3-Ethyl-6,8,8-trimethyl-3,4-nonanediol.—A solution of 133 g. (0.75 mole) of 2-hydroxy-4,6,6-trimethylheptanoic acid [α-hydroxydecanoic acid (Rohm and Haas)] in 750 ml. of absolute ethanol was saturated with dry hydrogen chloride at 0° and worked up in the usual way to give 109.1 g. (67.3%) of the **ethyl ester**, b. p. 89–94° (2 mm.), n^{23}D 1.4346. *Anal.* Calcd. for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 67.09; H, 11.43. Reaction with ethylmagnesium bromide gave the diol, n^{23}D 1.4518.

2,2-Diethyl-1-phenyl-1,3-propanediol.—**Ethyl 2,2-diethyl-3-hydroxy-3-phenylpropionate** was prepared in 72.0% yield by the reaction of benzaldehyde, ethyl diethylbromoacetate and zinc dust; the product distilled at 121–122° (0.6 mm.), n^{23}D 1.5050. *Anal.* Calcd. for $C_{15}H_{22}O_3$: C, 71.92; H, 8.86. Found: C, 71.68; H, 8.82. The diol, n^{23}D 1.5253, was obtained by reduction with lithium aluminum hydride.

2,2-Diethyl-3-hydroxypropyl Carbamate.—To a stirred solution of 66 g. (0.5 mole) of 2,2-diethyl-1,3-propanediol, 75 g. of dimethylaniline and 500 ml. of benzene, at 5 ± 2°, was added a solution of 50 g. of phosgene in 250 ml. of benzene. After an additional two hours of stirring at 5°, the liquid was decanted from dimethylaniline hydrochloride, treated with 250 ml. of concentrated ammonia, and stirred two additional hours at 5°. The benzene layer was separated, washed with water, dried and concentrated. The residual oil solidified and was recrystallized from benzene–hexane to give 2 g. (2.7%) of the product, m. p. 69–70°. *Anal.* Calcd. for $C_8H_{17}NO_3$: N, 7.99. Found: N, 7.88.

1-Phenyl-1,2,3-propanetriol.—A mixture of 40.2 g. (0.3 mole) of cinnamyl alcohol and 253.8 g. of 98–100% formic acid was cooled to 5° and treated all at once with 41.4 g. of 30% hydrogen peroxide. The mixture was warmed to 35° and kept at 35–40° for 22 hours, concentrated *in vacuo* and the residue saponified with a solution of 21 g. of potassium hydroxide in 95% ethanol. The ethanol was distilled and the residue extracted with ether. The dried ethereal solution was concentrated and distilled to give 8.5 g. (16.9%) of the product, b. p. 194° (6 mm.).

The $C_9H_{20}O$ Compound.—The sodium reduction procedure described by Hansley[5] was followed. A mixture of 210 g. of dry xylene, 80 g. of dry "Isobutylcarbinol" (Sharples) and 50 g. of diethyl ethyl-1-methylbutylmalonate was fed into a refluxing stirred suspension of 36.2 g. of sodium sand in 50 ml. of dry xylene contained in a 3-liter 3-necked flask equipped with a copper water cooled condenser and air stirrer. The addition required fifty minutes during which 4.34 liters of gas was evolved. After standing overnight the mixture was hydrolyzed by the cautious addition of 300 ml. of water, and then steam distilled. The organic layer in the steam distillate was separated and the water layer extracted with three 200-ml. portions of ether. The ether and organic layers were combined, dried and distilled to remove xylene and "Isobutylcarbinol," after which the residue was fractionated to give 9.5 g. (34%) of what is presumed to be 2-ethyl-3-methylhexanol, b. p. 76° (6 mm.). *Anal.* Calcd. for $C_9H_{20}O$: C, 74.93; H, 13.97. Found: C, 74.93; H, 13.91.

Summary

The preparative methods for a series of substituted alkanediols have been described.

NEW BRUNSWICK, NEW JERSEY
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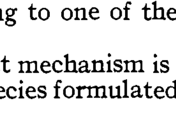
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MICHIGAN]

The Effect of Structure on the Course of the Schmidt Reaction on Unsymmetrical Ketones[1]

BY P. A. S. SMITH AND JEROME P. HORWITZ

The Schmidt reaction of hydrogen azide with ketones under the influence of strong acids is known to give amides: R—CO—R + $HN_3 \rightarrow$ R—CO—NH—R + N_2.[2] We have undertaken an investigation of the behavior of unsymmetrical ketones in this reaction and report here our observations on substituted benzophenones and certain aryl alkyl ketones, together with the interpretation according to one of the mechanisms recently proposed.[3]

A feature of that mechanism is the intermediate occurrence of a species formulated as



$$\left[\begin{array}{c} R—\underset{\underset{\displaystyle N—N_2}{\|}}{C}—R' \end{array}\right]^+$$

whose structure indicates the possibility of geometrical isomerism of the same type as encountered in oximes. If, as in the Beckmann rearrangement, the *trans* group (R) migrates from C to N, then the ratios of the *syn* and *anti* configurations of this intermediate would determine the relative extents of migration of R and R′. In the absence of such a geometrical effect, the factor determining the relative extents of migration would be expected to be the relative intrinsic rates of migration of R and R′. These different rates, commonly referred to as "migration aptitudes," are presumably the result of different activation energies of different groups undergoing the required transition. An indication as to their relative magnitudes is available from studies of the pinacol rearrangement[4] and the rates of migration of different groups in the Beckmann rearrangement.[5]

In order to obtain evidence as to whether the geometrical configuration of the intermediate or

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(1) Presented at the Meeting of the American Chemical Society, San Francisco, California, March 28–April 2. Part of this work was taken from part of the doctoral thesis of Jerome P. Horwitz, University of Michigan, 1949. This article antedates the paper of Smith and Ashby, THIS JOURNAL, **72**, 2503 (1950), which is a sequel to the present work. Reference 1 in that paper was intended to refer to the present article, but through error refers to an unrelated article.

(2) H. Wolff, "The Schmidt Reaction," in R. Adams, "Organic Reactions," Vol. III, John Wiley and Sons, New York, N. Y., 1946.

(3) P. A. S. Smith, THIS JOURNAL, **70**, 320 (1948); *cf.* M. S. Newman and H. Gildenhorn, *ibid.*, **70**, 317 (1948).

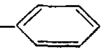
(4) For a summary of the work of various authors, see H. Adkins in Gilman, "Organic Chemistry," 2nd ed., John Wiley and Sons, New York, N. Y., 1943, p. 1067, and G. Wheland, "Advanced Organic Chemistry," John Wiley and Sons, New York, N. Y., 1949, p. 513.

(5) A. W. Chapman and F. A. Fidler, *J. Chem. Soc.*, 448 (1936).

the "migration aptitudes" of the migrating groups determines the ratio of the isomeric amides produced, a series of *para*-substituted benzophenones has been investigated. In such ketones, the environment in the neighborhood of the carbonyl group is the same on either side, and the geometrical isomers of the intermediate should be formed in nearly equal amounts. However, the different aryl groups used are ones known to have greatly different "migration aptitudes" in other rearrangements.

The results are listed in Table I, together with comparative information on the pinacol rearrangement, rates in the Beckmann rearrangement, and the ratios of geometrical isomers formed on oximation. The ratios of isomeric amides produced in the Schmidt reaction are seen to be all close to 1:1, very similar to the ratios of isomeric oximes, and in great disagreement with the values for "migration aptitudes." This result is consistent with the operation of a geometrical effect in the course of the reaction, and indicates that transmitted electric effects of the order of magnitude obtainable by *para*-substitution are of not more than secondary importance in determining the group which migrates.

TABLE I

COMPARATIVE EXTENTS OF MIGRATION OF R—— FOR THE SCHMIDT, BECKMANN AND PINACOL REARRANGEMENTS

R	Fractions migrating, R-C_6H_4- *vs.* C_6H_5- Schmidt	Beckmann	Pinacol	Migration rate in Beckmann[a]
Cl-	0.59:0.41	0.56:0.44[b]	0.40:0.60[c]	0.28
NO_2-	.51:0.49	.50:0.50[d]	....	$\ll$0.28
CH_3-	.54:0.46	.52:0.48[b]	.94:0.06[e]	8
CH_3O-	.61:0.39	.49:0.51[b]	.986:0.014[e]	$\gg$8
C_6H_5-	.52:0.48	.51:0.49[b]	.92:0.08[f]	....

[a] Comparative figures based on the rates of migration at 80° of the *trans* forms of the picryl ethers of benzophenone oximes, normalized to a basis of 1 for R = H; estimated from the work of Chapman and Fidler.[5] [b] W. E. Bachmann and M. X. Barton, *J. Org. Chem.*, **3**, 300 (1938). [c] P. J. Montagne, *Rec. trav. chim.*, **26**, 253 (1907). [d] L. E. Sutton and T. W. J. Taylor, *J. Chem. Soc.*, 2193 (1931). [e] W. E. Bachmann and F. H. Moser, THIS JOURNAL, **54**, 1124 (1932). [f] M. Gomberg and W. E. Bachmann, *ibid.*, **49**, 236 (1927).

In the investigation of this series, the conditions used were the same for each ketone, and consisted of treatment with sodium azide in fused trichloroacetic acid, with two molar equivalents of sulfuric acid as catalyst. While the conditions may not have been optimum in all cases, they were adhered to for the sake of comparability in the results. The composition of the products was determined by hydrolysis and actual separation of the pairs of acids and amines so produced, for the most part by methods which have been used in the past in similar investigations. The precision of such methods, while perhaps not as great as some indirect methods, was quite sufficient for the purpose required, and determinations such as these which result in the isolation of identifiable substances have a gross certainty not always associated with other methods.

One ketone, *p*-methylbenzophenone, had already been subjected to the Schmidt reaction by Sherk, *et al.*,[6] who reported an 80% yield of benz-*p*-toluidide. This is considerably in disagreement with the result we report here, but it should be noted that their reaction was carried out in a very different manner. A path is open for "migration aptitudes" to influence the ratios of migration, if the rate of interconversion of the *cis* and *trans* forms of the intermediate should compare in magnitude with the rate of migration of either R or R′. This condition does not appear to be satisfied in general, although it might obtain in special circumstances.

In order to gain evidence regarding the effect of changes in the steric environment of the carbonyl group on the course of the Schmidt reaction, a series of ketones was investigated of the type C_6H_5–CO–R, in which R is methyl, ethyl, isopropyl, or *t*-butyl. For the alkyl groups in this series, information of the type known for substituted phenyl groups regarding the comparative activation energies for migration is not available, although there have been expressions of opinion on the subject.[7] However, in view of our results with benzophenones, we felt justified in assuming that any large differences in ratios of migration which might be encountered among the alkyl phenyl ketones could be attributed to the steric effects of the groups concerned, rather than their "migration aptitudes." The migration ratios, as shown in Table II, show a progressive change from preferred phenyl-migration to preferred alkyl-migration as the alkyl group becomes increasingly branched at the α-position. This increase in branching also has a pronounced retarding effect on the reaction as a whole; as a result it was not possible to achieve complete reaction in a reasonable time for isobutyrophenone and pivalophenone. (The highly hindered methyl mesityl ketone and *t*-butyl mesityl ketone were found to be even more reluctant to undergo the Schmidt reaction.)

TABLE II

RELATIVE EXTENTS OF MIGRATION IN KETONES C_6H_5–CO–R

R	Fraction migrating C_6H_5-	R-	Total yield of amides, %
Methyl	0.95	0.05	81
Ethyl	.85	0.15	80
Isopropyl	.51	0.49	57
t-Butyl	.0	1.0	See exptl.

An additional effect of extreme branching at the α-position was observed in this series only with pivalophenone. Although the *t*-butyl group did

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[6] J. K. Sanford, F. T. Blair, J. Arroya and K. W. Sherk, THIS JOURNAL, **67**, 1941 (1945).

[7] A. D. McLaren, *Science*, **103**, 503 (1946).

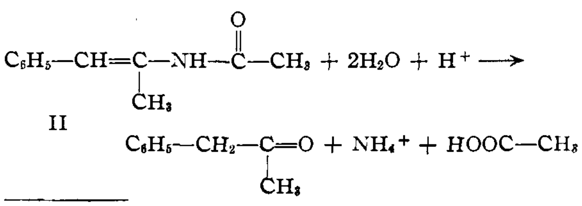
all of the detectable migrating, it became ultimately separated from the remainder of the molecule, and a mixture was obtained containing large amounts of benzonitrile along with benzamide, benzoic acid, N-*t*-butylbenzamide, ammonia and methylamine. No products resulting from migration of the phenyl group were detected. This cleavage, which is similar to that observed by Schuerch and Huntress[8] in the Schmidt reaction on pivalic acid, is analogous to the result of the Beckmann rearrangement of pivalophenone oxime.[9] We first encountered this phenomenon with the Schmidt reaction on pinacolone; a discussion of the theory of this cleavage and the analogous "second order" effect in the Beckmann rearrangement will be the subject of another communication.

As an attempt to separate the effect of changes in steric environment from transmitted electronic effects in migration-ratios in the Schmidt reaction, styryl methyl ketone, C_6H_5—CH=CH—CO—CH_3, and α-methyl-β-phenylvinyl methyl ketone, C_6H_5—CH=CCH_3—CO—CH_3, were studied. The product obtained from styryl methyl ketone was N-methylcinnamamide in 75% yield. This was also the only product found by Briggs, De Ath, and Ellis,[10] who, however, did not specify their yield. The interposition of a vinylene group between the phenyl and the carbonyl groups of acetophenone thus quite reverses the relative extents of migration. Since the vinylene group is known to be a fairly good transmitter of electronic effects, it would seem that the major difference between acetophenone and styryl methyl ketone with respect to the Schmidt reaction lies in the steric environment of the carbonyl group. To substantiate this, the bulk originally due to the phenyl group in acetophenone, and then displaced in styryl methyl ketone, was restored by adding a methyl group adjacent to the carbonyl, giving

$$C_6H_5\text{—}CH{=}CCH_3CO\text{—}CH_3$$

The result was consistent with these considerations; the only products detected were those arising from migration of the methylstyryl group (86% yield).

The initial product of the Schmidt reaction on α-methyl-β-phenylvinyl methyl ketone would be an N-vinyl compound (II), a type of substance which is easily hydrolyzed to a ketone



$$C_6H_5\text{—}CH{=}\underset{CH_3}{\underset{|}{C}}\text{—}NH\text{—}\overset{O}{\overset{\|}{C}}\text{—}CH_3 + 2H_2O + H^+ \longrightarrow$$

II

$$C_6H_5\text{—}CH_2\text{—}\underset{CH_3}{\underset{|}{C}}{=}O + NH_4^+ + HOOC\text{—}CH_3$$

The phenylacetone which results is itself highly susceptible to the Schmidt reaction, and gives as the terminal stage in the reaction sequence a mixture of N-benzylacetamide and N-methylphenylacetamide. These amides are resistant to mild acid hydrolysis, and could be isolated intact. Hydrolysis of the mixed amides and separation of the resulting pairs of acids and amines showed the ratio of the two components to be, within the estimated experimental error, the same as that obtained starting with known pure phenylacetone.

We do not intend to imply by the foregoing discussion that a bulk effect in the neighborhood of the carbonyl group will always enforce a *trans* configuration of the intermediate and thus result in favored migration of the bulky group. It is recognized that a departure from symmetry in the neighborhood of the carbonyl group might result in either a repulsion or an attraction by the bulkier side, depending on the electronic structure of the source of the bulk and its proximity to the carbonyl group. Indeed, it has already been shown[11] that, in the case of phenyl 1-phenanthryl ketone, the less bulky phenyl group migrates preferentially (ratio 0.83:0.17). The further study of structural influences on the Schmidt reaction, including *o*-substituted benzophenones, is in progress.

Experimental[12]

Aryl Alkyl Ketones.—The ketones acetophenone, propiophenone, isobutyrophenone, and pivalophenone were subjected to the Schmidt reaction on a scale of 0.02 mole by treatment with sodium azide in molten trichloroacetic acid, as described by Dice and Smith.[11] The amides thus produced were hydrolyzed by refluxing with methanolic potassium hydroxide, without prior purification. The basic and acidic fractions of the hydrolyzed mixtures were separated by standard procedures, during which the more volatile, aliphatic components were allowed to be lost. The aniline which remained in each case was converted to acetanilide for identification and weighing; the benzoic acid was weighed and identified as such.

Appreciable amounts of non-hydrolyzable oil were obtained from isobutyrophenone and pivalophenone; these were shown to be unreacted ketone by conversion to their dinitrophenylhydrazones.

The aqueous filtrates from the isolation of the mixed amides were treated with bromine in order to recover in the form of 2,4,6-tribromoaniline the small amounts of aniline formed by partial hydrolysis during the Schmidt reaction.

The results of these experiments are summarized in Table II, except that the reaction of pivalophenone is given separate description, because of its more complex result.

The ratios reported in Table II were calculated from the sum of the yields of acetanilide and tribromoaniline and the yield of benzoic acid, converted to mole-fraction of isolated product.

Pivalophenone.—Pivalophenone was prepared in 60% yield by the reaction of phenylmagnesium bromide with pivalyl chloride at 0°; b. p. 96–100° (10 mm.) (lit., 102° (12 mm.)[13]).

When the Schmidt reaction was applied to 3.24 g. of pivalophenone in trichloroacetic acid as with the previous ketones, there was obtained a heavy, water-insoluble oil having a strong odor of benzonitrile. This was freed of acid by washing with potassium carbonate solution, and

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[8] C. Schuerch, Jr., and E. H. Huntress, This Journal, **71**, 2233 (1949).

[9] G. Schroeter, *Ber.*, **44**, 1201 (1911).

[10] L. H. Briggs, G. C. De Ath and S. R. Ellis, *J. Chem. Soc.*, **61** (1942).

[11] J. R. Dice and P. A. S. Smith, *J. Org. Chem.*, **14**, 179 (1949).

[12] The melting points reported here are uncorrected.

[13] J. U. Nef, *Ann.*, **310**, 320 (1899).

Table III

Schmidt Reaction on Aryl Alkyl Ketones

Ketone	Aceto-phenone	Propio-phenone	Isobutyro-phenone
Weight, g.	2.40	2.68	2.96
Acetanilide, g.	1.45	1.64	0.69
Yield, %	54	61	25.5
Tribromoaniline, g.	1.00	0.13	...
Yield, %	15	2	...
Benzoic acid, g.	0.13	0.27	0.62
Yield, %	6	11	26

distilled at 25 mm. The distillate came over in the range 94–124°, and was collected in two imperfectly distinguished fractions, total weight 0.6–1.9 g. in different runs. These distillates were to a large extent hydrolyzable by acid or alkali, and yielded by such treatment benzoic acid, m. p. 120–122°, and ammonia, isolated as ammonium chloride and identified by Nessler reagent. The unhydrolyzed portion was pivalophenone.

The residue remaining in the still-pot after the distillation crystallized on cooling; weight 0.2–0.4 g., m. p. 100–110°. By crystallization from benzene, butyl ether, and ligroin, there was obtained benzamide, m. p. 125–128° alone and when mixed with authentic benzamide, and N-*t*-butylbenzamide, m. p. 133–135° alone and when mixed with an authentic sample.

The aqueous phase of the mixture resulting when the Schmidt reaction was drowned in water was made alkaline and distilled into hydrochloric acid. Evaporation of the distillate left 2.46 g. of mixed amine hydrochlorides. This mixture was extracted successively with *n*-butyl, isopropyl, and ethyl alcohols, and yielded 1.12 g. of pure ammonium chloride and 1.15 g. of impure methylamine hydrochloride, m. p. 205–210° (lit.[14] 232°). The crude methylamine hydrochloride was soluble in ethanol, slightly soluble in isopropyl alcohol, and insoluble in butanol. It was converted into its *p*-toluenesulfonyl derivative, m. p. 79–81°, in high yield. The absence of a butanol-soluble fraction in the mixed hydrochlorides showed the absence of *t*-butylamine.

Acidification of the alkaline residue in the still-pot gave 0.14 g. of benzoic acid, m. p. 121–122°. The almost total absence of aniline in the products of the Schmidt reaction was shown by the appearance of not more than an opalescence when any of the aqueous solutions were treated with excess bromine water. Because of the losses involved in many of the separations described, an accurate estimate of the yields of most of the products is not possible.

Benzalacetone.—The Schmidt reaction of this ketone was run in the presence of sulfuric acid, trichloroacetic acid, and hydrochloric acid, respectively. Although a small amount of N-methylcinnamamide was obtained from the sulfuric acid reaction, only the hydrochloric acid run gave really satisfactory results, and is described here.

To a mixture of 3.72 g. of benzalacetone and 17 cc. of concd. hydrochloric acid was added 2.5 g. of sodium azide in four portions over a period of one hour. The solution darkened and a vigorous and mildly exothermic reaction took place. A further 10 cc. of concd. hydrochloric acid was added, the mixture was heated momentarily on a hot-plate, decanted from some tar, and poured into *ca.* 150 cc. of water. The oil which separated was extracted with hot sodium bicarbonate solution, washed with water, and allowed to stand until crystalline, weight 2.35 g. The aqueous layer was extracted with benzene, and the benzene extracts washed with sodium bicarbonate solution. No water-insoluble acid was obtained on acidification of the washings. Evaporation of the benzene left 0.35 g. of crystals. A further 0.23 g. of crystals was obtained when the aqueous solution was alkalized and allowed to stand. The melting point of the solid, total weight 2.98 g. (75% yield), was 108–110°, both alone and when mixed with N-methylcinnamide prepared from cinnamoyl chloride and methylamine. Recrystallization from benzene raised this to 111–112°.

1-Benzal-1-methylacetone.[15]—Attempts to subject this ketone to the Schmidt reaction in fused trichloroacetic acid resulted only in the formation of tars, non-hydrolyzable oils, and difficultly fusible substances. Concentrated hydrochloric acid was found to be a satisfactory medium for the reaction, after many trials. Only the most successful is described.

To a mixture of 5.0 g. (0.031 mole) of 1-benzal-1-methylacetone and 20 ml. of concd. hydrochloric acid was added 2.5 g. of sodium azide in several portions spaced over a period of six hours, during which the mixture was frequently swirled. After twenty hours, the residual ketone had liquefied and darkened; 20 ml. more of concd. hydrochloric acid and an additional 2.5 g. of sodium azide was then added. After six more hours, during which the mixture was occasionally warmed to about 40°, significant gas evolution ceased, and the mixture was poured into cold water and extracted thrice with petroleum ether. Evaporation of the extracts left a dark gum, wt. 0.22 g., having a strong ketonic odor. Extraction of this gum with sodium bicarbonate solution yielded no acidic material. Repetition of these two steps, using benzene instead of petroleum ether, also produced no acids. The aqueous reaction mixture was alkalized with sodium hydroxide and extracted repeatedly with benzene. Evaporation of the benzene extracts left 3.99 g. of soft crystals (86% yield, calculated as $C_9H_{11}ON$).

The entire crop of crystalline amides was refluxed with 10 g. of potassium hydroxide in 60 ml. of methanol for seventeen hours. The mixture was then steam-distilled, and the distillates concentrated to remove most of the methylamine. Acidification of the distillates with hydrochloric acid and evaporation to dryness left 1.60 g. of acetone-washed amine salts. This could be converted into N-benzyl-*p*-toluenesulfonamide, m. p. 116–116.5° (lit.,[16] 116°) in 88% yield, accompanied by a trace of N-methyl-*p*-toluenesulfonamide. The original salt melted at 258° (lit.[17], 260°) after recrystallization from *n*-butyl alcohol, and also yielded a benzoyl derivative, m. p. 105–106° (lit.[16] 106°) both alone and when mixed with known N-benzyl-benzamide. The yield of benzylamine was calculated on the basis of the *p*-toluenesulfonamide assay as 0.010 mole (37% from amides).

The alkaline solution from the hydrolysis and steam-distillation was washed with ether, treated with decolorizing carbon, and acidified with hydrochloric acid. The precipitated acid was taken up in ether and the mother liquor was extracted with fresh ether; evaporation of the dried extracts left 2.06 g. (0.015 mole, 56.5% from amides) of phenylacetic acid; m. p. 74–76° (lit.,[18] 77–78°); no depression when mixed with known phenylacetic acid.

The total yield of hydrolysis products is 93.5%, and indicates a ratio of N-methylphenylacetamide to N-benzylacetamide of 60:40. The best figures we have obtained in a similar manner for the ratio of these substances formed by the Schmidt reaction on phenylacetone is 50:50. However, when phenylacetone is subjected in bulk to the conditions of the Schmidt reaction, much self-condensation occurs before reaction with hydrogen azide is completed. This results in somewhat erratic yields, and ratios between 60:40 and 40:60 have been obtained in different runs, with total yields near 80%.

Benzophenones.—The Schmidt reactions were conducted by treating 0.01 mole samples of the substituted benzophenone in 15 g. of trichloroacetic acid with 2 ml. (0.036 mole) of concd. sulfuric acid and 2 g. (0.03 mole) of sodium azide at 50–60° for six to twelve hours. The mixtures were then poured into 150 cc. of cold water,

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[14] M. Sommelet, *Compt. rend.*, **178**, 219 (1924).

[15] C. Harries and G. H. Muller, *Ber.*, **35**, 970 (1902).

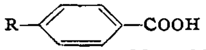
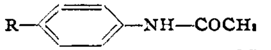
[16] Organic Reagents for Organic Analysis (Hopkin and Williams Research Laboratories), Chemical Publishing Co., Brooklyn, N. Y., 1946.

[17] A. E. Marrell and R. M. Herbst, *J. Org. Chem.*, **6**, 878 (9141).

[18] L. Wolff, *Ann.*, **394**, 43 (1912).

TABLE IV

PRODUCTS FROM *p*-SUBSTITUTED BENZOPHENONES

							
Substituent	Crude amides, g.	Mixed acids, g.	Wt.	M. p., °C.	Mixed acetanilides, g.	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.

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.

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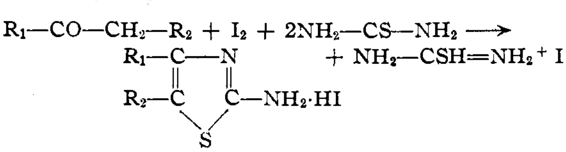
[19] Footnote *b* in Table I.

[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.



$$R_1{-}CO{-}CH_2{-}R_2 + I_2 + 2NH_2{-}CS{-}NH_2 \longrightarrow R_1{-}C{=}C(R_2){-}S{-}C(NH_2{\cdot}HI){=}N + NH_2{-}CSH{=}NH_2{}^+\ I^-$$

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

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[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).