[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

THE REACTION OF ORGANIC HALIDES WITH PIPERIDINE. II. CERTAIN ALPHA-BROMO-BETA-KETONIC ESTERS

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As a preliminary to some work which was contemplated in this Laboratory it was necessary to determine the course of the reaction of secondary amines, such as piperidine, with the three esters, ethyl α-bromobenzoylacetate, ethyl α-bromo-α-benzoylpropionate and ethyl α-bromo-α-phenylbenzoylacetate.

A study of the reaction of piperidine with a variety of alkyl bromides has been reported.[1] In this work it was found that the primary bromides were very much more reactive than the secondary or tertiary bromides and that the primary and secondary bromides, with the exception of cyclohexyl bromide, reacted with the piperidine to form tertiary amines, while cyclohexyl bromide and the tertiary bromides gave no tertiary amines but lost hydrogen bromide under the influence of the piperidine. The bromo esters mentioned above would seem to offer an interesting extension of this type of study, for the reason that they are secondary and tertiary bromides the reactivity of which would be considerably enhanced by the associated groups of each molecule.

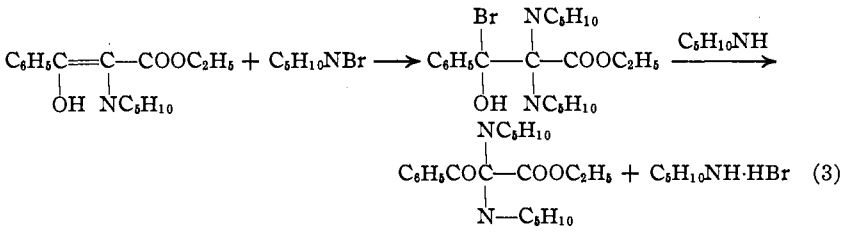
No attempt was made to carry out the reaction of these bromo esters with piperidine under similar conditions. Rather those conditions which produced a quite complete reaction as indicated by the yield of piperidine hydrobromide were found and used in each case. It was found that the optimum ratio of reactants was one mole of the bromo ester to three moles of piperidine.

Ethyl α-bromobenzoylacetate reacted rapidly with piperidine in dry ether and after a few hours 90% of the theoretical quantity of piperidine hydrobromide was precipitated. From the ethereal solution ethylbenzoyl acetate and a compound of the molecular formula, $C_{21}H_{30}O_3N_2$, which proved to be ethyl α,α-dipiperidinobenzoylacetate were isolated. The amounts of these two compounds which were obtained represented in the case of the former, 30% and in the case of the latter, 39% of the original bromo ester. Their formation may be illustrated by the following reactions

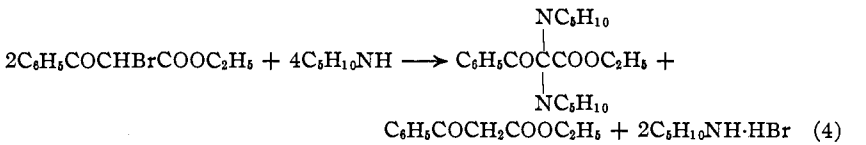
$$C_6H_5COCHBrCOOC_2H_5 + C_5H_{10}NH \longrightarrow C_5H_{10}NBr + C_6H_5COCH_2COOC_2H_5 \quad (1)$$

$$C_6H_5COCHBrCOOC_2H_5 + 2C_5H_{10}NH \longrightarrow C_5H_{10}NH\cdot HBr + C_6H_5CO\underset{\displaystyle NC_5H_{10}}{\underset{|}{C}H}COOC_2H_5 \quad (2)$$

[1] Semb and McElvain, THIS JOURNAL, 53, 690 (1931).

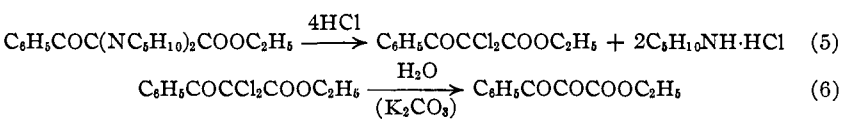


The sum of reactions 1, 2 and 3 gives the net reaction as



The bromination of piperidine by the bromo ester with the formation of ethyl benzoyl acetate and N-bromopiperidine (Reaction 1) is analogous to the behavior of diphenylbenzoylmethyl bromide as a brominating agent recently reported by Koelsch.[2] Reaction 2 is the normal reaction that would be expected between a secondary halide and piperidine.[1] Reaction 3 which involves the addition of N-bromopiperidine to the enol form of the monopiperidino compound seems probable from the work of Foldi,[3] who has shown that N-halogenated amines and amides add readily to the olefinic double bond. Such an addition product would be directly decomposed by the excess of piperidine present into the dipiperidino compound and piperidine hydrobromide.

The structure of the ethyl α,α-dipiperidinobenzoylacetate is shown by the following facts. As mentioned above, analyses and molecular weight determinations show it to have a molecular formula of $C_{21}H_{30}O_3N_2$. On alkaline hydrolysis it was converted into benzoic acid, ethyl alcohol and two moles of piperidine for each mole of the original compound. An ethereal solution of one mole of $C_{21}H_{30}O_3N_2$ when treated with dry hydrogen chloride yielded two moles of piperidine hydrochloride. From the resultant ethereal solution, after washing with potassium carbonate, ethyl benzoylglyoxalate, $C_6H_5COCOCOOC_2H_5$, was obtained. The formation of this latter compound may be explained by the following reactions:



Finally ethyl α,α-dipiperidinobenzoylacetate was prepared by the action of piperidine on ethyl α,α-dibromobenzoylacetate and was found to be

[2] (a) Koelsch, THIS JOURNAL, 53, 1147 (1931); (b) *cf.* also Goldschmidt and Nagel, *Ber.*, 63, 1212 (1930).

[3] Foldi, *ibid.*, 63, 2257 (1930).

identical with the compound obtained from the reaction of piperidine with ethyl α-bromobenzoylacetate.

The reaction of ethyl α-bromo-α-benzoylpropionate and piperidine in ether gave, after about seven hours, a 75% yield of piperidine hydrobromide. A longer period of reaction in ether solution did not increase the yield of this salt, but if the ether was distilled off and the remaining reactants heated at the temperature of the steam-bath for one hour, an additional 23% yield of piperidine hydrobromide was obtained. When the reaction mixture was worked up ethyl α-benzoylpropionate and a compound, melting at 132–133° and having the molecular formula $C_{22}H_{32}O_3N_2$ were isolated in yields that represented 35 and 28%, respectively, of the original bromo ester. The latter compound had a neutral equivalent of 187 and was ethyl α-benzoyl-α,β-dipiperidinopropionate. The reactions by which these products were formed may be illustrated thus

$$C_6H_5COCBr(CH_3)COOC_2H_5 + C_5H_{10}NH \longrightarrow C_6H_5COCH(CH_3)COOC_2H_5 + C_5H_{10}NBr \quad (7)$$

$$C_6H_5COCBr(CH_3)COOC_2H_5 + C_5H_{10}NH \longrightarrow C_6H_5COC(=CH_2)COOC_2H_5 + C_5H_{10}NH\cdot HBr \quad (8)$$

$$C_6H_5COC(=CH_2)-COOC_2H_5 + C_5H_{10}NBr \longrightarrow C_6H_5COC(CH_2Br)(NC_5H_{10})COOC_2H_5 \quad (9)$$

$$C_6H_5COC(CH_2Br)(NC_5H_{10})COOC_2H_5 + 2C_5H_{10}NH \longrightarrow C_6H_5COC(CH_2NC_5H_{10})(NC_5H_{10})COOC_2H_5 + C_5H_{10}NH\cdot HBr \quad (10)$$

The reactions 7, 8, 9 and 10 give as the net reaction,

$$2C_6H_5COCBr(CH_3)COOC_2H_5 + 4C_5H_{10}NH \longrightarrow C_6H_5COCH(CH_3)COOC_2H_5 + C_6H_5COC(CH_2NC_5H_{10})(NC_5H_{10})COOC_2H_5 + 2C_5H_{10}NH\cdot HBr \quad (11)$$

In reaction 7 the ethyl α-benzoylpropionate is formed as a result of the brominating action of the bromo ester. The loss of halogen acid from the ester (reaction 8) would be expected[1] from the fact that it is tertiary halide and the addition of N-bromopiperidine to the benzoylacrylic ester thus formed is analogous to reaction 3 and the reactions reported by Foldi.[3] The fact that the last portion of the halogen could not be obtained as piperidine hydrobromide until the temperature of reaction was raised to 100°, indicates that the bromo compound formed in reaction 9 is an unactivated primary bromide.[1]

Ethyl α-phenyl-α-bromobenzoyl acetate gave no precipitate of piperidine hydrobromide when refluxed in an ether solution of piperidine for seven hours. When, however, the ether was removed and the residue heated for two hours on a steam-bath a 95% yield of piperidine hydro-

bromide was obtained. When this salt was removed and the remainder of the reaction mixture worked up, a 10% yield of the ethyl α-phenylbenzoylacetate and a 60% yield of ethyl benzoate together with a small amount of ethyl phenylacetate were obtained. The residue from the distillation of these esters which had been extracted with both acid and alkali gave piperidine on hydrolysis. These results indicate that the bromo ester, by brominating the piperidine, is converted into the ethyl α-phenylbenzoylacetate, which reacts with piperidine under the conditions used to form an amide. The alcohol liberated in the latter reaction then splits the keto amide and keto ester. These reactions may be illustrated as

$$C_6H_5COCBr(C_6H_5)COOC_2H_5 + C_5H_{10}NH \longrightarrow C_6H_5COCH(C_6H_5)COOC_2H_5 + C_5H_{10}NBr \quad (12)$$

$$C_6H_5COCH(C_6H_5)COOC_2H_5 + C_5H_{10}NH \longrightarrow C_6H_5COCH(C_6H_5)CONC_5H_{10} + C_2H_5OH \longrightarrow C_6H_5COOC_2H_5 + C_6H_5CH_2CONC_5H_{10} \quad (13)$$

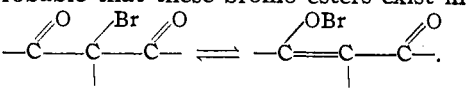
$$C_6H_5COCH(C_6H_5)COOC_2H_5 + C_2H_5OH \longrightarrow C_6H_5COOC_2H_5 + C_6H_5CH_2COOC_2H_5 \quad (14)$$

The piperidine hydrobromide which is obtained from the reaction quite probably results from a disproportionation of N-bromopiperidine. Lellmann[4] has shown that N-chloropiperidine in the presence of alkali loses hydrogen chloride to form tetrahydropyridine and piperidine hydrochloride and that on heating it disproportionates into N-chlorotetrahydropyridine and piperidine hydrochloride. It seems reasonable that N-bromopiperidine would follow a similar reaction course under the conditions used in the work now described. The following reaction, then, would explain the elimination of practically all of the bromine from the reactants as piperidine hydrobromide

$$C_5H_{10}NBr + C_5H_{10}NH \longrightarrow C_5H_9N + C_5H_{10}NH\cdot HBr \quad (15)$$

The action of piperidine on the three α-bromo-β-keto esters as described above is of some interest in connection with the previous work on the relation of structure to the course of the reaction of organic halides with piperidine. The replacement of the secondary halogen of ethyl α-bromobenzoylacetate to form a tertiary amine and of the tertiary halogen of ethyl α-bromo-α-benzoylpropionate to form the intermediate α-benzoylacrylic ester parallels the behavior of the simple secondary and tertiary bromides with piperidine.[1] The brominating action of each of the bromo esters is a separate and distinct competing reaction which has no counterpart in the case of the alkyl bromides. Ethyl α-phenyl-α-bromobenzoylacetate is a tertiary bromide which cannot lose hydrogen bromide. It is by far the least reactive of the three bromo esters studied and when it is forced into reaction with the secondary amine it shows only the brominating action. Professor C. S. Marvel of the University of Illinois has suggested to the authors that the brominating action of this type of bromo ester may be due to a hypobromite structure. If such be the case it would

[4] Lellmann, *Ber.*, **21**, 1924 (1888).

seem quite probable that these bromo esters exist in the following tautomeric forms,  .

Experimental

Materials Used.—The sodium ethoxide was prepared and the various esters which were used were purified by the procedure given by McElvain.[5] Piperidine was prepared by the catalytic reduction of purified pyridine in the presence of nickel.[6] Ethyl benzoylacetate was prepared by the procedure of Claisen and Lowman.[7] Ethyl α-benzoylpropionate was prepared in a similar manner by the condensation of ethyl benzoate with the ethyl propionate. This compound has been prepared previously[8] by the methylation of ethyl benzoylacetate.

Cyanodesoxybenzoin.—This compound has been prepared by Walther and Schickler[9] by the direct condensation of ethyl benzoate with benzyl cyanide. They obtained a yield of only 10% of the theoretical. In the present work the following procedure, which gave a yield of 47% of cyanodesoxybenzoin, was used. A mixture of 80 g. (1 mol) of benzyl cyanide, 300 g. (3 mols) of ethyl benzoate and 46 g. of sodium ethoxide were placed in a flask equipped with an efficient mechanical stirrer and a condenser set for downward distillation. The mixture was stirred rapidly and gradually heated to 220° on an oil-bath. The alcohol distilled as formed and was collected. At the end of seven hours no more alcohol came over and the mixture was allowed to cool. A yield of 29 g. (48.5%) of alcohol was obtained. The red gelatinous mass in the flask was shaken with a mixture of ice water and ether until all the salt had dissolved. The ether layer was separated and the water layer again extracted with ether. After separation of the ether layer, the aqueous portion was acidified with dilute sulfuric acid. A mixture of benzoic acid and cyanodesoxybenzoin separated as an oil which later solidified. The solid mixture was filtered and recrystallized from 95% alcohol. The remaining benzoic acid was effectively removed by suspending the solid in a saturated solution of sodium bicarbonate and shaking vigorously. The undissolved cyanodesoxybenzoin was filtered and washed with water. After drying it weighed 71 g. (47.5%) and melted at 89–90°.

Ethyl α-Phenylbenzoylacetate.—This compound has been prepared by Walther and Schickler[9] and by Scheibler[10] by the alcoholysis of cyanodesoxybenzoin. Since neither of these investigators gave satisfactory experimental details or yield of product, the following method of preparation, which was used in the present work, is given. A solution of 55 g. of cyanodesoxybenzoin in 300 g. of absolute alcohol was cooled to 0° and saturated with dry hydrogen chloride. After standing overnight at room temperature the alcohol was removed by distillation under reduced pressure and the solid imino ester hydrochloride taken up in 100 cc. of alcohol to which 10 cc. of water had been added. The resulting mixture was refluxed for one hour, after which it was poured into 3 liters of ice water. The ethyl α-phenylbenzoylacetate separated out and was filtered. After recrystallization from 95% alcohol it melted at 89–90°. The yield was 41.8 g. (63%).

[5] McElvain, THIS JOURNAL, 51, 3124 (1929).

[6] The authors are indebted to Messrs. K. A. Folkers and R. A. Connor for this preparation.

[7] Claisen and Lowman, *Ber.*, **20**, 651 (1887).

[8] Perkin and Calmen, *J. Chem. Soc.*, **49**, 156 (1886).

[9] Walther and Schickler, *J. prakt. Chem.*, [2] **55**, 308 (1897).

[10] Scheibler, *Ber.*, **63**, 1564 (1930).

Bromination of the Keto Esters.—Each of the keto esters mentioned above was brominated by the gradual addition of the theoretical quantity of bromine to the ester in boiling carbon tetrachloride solution. After the bromine had been absorbed the solvent was removed by distillation and the residue distilled under diminished pressure. The yields, physical constants and analyses of the bromo esters are summarized in the following table.

Compound, ethyl	Yield, %	B. p. (1 mm.), °C.	d_{20}^{20}	n_D^{20}	Analyses, % Br Calcd.	Found
α-Bromo benzoylacetate	90	135–137	1.4092	1.5470	29.49	29.40
α-Dibromo benzoylacetate	71	153–154	1.7127	1.5703	45.71	43.91[a]
α-Bromo benzoylpropionate	79	148–150	1.3499	1.5340	28.07	28.27
α-Bromophenylbenzoylacetate[b]	85	189–190	....	....	23.07	24.02

[a] The analyses for this compound were low due to the fact that it was not possible to separate all of the monobromo ester from it by fractional distillation. [b] All analyses of this compound were high because of traces of hydrogen bromide which could not be removed. This bromo ester has not been described heretofore in the literature although the possibility of its formation has been mentioned by Scheibler.[10] It is quite unstable and appears to decompose in a few hours. It is a heavy, yellow, viscous oil with a slight lachrymatory effect.

Reaction of the α-Bromo-β-keto Esters with Piperidine.—In the case of ethyl α-bromobenzoylacetate a solution of 100 g. (1 mol) of the bromo ester in 100 cc. of ether was added slowly from a dropping funnel to a solution of 97 g. (3 mols) of piperidine in 300 cc. of ether contained in a 1-liter flask which was fitted with an efficient reflux condenser. The reaction was sufficiently exothermic to cause vigorous boiling of the ether at the beginning of the addition. An immediate precipitation of piperidine hydrobromide occurred. After stirring for seven hours the salt was filtered, dried and weighed. A yield of 57 g. of the hydrobromide, representing 90% of the bromine in the reaction mixture, was obtained. The ether was distilled from the filtrate and the last traces removed by a water pump. A pasty yellow mass, consisting of a crystalline substance and an oil, remained in the flask. To this residue 100 cc. of 95% alcohol was added whereupon the oil went into solution and the crystals remained undissolved. The latter were filtered off and recrystallized from light petroleum ether. A yield of 53.25 g. of pale yellow crystals which melted at 131–132° was obtained. The alcoholic filtrate was evaporated under reduced pressure and the residue again taken up in ether and the ethereal solution washed first with dilute sulfuric acid then with dilute potassium carbonate solution. The solution was dried with sodium sulfate, the ether evaporated and the residue distilled under reduced pressure. A yield of 22.1 g. of ethyl benzoylacetate boiling at 118–120° (1 mm.) was obtained.

The pale yellow crystals which were insoluble in alcohol were identified as ethyl α,α-dipiperidinobenzoylacetate. This compound was basic and dissolved readily in dilute hydrochloric acid but could not be recovered when the solution was made alkaline. Long boiling with 30% alkali and steam distillation gave 93% of *two* moles of piperidine for each mole of the solid compound. This piperidine was isolated as the benzene sulfonamide, m. p. 94°. Benzoic acid and ethyl alcohol were also obtained from this hydrolysis. On passing dry hydrogen chloride into an ethereal solution of 10 g. of the substance, 6.6 g. of piperidine hydrochloride was obtained. This amount of piperidine hydrochloride indicated that the two piperidine nuclei had been split out of the molecule and recovered in a 98% yield.

Nothing definite could be isolated from the ethereal solution directly after the treatment with hydrogen chloride except a small amount of a viscous lachrymatory oil, but

when the ethereal solution was washed with potassium carbonate solution, evaporation of the ether and distillation yielded 4.5 g. of a yellow-orange oil boiling at 128–130° (1 mm.). This oil was identified as ethyl benzoylglyoxalate. On hydrolysis with 15% hydrochloric acid, 0.840 g. of the oil gave 0.47 g. of benzoic acid and 0.1754 g. of carbon dioxide which represent 95 and 98% yields, respectively. The identification was completed by the preparation of the mono-oxime, which melted at 123°.[11]

Ethyl α,α-dipiperidinobenzoylacetate was prepared also from ethyl α,α-dibromobenzoylacetate in the following manner. A solution of 5 g. of the dibromo ester in 50 cc. of ether was treated with 6 g. of piperidine and the mixture refluxed for fifty hours. After this time the piperidine hydrobromide was filtered off and from the ethereal solution 1.6 g. of a compound was isolated which proved to be identical with the ethyl α,α-dipiperidinobenzoylacetate obtained above by the action of piperidine on the ethyl α-bromobenzoylacetate.

In the case of ethyl α-bromo-α-benzoylpropionate a solution of 43.5 g. (1 mol) of the bromo ester and 39 g. (3 mols) of piperidine in 500 cc. of ether was placed in a 1-liter flask fitted with a reflux condenser. Precipitation of piperidine hydrobromide began immediately. After stirring for seven hours the hydrobromide was filtered and weighed. About 75% of the theoretical amount was formed at that time. Continued stirring of the solution gave no further precipitation of piperidine hydrobromide, so the flask was transferred to a steam-bath and the ether removed by distillation. The residue was heated on the steam-bath for one hour and again taken up in ether. Another portion of piperidine hydrobromide precipitated and was filtered from the solution. The total yield of this salt was 25 g., which represented 98% of the bromine in the original solution. When the ether was distilled from the solution, a pasty yellow mass remained in the flask. The addition of 100 cc. of alcohol caused the oily portion of this residue to dissolve, leaving a crystalline substance suspended in the solution. These crystals were filtered off and recrystallized from 95% alcohol. A yield of 16 g. of pale yellow crystals which melted at 132–133° was obtained. Removal of the alcohol from the filtrate gave a heavy red oil which was taken up in ether and washed with dilute sulfuric acid and then with dilute potassium carbonate solution. On evaporation of the ether and distillation of the oily residue 11 g. of ethyl α-benzoylpropionate was obtained.

The yellow crystals were identified as ethyl α,β-dipiperidino-α-benzoylpropionate. On hydrolysis they gave benzoic acid and piperidine. The substance was basic and had a neutral equivalent of 187. The molecular weight as determined in benzene was 366 (calcd. 372) which together with the neutral equivalent showed it to be a diacid base.

The yields, melting points and analytical data of the products obtained from the reaction of piperidine and ethyl α-bromobenzoylacetate and ethyl α-bromo-α-benzoylpropionate are summarized in the following table.

Compound, ethyl ( )-dipiperidino-benzoyl-	Yield,[a] %	M. p., °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
α,α-acetate	39	131–132	70.31	8.37	7.82	70.14	8.31	7.37
α,β-propionate	28	132–133	70.95	8.60	7.52	70.60	8.64	7.91

The unbrominated esters, ethyl benzoylacetate and ethyl α-benzoylpropionate, were prepared in yields of 30 and 35%, respectively,[a] based on the amounts of bromo ester put into the reaction.

[a] Based on the amount of bromo ester put into the reaction.

In the case of ethyl α-bromo-α-phenylbenzoylacetate a solution of 22.1 g. (1 mol) of the bromo ester and 16 g. (3 mols) of piperidine in 300 cc. of ether was stirred in a

[11] Wahl, *Bull. soc. chim.*, [4] **1**, 461 (1907).

flask at room temperature for seven hours under a reflux condenser. No apparent reaction could be detected. The flask was placed on a steam-bath, the ether distilled and the residue heated for two hours. It was again taken up in ether and the precipitated piperidine hydrobromide removed by filtration. The yield of this salt was 10 g. (representing 95% of the bromine in the original bromo ester). The solution was washed with dilute sulfuric acid and then with dilute potassium carbonate. The ether solution was dried, the ether removed by distillation, and the residue fractionated. This fractionation yielded 1.7 g. of ethyl α-phenylbenzoylacetate, m. p. 89–90°, 6 g. of ethyl benzoate and 2–3 g. of ethyl phenylacetate. The two latter esters were mixed when distilled. They were identified by hydrolysis and fractional crystallization of the acids from water. The yield of ethyl benzoate was calculated from the amount of benzoic acid obtained. The residue from the distillation of the above esters was hydrolyzed with 30% potassium hydroxide and the mixture steam distilled. A small quantity of piperidine was obtained. This yield of piperidine from the hydrolysis of the residue indicated that amide formation had taken place in the reaction mixture. Amide formation was demonstrated by the fact that when 5 g. of the unbrominated ester was heated with 5 g. of piperidine on the steam-bath for two hours without a solvent and the reaction mixture worked up in the same manner as that described above, 1.2 g. of a mixture of ethyl benzoate and ethyl phenylacetate was obtained. Hydrolysis of the residue from the distillation with 30% potassium hydroxide gave 0.3 g. of piperidine after steam distillation. This yield represents 20% of amide formation.

Summary

The reactions of piperidine with ethyl α-bromobenzoylacetate, ethyl α-bromo-α-benzoylpropionate and ethyl α-bromo-α-phenylbenzoylacetate have been studied. In the case of each of the first two of these bromo esters the unbrominated ester and a dipiperidino compound were the reaction products. The former product results from the brominating action of the bromo ester while the formation of the latter product is best explained as a secondary reaction product resulting from the action of the brominated piperidine on the normal reaction product of piperidine and a secondary or tertiary bromide. Ethyl α-bromo-α-phenylbenzoylacetate, a tertiary bromide which cannot lose hydrogen bromide, reacts only as a brominating agent since the unbrominated ester and its cleavage products were the only products obtained from the reaction of this bromo ester with piperidine.

Improved methods are given for the preparation of cyanodesoxybenzoin and ethyl α-phenylbenzoylacetate. The following compounds have been prepared and described for the first time: ethyl α-bromobenzoylacetate, ethyl α-bromo-α-benzoylpropionate, ethyl α-bromo-α-phenylbenzoylacetate, ethyl α,α-dibromobenzoylacetate, ethyl α,α-dipiperidinobenzoylacetate and ethyl α,β-dipiperidino-α-benzoylpropionate.

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