supernatant fluids and purified by recrystallization, was found to contain no iodine.

Iodination of Casein.—The method was that of Reineke and Turner[7b] except that a solution of iodine was used instead of powdered iodine. To 1-g. portions of casein in 40 cc. of 0.7% sodium bicarbonate solutions containing 0, 0.00025, 0.0005 and 0.001 equivalent of 2-thiouracil was added 0.0014 equivalent of iodine in the form of a 0.28 *N* solution (in aqueous potassium iodide). One fifth of the iodine solution was added slowly every fifteen minutes with stirring which was continued for a total of four hours. To prevent oxidation of iodide by the 2-thiouracil disulfide present, acidification was avoided and the casein was precipitated with 2 *M* ammonium sulfate. After washing the protein free of iodide it was further purified by isoelectric precipitation followed by drying with acetone. Iodine determinations[5] on the purified protein gave the values shown in Table II.

Acknowledgment.—The measurement and interpretation of the ultraviolet spectral data were made by Paul H. Bell and J. Foster Bone of the Chemotherapy Division.

Summary

A study of the reaction between iodine and 2-thiouracil and related compounds has been carried out. The disulfides of the isomeric 2-thiouracil and 4-thiouracil were obtained by iodine oxidation. The former compound was very unstable and was isolated only as the disodium salt while the latter was obtained as the stable free acid.

The mercapto compounds have been found to react with several equivalents of iodine at *p*H 6.8. In the case of 2-thiouracil, this reaction rate was such that tyrosine and casein were protected against iodination by this compound. These facts support the hypothesis that the thio compounds may prevent thyroid hormone synthesis in the gland by blocking the iodination of hormone precursors.

STAMFORD, CONN. RECEIVED AUGUST 29, 1945

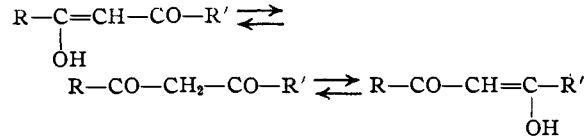
[CONTRIBUTION FROM THE THOMPSON LABORATORY OF THE PHILLIPS EXETER ACADEMY]

The Alkaline Cleavage of Unsymmetrical β-Diketones

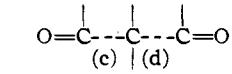
BY CHARLES L. BICKEL

β-Diketones are cleaved both by bases[1,2] and by acids.[2,3] Unsymmetrical β-diketones, R—CO—CH_2—CO—R′, can be cleaved in either of two ways and an analysis of the products of fission can be used to find the direction of the cleavage.

β-Diketones with terminal aryl groups are highly enolic and the solution of an unsymmetrical diaryl β-diketone may consist of an equilibrium mixture of the two enolic forms and the diketonic form



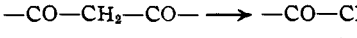
It is therefore possible that the direction of cleavage is determined by the proportion of the two enolic forms present in the mixture. Bradley and Robinson,[1] using aqueous sodium hydroxide, concluded (1) that the direction of cleavage is determined by the strength of the two possible aryl acids, the stronger acid being formed in the larger proportion, and (2) that the direction of enolization is not a factor in the fission. However, Adkins and co-workers,[2,3] using alcoholic hydrogen chloride, concluded that the acid cleavage is probably directed by the enolic forms and that the strength of the two acids has little to do with the course of the reaction. Most significant, however, is the final conclusion of Adkins,[4] based on a great deal of evidence, that "the relative lability of the two bonds (c) and (d)



in an unsymmetrical diketone seems to be approximately the same irrespective of whether the reaction is alcoholysis, hydrolysis or hydrogenolysis."

Bradley and Robinson's conclusions were based on the analysis of the mixture of the two aryl acids formed by alkaline cleavage. As will be shown in the experimental section of this paper, a rather large quantity of sodium chloride was present as an impurity in the mixtures which they analyzed. In consequence, their analytical results were in error and the validity of the conclusions based on these results is open to question. It therefore seemed advisable to check Bradley and Robinson's results[5] and also to attack the problem in a different way.

When one of the central hydrogen atoms of a β-diketone is replaced by an alkyl group, for example



the enolization is almost completely suppressed. Under the ordinary conditions, these alkylated compounds give no coloration with ferric chloride and do not yield copper salts.[6,7]

This paper is concerned with the alkaline cleavage of certain diaryl β-diketones and their methyl

(1) Bradley and Robinson, *J. Chem. Soc.*, **129**, 2356 (1926).
(2) Kutz and Adkins, THIS JOURNAL, **52**, 4036, 4391 (1930).
(3) Adkins, Kutz and Coffman, *ibid.*, **52**, 3212 (1930).
(4) Sprague and Adkins, *ibid.*, **56**, 2675 (1934).
(5) In the experimental part of this paper.
(6) Kohler, Tishler and Potter, THIS JOURNAL, **57**, 2518 (1935).
(7) Sprague and Adkins, *ibid.*, **56**, 2672 (1934).

derivatives. The methyl compounds are cleaved smoothly and completely by the method used by Bradley and Robinson. For example, methyldibenzoylmethane gives a quantitative yield of benzoic acid. Three unsymmetrical diketones (*p*-chlorodibenzoylmethane, *p*-bromodibenzoylmethane and *p*-methoxydibenzoylmethane) and their methyl derivatives were cleaved by one per cent. aqueous sodium hydroxide. The results are shown in Table I.

TABLE I

Substance	X-$C_6H_4CO_2H$,[a] moles/100 moles diketone
p-$ClC_6H_4COCH_2COC_6H_5$	60[b]
p-$BrC_6H_4COCH_2COC_6H_5$	62
p-$CH_3OC_6H_4COCH_2COC_6H_5$	42[c]
p-$ClC_6H_4COCH(CH_3)COC_6H_5$	63
p-$BrC_6H_4COCH(CH_3)COC_6H_5$	62
p-$CH_3OC_6H_4COCH(CH_3)COC_6H_5$	41

[a] The para substituent is represented by X. [b] Bradley and Robinson reported 63.7 moles of *p*-chlorobenzoic acid but their analytical results indicate 74 moles of the acid. [c] Bradley and Robinson reported 50.2 moles of anisic acid.

The results indicate clearly that the cleavage takes the same course whether the methyl group is present or not. It is therefore apparent that the enolization of the diketone is not a deciding factor in the cleavage unless the methylated diketone is easily and completely enolized in the presence of the alkali. Such a possibility appears to be untenable but cannot be ruled out *a priori* since these substances can be induced to enolize under the proper stimulus.[6,8,9]

The effect of the amount and the concentration of alkali on the extent and direction of cleavage was also examined in the case of *p*-bromodibenzoylmethane. The results appear in Table II.

TABLE II

Concn. of NaOH	Moles NaOH/mole diketone	Moles *p*-$BrC_6H_4CO_2H$/100 moles diketone
1%	0.5	59
1%	1.0	62
1%	2.5	64
10%	10	65
..	2.5[a]	61

[a] The sodium hydroxide solution was added dropwise to a suspension of the diketone in boiling water.

An increase in the amount of alkali does result in a slightly larger proportion of *p*-bromobenzoic acid but it is evident that neither the amount nor the concentration of alkali has a pronounced effect on the direction of cleavage. This evidence supports the contention of Bradley and Robinson that alkaline cleavage takes place through the ketonic rather than the enolic forms of the diketone.

Experimental

Preparation of the Diketones.—Dibenzoylmethane, *p*-chlorodibenzoylmethane, *p*-bromodibenzoylmethane and *p*-methoxydibenzoylmethane were prepared by brominating the benzalacetophenones, treating the dibromides with methyl alcoholic potassium hydroxide, acidifying the resulting products and purifying the diketones by way of the copper salts. The properties of these compounds have been described elsewhere.

Preparation of the Methyl Derivatives.—The methyl derivatives of the above diketones were prepared by the method outlined in a previous paper.[10] In each case the yield was about 80%. Methyl dibenzoylmethane[11] and methyl-*p*-methoxydibenzoylmethane[10] have been prepared previously.

Methyl-*p*-chlorodibenzoylmethane is soluble in the common solvents but only sparingly soluble in petroleum ether. It crystallizes as colorless needles and melts at 99°. A methyl alcoholic solution of the substance gives no ferric chloride coloration during a period of twelve hours. An ether solution shaken with saturated cupric acetate solution for four days gives no evidence of a copper salt.

Anal. Calcd. for $C_{16}H_{13}O_2Cl$: C, 70.5; H, 4.8. Found: C, 70.4; H, 4.8.

Methyl-*p*-bromodibenzoylmethane resembles the *p*-chloro compound but it melts at 83°.

Anal. Calcd. for $C_{16}H_{13}O_2Br$: C, 60.6; H, 4.1. Found: C, 60.6; H, 4.0.

Bradley and Robinson's Method of Analysis.—After hydrolysis was complete, Bradley and Robinson extracted the neutral material (the acetophenones) with ether, concentrated the aqueous solution to 5–7 cc., acidified at 0° with 32% hydrochloric acid, collected the precipitate and washed it with ice-cold 10% hydrochloric acid. The solid was then dried to constant weight and a sample analyzed.

In order to check the above, 1.00 g. of *p*-chlorobenzoic acid and 0.50 g. of benzoic acid were dissolved in 42 cc. of 1% sodium hydroxide solution. The solution was extracted with ether; the ether extract contained no organic material. The aqueous solution was then boiled down to 7 cc., acidified with 2 cc. of 32% hydrochloric acid and kept at 0° for one hour. The solid was filtered, washed with 30 cc. of ice-cold 10% hydrochloric acid, air dried for two days and finally brought to constant weight over solid potassium hydroxide in a desiccator. The weight of solid was 1.63 g.

The above solid was powdered, leached with 50 cc. of distilled water, filtered and washed with 50 cc. of distilled water. Addition of 5 cc. of normal silver nitrate solution to the filtrate and washings gave 0.44 g. of silver chloride, which is equivalent to 0.18 g. of sodium chloride.

Exactly one gram of *p*-chlorobenzoic acid was recovered from the leached solid. Thus, by difference, only 0.45 g. of benzoic acid was contained in the dried solid and 0.05 g. of benzoic acid was lost during the filtration. By analysis, the mixture contained 20.7% chlorine whereas the original mixture of acids contained only 15.2% chlorine. The difference is due to the sodium chloride.

Method of Cleavage and Analysis.—The general procedure for all of the substances is outlined below while the individual compounds and the results are listed in Table III.

The diketone was refluxed with aqueous sodium hydroxide until cleavage was complete (five to eight hours). A slight excess of sodium hydroxide was then added, the mixture cooled and extracted with ether to remove the acetophenones or propiophenones. The ether-extracted aqueous solution of the acid products was heated to remove the dissolved ether, diluted with distilled water to a volume which would dissolve all of the benzoic acid, cooled and a slight excess of concentrated hydrochloric acid added. After standing overnight, the substituted benzoic acid was filtered off and dried to constant weight. A correction was applied for the solubility of the acid in the filtrate.

The filtrate, which contained the benzoic acid and a small

(8) Bartlett and Cohen, *J. Org. Chem.*, **4**, 88-94 (1939).
(9) Weygand, *Ber.*, **61**, 687 (1928).
(10) Bickel, THIS JOURNAL, **67**, 2045 (1945).
(11) Abell, *J. Chem. Soc.*, **101**, 989 (1912).

amount of the substituted benzoic acid, was extracted with ether. The ether solution was dried over anhydrous sodium sulfate, filtered, the ether removed and the solid residue heated to constant weight. A correction was applied for the presence of the substituted benzoic acid.

In all cases where at least one mole of sodium hydroxide was used per mole of diketone, the acids obtained accounted for at least 95% of the diketone used. In none of these cases was any diketone recovered from the ether extract.

In the case of methyl dibenzoylmethane the above procedure was modified since benzoic acid is the only acid product. The whole of the acidified solution was extracted with ether and the benzoic acid isolated as above from the ether solution.

TABLE III

Substance[a]	Wt., g.	NaOH soln., cc.	NaOH soln., %	X-$C_6H_4CO_2H$, g.	$C_6H_5CO_2H$, g.	Diketone accounted for as acids, %
I	2	35	1	..	1.02	100
II	3	50	1	0.72	0.79	95
III	3	48	1	0.70	.80	99
IV	3	50	1	1.06	.56	98
V	3	47	1	1.06	.49	98
VI	3	20	1	0.66	.31	59[c]
VI	3	40	1	1.22	.45	99
VI	3	100	1	1.22	.42	96
VI	3	40	10	1.28	.42	99
VI	3	added dropwise[b]		1.15	.45	96
VII	3	39	1	1.17	.43	98

[a] I, Methyldibenzoylmethane; II, *p*-methoxydibenzoylmethane; III, methyl *p*-methoxydibenzoylmethane; IV, *p*-chlorodibenzoylmethane; V, methyl *p*-chlorodibenzoylmethane; VI, *p*-bromodibenzoylmethane; VII, methyl *p*-bromodibenzoylmethane. [b] Thirty-seven per cent. of the diketone was recovered unchanged, thus accounting for 96% of the starting material. [c] Sixty cc. of solution containing one gram of sodium hydroxide was added over a period of five hours to the diketone refluxed with 40 cc. of distilled water.

Summary

The alkaline cleavage of three unsymmetrical diaryl beta diketones and their monomethyl derivatives is reported. The introduction of the methyl group does not affect the direction of the cleavage.

Varying amounts and concentrations of sodium hydroxide solution had little effect on the direction of cleavage of *p*-bromodibenzoylmethane.

The results support the conclusion of Bradley and Robinson that the alkaline cleavage of beta diketones is concerned with the ketonic form rather than the enolic forms.

EXETER, NEW HAMPSHIRE RECEIVED OCTOBER 3, 1945

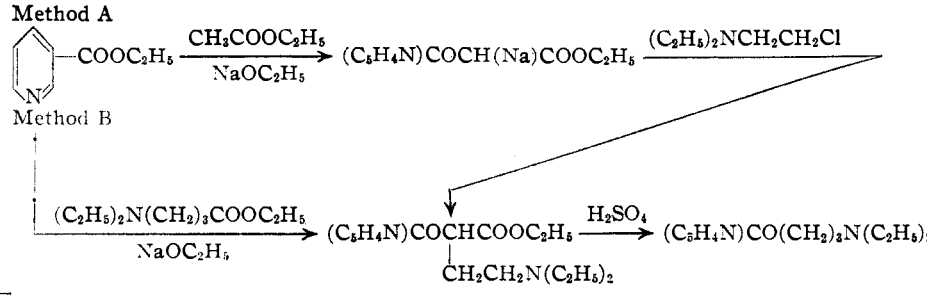
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

Synthesis of Antimalarials. III.[1] The Synthesis of Certain Quinacrine Analogs Having N-Heterocyclic Groups in the α-Position of the Side Chain[2]

BY MELVIN S. BLOOM, DAVID S. BRESLOW AND CHARLES R. HAUSER

In continuation of our work on the preparation of quinacrine analogs having various α-substituents in the side chain,[1] we have synthesized four new diamines of the type $RCH(NH_2)CH_2CH_2CH_2N(C_2H_5)_2$ in which R is α-, β- or γ-pyridyl or 2-pyrazyl. Two of these compounds, in which R is α- and γ-pyridyl, have been coupled with 2-methoxy-6,9-dichloroacridine to form quinacrine analogs.

The diamines were prepared by the reduction of the oximes of the corresponding ketones, which were synthesized by the usual[1a] acetoacetic ester method (Method A) or, preferably, by a modification of this method (Method B). In Method A, pyridyl esters were condensed with ethyl acetate[3,4,5] and the resulting pyridoylacetic esters were alkylated with β-diethylaminoethyl chloride and cleaved. In Method B, the heterocyclic esters were condensed with ethyl γ-diethylaminobutyrate and the resulting β-keto esters were cleaved. These two methods may be illustrated by the preparation of 4-diethylamino-1-(β-pyridyl)-1-aminobutane starting from ethyl nicotinate



Method A has given only poor to fair yields of

(1) For previous papers of this series see (a) Breslow, Yost, Walker and Hauser, THIS JOURNAL, **66**, 1921 (1944); (b) Breslow, Walker, Yost and Hauser, *ibid.*, **67**, 1472 (1945).

(2) The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Duke University.

(3) Hurd and Webb, THIS JOURNAL, **49**, 546 (1927).

(4) Pinner, *Ber.*, **34**, 4234 (1901).

(5) Koelsch, *J. Org. Chem.*, **10**, 34 (1945); THIS JOURNAL, **65**, 2460 (1943).