[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

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

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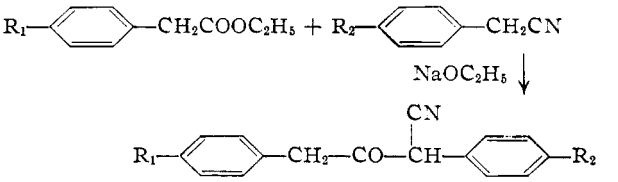
The synthesis of six new unsymmetrically *p*-substituted 1,3-diphenyl-2-propanones has been carried out by condensing ethyl phenylacetate with phenylacetonitrile—the substituent being in either the ester or the nitrile—and hydrolyzing and decarboxylating the intermediate acetoacetonitrile. 1-(2′,4′-Dinitrophenyl)-3-benzyl-4-phenyl-2-aminopyrazoles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

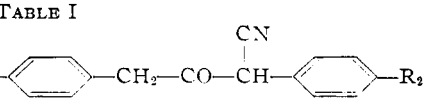
In the course of our studies on the synthesis and absorption spectra of tetracyclones,[2] it was necessary to prepare unsymmetrically substituted 1,3-diphenyl-2-propanones as intermediates. It appeared expedient to us to modify and attempt to standardize the reported Claisen condensation[3-5] whereby 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.



of the intermediate acetoacetonitriles. Derivatives of the β-ketonitriles were prepared in the form of their 2,4-dinitrophenylhydrazones. It was necessary to allow the mixture of ketonitrile and 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-

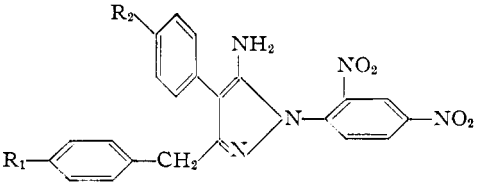
TABLE I

DIPHENYLACETOACETONITRILES 

Acetoacetonitrile R₁	R₂	Yield, %	M.p., °C.	Empirical formula	Analyses, % Calcd. C	H	N	Hal. or S	Found C	H	N	Hal. or S
From phenylacetonitrile and an ethyl 4-substituted phenylacetate												
H	H	82	79.4–80.0[a]	$C_{16}H_{13}NO$	81.68	5.57	5.96	...	81.98	5.35	5.82	...
CH_3	H	84	88.0–89.0	$C_{17}H_{15}NO$	81.90	6.06	5.62	...	82.02	6.29	5.36	...
CH_3O	H	81	69.5–70.4	$C_{17}H_{15}NO_2$	76.96	5.70	5.28	...	77.24	6.00	5.25	...
Br	H	80	94.0–95.0	$C_{16}H_{12}BrNO$	61.16	3.85	4.46	25.44	61.62	4.13	4.28	25.24
CH_3S	H	85	85.0–85.2	$C_{17}H_{15}NOS$	72.56	5.37	4.98	11.40	72.39	5.27	5.02	11.25
From a 4-substituted phenylacetonitrile and ethyl phenylacetate												
H	Cl	59	31.0–31.2	$C_{16}H_{12}ClNO$	...	..	5.19	13.14	...	..	5.28	13.08
H	F	75	111.8–112.0	$C_{16}H_{12}FNO$	75.87	4.77	5.53	...	76.00	4.75	5.83	...

[a] Reported m.p. 85–86°, see reference 4.

TABLE II

1-(2′,4′-DINITROPHENYL)-3-BENZYL-4-PHENYL-2-AMINOPYRAZOLES 

R₁	R₂	M.p., °C.	Empirical formula	Analyses, % Calcd. C	H	N	Hal. or S	Found C	H	N	Hal. or S
H	H	127.2–128.2	$C_{22}H_{17}N_5O_4$	63.61	4.13	16.84	..	64.14	3.86	17.08	..
CH_3	H	140.0–141.0	$C_{23}H_{19}N_5O_4$	64.33	4.46	16.31	..	64.52	4.50	15.95	..
CH_3O	H	113.8–114.5	$C_{23}H_{19}N_5O_5$	...	..	15.72	..	...	..	15.54	..
Br	H	154.8–155.2	$C_{22}H_{16}BrN_5O_4$	...	..	14.17	..	...	..	14.17	..
H	Cl	155.0–156	$C_{22}H_{16}ClN_5O_4$	58.74	3.59	15.57	7.88	59.21	3.55	15.30	8.12
H	F	175.4–176.4	$C_{22}H_{16}FN_5O_4$	...	..	16.16	..	...	..	15.56	..

Table I summarizes the results for the preparation

(1) Taken from the Dissertation of S. B. Coan presented to the Graduate Faculty of the Polytechnic Institute in partial fulfillment of the requirements for the Ph.D. degree.

(2) S. B. Coan, D. E. Trucker and E. I. Becker, THIS JOURNAL, **75**, 900 (1953).

(3) C. von Meyer, *J. prakt. Chem.*, [2] **52**, 115 (1895).

(4) R. Walther and P. G. Schickler, *ibid.*, [2] **55**, 348 (1897).

(5) R. Walther and L. Hirschberg, *ibid.*, [2] **67**, 390 (1903).

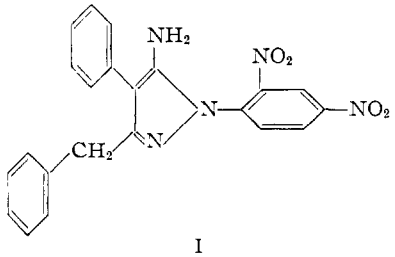
TABLE III

1,3-DIPHENYL-2-PROPANONES R—C$_6$H$_4$—CH$_2$—CO—CH$_2$—C$_6$H$_5$

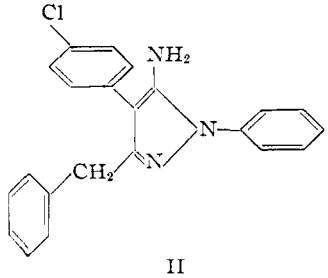
R	M.p., °C.	Yield	Empirical formula	Analyses, % Calcd. C	H	Hal. or S	Found C	H	Hal. or S
CH_3	30.8–31.2	66	$C_{16}H_{16}O$	85.67	7.19	...	85.49	7.30	...
CH_3O	46.6–47.4	19[a]	$C_{16}H_{16}O_2$	79.98	6.70	...	80.10	6.96	...
F	36.0–36.5	50	$C_{15}H_{13}FO$	78.93	5.74	14.49	79.03	5.83	...
Cl	35.9–36.5	71	$C_{15}H_{13}ClO$	73.62	5.35	...	74.00	5.47	13.97
Br	53.8–54.2	50	$C_{15}H_{13}BrO$	62.30	4.53	...	62.59	4.67	...
CH_3S	43.9–44.2	40	$C_{16}H_{16}OS$	74.96	6.29	12.51	75.18	6.39	12.26
$CH_3SO_2^-$	104.6–105.2	70	$C_{16}H_{16}O_3S$	66.64	5.59	11.12	66.89	5.80	11.03

[a] Prepared by refluxing a solution of 5 ml. of glacial acetic acid and 5 ml. of 20% aqueous hydrochloric acid with 1.0 g. of the β-ketonitrile until evolution of carbon dioxide ceased.

firming the suspicion that the dinitrophenylhydrazone was an aminopyrazole (I), rather than a simple hydrazone.



I



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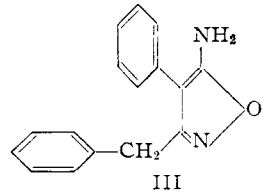

III

This conclusion corroborates the suggestion of Walther, *et al.*,[5] who noted the stability of the phenylhydrazone of α-(*p*-chlorophenyl)-γ-phenylacetoacetonitrile to acid hydrolysis and suggested that the derivative was II. Further analogy for this cyclic structure is taken from Walther and Schickler[4] who reported that the compound obtained by treating α,γ-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 1-(*p*-methoxyphenyl)-3-phenyl-2-propanone 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,[6] it is likely that after hydrolysis of the nitrile cyclization occurred.

Experimental

Materials.—The known intermediary substituted ethyl phenylacetates and phenylacetonitriles were prepared according to methods in the literature. Commercial 2B ethanol was found satisfactory as solvent for the condensation.

The preparations described below are typical of the procedures employed.

Ethyl *p*-Methylmercaptophenylacetate.—A solution of 27 g. (0.15 mole) of *p*-methylmercaptophenylacetic acid[7] 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 $C_{11}H_{14}O_2S$: C, 62.82; H, 6.71; S, 15.25. Found: C, 62.93; H, 6.18; S, 15.20.

α-(4-Chlorophenyl)-γ-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 4-chlorophenylacetonitrile and 50.8 g. (0.31 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-

TABLE IV

OXIMES OF 1,3-DIPHENYL-2-PROPANONES

R	M.p., °C.	Empirical formula	Analyses, % Calcd. N	Hal. or S	Found N	Hal. or S
CH_3	91.5–93.0	$C_{16}H_{17}NO$	5.85	...	5.74	...
CH_3O	98.8–99.5	$C_{16}H_{17}NO_2$	5.49	...	5.60	...
Cl	92.0–93.0	$C_{15}H_{14}ClNO$	5.39	13.65	5.17	13.65
Br	87.4–88.2	$C_{15}H_{14}BrNO$	4.61	...	4.41	...

TABLE V

2,4-DINITROPHENYLHYDRAZONES OF 1,3-DIPHENYL-2-PROPANONES

R	M.p., °C.	Empirical formula	Analyses, % Calcd. N	Hal. or S	Found N	Hal. or S
CH_3	132.2–132.8	$C_{22}H_{20}N_4O_4$	13.85	...	13.58	...
CH_3O	132.5–133.5	$C_{22}H_{20}N_4O_5$	13.33	...	13.50	...
F	114.5–115.0	$C_{21}H_{17}FN_4O_4$	13.72	...	13.90	...
Cl	124.5–125.0	$C_{21}H_{17}ClN_4O_4$	13.19	8.36	12.92	7.98
Br	134.8–136.2	$C_{21}H_{17}BrN_4O_4$	11.94	17.04	11.50	16.83
CH_3S	146.5–147.0	$C_{22}H_{20}N_4O_4S$	12.84	7.34	12.33	7.44
CH_3SO_2	122.0–123.0	$C_{22}H_{20}N_4O_6S$	11.95	6.85	11.78	6.70

(6) H. E. Zaugg, R. T. Rapala and M. T. Leffler, THIS JOURNAL, **70**, 3224 (1948). These authors cyclized α,γ-diarylacetoacetonitriles with concentrated sulfuric acid to yield the corresponding 2-aryl-1,3-naphthohydroquinones.

(7) Prepared in 20% yield according to the procedure of J. W. Corse, R. G. Jones, Q. F. Soper, C. W. Whitehead and O. K. Behrens, THIS JOURNAL, **70**, 2841 (1948).

tion once with 100 ml. of water, twice with 100 ml. each of 10% sodium bicarbonate solution and once with 100 ml. of water and discarding the aqueous extracts in turn, the organic phase was dried with anhydrous sodium sulfate, filtered through a fluted filter and distilled to dryness on a steam-bath. The yield of product was 60 g. (90%), m.p. 128.5–130°. Recrystallization from aqueous methanol raised the melting point to 131.0–131.2° (reported[5] m.p. 127°).

1-(4′-Chlorophenyl)-3-phenyl-2-propanone.—A mixture of 25 g. (0.093 mole) of crude α-(4-chlorophenyl)-γ-phenylacetoacetonitrile and 75 ml. of 60% sulfuric acid was stirred and refluxed until the evolution of carbon dioxide ceased. After cooling, the mixture was poured into 200 ml. of water and extracted three times with 150-ml. portions of ether. The ether was washed with dilute alkali and water and then dried over anhydrous sodium sulfate. After filtering, the solvent was removed by distillation to yield 16 g. (71%) of product, m.p. 34.5–35.5°. Recrystallization from petroleum ether (b.p. 40–60°) raised the melting point to 35.9–36.5°.

1-(4′-Methylsulfonylphenyl)-3-phenyl-2-propanone.—To a solution of 1.024 g. (4 mmoles) of 1-(4′-methylmercaptophenyl)-3-phenyl-2-propanone in 5 ml. of glacial acetic acid was added 1.4 g. (2 mmoles) of 30% hydrogen peroxide. The solution was refluxed for 20 hours and after cooling a few milliliters of water was added to induce crystallization. The cream-colored crystals were removed by filtration, washed with water and dried to yield 800 mg. (2.78 mmoles, 70%), m.p. 99–101°. Recrystallization from benzene–petroleum ether yielded 400 mg. (1.39 mmoles, 35%), m.p. 104.6–105.2°.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF BARNARD COLLEGE]

Enol-lactone Tautomers of β-Bromobenzylidenepyruvic Acids

BY EMMA DIETZ STECHER AND ANN CLEMENTS

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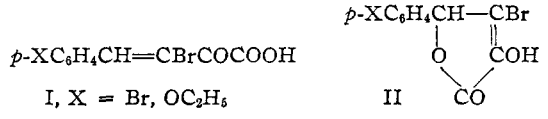
Previously described isomers of *p*-bromo- and *p*-ethoxy-β-bromobenzylidenepyruvic acid (I) have been shown to be enol-lactone tautomers (II) from which stable acetoxy derivatives have been prepared. The enols, their acetates and ethers all have strong lactone absorption bands at 5.60–5.65 μ in the infrared. Ionization constants determined in 50% methanol–0.2 *M* LiCl are 2.8 and 2.3 × 10^{-6} for the *p*-bromo- and *p*-ethoxyenol lactones, and 5.5 ± 0.3 × 10^{-3} for both keto acids. Ultraviolet absorption spectra in isoöctane solution are reported for all compounds.

In her investigation of β-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 and esters were also reported. Reimer considered the possibility of *cis–trans* isomerism but

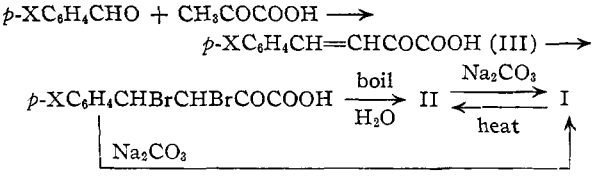


favored hydrogen bond structures for one series of compounds. On the basis of existing evidence Brown[3] suggested that the colorless isomers might be γ-lactones capable of enolization (II).

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) H. C. Brown, *ibid.*, **63**, 882 (1941).



Yellow *p*-bromo- and *p*-ethoxy-β-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 ± 0.3 × 10^{-3} 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 × 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 × 10^{-3},[5] 3.2 × 10^{-3}, [6]). Our results are consistent with the keto acid structure of the yellow acids. Since *p*-ethoxy-β-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 β-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).
(5) A. Hantzsch and A. Moliati, *Z. physik. Chem.*, [A] **10**, 8 (1892).
(6) M. H. Böeseken, L. W. Hansen and S. H. Bertram, *Rec. trav. chim.*, **35**, 313 (1916); E. G. Clair and K. Wiesner, *Nature*, **165**, 202 (1950).