TABLE IV

PRODUCTS FROM *p*-SUBSTITUTED BENZOPHENONES

Substituent	Crude amides, g.	Mixed acids, g.	R—C$_6$H$_4$—COOH Wt.	M. p., °C.	Mixed acetanilides, g.	R—C$_6$H$_4$—NH—COCH$_3$ Wt.	M. p., °C.
Cl–	2.17	0.98	0.48	225–230	1.35	0.90	166–170
NO_2–	2.26	1.07	.45[a]	117–119[a]	0.55[b]	.57[c]	140–143[c]
CH_3–	1.87	0.96	.50[d]	300[d]	1.18	[e]	
C_6H_5–	2.67	1.01	.59	222–224	1.58	.88	166–168
CH_3O–	2.06	1.10	.40[f]	204–207	0.42[b]		

[a] Benzoic acid isolated. [b] Acetanilide isolated. [c] *p*-Nitroaniline. [d] Terephthalic acid. [e] No satisfactory separation of aniline and *p*-toluidine could be found. [f] *p*-Hydroxybenzoic acid. There was also isolated 0.59 g. benzoic acid, m. p. 111–115°.

neutralized with ammonium hydroxide, and filtered. The crude amides were washed on the filter with water and petroleum ether, and then hydrolyzed by refluxing for 24 to 48 hours with a mixture of glacial acetic and concd. hydrochloric acids.

The acidic products of hydrolysis were isolated and weighed, after separation from any neutral material by solution in sodium bicarbonate and reprecipitation with hydrochloric acid. Several of the substituted benzoic acids are insoluble in water; mixtures containing them were therefore separated by extraction with warm water, the insoluble acid being identified and weighed. The exceptions were: *p*-nitrobenzoic acid, which was hydrogenated to *p*-aminobenzoic acid for separations; *p*-toluic acid, which was first oxidized[19] to water-insoluble terephthalic acid; and the products from *p*-methoxybenzophenone, which are given separate treatment in the following paragraph. The basic products of the hydrolysis were isolated as their acetyl derivatives obtained by treatment with acetic anhydride. The acetanilide was extracted from each mixture by warm water, and the residual substituted acetanilide identified and weighed. *p*-Nitroaniline was isolated without acetylation, however, since its feeble basicity makes it insoluble in dilute acid.

The amides from *p*-methoxybenzophenone were hydrolyzed and simultaneously demethylated by heating with a 30% solution of hydrogen bromide in glacial acetic acid in a sealed tube at 100° for twenty-four hours. The mixture of benzoic and *p*-hydroxybenzoic acids obtained from this was separated by extraction with benzene or carbon disulfide, in which only benzoic acid is soluble. This procedure was tested by subjecting a mixture of equal parts of *p*-anisic acid and benzoic acid first to the hydrolysis procedure, and then to the separation. A 91% recovery of *p*-hydroxybenzoic acid and 96% of benzoic acid was obtained. From the basic products of hydrolysis the aniline was recovered by extraction with benzene from the alkalized aqueous solution, and was converted to acetanilide for identification and weighing.

The detailed results of these procedures are given in Table IV.

(19) Footnote *b* in Table I.

Summary

A study has been made of the Schmidt reaction on a series of *para*-substituted benzophenones, a series of phenyl alkyl ketones, and two unsaturated aralkyl ketones. The ratios of the two isomeric amides formed in each case are nearly independent of para-substituents, but are greatly affected by changes in the steric environment of the carbonyl group. These observations are correlated with existing theory.

ANN ARBOR, MICHIGAN RECEIVED OCTOBER 21, 1949

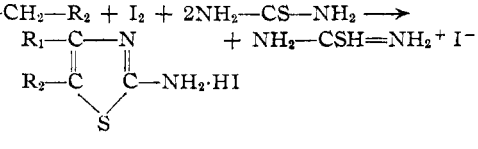
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Reaction of Ketones with Iodine and Thiourea[1]

BY L. CARROLL KING AND ROBERT J. HLAVACEK

Recent papers from this Laboratory[2] have described the formation of aminothiazoles by means of the reaction.

$$R_1—CO—CH_2—R_2 + I_2 + 2NH_2—CS—NH_2 \longrightarrow$$



$$+ NH_2—CSH=NH_2^+ I^-$$

This reaction has now been examined as a preparative method for aminothiazoles. The 2-aminothiazoles and the corresponding 2-acetaminothiazoles prepared from a variety of ketones where R_1 and R_2 are separate groups, are listed in Table I. Thiazoles and acetaminothiazoles prepared from ketones where $R_1CO–CH_2–R_2$ is a cyclic ketone are listed on Table II.

The method described was not found to be useful for preparation of thiazoles from aldehydes or from certain ketones such as *o*-nitroacetophenone, 2-methylcyclohexanone, cyclopentanone and acetomesitylene. In the case of acetomesitylene the reaction gives the isothiuronium salt II, but this compound will not cyclize to form the thiazole.[3]

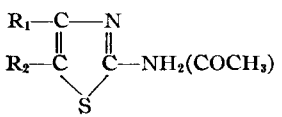
In the case of 3-methylcyclohexanone a poor yield of a single product was obtained. It was

(1) This investigation was partially supported by a grant from the Abbott Fund of Northwestern University.

(2) Dodson and King, THIS JOURNAL, **67**, 2242 (1944); *ibid.*, **68**, 871 (1946); King and Ryden, *ibid.*, **69**, 1813 (1947).

(3) This is in line with other reactions of acetomesitylene wherein *normal* ketone reactions are absent; see Kadesch, THIS JOURNAL, **66**, 1206 (1944).

TABLE I



R_1	R_2	2-Aminothiazole Formula	M. p., °C.[a] Found	Yield,[b] %	Analyses, % Calculated	Found	2-Acetaminothiazole Formula	M. p., °C.[a]	Analyses, % Calculated	Found
p-Cl–C_6H_4–	H–	$C_9H_7ClN_2S$	163–164	89	N, 13.3	13.37	$C_{11}H_9N_2OSCl$	254–255	N, 11.08	11.0
p-Br–C_6H_4–	H–	$C_9H_7BrN_2S$	180–181	93	N, 11.0	10.8	$C_{11}H_9N_2OSBr$	277–278	N, 9.43	9.26
p-I–C_6H_4–	H–	$C_9H_7IN_2S$	176–177	97	N, 9.27	9.18	$C_{11}H_9N_2OSI$	302–303	N, 8.13	8.03
p-CH_3–O–C_6H_4–	H–	$C_{10}H_{10}N_2OS$	204–205	72	N, 13.6	13.6	$C_{12}H_{12}N_2O_2S$	287–288	N, 11.3	11.65
p-CH_3–S–C_6H_4–	H–	$C_{10}H_{10}N_2S_2$	180–182	67	N, 12.6	12.3	$C_{12}H_{12}N_2OS_2$	232–233	N, 10.6	10.1
p-NH_2–C_6H_4–	H–	$C_9H_9N_3S$	174–175	63	C, 56.52 H, 4.74	56.80 4.85	$C_{13}H_{13}N_3O_2S$[c]	284–286	C, 56.71 H, 4.76	56.72 5.34
p-C_6H_5–C_6H_4–	H–	$C_{15}H_{12}N_2S$	207–208	99	C, 71.40 H, 4.79	71.27 5.10	$C_{17}H_{14}N_2OS$	252–253	N, 9.52	8.92
p-CH_3–C_6H_4–	H–	$C_{10}H_{10}N_2S$	124–125	84	C, 63.07 H, 5.30	62.96 5.23	$C_{12}H_{12}N_2OS$	204–205	C, 62.04 H, 5.21	62.04 5.31
m-CH_3–C_6H_4–	H–	$C_{10}H_{10}N_2S$	79– 92	64	C, 63.07 H, 5.30	64.02 5.85	$C_{12}H_{12}N_2OS$	211–212	C, 62.12 H, 5.21	61.39 5.15
o-CH_3–C_6H_4–	H–	$C_{10}H_{10}N_2S$	81– 82	70	C, 63.07 H, 5.30	63.27 5.41	$C_{12}H_{12}N_2OS$	143–144	C, 62.04 H, 5.21	61.98 5.36
p-NO_2–C_6H_4–	H–	$C_9H_7N_3O_2S$	285–286	99	C, 48.86 H, 3.19	48.92 3.09	$C_{11}H_9N_3O_3S$	306–307	C, 50.18 H, 3.45	50.04 3.34
m-NO_2–C_6H_4–	H–	$C_9H_7N_3O_2S$[d]	188–190	84	C, 48.86 H, 3.19	48.98 3.15	$C_{11}H_9N_3O_3S$[e]	312–314	C, 50.18 H, 3.44	50.33 3.34
β-Naphthyl-	H–	$C_{13}H_{10}N_2S$	153–154	99	N, 12.38	12.28	$C_{15}H_{12}N_2OS$	239–240	N, 10.44	10.1
2-Phenanthryl–	H–	$C_{17}H_{12}N_2S$	243–244	87	N, 10.14	10.1	$C_{19}H_{14}N_2OS$	304–305	N, 8.80	8.61
2-Thienyl–	H–	$C_7H_6N_2S_2$	127–130	91	C, 46.13 H, 3.32	45.90 3.23	$C_9H_8N_2OS_2$	199–207	C, 48.19 H, 3.60	48.12 3.64
t-Butyl	H–	$C_7H_{12}N_2S$[f]	98– 99	71	C, 53.81 H, 7.74	54.34 8.01	$C_9H_{14}N_2OS_2$[g]	173–174	C, 54.51 H, 7.12	54.75 7.45
C_6H_5–	Ethyl–	$C_{11}H_{12}N_2S$	68– 69	65	N, 13.71	14.3	$C_{13}H_{14}N_2OS$	175–176	N, 11.37	11.36
C_6H_5–	Propyl–	$C_{12}H_{14}N_2S$	103–104	54	N, 12.83	12.6	$C_{14}H_{16}N_2OS$	135–136	N, 10.76	10.8
C_6H_5–	Butyl–	$C_{13}H_{16}N_2S$	60– 61	43	N, 12.06	11.8	$C_{15}H_{18}N_2OS$	187–188	N, 10.21	10.0
Benzyl–	C_6H_5–	$C_{16}H_{14}N_2S$	139–140	83	N, 10.52	10.68	$C_{18}H_{16}N_2OS$	164–165	N, 9.08	9.17
C_6H_5–	C_6H_5–	$C_{15}H_{12}N_2S$[h]	184–185	99	N, 11.10	10.9	$C_{17}H_{14}N_2OS$	208–209	N, 9.52	9.23
C_6H_5–	Benzoyl–	$C_{16}H_{12}N_2OS$	215–216	18	N, 9.99	10.1	$C_{18}H_{14}N_2O_2S$	237–238	N, 8.69	8.27
o-HO–C_6H_4–	H–	$C_9H_8N_2OS$	139–140	37[i]	C, 56.23 H, 4.20	56.23 4.41	$C_{13}H_{12}N_2O_3S$[l]	200–203	C, 56.51 H, 4.38	56.43 4.58
m-HO–C_6H_4–	H–	$C_9H_8N_2OS$	136–138	59[j]	C, 56.29 H, 4.20	55.92 4.55	$C_{13}H_{12}N_2O_3S$[l]	186–187	C, 56.56 H, 4.38	56.49 4.49
p-HO–C_6H_4–	H–	$C_9H_8N_2OS$	198–200	62[k]	C, 56.29 H, 4.20	56.65 4.29	$C_{13}H_{12}N_2O_3S$[l]	235–237	C, 56.56 H, 4.38	56.55 4.52

[a] All melting points were observed with a Fisher–Johns melting point block. [b] Based on the ketone. [c] Both amino groups are converted to the corresponding acetamido derivatives. [d] Calculated: N, 19.00. Found: N, 18.5. Previously reported by Dodson and King, THIS JOURNAL, **67**, 2242 (1945), m. p. 188–190°, and by Hurd and Kharasch, *ibid.*, **68**, 656 (1946), m. p. 189–191°. [e] Hurd and Kharasch reported the m. p. of this compound as 310–314°. [f] Calcd.: N, 17.93. Found: N, 17.2. [g] Calcd.: N, 14.13. Found: N, 14.0. [h] Hubacher, *Ann.*, **259**, 228 (1890), reported this compound, m. p. 185–186°. [i] Based on the quantity of 2-amino-4-(2-hydroxyphenyl)-thiazole hydriodide isolated, m. p. 220–223°. *Anal.* Calcd. for $C_9H_9N_2OSI \cdot H_2O$: I, 37.53. Found: I, 37.6. [j] Based on the quantity of 2-amino-4-(3-hydroxyphenyl)-thiazole hydriodide isolated, m. p. 95–97°. *Anal.* Calcd. for $C_9H_9N_2OSI \cdot H_2O$: I, 37.53. Found: I, 37.8. [k] Based on the quantity of 2-amino-4-(4-hydroxyphenyl)-thiazole hydriodide isolated, m. p. 240–242°. *Anal.* Calcd. for $C_9H_9N_2OSI \cdot H_2O$: I, 37.53. Found: I, 38.0. [l] Note both the amino group and the hydroxyl group are acetylated.

TABLE II[a]

Starting ketone	Aminothiazole: Formula	M. p., °C.[b]	Yield,[c] %	Calculated	Found	Acetaminothiazole: Formula	M. p., °C.	Calculated	Found
Cyclohexanone	$C_7H_{10}N_2S$[e]	87–88	65	N, 18.16	18.03	$C_9H_{12}N_2OS$[e]	140–141	N, 14.28	14.25
4-Methylcyclohexanone	$C_8H_{12}N_2S$	98–99	66	N, 16.55	15.74	$C_{10}H_{14}N_2OS$[d]	162–163	C, 57.07 H, 6.71	57.79 6.34
3-Methylcyclohexanone	$C_8H_{12}N_2S$	110–111	24	C, 57.10 H, 7.19	57.25 7.31	$C_{10}H_{14}N_2OS$	150–151	C, 57.07 H, 6.71	57.12 6.64
Cycloheptanone	$C_8H_{12}N_2S$	75–76	60	C, 57.10 H, 7.19	56.27 7.14	$C_{10}H_{14}N_2OS$	124–125	C, 57.07 H, 6.71	57.07 6.81
Hydrindone	$C_{10}H_8N_2S$[f]	213–214	53	C, 63.75 H, 4.28	63.75 4.28	$C_{12}H_{10}N_2OS$[g]	284–285	C, 62.59 H, 4.38	62.65 4.34
α-Tetralone	$C_{11}H_{10}N_2S$	133–134	52	N, 13.85	13.7	$C_{13}H_{12}N_2OS$	233–234	N, 11.47	11.49
Acenaphthenone[h]	$C_{13}H_8N_2S$[i,j]	205–207	99	C, 69.62 H, 3.60	69.76 3.63	$C_{15}H_{10}N_2OS$	309–311	C, 67.65 H, 3.79	67.23 3.87

[a] The structure of the thiazole is apparent from the starting ketone, except in the case of 3-methylcyclohexanone. From this substance either 2-amino-5-methyl-4,5,6,7-tetrahydrobenzothiazole or the corresponding 7-methyl derivative could result. Our experiments provide no method for distinguishing between the two substances. [b] All melting points were observed on a Fisher–Johns melting point block. [c] Based on the ketone. [d] Calcd.: N, 13.32. Found: N, 12.75. [e] Kucherova and Kochesh-kov, *J. Gen. Chem.* (*U. S. S. R.*), **16**, 1701 (1946), reported these compounds with identical melting points. The thiazole was also reported by Erlenmeyer and Schoenauer, *Helv. Chim. Acta*, **24**, 172 (1941). [f] Calcd.: N, 14.88. Found: N, 13.50. [g] Calcd.: N, 12.17. Found: N, 12.17. [h] This thiazole was converted to the hydrobromide, $C_{13}H_8N_2S{\cdot}HBr$, m. p. 238–244°. *Anal.* Calcd.: Br, 26.18. Found: Br, 25.1. [i] 8-Aminoacenaphtho-1,2-thiazole is a bright red crystalline substance.

II

not determined whether this substance was 2-amino-5-methyl-4,5,6,7-tetrahydrobenzothiazole, or the corresponding 7-methyl derivative. In all other cases reported, the structure of the thiazole is apparent from the method of preparation.

Experimental

Preparation of Starting Materials.—The thiourea was White Label Grade obtained from Eastman Kodak Company. The iodine was U.S.P. resublimed crystals. Many of the ketones were obtained from commercial sources. The others were prepared by known methods. The homogeneity of each ketone was established by conventional methods (b.p., m.p., etc.), before using it in the reaction. In all cases the physical constants of the ketones were in good agreement with values given in the literature.

Preparation of the Substituted 2-Aminothiazoles.—General Procedure: A mixture consisting of 0.1 mole of ketone, 0.2 mole of thiourea and 0.1 mole of iodine was heated overnight on the steam-bath. This crude reaction mixture was cooled and extracted with ether to remove unreacted ketone and iodine. The residue was then dissolved in boiling water[4,5] and filtered to remove sulfur. The solution was then cooled somewhat and made basic with concentrated ammonium hydroxide. The aminothiazole which separated was recrystallized from water–alcohol.

If the free aminothiazole separated from the aqueous solution as an uncrystallizable oil, a characteristic of those compounds finally melting below 100°, the oil was separated and taken up in hot Skellysolve C. Most of the low melting thiazoles crystallized from the Skellysolve C solution as it cooled.

The 2-acetamido derivative of each of the thiazoles was obtained by heating the thiazole with acetic anhydride and crystallizing the product from alcohol–water.

Preparation of 2-Aminothiazoles from Hydroxyacetophenones.—The reactions were carried out as described above. The crude reaction mixture after extraction with ether was taken up in hot water, filtered to remove sulfur, and cooled. The 2-amino-(hydroxyphenyl)-thiazole hydriodide crystallized as slender needles. The yield data given in Table I are based on the amount of this hydriodide isolated. Analytical samples of these materials were prepared by crystallization from acetone–water (1–2) (see notes *i*, *j*, and *k*, Table II).

The free aminothiazoles were prepared from the pure hydriodides by adding concentrated ammonia to a concentrated solution of the hydriodide salt until the solution was neutral. The aminothiazole separated on cooling, and was recrystallized from water.

The diacetyl derivatives were prepared by heating the hydriodide salt with acetic anhydride. The reaction mixture was poured into ice water and the product crystallized from 95% alcohol.

2,4,6-Trimethylphenacylisothiuronium Bromide.—A mixture consisting of 1.4 g. of thiourea and 4.6 g. of bromoacetomesitylene[6] in ethanol was refluxed for several hours. On concentrating and cooling, the salt crystallized; yield 3.8 g. m. p. 260–280°. After recrystallization three times the melting point was 280–282°.

(4) If this solution were appreciably colored it was treated with norite A and filtered again.

(5) Some salts proved virtually water insoluble. In such cases, the residue was treated directly with ammonium hydroxide.

(6) Jacobs and Heidelberger, *J. Biol. Chem.*, **21**, 459 (1915).

Anal. Calcd. for $C_{11}H_{17}OBrN_2S$: Br, 27.09. Found: Br, 26.4.

Summary

The formation of 2-aminothiazoles by action of iodine and thiourea on ketones has been examined as a preparative method.

EVANSTON, ILLINOIS RECEIVED FEBRUARY 2, 1950

[CONTRIBUTION FROM ROHM AND HAAS COMPANY]

Reaction of β-Alkoxyacrylic Esters with Secondary Amines

BY PETER L. DE BENNEVILLE AND JANE H. MACARTNEY

Replacement of an ether group with an amino group requires a particularly favorable structural condition in the molecule. Cook and Dixon[1] have succeeded in so replacing the ether group by heating β-alkoxypropionitriles with amines in an autoclave to temperatures generally in the neighborhood of 200°. This reaction can be attributed to the presence of the cyanide group in a neighboring position to the alkoxy group, with consequent weakening of the carbon–oxygen bond. A very labile system which has been known for some years is represented by the group of compounds of the structure $ROCH{=}C\langle^{X}_{Y'}$ where both X and Y are the customary labilizing groups —COR, —COOR and —CN.[2,3] Replacement of the alkoxy group with amino- and anilino- groups is readily carried out in these cases at temperatures ranging from room to 100°.

We have found that a single labilizing group, as found in the β-alkoxyacrylic esters, is sufficiently active to promote the replacement of the alkoxy group by a number of secondary amino groups, at temperatures generally no higher than 100°. At these temperatures no replacement of the ester alkoxy group was obtained; however, in reactions requiring higher temperatures, such a replacement might occur. The reaction did not take place with all secondary amines. A notable exception was the case of diisopropylamine, which gave no reaction. This would indicate that highly hindered bases or weak bases,[4] as in the aromatic series, would not react under such favorable conditions. Since the β-alkoxyacrylic esters are available from the reaction of acetylene and dialkyl carbonates,[5] this represents a superior method of obtaining the β-aminoacrylic esters.

The amination is readily carried out by heating molecular equivalents of the β-alkoxyacrylic ester and the amine at reflux or steam-bath temperature, depending on boiling point of the amine. A potassium carbonate catalyst was used in most of the reactions, but since omission of the catalyst gave only slightly lower yields in the one case where it was tried, the necessity for this catalyst is questionable. The alcohol may be removed by distillation as the reaction progresses, but this is unnecessary. The results of typical aminations are given in the accompanying table.

TABLE I

TRANSAMINATION REACTIONS,[a] $ROCH{=}CHCOOR' \rightarrow {>}NCH{=}CHCOOR'$

R	R'	Amine	Yield, %	B. p., °C. uncor.	at mm.	Nitrogen, % Found	Nitrogen, % Calcd.	Neutralization equivalent Found	Neutralization equivalent Calcd.	Sp. gr. 20/20	$n^{20}D$
CH_3	CH_3	Morpholine	50[b]	M. p. 76–78°		8.20	8.18	174	171	....	....
C_2H_5	C_2H_5	Morpholine	69	138–142	0.8	7.67	7.57	185	185	1.1077	1.5309
C_2H_5	C_2H_5	Morpholine[c]	52	141–145	1.2	..	..	187	185	....	....
C_2H_5	C_2H_5	$(CH_3)_2NH$	53	84–85	1.4	9.32	9.78	145	143	0.9947	1.5114
C_2H_5	C_2H_5	$C_9H_{19}NHCH_3$	64	164–165	4.0	5.28	5.48	[d]	255	0.9196	1.4897
C_2H_5	C_2H_5	Piperidine	79	123–124	1.1	7.62	7.64	187	183	1.0293	1.5334
C_2H_5	C_2H_5	$(HOCH_2CH_2)_2NH$	82	Decomposed[e]		7.30	7.40	[d]	203	[e]	1.5021
C_4H_9	C_4H_9	Morpholine	26	165–175	2	5.94	6.59	230	213	1.0357	1.5056

[a] Anhydrous potassium carbonate used as catalyst except when indicated. [b] Product recrystallized from methanol. [c] No catalyst used. [d] Too weakly basic to titrate with indicator. [e] Product isolated by water wash to remove unreacted materials and stripping on the steam-bath under good water vacuum to remove low-boiling products. It was a thick almost glassy material at room temperature.

The β-dialkylaminoacrylic esters so produced were stable but very weak bases. For example, titration with hydrochloric acid to a brom phenol blue end-point led to a disappearing end-point which drifted back to the basic side until the neutral point was reached, which in almost all cases corresponded to the theoretical neutral equivalent for the compound. This basicity distinguishes these compounds from the other possible products of the reaction, the alkoxyacrylamides. Cold dilute hydrochloric acid slowly hydrolyzed ethyl

(1) Cook and Dixon, U. S. Patent 2,425,693.
(2) Claisen, *Ann.*, **297**, 1 (1897).
(3) de Bollemont, *Bull. soc. chim.*, [3] **25**, 29 (1901).
(4) Methylaniline also did not give the expected product in this reaction (Dr. J. O. Van Hook, private communication).
(5) Croxall and Schneider, THIS JOURNAL, **71**, 1257 (1949).