phosphorus, 46.0 g. (0.2 mole) of 1,5-dibromopentane and 250 ml. of dry dimethylformamide was refluxed with stirring under a nitrogen atmosphere for 16 hr., at which time about 130 ml. of solvent was removed by distillation. The residue was allowed to cool and then poured into 500 ml. of dry benzene. The supernatant liquid was poured away from the resulting pasty material and an additional 200 ml. of dry benzene added to the paste whereupon immediate crystallization of the product occurred. The solid was broken up and, after washing on the filter with dry benzene and dry ether, was recrystallized from ethanol–isopropyl ether solvent pair to yield 100 gm. (66% yield) of the diphosphonium salt of m.p. 240–244°.

Anal. Calcd. for $C_{41}H_{40}P_2Br_2$: C, 65.26; H, 5.34; P, 8.21. Found: C, 65.41; H, 5.38; P, 7.83.

B. 1,6-Heptadiene.—The olefin, b.p. 89–90°, $n^{18}D$ 1.4151 (lit.,[24] b.p. 90°, $n^{20}D$ 1.4142), was obtained in 45% yield[14] *via* condensation of pentamethylenebis(triphenylphosphonium bromide) with formaldehyde (see Styrene; procedure A). The diene exhibited characteristic infrared absorption bands[8] at 1640, 990, and 910 cm.$^{-1}$.

***p*-Divinylbenzene.**—The olefin, b.p. 62–63°/6 mm. (lit.,[25] 85–86°/16 mm.), was obtained in 42% yield *via* condensation of the diphosphorane derived from *p*-xylenebis(triphenylphosphonium chloride)[26] and paraformaldehyde (see Styrene: procedure B).

Anal. Calcd. for $C_{10}H_{10}$: C, 92.26; H, 7.74. Found: C, 91.92; H, 8.02.

The diene exhibited characteristic infrared absorption bands[8] at 1625, 980, and 900 cm.$^{-1}$.

(25) Lespieau and Deluchat, *Compt. rend.*, **190**, 683 (1930).

(26) T. W. Campbell and R. N. McDonald, *J. Org. Chem.*, **24**, 1246 (1959).

β-Diketones. IV. Synthesis of Monosubstituted Benzoylcyclopentanones[1]

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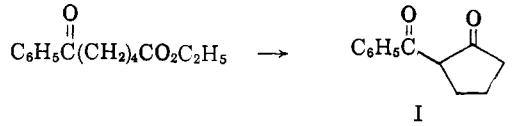
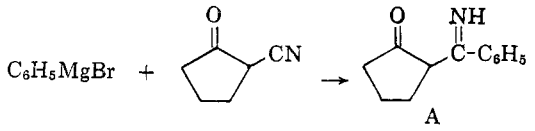
A series of seventeen monosubstituted benzoylcyclopentanones has been prepared by condensation of the pyrrolidene–enamine of cyclopentanone with substituted benzoyl chlorides. The yields ranged from 28 to 76%. In some cases, the 2,5-dibenzoylcyclopentanone was isolated. Other methods of condensation of cyclopentanone with benzoate esters were studied; larger amounts of by-products and lower yields of benzoylcyclopentanones resulted. Keto–enol equilibrium data are presented and discussed.

In a continuing study[1,3,4] of benzoylcyclanones it was desirous to prepare a number of monosubstituted benzoycylopentanones. The parent compound 2-benzoylcyclopentanone (I) was first prepared[5] by Bauer, in a Dieckmann ring closure, employing sodium amide as catalyst. Sodium ethoxide has also been used.[6] The diketone I was reported[5,6] to melt at 41–42°.



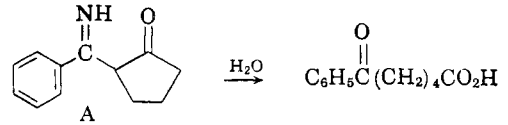
I

The reaction of 2-cyanocyclopentanone with phenylmagnesium bromide gave a product, m.p. 117°, erroneously identified[7] as I. The product melting at 117°



A

has since been shown[8] to be the imine intermediate (structure A). Hydrolysis of A gives ring opening,



A

rather than I. The direct benzoylation of cyclopentanone by benzoyl chloride in the presence of sodium amide was reported[9] to give I in 53% yield. When *p*-methoxybenzoyl chloride was used only a 22% yield of the diketone was formed. Self-condensation of cyclopentanone was found to occur under the reaction conditions, decreasing the yield of diketone. When methyl benzoate was employed, no diketone I was formed, and complete self-condensation occurred.[10]

The synthetic method which we found to be useful in the series of monosubstituted benzoylcyclopentanones was the condensation of N-cyclopentenylpyrrolidene with benzoyl chloride or its monosubstituted derivatives. Stork[11] reported the preparation of 2-benzoylcyclohexanone by this method, but no conditions or yield were given. Eistert[12] reported the synthesis of I in 42% yield employing N-cyclopentenylmorpholine.[13] This method was found suitable for benzoylcyclanones of larger ring size.[12]

We found it possible to prepare monosubstituted benzoylcyclopentanones in satisfactory yields, by use of the Stork enamine method.[11] Seventeen compounds prepared this way are listed in Table I with pertinent data. The reaction procedure was essentially that used by others.[11–13] The intermediate amino ketone was not isolated. It was hydrolyzed immediately to give the substituted benzoylcyclopentanone (I-XVII).

The diketone resulting from hydrolysis was isolated by three different procedures. Diketones, I, XIII, and XVII, were obtained in sufficient purity by distilling the ether extract of the hydrolysis mixture (pro-

(1) Previous paper in this series, R. D. Campbell and H. M. Gilow, *J. Am. Chem. Soc.*, **84**, 1440 (1962). Taken in part from the M.S. thesis of W. L. H., 1962. Presented in part at the 141st National Meeting of the American Chemical Society, Washington, D.C., 1962.

(2) Monsanto Research Fellow, Summer Session, 1961.

(3) R. D. Campbell and H. M. Gilow, *J. Am. Chem. Soc.*, **82**, 2389 (1960).

(4) R. D. Campbell and H. M. Gilow, *ibid.*, **82**, 5426 (1960).

(5) E. Bauer, *Ann. Chim. Phys.*, 9, **1**, 393 (1914).

(6) S. Grateau, *Compt. rend.*, **191**, 947 (1930).

(7) O. Riobe and L. Gouin, *ibid.*, **234**, 1889 (1952).

(8) B. Eistert and H. Wurzler, *Ann.*, **650**, 157 (1961).

(9) B. O. Linn and C. R. Hauser, *J. Am. Chem. Soc.*, **78**, 6066 (1956).

(10) C. R. Hauser, B. I. Ringler, F. W. Swamer, and W. F. Thompson, *ibid.*, **69**, 2649 (1947).

(11) G. N. Stork, R. Terrell, and J. Szmuszkovicz, *ibid.*, **76**, 2029 (1954); see also *Chem. Abstr.*, **51**, 9703e (1957).

(12) B. Eistert, W. Reiss, and H. Wurzler, *Ann.*, **650**, 133 (1961).

(13) S. Hünig and W. Lendle, *Ber.*, **93**, 909 (1960).

TABLE I

2-BENZOYLCYCLOPENTANONES

Compound	X	M.p.,[a] °C.	B.p., °C.	Yield,[b] %	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Isolation[a] method
I	None		132/2 mm.	53	76.57	76.97	6.43	6.09	A
II	*p*-F		122–125/2 mm.	40	69.89	69.55	5.38	5.33	C
III	*p*-Cl	64–65		57	64.73	65.21	4.98	4.99	C
IV	*p*-Br	94–96		76	53.95	53.77	4.15	4.15	C
V	*p*-I	117–118		48	45.88	45.76	3.53	3.57	C
VI	*p*-CH_3	47–48		63	77.20	76.80	6.98	6.97	C
VII	*p*-OCH_3[d]	70–72		43	71.54	71.51	6.47	6.48	C
VIII	*p*-NO_2[e]	79–80		37	61.80	61.35	4.75	5.40	C
IX	*m*-F	61–63		58	69.89	68.89	5.38	4.82	C
X	*m*-Cl	64–65		72	64.73	64.69	4.98	4.80	C
XI	*m*-CH_3		138/2 mm.	35	77.20	77.10	6.98	7.21	A
XII	*o*-F		106–108/1 mm.	48	69.89	68.99	5.38	5.64	B
XIII	*o*-Cl		122–128/1 mm.	50	64.73	64.33	4.98	5.25	A or C
XIV	*o*-Br		142–145/1 mm.	32	53.95	53.73	4.15	3.87	B
XV	*o*-I[c]		120–122/0.1 mm.	35	45.88	46.12	3.53	3.28	C
XVI	*o*-CH_3	44–46		35	77.20	77.10	6.98	6.57	B
XVII	*o*-OCH_3		120–124/1 mm.	28	71.54	71.78	6.47	6.58	A

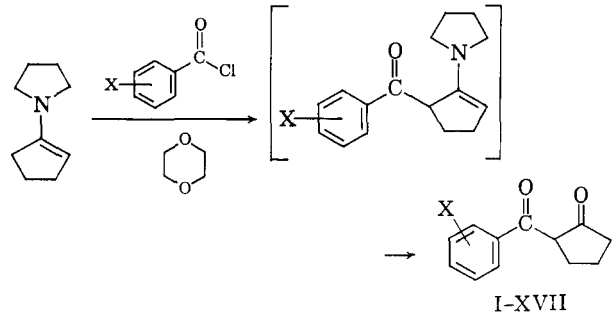
[a] See Experimental. [b] By isolation method listed. Other isolation methods gave poorer yields. [c] Tends to decompose when distilled at higher pressure. [d] Keto form m.p. 63–64°. [e] Enol form m.p. 88–90°. Found: C, 61.72; H, 5.23; N, 5.99. Calcd.: N, 6.01.

TABLE II

TAUTOMERIC EQUILIBRIUM AND HAMMETT SUBSTITUENT CONSTANT

Compound	Subst.	Enol, %	*K*	Relative[a] error, %	log K/K_0	Absolute[b] error limits	σ[c]
I	None	38.7 ± 0.8	0.630	3	0.00	±0.024	000
II	*p*-F	38.7 ± 0.1	.630	1	.00	± .017	0.062
III	*p*-Cl	48.1 ± 1.2	.927	2	.167	± .020	.227
IV	*p*-Br	57.6 ± 1.0	1.36	4	.333	± .029	.232
V	*p*-I	49.3 ± 0.1	0.976	0.2	.189	± .014	.276
VI	*p*-CH_3	30.7 ± 1.2	.443	5.3	− .154	± .035	− .170
VII	*p*-OCH_3	20.7 ± 0.1	.261	.6	− .383	± .015	− .268
VIII	*p*-NO_2	74.8 ± 0.4	2.97	1.2	.672	± .018	.778
IX	*m*-F	52.9 ± 0.4	1.130	0.8	.253	± .016	.337
X	*m*-Cl	53.5 ± 0.2	1.150	.4	.261	± .014	.373
XI	*m*-CH_3	30.3 ± 0.6	0.435	2.1	− .157	± .022	− .069
XII	*o*-F	68.2 ± 0.2	2.14	1.0	.531	± .017	.937
XIII	*o*-Cl	74.9 ± 0.3	2.99	1.4	.676	± .019	1.260
XIV	*o*-Br	86.0 ± 0.3	6.14	2.3	.988	± .022	1.348
XVI	*o*-CH_3	77.9 ± 0.4	3.53	2.5	.748	± .023	0.292
XVII	*o*-OCH_3	48.5 ± 0.1	0.942	0.4	.173	± .014	.109

[a] Relative size of maximum error of all determinations taken for each compound. [b] Actual size of error limits including limits for *K* and for K_0. [c] Values for *ortho*-substituents calculated from benzoic acid ionization constants.



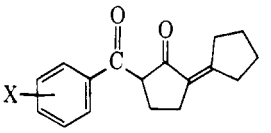
I-XVII

cedure A). These compounds and the remaining *ortho*-substituted diketones were further purified after distillation: The distillate was converted to the copper chelate, which was then decomposed to afford purer diketone upon redistillation (procedure B). In a third method (procedure C), the diketone in the ether extract from the hydrolysis reaction was converted directly to the copper chelate. The latter was then decomposed, and the resulting diketone was either distilled or recrystallized depending on whether it was liquid or solid.

In procedure C, small amounts of copper chelate remained undecomposed after the usual treatment with aqueous acid. This residual chelate was the derivative of the dibenzoylated cyclopentanone. Dibenzoylcyclopentanone (XX) was isolated directly in the preparation of I by crystallization from the crude oil.

Other methods of benzoylating cyclopentanone were explored and found unsatisfactory. Condensation of benzoyl chloride and cyclopentanone catalyzed by sodium hydride yielded a trace of I, and substantial recovery of starting material. No cyclopentylidenecyclopentanone was detected. When methyl benzoate and sodium methoxide, or phenyl anisoate and sodium amide were employed, combined aroylation and self-condensation of cyclopentanone occurred, forming XXI and XXII, respectively.[1,10] These methods were not pursued further since our goal was the preparation of the benzoylcyclopentanone series.

The Keto–Enol Equilibrium.—Each of the monosub-



XXI (X = H); XXII (X = OCH_3)

stituted benzoylcyclopentanones was allowed to equilibrate in methanol, in approximately 0.4% concentration. To ensure equilibrium, the previously employed method was modified by extending the equilibration time to forty-eight hours. Determination of enol percentage gave the results shown in Table II. From these data were calculated the equilibrium constants for the reaction: keto $\rightleftharpoons$ enol. The limits of error listed represent the maximum deviation of single determinations from the average of two to seven determinations for each compound. A total of forty-nine determinations was made.

A measure of the precision of the enol determinations was obtained by the usual statistical treatment.[14] The standard deviation of individual determinations from the average for each set (compound), taken over all sets, was found to be 0.79%. The confidence limit (95% level) is ±1.6%. That is, only one determination in 20 will differ from the average by more than 1.6%. The confidence limit (95% level) for the values of log K/K_0 is ±0.037. Thus the data are quite suitable for determining the statistics of a straight line correlation of log K/K_0 with the Hammett σ function.[15]

On Fig. 1 are plotted the equilibrium data as log K/K_0 for the enolization reaction as ordinate, and the Hammett σ function as abscissa. It is seen that the *meta*- and *para*-substituted derivatives follow the Hammett equation closely, and as expected[15] the *ortho*-substituted derivatives scatter substantially, as they did in the benzoylcyclohexanone series.[4] The values for slope and intercept were calculation by the least squares method[14]:

$$\bar{y} = b\bar{x} + a \qquad b = \frac{n\Sigma xy - \Sigma x \Sigma y}{n\Sigma x^2 - (\Sigma x)^2} \tag{1}$$

These values were calculated for three sets: (a) all compounds in the series (equation 2); (b) the *meta* and *para* compounds (equation 3); (c) the *ortho* compounds alone (equation 4).

$$\log K/K_0 = 0.676\,\sigma - 0.045 \tag{2}$$
$$\rho = 0.676 \pm 0.12$$
$$\log K/K_0 = 0.934\,\sigma - 0.039 \tag{3}$$
$$\rho = 0.934 \pm 0.088$$
$$\log K/K_0 = 0.254\,\sigma + 0.457 \tag{4}$$
$$\rho = 0.254 \pm 0.266$$

It is obvious from the statistical determination of the standard deviation of the slope that the *ortho*-substituted compounds do not fit the correlation well, and that at least one additional parameter will be required to obtain a fit. A study in search of such a parameter is planned. The values of σ for *ortho* substituents were obtained from benzoic acid dissociation data, as before.[4] The failure of the correlation for the

(14) W. J. Youden, "Statistical Methods for Chemists," John Wiley and Sons, Inc., New York, N. Y., chap. 1, 2, and 5.

(15) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 186 ff.

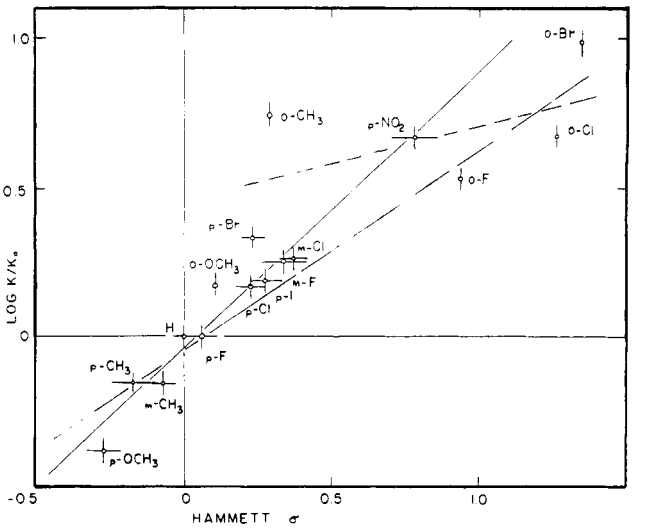


Fig. 1.—Log K/K_0 for keto–enol equilibrium of benzoylcyclopentanones, and the Hammett equation. Equation 2, ———; equation 3, ———; equation 4, – – – –.

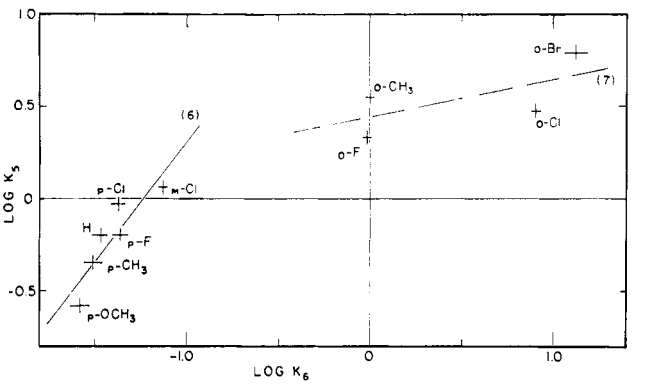


Fig. 2.—Comparison of keto–enol equilibrium in the benzoylcyclopentanone and benzoylcyclohexanone series. Lines for equations 6 and 7 are shown.

ortho-substituted compounds is quantitative, and not qualitative, in the present series as well as in the previously reported[4] cyclohexanone series. Substituents in the *ortho* position tend to result in behavior much less predictable than is seen here.

The Hammett Reaction Constant.—The value of the reaction constant ρ for the *meta*- and *para*-substituted compounds (I–XI) is +0.934 ± 0.088. The sign of ρ is positive. This means that electron donor substituents (methyl, methoxyl) lend more stability to the keto form than to the enol form. It is logical to conclude that *the enol system is less electron deficient (electron demanding) than is the single carbonyl group.* The magnitude of the reaction constant ρ is, within statistical limits, the same as the reaction constant for benzoic acid ionization (1.000). The structural similarity between the benzoic acid–benzoate system and the keto–enol system of the benzoylcyclanone class has been pointed out.[4] In the compounds of the present study the effects of coplanarity, resonance, inductive and dipole interaction, solvation, and bulk steric effects appear to be parallel to the same effects in the benzoic acid ionization equilibrium and the benzoylcyclohexanone tautomeric equilibrium.[4]

In Fig. 2 are plotted values of log K_5 for the benzoylcyclopentanones against log K_6 for the benzoylcyclohexanones, to compare the substituent effects upon the

TABLE III
COMPARISON OF FIVE-RING AND SIX-RING TAUTOMERIC EQUILIBRIUM

		Five-ring			Six-ring		
Compound	X	Enol, %	K_6	log K_6	Enol,[a] %	K_6	log K_6
I	None	38.7	0.630	−0.200	3.3	0.0342	−1.466
II	*p*-F	38.7	.630	− .200	4.2	.0438	−1.359
III	*p*-Cl	48.1	.927	− .033	4.1	.0428	−1.369
VI	*p*-CH_3	30.7	.443	− .354	3.0	.0309	−1.510
VII	*p*-OCH_3	20.7	.261	− .583	2.6	.0267	−1.574
X	*m*-Cl	53.5	1.15	.061	6.9	.0741	−1.130
XII	*o*-F	68.2	2.14	.330	48.7	.0949	−0.023
XIII	*o*-Cl	74.9	2.99	.475	88.8	7.93	.899
XIV	*o*-Br	86.0	6.14	.788	92.9	13.1	1.117
XVI	*o*-CH_3	77.9	3.53	.548	50.0	1.0	0.00

tautomeric equilibrium in the two series. The data are listed in Table III. The ten sets of values best fit a straight line indicated by equation 5; the *meta*- and *para*-substituted compounds comprise a set with equation 6, and the *ortho*-substituted compounds comprise a set with equation 7. The number of values is not sufficient for a meaningful determination of standard deviations.

$$\log K_5 = 0.387 \log K_6 + 0.333 \quad (5)$$

$$\log K_5 = 1.302 \log K_6 + 1.607 \quad (6)$$

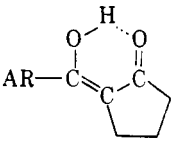
$$\log K_5 = 0.219 \log K_6 + 0.421 \quad (7)$$

The slope of the straight line (equation 6) for the *meta*- and *para*-substituted compounds is 1.302. This indicates that the benzoylcyclopentanone series responds more to substituent effects than does the benzoylcyclohexanone series. From previous evidence[1] it was seen that a higher degree of coplanarity is present in the benzoylcyclopentanone enol than in the benzoylcyclohexanone enol. This difference in coplanarity provides an entirely consistent explanation of the results of the present study as seen in Fig. 2 and equation 6.

The relationship just described between the five-ring and six-ring series breaks down for the *ortho*-substituted compounds. This result is expected because the groups in the *ortho* position exert a bulk steric effect which overrides the less powerful steric effect of ring size.[1]

The ultraviolet spectra for the benzoylcyclopentanones follow the general pattern of the six-ring series and will be the subject of a future article.

The infrared spectra of benzoylcyclopentanones exhibit the following features: (a) complete absence of any O—H stretching frequency; (b) the cyclopentanone carbonyl band at 1735–1745 cm.$^{-1}$; (c) the benzoyl carbonyl band at 1668–1682 cm.$^{-1}$; (d) a complex of multiple absorption bands in the 1600–1670-cm.$^{-1}$ region. The first three characteristics were seen also in the six-ring series.[4] In respect to the last characteristic the two series differ markedly. In the six-ring series, a broad intense absorption is found in the 1550–1650-cm.$^{-1}$ region and is taken as evidence of a strongly chelated enol structure. The multiple bands, well resolved, seen for the five-ring series in this region, indicate weaker hydrogen chelation[16] in the enol forms of the latter series. The weaker hydrogen chelation is expected because the internal bond angles of the five-ring tend to be 108°, increasing the internal angles of the chelate ring beyond the normal 120°. The result is a greater oxygen–oxygen distance, approaching the limiting distance for hydrogen chelation.[17] High resolution studies of these compounds in the 1550–1700-cm.$^{-1}$ region are in progress and will be reported in a subsequent paper.



Experimental[18]

Preparation of Substituted 2-Benzoylcyclopentanones.—N-Cyclopentenylpyrrolidine[11,19] was prepared in 85% yield by direct condensation of pyrrolidine with cyclopentanone in refluxing benzene, employing a Dean–Stark trap.

An anhydrous dioxane solution of 27.4 g. (0.2 mole) of N-cyclopentenylpyrrolidine was stirred at 0–10°. A dioxane solution containing the appropriate benzoyl chloride (0.1 mole) was added over a 2–4-hr. period. The mixture was allowed to stand at room temperature 10–12 hr. (overnight). The mixture was refluxed for 1 hr. After 100 ml. of 1 *N* hydrochloric acid was added, the mixture was refluxed one more hour. The mixture was cooled and extracted with ether. Aqueous sodium chloride was added if necessary to aid in separation of phases. The ether extract was washed twice with aqueous sodium bicarbonate solution, twice with water, and then dried over anhydrous sodium sulfate. The ether solution was treated by one of the following procedures to isolate the diketone. The results are listed in Table I.

Procedure A.—The ether solution was flash distilled. The residue was fractionally distilled at reduced pressure (1 mm.) to give liquid diketone.

Procedure B.—The diketone was isolated by fractional distillation at reduced pressure as in procedure A. The oil was then taken up in ether and shaken with an excess of aqueous copper acetate. The mixture was allowed to stand overnight. The chelate was isolated by filtration, washed with ether, and dried. The copper chelate was shaken with ether and dilute hydrochloric acid (1 *N* was found most satisfactory). The ether layer was washed with water, dried, and flash distilled. The residue was crystallized from hexane, pentane, or ligroin to give crystalline diketone. In those cases in which crystallization did not occur, the residue was fractionally distilled at reduced pressure to obtain pure liquid diketone.

Procedure C.—The ether solution was shaken with excess aqueous copper acetate, and allowed to stand overnight. The chelate was separated by filtration, washed with ether, and dried. It was decomposed as in procedure B, and isolated from

(16) Compare R. D. Campbell and C. L. Pitzer, *J. Org. Chem.*, **24**, 1531 (1959).

(17) Calculated to be 2.5–2.6 Å. by R. Blinc and D. Hadzi in "Symposium on Hydrogen Bonding," D. Hadzi, ed., Pergamon Press, London, 1957, p. 147.

(18) All melting points are corrected. Elemental analyses were determined by R. T. Foster using the Coleman apparatus.

(19) E. D. Bergmann and R. Ikan, *J. Am. Chem. Soc.*, **78**, 1482 (1956).

TABLE IV

INFRARED SPECTRA OF SOME BENZOYLCYCLOPENTANONES

Compound	X	Tautomer[a]	M.p., °C.	C=O unconj.	C=O conj.	C=C region
I	H	Keto[b]	Liq.	1742 s	1688 s	1640-1510[d]
VII	p-OCH_3	Enol[c]	70–72	1738 vw		1640 m, 1605 s, 1600 m
VII	p-OCH_3	Keto[b]	63–64	1740 s	1682 s	1605 s
VIII	p-NO_2	Enol[b]	79–80			1640 s, 1605 m
VIII	p-NO_2	Keto[b]	88–89		1685	1650, 1615

[a] No OH band in the 3000–4000-cm.$^{-1}$ region for either tautomer. [b] Colorless. [c] Yellow. [d] Hyphen indicates overlapping bands.

the resulting ether extract. Compounds II and XV were distilled; in all other cases employing this procedure the product crystallized directly from hexane, pentane, or ligroin

Isolation of 2,5-Dibenzoylcyclopentanone (XX).—When the preparation of I was carried out as above, the ether extract from the decomposed reaction mixture was flash distilled and the residue taken up in hot methanol. Cooling of the methanol yielded a trace of yellow crystals of XX,[1] m.p. 121–122°.

Alternative Benzoylation Methods. Acid Chloride.—A solution of 13.9 g. (0.165 mole) of cyclopentanone and 23.0 g. (0.165 mole) of benzoyl chloride in 200 ml. of dry benzene was stirred at 0° under dry nitrogen. Sodium hydride[20] (15 g., 0.33 mole) was added in ten portions with cooling and stirring. The mixture was refluxed for 3 hr. Decomposition and isolation in the usual manner yielded 4 g. of cyclopentanone (2,4-DNP, m.p. 143°), 6 g. of benzoyl chloride, and a few drops of I (b.p. 150–155°/7 mm.).

Methyl Ester Method.—A dispersion of 17.8 g. (0.33 mole) of sodium methoxide in 300 ml. of benzene was stirred as 13.9 g. (0.165 mole) of cyclopentanone was added over a 10-min. period. After 5 min. more, 22.5 g. (0.165 mole) of methyl benzoate was added over a 10 min. period. The mixture was allowed to stand for 0.5 hr. and heated on a steam bath overnight. The mixture was decomposed and the product isolated by procedure C above. Yellow crystals from *n*-hexane were identified as 2-benzoyl-5-cyclopentylidenecyclopentanone (XXI), 2 g., m.p. 99–100°.[10] No other product was isolated.

Phenyl Ester Method.—The procedure for preparation of aroylcyclohexanones[3] was applied to phenyl anisoate and cyclopentanone. Isolation procedure C above yielded 7 g. of copper chelate, from which 4 g. of 2-(*p*-anisoyl)-5-cyclopentylidenecyclopentanone (XXII) was isolated, m.p. 104–106°.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.90; H, 7.52.

Determination of Percentage Enol.—The enol content was determined at equilibrium. A weighed sample of diketone (approximately 0.2 g.) was dissolved in 50 ml. of anhydrous absolute methanol. The solution was allowed to stand for 48 hr. at room temperature in the dark. The modified bromine titration[2,21] procedure was used to determine percentage enol. Due to a shifting end point, the titration was carried out rapidly, arriving at the end point within 2 min. for consistent results. The results of the determinations are listed in Table II.

Measurement of Spectra.—The infrared spectra were measured using a Perkin–Elmer Model 21 double-beam recording spectrophotometer with a sodium chloride prism. The control settings were maintained constant at: resolution, 926; response 1; gain, 5; speed, 4; suppression, 4. The concentration used was 40 mg./ml. Matched 0.1-mm. cells were used in standard double-beam operation. Data obtained are listed in Table IV.

(20) A 52% mineral oil dispersion was first washed with benzene in a dry nitrogen atmosphere to give oil-free sodium hydride, which was used immediately.

(21) W. T. Smith, Jr., and R. L. Shriner, "The Examination of New Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 101.

The Synthesis of Hydroxycotinine and Studies on Its Structure[1]

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Hydroxycotinine, an optically active metabolite which arises *in vivo* from (−)-nicotine by way of the intermediate (−)-cotinine, was converted to chlorocotinine by reaction with thionyl chloride. The resultant chlorocotinine yielded (−)-cotinine upon hydrogenolysis. γ-(3-Pyridyl)-γ-oxo-α-acetamidobutyric acid, prepared from acetamidomalonic ester and bromomethyl 3-pyridyl ketone, was converted with methylamine and hydrogen in the presence of Raney nickel to acetamidocotinine. Aminocotinine from hydrolysis of the latter afforded two isomeric pairs of hydroxycotinine. The dextrorotatory form obtained by resolution of one of these pairs corresponded in melting point, mixed melting point, and infrared absorption spectra to metabolic hydroxycotinine.

In the metabolism of (−)-nicotine in the dog, oxidation of the pyrrolidine ring leads to the formation of (−)-cotinine, 5-(3′-pyridyl)-1-methylpyrrolidone-2.[4] Metabolism of (−)-cotinine gives rise[5–7] in turn to a number of additional pyridino compounds which, through the ubiquitousness[8] of cotinine, may be common to a number of species.

During early studies[5] on the metabolism of (−)-cotinine in the dog a fraction giving a strong Koenig reaction and containing two components was obtained. One component was identified in crystalline form as (−)-demethylcotinine. The other metabolic component was acetylated with acetic anhydride in pyridine and then yielded a crystalline picrate, $C_{18}H_{17}N_5O_{10}$. The acetylated metabolite, acetoxycotinine, gave[7] upon acidic hydrolysis a colorless alcohol, hydroxy-

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(8) (a) F. E. Guthrie, R. L. Ringer, and T. G.Bowery, *J. Econ. Entomol.*, **50**, 822 (1957); (b) H. B. Hucker, J. R. Gillette, and B. B. Brodie, *Nature*, **183**, 47 (1959); (c) R. Truhaut and M. de Clercq, *Bull. soc. chim. biol.*, **41**, 1693 (1959).