

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF KANSAS]

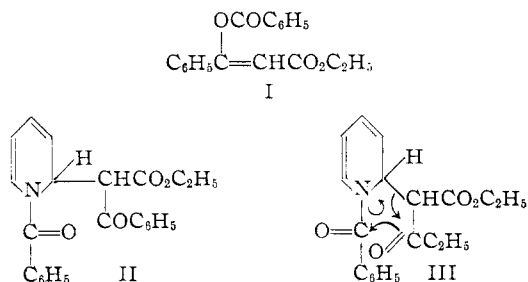
Benzoylation of Ethyl Benzoylacetate in the Presence of Various Tertiary Amines<sup>1</sup>

BY PAUL E. WRIGHT AND WILLIAM E. McEWEN

RECEIVED MARCH 11, 1954

The condensation of benzoyl chloride with ethyl benzoylacetate has been carried out in each of four different tertiary amines as solvents. The exclusive product with dimethylaniline as the solvent was ethyl dibenzoylacetate (IV). A reaction in pyridine for two hours at room temperature afforded a 75.8% yield of ethyl  $\beta$ -benzoxycinnamate (I) and 2.6% of IV. Under the same conditions, with triethylamine as the solvent, there was obtained 49% of I and 29% of IV. Finally, with quinoline, there was obtained a 17.5% yield of IV and a 43.5% yield of a product,  $C_{27}H_{23}NO_4$ , tentatively assumed to be ethyl benzoyl-(1-benzoyl-1,2-dihydro-2-quinolyl)-acetate (V).

On the basis of kinetic evidence<sup>2</sup> and analogy with other, closely related reactions,<sup>3</sup> it has been claimed that pyridine as a solvent plays a unique role in the O-acylation of a  $\beta$ -ketoester by means of an acid chloride. In the reaction of benzoyl chloride with ethyl benzoylacetate in pyridine, for example, it has been suggested that the major product, ethyl  $\beta$ -benzoxycinnamate (I), which has been obtained in as high a yield as 83%,<sup>4</sup> arises from an intermediate condensation product, ethyl benzoyl-(1-benzoyl-1,2-dihydro-2-pyridyl)-acetate (II), rearranging *via* the quasi six-membered ring transition species, III, to give I and pyridine.



It was felt that an investigation of the effect of other tertiary amines besides pyridine on the course of the condensation reaction between benzoyl chloride and ethyl benzoylacetate might provide additional information as to whether pyridine is truly a unique solvent for O-acylation. Triethylamine, dimethylaniline and quinoline were chosen as the comparison solvents for the following reasons: (1) There are no outstanding differences in the abilities of the four tertiary amines to form adducts with acid chlorides. Crystalline, quaternary acylammonium chlorides of varying degrees of purity have been obtained under relatively mild conditions from each of the four amines with a variety of acid chlorides.<sup>5</sup> Therefore adduct formation would not be a limiting condition for O-acylation in pyridine.

(2) Triethylamine is a distinctly stronger base than pyridine, quinoline or dimethylaniline. Thus

(1) Abstracted from the M.S. thesis of Paul E. Wright, Kansas University, 1953.

(2) W. R. Gilkerson, W. J. Argersinger, Jr., and W. E. McEwen, *THIS JOURNAL*, **76**, 41 (1954).

(3) W. von E. Doering and W. E. McEwen, *ibid.*, **73**, 2104 (1951).

(4) S. M. McElvain and D. M. Kundiger, *ibid.*, **64**, 254 (1942).

(5) H. Adkins and Q. E. Thompson, *ibid.*, **71**, 2242 (1949); V. Prey, *Ber.*, **75**, 537 (1942); W. M. Dehn, *THIS JOURNAL*, **34**, 1399 (1912); W. M. Dehn and A. Ball, *ibid.*, **36**, 2091 (1914); G. L. Schwartz and W. M. Dehn, *ibid.*, **39**, 2444 (1917); S. I. Lur'e, *J. Gen. Chem. (U.S.-S.R.)*, **18**, 1517 (1948); H. E. Baumgarten, *THIS JOURNAL*, **75**, 1239 (1953).

if the base strength of the solvent were to have any important bearing on the course of the reaction its effect would show up most strongly with triethylamine.

(3) Quinoline is better able than pyridine to react with an acid chloride and a nucleophilic agent to form a stable dihydro condensation product. For example, quinoline (but not pyridine) forms an addition product, a 1-acyl-1,2-dihydroquinolaldehyde, on reaction with an acid chloride and the cyanide ion.<sup>6</sup> Another example involves the reaction of benzoyl chloride, quinoline and dimethylaniline to form 1-benzoyl-2-(*p*-dimethylaminophenyl)-1,2-dihydroquinoline, whereas pyridine with benzoyl chloride and dimethylaniline gives 4-*p*-dimethylaminophenylpyridine plus some benzaldehyde. The presumed intermediate, 1-benzoyl-4-*p*-dimethylaminophenyl-1,4-dihydropyridine, cannot be isolated, even when the reaction is carried out under the mildest possible conditions.<sup>7</sup> It was therefore thought that quinoline might react with benzoyl chloride and ethyl benzoylacetate to give an isolable condensation product analogous to II. In view of the demonstrated stability of 1-benzoyl-2-(*p*-dimethylaminophenyl)-1,2-dihydroquinoline compared to the hypothetical 1-benzoyl-4-*p*-dimethylaminophenyl-1,4-dihydropyridine, however, it would not necessarily follow that such a condensation product in the quinoline series would rearrange to give ethyl  $\beta$ -benzoxycinnamate (I) and quinoline.

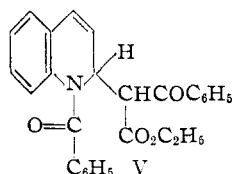
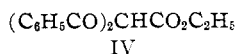
(4) From the point of view of basicity and ability to form an adduct with an acid chloride, dimethylaniline is quite similar to pyridine. The major difference between the two, when used as solvents for the acylation of a  $\beta$ -ketoester, is that pyridine is structurally capable of forming an intermediate dihydro addition product, such as II, whereas dimethylaniline is not. If the formation of such an intermediate plays an important role in the mechanism of the reaction with pyridine as the solvent, then a noticeable difference might be anticipated in a comparison of the two solvents. If, on the other hand, an intermediate such as II plays no important role in the mechanism of the reaction in pyridine, then no outstanding difference would be anticipated in a comparison of the two solvents.

The results of the acylation reactions carried out in each of the four tertiary amines as solvents do not invalidate in any way the contention that the mechanism in pyridine involves the transition

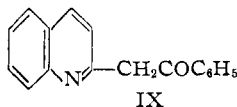
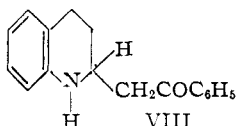
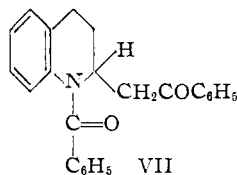
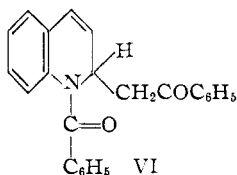
(6) A. Reissert, *Ber.*, **38**, 1603 (1905); **38**, 3415 (1905).

(7) E. Koenigs and E. Ruppelt, *Ann.*, **509**, 142 (1934); W. E. McEwen, R. H. Tiers and I. W. Elliott, *THIS JOURNAL*, **74**, 3605 (1952).

species III and lend some support to that contention. The reaction of benzoyl chloride with ethyl benzoylacetate in pyridine at room temperature for two hours afforded a 75.8% yield of ethyl  $\beta$ -benzoxycinnamate (I) plus a 2.6% yield of ethyl dibenzoylacetate (IV). With triethylamine under the same conditions there was obtained a 49% yield of I and a 29% yield of IV. With dimethylaniline at room temperature for 24 hours there was formed no I and a 90% yield of IV.<sup>8</sup> Finally, with quinoline as the solvent and a reaction period of two hours at room temperature, there was formed no I, a 17.5% yield of IV and a 43.5% yield of a crystalline solid,  $C_{27}H_{23}NO_4$ . The proof of structure and chemical properties of the latter compound will be the subject of a future paper. For the present, however, the compound is tentatively assigned the structure V, ethyl benzoyl-(1-benzoyl-1,2-dihydro-2-quinolyl)-acetate, in analogy with the other products mentioned above obtained by the reaction of benzoyl chloride and quinoline with nucleophilic reagents. The argument in favor of structure V was further strengthened by the results of an analogous condensation reaction described below.



An even more closely related dihydroquinoline condensation product, 1-benzoyl-2-phenacyl-1,2-dihydroquinoline (VI), or an isomer thereof differing in the position of the 3,4-double bond, was obtained from a condensation reaction involving acetophenone, benzoyl chloride and quinoline. The proof of structure of VI involved the following steps: (1) catalytic hydrogenation of VI produced 1-benzoyl-2-phenacyl-1,2,3,4-tetrahydroquinoline (VII); (2) an authentic specimen of VII was prepared by benzoylation of 2-phenacyl-1,2,3,4-tetrahydroquinoline (VIII); (3) the latter compound (VIII) was prepared by catalytic hydrogenation of 2-phenacylquinoline (IX), a known compound,<sup>9</sup> in an acidic medium.



(8) The longer reaction period has no bearing on the fact that ethyl dibenzoylacetate (IV) is the sole reaction product. At shorter periods of time IV is still the only product, but the yields are lower.

(9) (a) G. Scheuing and L. W. Winterhalter, German Patent 594,849, March 22, 1934; C. A., **28**, 4541 (1934); (b) F. W. Bergstrom and A. Moffat, THIS JOURNAL, **59**, 1494 (1937); (c) M. J. Weiss and C. R. Hauser, *ibid.*, **71**, 2023 (1949).

## Experimental<sup>10</sup>

**Reaction of Triethylamine, Benzoyl Chloride and Ethyl Benzoylacetate.**—To a mixture of 101.2 g. (1.00 mole) of freshly distilled, anhydrous triethylamine and 96.1 g. (0.50 mole) of freshly distilled (b.p. 165–166° at 20 mm.) ethyl benzoylacetate was added dropwise with mechanical stirring 70.3 g. (0.50 mole) of "J. T. Baker Analyzed" benzoyl chloride over a 45-minute period. Stirring was continued for a total of two hours, and the color of the solution, initially yellow, gradually changed to orange-brown. Triethylamine hydrochloride which precipitated was collected by filtration and washed with ether, 67.5 g.

The combined filtrate and ether wash solution was extracted with ice-cold 10% hydrochloric acid. Triethylamine, 39 cc., was recovered upon making the acid solution basic with sodium hydroxide solution.

The ether solution was then extracted thoroughly with ice-cold 10% sodium hydroxide solution. Some ethyl  $\beta$ -benzoxycinnamate (I) precipitated from the ether solution at this stage and more was obtained upon concentration of the ether solution, 72.6 g. (49%), m.p. 78–83°. Recrystallization from acetone and then ethanol gave colorless needles, m.p. 82.5–83.7° (reported<sup>4</sup> m.p. 84–85°), also in admixture with an authentic specimen<sup>4</sup> of ethyl  $\beta$ -benzoxycinnamate (I).

After acidification of the sodium hydroxide solution, orange-red in color, with concentrated hydrochloric acid, there was obtained 43.3 g. (29.2%) of ethyl dibenzoylacetate (IV), m.p. 108.0–109.6° after recrystallization from acetone and then ethanol (reported<sup>11</sup> m.p. 112°). There was no depression in a mixed m.p. test with an authentic<sup>11</sup> specimen of ethyl dibenzoylacetate (IV).

**Reaction of Dimethylaniline, Benzoyl Chloride and Ethyl Benzoylacetate.**—To a mixture of 121.2 g. (1.00 mole) of dimethylaniline and 96.1 g. (0.50 mole) of ethyl benzoylacetate was added dropwise with mechanical stirring 70.3 g. (0.50 mole) of benzoyl chloride over a 45-minute period. There was no noticeable evolution of heat as in the previous reaction nor any precipitation of amine hydrochloride. Therefore the deeply colored solution was allowed to stand at room temperature with occasional stirring for 24 hours. Ether was added to the homogeneous reaction mixture, which was then extracted thoroughly with cold 10% hydrochloric acid. Dimethylaniline, 88 cc., was recovered on making the acid extract basic with sodium hydroxide solution.

The ether solution was extracted thoroughly with cold 10% sodium hydroxide solution. Evaporation of the ether afforded no ethyl  $\beta$ -benzoxycinnamate (I).

Acidification of the sodium hydroxide solution with concentrated hydrochloric acid caused precipitation of 133.9 g. (90.4%) of ethyl dibenzoylacetate, which was purified and identified as described above.

**Reaction of Quinoline, Benzoyl Chloride and Ethyl Benzoylacetate.**—To a mixture of 129.2 g. (1.00 mole) of freshly distilled, anhydrous quinoline and 96.1 g. (0.50 mole) of ethyl benzoylacetate was added dropwise with mechanical stirring 70.3 g. (0.50 mole) of benzoyl chloride over a period of 45 minutes. Stirring was continued for two hours and then 50 cc. of ether and 50 cc. of water were added to the yellow-white semi-solid mass. The resulting suspension was filtered through a sintered glass funnel and the white precipitate was washed successively with 10% hydrochloric acid, 10% sodium hydroxide solution and finally water. After drying over anhydrous calcium chloride in a vacuum desiccator the solid material, tentatively assigned the structure of ethyl benzoyl-(1-benzoyl-1,2-dihydro-2-quinolyl)-acetate (V), weighed 48.6 g. (22.9%), m.p. 126–132°. Recrystallization first from acetone and then several times from absolute ethanol raised the m.p. to 145.8–147.4°.

*Anal.* Calcd. for  $C_{27}H_{23}NO_4$ : C, 76.22; H, 5.45; N, 3.29. Found: C, 76.50; H, 5.11; N, 3.33.

The filtrate was extracted thoroughly with cold 10% hydrochloric acid and the acid solution was combined with the acid washings of the above precipitate. After making the acid solution basic with sodium hydroxide solution, 62.7 g. of quinoline was recovered.

(10) All m.p.'s are corrected; analyses by Weiler and Strauss, Oxford, England.

(11) W. H. Perkin and J. Stenhouse, *J. Chem. Soc.*, **59**, 996 (1891).

The ether solution was next extracted thoroughly with cold 10% sodium hydroxide solution. A solid separated from the ether solution, which proved to be the compound  $C_{27}H_{23}NO_4$ . More of the same material was obtained on concentration of the ether solution, 43.8 g. (20.6%).

Following acidification of the sodium hydroxide solution there was obtained 25.9 g. (17.5%) of ethyl dibenzoylacetate (IV).

**Reaction of Pyridine, Benzoyl Chloride and Ethyl Benzoylacetate.**—This reaction has been described previously.<sup>4</sup> The only essential difference in this run is that an effort was made to isolate any ethyl dibenzoylacetate (IV) which had been formed. After a two-hour reaction period at room temperature there was obtained a 75.8% yield of ethyl  $\beta$ -benzoxycinnamate (I) and a 2.6% yield of ethyl dibenzoylacetate (IV).

**Reaction of Quinoline, Benzoyl Chloride and Acetophenone.**—To a solution of 93.5 g. (0.672 mole) of freshly distilled benzoyl chloride in 173.2 g. (1.344 moles) of quinoline, dried over anhydrous barium oxide and also freshly distilled, was added 80.6 g. (0.672 mole) of acetophenone. Solid material precipitated after a period of 12 hours, and the mixture gradually assumed a reddish color. After having stood in a tightly stoppered flask at room temperature for a period of a month, the half-solid reaction mixture was mixed with 750 cc. of ether. A colorless, hygroscopic solid, 58 g., was filtered off. This apparently consisted of a mixture of quinoline hydrochloride and benzoylquinolinium chloride; for, on mixing with water, most of the material went into solution, but several cc. of benzoyl chloride separated from the aqueous solution. The benzoyl chloride was identified by its odor and by its reaction with aniline to give benzanilide.

The ether filtrate was extracted with four 125-cc. portions of ice-cold 3 *M* hydrochloric acid. Colorless 1-benzoyl-2-phenacyl-1,2-dihydroquinoline (VI) precipitated during this extraction procedure and was collected by filtration, 17.0 g. (7.2%), m.p. 135–143°. Crystallization from acetone afforded 8.05 g. of colorless prisms, m.p. 147.5–150.0°. Two additional recrystallizations from acetone afforded material of m.p. 149.0–150.5°.

*Anal.* Calcd. for  $C_{24}H_{19}NO_2$ : C, 81.56; H, 5.42; N, 3.96. Found: C, 81.76; H, 5.77; N, 3.70.

The ether solution was washed with 10% sodium carbonate solution, then water. On standing for a period of 24 hours, an additional 5.01 g. (2.1%) of crude 1-benzoyl-2-phenacyl-1,2-dihydroquinoline (VI) precipitated from the ether solution. Another 2.52 g. (1.1%) of the same material was obtained on concentration of the ether solution.

All of the remaining ether was removed by distillation, and the liquid residue was then vacuum distilled. After a small forerun, there was collected 67.5 g. (84%) of acetophenone. No additional VI could be obtained from the brown, tarry distillation residue.

**Hydrogenation of 1-Benzoyl-2-phenacyl-1,2-dihydroquinoline (VI).**—To a mixture of 2.00 g. (0.00566 mole) of 1-benzoyl-2-phenacyl-1,2-dihydroquinoline (VI) and 60 cc. of absolute ethanol was added 0.10 g. of Adams catalyst. The mixture was hydrogenated at atmospheric pressure and room temperature until one equivalent (0.00655 mole) of hydrogen had been absorbed. The mixture was heated to the boiling point and filtered. Colorless crystals of 1-benzoyl-2-phenacyl-1,2,3,4-tetrahydroquinoline (VII) were obtained on cooling the filtrate, 1.65 g. (82%), m.p. 148–151°. Two recrystallizations from absolute ethanol afforded colorless leaflets, m.p. 151.5–152.4°, also in admixture with an authentic sample of 1-benzoyl-2-phenacyl-1,2,3,4-tetrahydroquinoline (VII).

*Anal.* Calcd. for  $C_{24}H_{21}NO_2$ : C, 81.10; H, 5.96; N, 3.94. Found: C, 81.00; H, 6.04; N, 3.70.

**2-Phenacylquinoline (IX).**—The following procedure is substantially that described in sketchy form by Scheuing and Winterhalter.<sup>2a</sup> To 97.8 g. (0.25 mole) of 2-styryl-

quinoline dibromide suspended in 300 cc. of anhydrous benzene was added 42.0 g. (0.75 mole) of potassium hydroxide dissolved in 750 cc. of absolute ethanol. The mixture was heated on the steam-bath, and about half of the solvent was distilled in the course of an hour. The potassium bromide which had precipitated was removed by filtration and washed with ethanol and benzene. The combined filtrate and wash solution was distilled *in vacuo* until all the solvent was removed. The residual oil was dissolved in 500 cc. of 50% sulfuric acid, the solution heated to the boiling point and refluxed for ten minutes, then cooled and added to 500 cc. of water. The solution was made alkaline with sodium carbonate, and the resulting mixture was extracted with four 500-cc. portions of ether. Distillation of the ether solution, dried over anhydrous sodium sulfate, afforded a dark oil. This was dissolved in hot 95% ethanol and treated with Norit. A yellow-brown solid crystallized from the ethanol solution on cooling, and this was washed with small portions of ether until a yellow solid remained. Recrystallization from 95% ethanol afforded 10.75 g. (17.4%) of 2-phenacylquinoline (IX), yellow crystals, m.p. 116–117.5° (reported 116°,<sup>2a</sup> 116.4–117.1°,<sup>2b</sup> 114–116°.<sup>2c</sup>)

The ethanol mother liquor was treated with an excess of ethanolic picric acid, thereby providing 49.0 g. (41.2%) of crude 2-phenacylquinoline picrate, m.p. 147–160°. Several recrystallizations from ethanol afforded material of m.p. 175–177° dec.; reported<sup>2b</sup> 171.5–172.5° (uncor.).

**1-Benzoyl-2-phenacyl-1,2,3,4-tetrahydroquinoline (VII).**—To a solution of 1.00 g. (0.00405 mole) of 2-phenacylquinoline (IX) in 50 cc. of absolute ethanol was added 0.10 g. of Adams catalyst and ten drops of concentrated hydrochloric acid. The solution was hydrogenated at atmospheric pressure and room temperature until three equivalents (0.01215 mole) of hydrogen had been absorbed.<sup>12</sup> The solution was filtered, and the alcohol was distilled *in vacuo*. The residue was made alkaline with sodium carbonate and extracted with benzene. The benzene solution was distilled until the distillate was no longer turbid, then one cc. of benzoyl chloride was added to the benzene solution. The benzene solution was distilled until a residue of about 15 cc. remained. Ether was added, and the solution was extracted with 10% sodium carbonate solution. The ether solution was then extracted with 3 *M* hydrochloric acid. A yellow solid precipitated on making the acid extract alkaline, and this was taken up in ether. Evaporation of the ether solution, dried over anhydrous sodium sulfate, left a gum. This was converted to the crude picrate, 0.49 g., m.p. 110–115° dec., by means of ethanolic picric acid. The picrate was not investigated further. This product evidently resulted from hydrogenation of the keto group of the side chain of 2-phenacylquinoline (IX) without reduction of the quinoline ring.

Distillation of the original ether solution of the neutral fraction, dried over anhydrous sodium sulfate, afforded a half-solid mass. This was dissolved in hot 95% ethanol, cooled and seeded with the product of m.p. 151.5–152.4°, obtained from the hydrogenation of 1-benzoyl-2-phenacyl-1,2-dihydroquinoline (VI). Colorless leaflets of 1-benzoyl-2-phenacyl-1,2,3,4-tetrahydroquinoline (VII) formed, 0.13 g. (9%), m.p. 143–147°. Two recrystallizations from 95% ethanol afforded colorless leaflets, m.p. 151.5–152.4°. The infrared spectrum in chloroform solution showed carbonyl peaks at 1635 and 1684  $\text{cm}^{-1}$  and was identical in all respects with the infrared spectrum of the compound, m.p. 151.5–152.4°, obtained from the hydrogenation of 1-benzoyl-2-phenacyl-1,2-dihydroquinoline (VI). A mixed m.p. test of the two products showed no depression.

LAWRENCE, KANSAS

(12) It was found that the addition of three equivalents of hydrogen at this stage eventually led to a higher yield of the desired final product, 1-benzoyl-2-phenacyl-1,2,3,4-tetrahydroquinoline (VII), than was obtained by the addition of only two equivalents of hydrogen.