Synthesis of Unsymmetrical 1,3-Diphenyl-2-propanones

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The synthesis of six new unsymmetrically p-substituted 1,3-diphenyl-2-propanones has been carried out by condensing ethyl phenylacetate with phenylacetonitrile—the substituent being in either the ester or the nitrile—and hydrolyzing and decarboxylating the intermediate acetoacetonitrile. 1-(2',4'-Dinitrophenyl)-3-benzyl-4-phenyl-2-aminopyrazoles have been used to characterize the acetoacetonitriles and oximes and 2,4-dinitrophenylhydrazones for the 1,3-diphenyl-2-propanones.

In the course of our studies on the synthesis and absorption spectra of tetracyclones, it was necessary to prepare unsymmetrically substituted 1,3-diphenyl-2-propanones as intermediates. It appeared expedient to us to modify and attempt to standardize the reported Claisen condensation, where a phenylacetonitrile is condensed with an ethyl phenylacetate in the presence of sodium ethoxide; the isolated disubstituted acetoacetonitrile being ultimately hydrolyzed and decarboxylated to yield the desired ketone.

### Table I

<table>
<thead>
<tr>
<th>Acetoacetonitrile R₁ R₂</th>
<th>Yield, %</th>
<th>M.P., °C</th>
<th>Empirical formula C₁₃H₁₃N₂O₂</th>
<th>Analyses, %</th>
<th>C</th>
<th>H</th>
<th>N</th>
<th>Hal. or S</th>
<th>C</th>
<th>H</th>
<th>N</th>
<th>Hal. or S</th>
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</thead>
<tbody>
<tr>
<td>From phenylacetonitrile and an ethyl 4-substituted phenylacetate</td>
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<tr>
<td>H H 82</td>
<td>79.4–80.0</td>
<td>C₁₈H₁₆N₂O₂</td>
<td>81.68 5.57 5.96</td>
<td>...</td>
<td>81.98</td>
<td>5.35</td>
<td>5.82</td>
<td>...</td>
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<tr>
<td>CH₃ H 84</td>
<td>88.0–89.0</td>
<td>C₁₈H₁₆N₂O₂</td>
<td>81.90 6.05 5.62</td>
<td>...</td>
<td>82.02</td>
<td>6.29</td>
<td>5.36</td>
<td>...</td>
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<tr>
<td>CH₃O H 81</td>
<td>69.5–70.7</td>
<td>C₁₈H₁₆N₂O₂</td>
<td>76.96 5.70 5.28</td>
<td>...</td>
<td>77.24</td>
<td>6.00</td>
<td>5.25</td>
<td>...</td>
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<tr>
<td>Br H 80</td>
<td>94.0–95.0</td>
<td>C₁₈H₁₆N₂O₂</td>
<td>61.16 3.85 4.46</td>
<td>25.44</td>
<td>61.62</td>
<td>4.13</td>
<td>4.28</td>
<td>25.24</td>
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<tr>
<td>CH₃S H 85</td>
<td>85.0–85.2</td>
<td>C₁₈H₁₆N₂O₂</td>
<td>72.36 5.37 4.98</td>
<td>11.40</td>
<td>72.39</td>
<td>5.27</td>
<td>5.02</td>
<td>11.25</td>
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</table>

From a 4-substituted phenylacetonitrile and ethyl phenylacetate

| H Cl 59 | 31.0–31.2 | C₂₂H₁₄N₂O₄ | ... | ... | 5.19 | 13.14 | ... | 5.28 | 13.08 |
| H F 75 | 111.8–112.0 | C₂₂H₁₄F₂N₂O₄ | 75.87 4.77 5.33 | ... | 76.00 | 4.75 | 5.83 | ... |

Table I summarizes the results for the preparation

1-\{(2',4'-Dinitrophenyl)-3-benzyl-4-phenyl-2-aminopyrazoles

<table>
<thead>
<tr>
<th>R₁ R₂</th>
<th>M.P., °C</th>
<th>Empirical formula C₂₂H₁₄N₂O₄</th>
<th>Analyses, %</th>
<th>C</th>
<th>H</th>
<th>N</th>
<th>Hal. or S</th>
<th>C</th>
<th>H</th>
<th>N</th>
<th>Hal. or S</th>
</tr>
</thead>
<tbody>
<tr>
<td>H H 127.2–128.2</td>
<td>C₂₂H₁₄N₂O₄</td>
<td>63.61 4.13 16.84</td>
<td>...</td>
<td>64.14</td>
<td>3.86</td>
<td>17.08</td>
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<tr>
<td>CH₃ H 140.0–141.0</td>
<td>C₂₂H₁₄N₂O₄</td>
<td>64.35 4.46 16.31</td>
<td>...</td>
<td>64.52</td>
<td>4.50</td>
<td>15.96</td>
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<tr>
<td>CH₃O H 112.8–114.5</td>
<td>C₂₂H₁₄N₂O₄</td>
<td>...</td>
<td>15.72</td>
<td>...</td>
<td>...</td>
<td>15.54</td>
<td></td>
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<tr>
<td>Br H 154.8–155.2</td>
<td>C₂₂H₁₄BrN₂O₄</td>
<td>...</td>
<td>14.17</td>
<td>...</td>
<td>...</td>
<td>14.17</td>
<td></td>
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</tr>
<tr>
<td>H Cl 155.0–156</td>
<td>C₂₂H₁₄ClN₂O₄</td>
<td>58.74 3.59 15.57</td>
<td>7.88</td>
<td>59.21</td>
<td>3.55</td>
<td>15.30</td>
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<tr>
<td>H F 175.4–176.4</td>
<td>C₂₂H₁₄F₂N₂O₄</td>
<td>...</td>
<td>16.16</td>
<td>...</td>
<td>...</td>
<td>15.56</td>
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</tbody>
</table>

Table II

2,4-Dinitrophenylhydrazone in ethanol-sulfuric acid to stand overnight, after warming, before crystals appeared. The data for these derivatives are shown in Table II.

Infrared studies on selected 2,4-dinitrophenylhydrazones invariably showed the absence of a band in the 4.52–4.55 μ region. These results indicate the absence of the —C≡N group, con-
firming the suspicion that the dinitrophenylhydrazone was an aminopyrazole (I), rather than a simple hydrazone.

This conclusion corroborates the suggestion of Walther, et al., who noted the stability of the phenylhydrazone of \( \alpha \)-\( \beta \)-chlorophenyl-\( \gamma \)-phenylacetoacetonitrile to acid hydrolysis and suggested that the derivative was II. Further analogy for this cyclic structure is taken from Walther and Schickler who reported that the compound obtained by treating \( \alpha \)-\( \gamma \)-diphenylacetoacetonitrile with hydroxylamine hydrochloride was III.

Hydrolysis and decarboxylation in one step was conveniently effected by refluxing the ketonitrile with 60% aqueous sulfuric acid. However, in the preparation of \( \text{I} \), phenyl-\( \beta \)-methoxyphenyl-\( \gamma \)-phenylacetoacetonitrile low yields (see Table III) were obtained even when milder conditions such as acetic acid-aqueous hydrochloric acid were employed. Invariably substantial quantities of dark colored tarry matter formed along with the ketone. On the basis of the work done by Zaugg, it is likely that after hydrolysis of the nitrile cyclization occurred.

### Experimental

**Materials**.—The known intermediary substituted ethyl phenylacetates and phenylacetanilides were prepared according to methods in the literature. Commercial 29 ethanol was found satisfactory as solvent for the condensation.

The preparations described below are typical of the procedures employed.

**Ethyl \( \beta \)-Methylmercaptophenylacetate.**—A solution of 27 g. (0.25 mole) of \( \beta \)-methylmercaptophenylacetic acid and 25 ml. of concentrated sulfuric acid in 250 ml. of absolute ethanol was refluxed for four hours and allowed to stand overnight. After pouring over 300 g. of ice, the mixture was extracted with ether. The ether extracts were washed thoroughly with water and sodium bicarbonate solution and dried over anhydrous sodium sulfate. Removal of the solvent by evaporation on a steam-bath yielded 27 g. (0.13 mole, 86%) of an oil which crystallized upon cooling, m.p. 52.0-53.0°. Recrystallization from 100 ml. of petroleum ether (b.p. 35-50°) yielded 24 g. (0.115 mole, 77%) of white needles, m.p. 55.5-56.2°.

**Anal.** Calcd. for \( \text{C}_{13} \text{H}_{14} \text{NS}_{2} \): C, 66.89; H, 5.80; S, 17.14. Found: C, 66.98; H, 5.80; S, 17.15.

**Ethyl \( \alpha \)-Chlorophenyl-\( \beta \)-phenylacetoacetonitrile.**—To a stirred and refluxing solution of sodium ethoxide in ethanol prepared from 11.5 g. (0.5 atom) of sodium and 150 ml. of ethanol was slowly added a mixture of 37.8 g. (0.25 mole) of \( \alpha \)-chlorophenylacetonitrile and 50.8 g. (0.51 mole) of ethyl phenylacetate. After refluxing for three hours, the solution was cooled and poured into 600 ml. of ice-water. The aqueous alkaline mixture was thoroughly extracted with ether and then acidified with cold dilute hydrochloric acid. The acidified mixture was then extracted three times with 200-ml. portions of ether. After extracting the ether solu-

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(6) H. E. Zaugg, R. T. Rapala and M. T. Leffer, *This Journal*, 70, 3224 (1948). These authors cyclized \( \alpha \)-\( \gamma \)-diphenylacetoacetonitriles with concentrated sulfuric acid to yield the corresponding 2-aryl-1,3-naphthohydroquinones.

Enol-lactone Tautomers of $\beta$-Bromobenzylidenepyruvic Acids

By Emma Dietz Stecher and Ann Clements

Received August 3, 1953

Previously described isomers of $p$-bromo- and $p$-ethoxy-$\beta$-bromobenzylidenepyruvic acid (I) have been shown to be enol-lactone tautomers (II) from which stable acetoxyl derivatives have been prepared. The enols, their acetates and ethers all have strong lactone absorption bands at 3.90-3.95 $\mu$ in the infrared. Ionization constants determined in 50% methanol-0.2 $M$ LiCl are 2.8 and 2.3 $\times 10^{-6}$ for the $p$-bromo- and $p$-ethynyl lactones, and 5.5 $\pm$ 0.3 $\times 10^{-4}$ for both keto acids. Ultraviolet absorption spectra in isooctane solution are reported for all compounds.

In her investigation of $\beta$-bromobenzylidenepyruvic acids, Marie Reimer$^{1,2}$ reported instances of a type of isomerism which was not easily explained. The $p$-bromo- and $p$-ethoxy acids (I) were each obtained in a colorless and a yellow form with different melting points. Corresponding isomeric sodium salts were also reported. Reimer considered the possibility of cis-trans isomerism but favored hydrogen bond structures for one series of compounds. On the basis of existing evidence Brown$^3$ suggested that the colorless isomers might be $\gamma$-lactones capable of enolization (II).

By a further study of these compounds, chiefly through infrared spectra and the formation of new derivatives, we have been able to show definitely that the yellow isomers are unsaturated keto acids, whereas the colorless compounds are enolized lactones tautomeric with these as suggested by Brown.

Table I lists the acids and esters prepared for this study. The required benzylidenepyruvic acids were synthesized by condensing the substituted benzaldehyde with pyruvic acid in an alkaline medium. Bromination readily produced the dibromides which were converted to the isomers by removal of hydrogen bromide. In an acid medium (boiling with water) the lactone formed readily, whereas shaking with sodium carbonate solution slowly produced the salt of the keto acid.

Acknowledgement.—The Authors wish to express their appreciation to Dr. F. J. Villani for helpful discussions.

Brooklyn 1, New York

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF BARNARD COLLEGE]

Enol-lactone Tautomers of $\beta$-Bromobenzylidenepyruvic Acids

BY EMMA DIETZ STECHER AND ANN CLEMENTS

PREVIOUSLY DESCRIBED ISOMERS OF $p$-BROMO- AND $p$-ETHOXY-$\beta$-BROMOBENZYLIDENEPYRUVIC ACID (I) HAVE BEEN SHOWN TO BE ENOL-LACTONE TAUTOMERS (II) FROM WHICH STABLE ACETOXYL DERIVATIVES HAVE BEEN PREPARED. THE ENOLS, THEIR ACETATES AND ETHERS ALL HAVE STRONG LACTONE ABSORPTION BANDS AT 3.90-3.95 $\mu$ IN THE INFRARED. IONIZATION CONSTANTS DETERMINED IN 50% METHANOL-0.2 $M$ LiCl ARE 2.8 AND 2.3 $\times 10^{-6}$ FOR THE $p$-BROMO- AND $p$-ETHYNYL LACTONES, AND 5.5 $\pm$ 0.3 $\times 10^{-4}$ FOR BOTH KETO ACIDS. ULTRAVIOLET ABSORPTION SPECTRA IN ISOOCTANE SOLUTION ARE REPORTED FOR ALL COMPOUNDS.

IN HER INVESTIGATION OF $\beta$-BROMOBENZYLIDENEPYRUVIC ACIDS, MARIE REIMER$^{1,2}$ REPORTED INSTANCES OF A TYPE OF ISOMERISM WHICH WAS NOT EASILY EXPLAINED. THE $p$-BROMO- AND $p$-ETHOXY ACIDS (I) WERE EACH OBTAINED IN A COLORLESS AND A YELLOW FORM WITH DIFFERENT MELTING POINTS. CORRESPONDING ISOMERIC SODIUM SALTS WERE ALSO REPORTED. REIMER CONSIDERED THE POSSIBILITY OF cis-trans ISOMERISM BUT FAVORED HYDROGEN BOND STRUCTURES FOR ONE SERIES OF COMPOUNDS. ON THE BASIS OF EXISTING EVIDENCE BROWN$^3$ SUGGESTED THAT THE COLORLESS ISOMERS MIGHT BE $\gamma$-LACTONES CAPABLE OF ENOLIZATION (II).

BY A FURTHER STUDY OF THESE COMPOUNDS, CHIEFLY THROUGH INFRARED SPECTRA AND THE FORMATION OF NEW DERIVATIVES, WE HAVE BEEN ABLE TO SHOW DEFINITELY THAT THE YELLOW ISOMERS ARE UNSATURATED KETO ACIDS, WHEREAS THE COLORLESS COMPOUNDS ARE ENOLIZED LACTONES TAUTOMERIC WITH THESE AS SUGGESTED BY BROWN.

TABLE I LISTS THE ACIDS AND ESTERS PREPARED FOR THIS STUDY. THE REQUIRED BENZYLIDENEPYRUVIC ACIDS WERE SYNTHESIZED BY CONDENSING THE SUBSTITUTED BENZALDEHYDE WITH PYRUVIC ACID IN AN ALKALINE MEDIUM. BROMINATION READILY PRODUCED THE DIBROMIDES WHICH WERE CONVERTED TO THE ISOMERS BY REMOVAL OF HYDROGEN BROMIDE. IN AN ACID MEDIUM (BOILING WITH WATER) THE LACTONE FORMED READILY, WHEREAS SHAKING WITH SODIUM CARBONATE SOLUTION SLOWLY PRODUCED THE SALT OF THE KETO ACID.

(1) M. Reimer and E. Tobin, THIS JOURNAL, 62, 2515 (1940).
(2) M. Reimer and A. L. Morrison, ibid., 63, 236 (1941).
(3) G. C. Brown, ibid., 85, 883 (1941).

Yellow $p$-bromo- and $p$-ethoxy-$\beta$-bromobenzylidenepyruvic acids and their colorless enolic isomers are all acids which dissolve in very dilute sodium carbonate solution and form stable crystalline sodium salts. Table II summarizes $pK'$ determinations in 50% methanol-0.2 $M$ LiCl as a solvent. It was found that the two yellow compounds are very strong acids. $K'$ is $5.5 \pm 0.3 \times 10^{-4}$ and is the same for both within the experimental error. These acids are somewhat stronger than the benzylidenepyruvic acids (III) (without the bromine atom) for which the average $K'$ is $3.0 \times 10^{-3}$ as reported in a previous paper.$^4$ These acid strengths are comparable to that of unsubstituted pyruvic acid ($K'$ in water = $5.6 \times 10^{-3},^5 3.2 \times 10^{-3},^4$).

Our results are consistent with the keto acid structure of the yellow acids. Since $p$-ethoxy-$\beta$-bromobenzylidenepyruvic acid changes to the colorless isomer on standing, its ionization constant was determined on fresh solutions, or by titrating back the stable sodium salt with acid. It is interesting to note that the $\beta$-bromine atom nearly doubles the acid strength. Also, as was previously observed,$^4$ groups substituted on the benzene ring have little effect on the acidity.

(4) E. D. Stecher and H. F. Ryder, ibid., 74, 4392 (1952).