone to form β-diketone X. To a stirred suspension of 0.19 mole of sodium amide in 300 ml. of liquid ammonia[11] was added through a powder funnel 8.65 g. (0.063 mole) of *p*-hydroxyacetophenone. After 1 hr., 17.3 g. (0.127 mole) of methyl benzoate in an equal volume of dry ether was added over 15 min., and the liquid ammonia replaced by dry ether. The resulting ether suspension was stirred and refluxed for 2.5 hr. Dry benzene (250 ml.) was then added, and most of the ether distilled off. The resulting benzene suspension was refluxed for 24 hr. The mixture was added to crushed ice. After the ice had melted, the water layer was separated and filtered through Amend hyflo supercell (on a filter paper in a Büchner funnel) and then acidified with iced 6*N* hydrochloric acid. The precipitated oil was taken up in ether and dried over magnesium sulfate. The solvent was removed to give 13.3 g. of golden oil which gave, on recrystallization from benzene, 3.30 g. of 1-*p*-hydroxyphenyl-3-phenylpropane-1,3-dione (X), m.p. 146–153°. More (2.3 g.) of β-diketone X was isolated from the mother liquor through the copper chelate; total yield, 37%. Two recrystallizations from benzene raised the melting point of X to 154–156°.

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 75.33; H, 5.05.

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[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

Orientation in Friedel-Crafts Reactions with 2-Methoxy-1-methylnaphthalene

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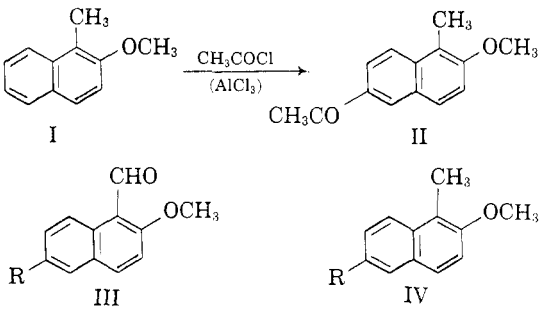
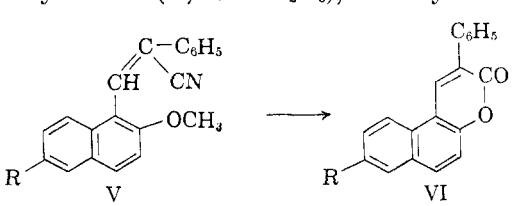
The acyl group in the Friedel-Crafts acetylation product (II) of 2-methoxy-1-methylnaphthalene in nitrobenzene is shown to enter position 6. The proof is based on the identity of the Kishner-Wolff reduction product of II and that of 1-formyl-2-methoxy-6-ethylnaphthalene, prepared by formylation of 2-methoxy-6-ethylnaphthalene. In the course of this work, a number of new homologs of 6-substituted naphthols, naphthaldehydes, naphthalene ketones, and their derivatives were prepared.

2-Methoxynaphthalene is known to undergo Friedel-Crafts acylations with aliphatic acid chlorides in nitrobenzene medium to give, as the isolated products, primarily the 6-acyl derivative, and some of the 8-acyl isomer; with carbon disulfide as solvent, substitution takes place predominantly in position 1.[1] It was of interest to investigate the behavior of 1-alkyl-2-naphthols in similar Friedel-Crafts reactions.

A convenient intermediate was 2-methoxy-1-methylnaphthalene (I), readily prepared by Kishner-Wolff reduction of 2-methoxy-1-naphthaldehyde. Acetylation of compound I, effected in nitrobenzene medium by Robinson and Weygand,[2] afforded a reaction product which, without proof of constitution, they considered to be 6-methoxy-5-methylacetonaphthone (II). Such a proof was now provided, by Kishner-Wolff reduction of this ketone to 6-ethyl-2-methoxy-1-methylnaphthalene (IV; R = C_2H_5), which was found to be identical with a sample prepared by Kishner-Wolff reduction of 6-ethyl-2-methoxy-1-naphthaldehyde (III; R = C_2H_5). The latter aldehyde was



readily prepared by formylation[3] of 6-ethyl-2-methoxynaphthalene with dimethylformamide in the presence of phosphorus oxychloride. The position taken by the formyl group in this reaction was ascertained by condensation of the aldehyde (III; R = C_2H_5) with benzyl cyanide to give the diarylacrylonitrile (V; R = C_2H_5), which yielded on



demethylation with pyridine hydrochloride 3′-

(1) L. Gattermann, R. Ehrhardt, and H. Maisch, *Ber.*, **23**, 1199 (1890); M. L. Rousset, *Bull. soc. chim. Belges*, [3] **15**, 633 (1896); R. R. Galle, *J. Gen. Chem. U.S.S.R.*, **8**, 402 (1938).

(2) R. Robinson and F. Weygand, *J. Chem. Soc.*, 389 (1941).

(3) For similar formylations of naphthol ethers with dimethylformamide, see N. P. Buu-Hoï and D. Lavit, *J. Chem. Soc.*, 2776 (1955).