The Schmidt and Beckmann Reactions of α-Trisubstituted Ketones and Ketoximes. The Synthesis of Isotopically Labeled Aniline[1]

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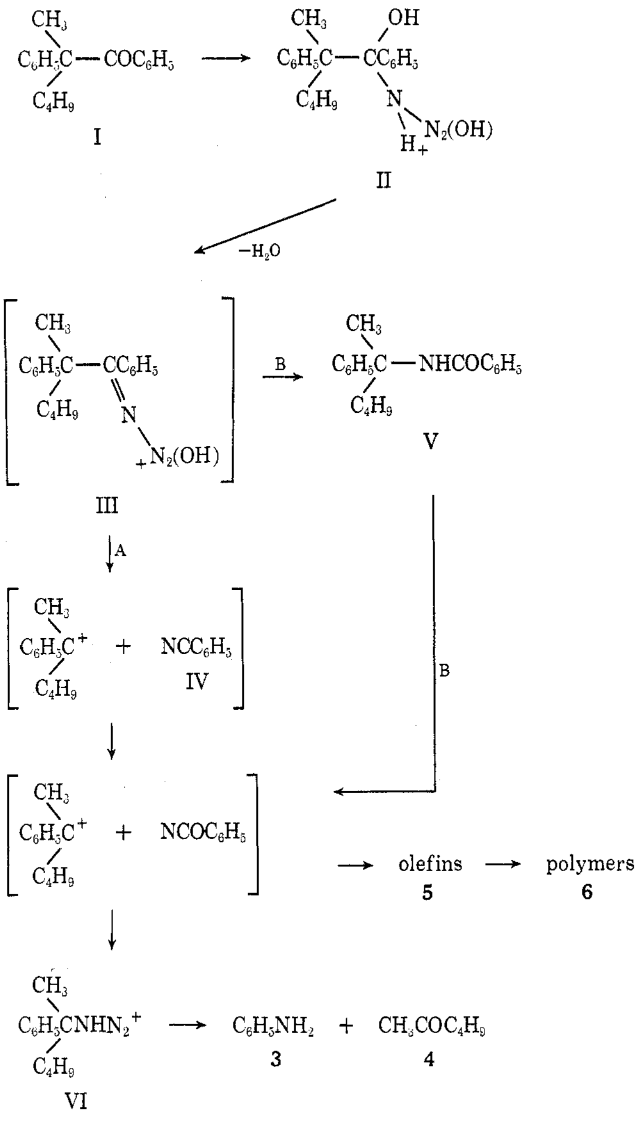
Similarities in the behavior of α-trisubstituted aralkyl ketones and ketoximes were observed during the Schmidt reaction and Beckmann rearrangement in polyphosphoric acid. Both reactions involve fragmentation to carbonium ion and nitrile or amide. The carbonium ion will react with azide to yield an aralkyl azide which rearranges to form aniline. The mechanism is discussed.

Our interest in the Beckmann and Schmidt reaction had as its focal point the behavior of α-trisubstituted aralkyl ketones and ketoximes under rearrangement conditions, particularly those considered strongly acidic such as polyphosphoric acid. Only a limited number of examples of α-trisubstituted aralkyl ketoxime systems have been examined in the case of the Beckmann rearrangement.[4,5] No studies of the Schmidt reaction of aralkyl ketones have been reported in this medium. Both reactions have certain similarities provided that they are compared on common grounds, *i.e.*, analogous ketone and ketoxime structures under the same reaction conditions.

Results and Discussion

Our previous report[6] described the fate of α-aralkyl substituted carboxylic acid under Schmidt reaction conditions. The reaction products obtained when 3-phenyl-3-methylheptanone-2 (**2**) was treated with sodium azide in polyphosphoric acid at 50° for 8 hr were almost identical with those obtained by the Schmidt reaction of 2-phenyl-2-methylhexanoic acid,[6] namely, aniline (**3**), 2-hexanone (**4**), olefins (**5**), and polymer[6] (**6**), as well as 25% of the recovered ketone. Similarly 2-methyl-2-phenylhexophenone (I) under the identical conditions gave aniline (**3**), 2-hexanone (**4**), olefins (**5**), polymer (**6**), starting ketone, and benzamide. Since both starting ketones could be recovered unchanged after being heated at 50° in polyphosphoric acid for 8 hr and since benzamide was isolated on attempted Schmidt reaction, it would appear that the observed fragmentation could have occurred by either of two pathways (Chart I). If we postulate that hydrazoic acid adds to the protonated carbonyl followed by dehydration to an iminodiazonium ion, III, as proposed by Smith[7] and confirmed in spiro ketone systems,[8] then, under the reaction conditions, the iminodiazonium ion, III, would be expected to lose nitrogen to form the nitrile, IV, and carbonium ion as proposed by Conley and Nowak[8] (Chart I, pathway A). If generalized, this postulate can be correlated to both the abnormal Schmidt and Beckmann reactions. The nitrile was then hydrolyzed to amide and the carbonium ion was attacked by azide ion to form the tertiary aralkyl azide VI, which rearranged to aniline and ketone. On the other hand, if we consider that the rearrangement has occurred simultaneously with the loss of nitrogen (Chart I, pathway B), then the resulting secondary amide V could undergo cleavage to a carbonium ion and benzamide. The aniline produced could be accounted for by the same aralkyl azide intermediate VI as previously proposed for α-trisubstituted acids.[6]

CHART I



In order to test the two mechanistic pathways, each of the secondary amides was subjected to hot poly-

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[4] T. T. Conley and T. M. Tencza, *Tetrahedron Lett.*, **No. 26**, 1781 (1963).

[5] R. T. Conley, *J. Org. Chem.*, **28**, 278 (1963).

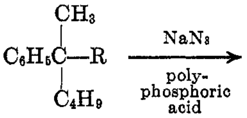
[6] R. M. Palmere and R. T. Conley, *ibid.*, **35**, 2703 (1970).

[7] P. A. S. Smith, *J. Amer. Chem. Soc.*, **70**, 320 (1948).

[8] R. T. Conley and B. E. Nowak, *J. Org. Chem.*, **26**, 692 (1961).

TABLE I

REACTIONS OF α-TRISUBSTITUTED ARALKYL COMPOUNDS WITH SODIUM AZIDE AT 50°



$$C_6H_5C(CH_3)(C_4H_9)\text{—}R \xrightarrow[\text{polyphosphoric acid}]{NaN_3}$$

Registry no.	R	Sodium azide, equiv	Unreacted material, %	Olefin, %	Polymer, %	Aniline, %
	COOH[a]	None	None	10.8	79.7	None
	COOH	1[b]	0.01	6.3	34.6	57.7[c]
36789-50-1	$COCH_3$	None	98.6	None	None	None
	$COCH_3$	1	25.0	7.0	26.0	40.8
36789-51-2	COC_6H_5	None	98.9	None	None	None
	COC_6H_5	1	58.0	8.0	5.0	24.3
20826-78-2	$NHCOCH_3$	1	None	13.6	75.7	10.7
36789-53-4	$NHCOC_6H_5$	1	None	8.2	70.1	8.0
36789-54-5	$HON{=}CCH_3$	None	None	98.3	1.2	None
		1	None	1.0	51.0	54.0[d]
36789-55-6	$HON{=}CC_6H_5$	None	None	17.7	82.5	None[e]
		1[f]	None	6.0	46.4	40.0[g,h]

[a] Reference 6. [b] Isotopically labeled ^{15}N sodium azide. [c] Contained 47.345 atom % ^{15}N greater than the theoretical naturally occurring ^{15}N. [d] Isolated as aniline hydrochloride. [e] 72.4% benzamide isolated. [f] Isotopically labeled ^{15}N sodium azide. [g] Contained 46.790 atom % ^{15}N greater than the theoretical naturally occurring ^{15}N. [h] 81.6% benzamide isolated.

phosphoric acid and sodium azide. When 2-acetamido-2-phenylhexane was heated at 50° with 1 molar equiv of sodium azide for 8 hr, none of the amide was isolated. The products of the reaction were aniline (11%), *trans*-2-phenyl-2-hexane, and polymer. Although acetamide should have been found,[9] no isolation attempt was made. On the other hand, when 2-benzamido-2-phenylhexane was subjected to the identical conditions, the reaction products were aniline (8%), 2-hexanone, *trans*-2-phenyl-2-hexene, polymer, and benzamide. Since the yields of aniline were only 11 and 8% obtained from the amides as compared with 40 and 24% obtained from the ketones, we can consider any product due to amide cleavage of secondary importance. Therefore, it appears that the operating mechanism parallels that proposed by Hill and Conley[10] for fragmentation in the Beckmann rearrangement of ketoximes but that the reaction is complicated by the aralkyl azide formed (VI).

The ketoximes of **1** and **2** were subjected to Beckmann rearrangement conditions using a variety of catalysts and solvents; however, only fragmentation products were isolated. When 3-phenyl-3-methylheptanone-2 oxime was treated with polyphosphoric acid, either at room temperature for 2 hr or at 110° for 10 min, the three isomeric olefins (2-phenyl-1-hexene, *trans*-2-phenyl-2-hexene, and *cis*-2-phenyl-2-hexene) and polymer were isolated. If 1 molar equiv of sodium azide is added to the reaction in polyphosphoric acid, at 50° for 8 hr, then aniline (54%), 2-hexanone, *trans*-2-phenyl-2-hexene, and polymer are the products. The reactions performed in polyphosphoric acid are summarized in Table I.

Theoretically, the sum of olefin, polymer, and aniline in the tables should total 100% and the amount of 2-hexanone should equal the amount of aniline. The discrepancies result from analysis by two distinct procedures, determination of aniline by hydrochloride formation and the other products by vpc.

Since Hill, Conley, and Chortyk[11,12] have shown in their crossover experiment that the amide product of the Beckmann rearrangement of 3-phenyl-3-methylbutanone-2 does undergo fragmentation and recombination in polyphosphoric acid, it would appear (despite the low yields observed) that the butyl chain in the ketones here investigated sterically interferes with the recombination process. The recombination of fragments did not occur in our case since the expected amide undergoes fragmentation under these conditions.

Furthermore, when 2-methyl-2-phenylhexaphenone oxime was allowed to react with polyphosphoric acid containing 1 molar equiv of sodium azide at 50° for 8 hr, aniline (40%), *trans*-2-phenyl-2-hexene, polymer, and benzamide (80%) were found. Thus, the amount of aniline formed indicates that cleavage of oxime to carbonium ion and nitrile is the major course of reaction.

Since the results of both the Schmidt and Beckmann reactions in polyphosphoric acid are consistent with a common mechanism, *i.e.*, essentially fragmentation being the underlying course of reaction, it was reasonable to assume that isotopically labeled aniline or amides could be prepared by this method. Both 2-phenyl-2-methylhexanoic acid and 2-methyl-2-phenylhexaphenone oxime were treated with polyphosphoric acid and 1 molar equiv of sodium azide containing ^{15}N. The results of these studies are summarized in Table I. The degree of incorporation of the ^{15}N into aniline from 2-phenyl-2-methylhexanoic acid as well as from phenyl ketoxime was determined by mass spectrometry. The results described in Table I suggests that the method could be used for ^{15}N aniline derivatives in general. Furthermore, the benzamide isolated from the reaction of 2-methyl-2-phenylhexaphenone oxime and ^{15}N sodium azide contained 0.1718 atom % more than theoretical naturally occurring ^{15}N, indicating that a very small portion of the oxime must have hydrolyzed to ketone during reaction. Therefore, if ^{15}N sodium azide were treated directly with the ketone, isotopically labeled benzamide would have been formed.

Experimental Section

Melting and boiling points are uncorrected. Infrared spectra were obtained with a Beckman IR-10 grating spectrophotometer

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(9) A. G. Mohan and R. T. Conley, *J. Org. Chem.*, **34**, 3529 (1969).

(10) R. K. Hill and R. T. Conley, *J. Amer. Chem. Soc.*, **82**, 645 (1960).

(11) R. T. Conley, *J. Org. Chem.*, **28**, 278 (1963).

(12) R. K. Hill, R. T. Conley, and O. T. Chortyk, *J. Amer. Chem. Soc.*, **87**, 5646 (1965).

and were consistent with the structure. Vpc was performed on an F & M Model 720 gas chromatograph as follows: 6 ft × 0.25 in. in 10% silicone gum nitrile on Chromosorb P, programmed from 60 to 220° at 20°/min with a helium flow rate of 60 cm^3/min, 185° isothermal.

2-Phenyl-2-methylhexanoic Acid.—The acid was prepared in 89% yield as previously described,[6] bp 154–156° (4 mm)

3-Phenyl-3-methylheptanone-2.—An ethereal solution of 0.7 *M* methyllithium (85 ml) was added slowly over a 1.5-hr period to a solution of 6.0 g (0.029 mol) of 2-methyl-2-phenylhexanoic acid in 150 ml of anhydrous ether cooled in an ice bath. The red solution was stirred for an additional 30 min and quenched with 100 ml of water, and the ethereal layer was separated. The aqueous portion was extracted twice with 100-ml portions of ether. The ethereal portions were combined, washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to give 4.5 g (80%) of 3-phenyl-3-methylheptanone-2. The crude ketone was distilled to give 4.28 g, bp 124–126° (3.5 mm).

Vpc (20 ft, 30% SE-30) analysis indicated 98% purity. An analytical sample was trapped.

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.81. Found: C, 82.18; H, 9.77.

3-Phenyl-3-methylheptanone-2 oxime (7.0 g) was prepared by literature procedure[13,14] and after three recrystallizations gave 5.42 g of 3-phenyl-3-methylheptanone-2 oxime, mp 66.5–67.5°.

Anal. Calcd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.39. Found: C, 76.50; H, 9.70; N, 6.30.

The 2,4-dinitrophenylhydrazone was prepared as described by Schriner, Fuson, and Curtin.[13] After four recrystallizations from dilute alcohol, the purified derivative had mp 126–128°.

Anal. Calcd for $C_{20}H_{24}N_4O_4$: C, 62.48; H, 6.29; N, 14.58. Found: C, 62.48; H, 6.31; N, 14.33.

2-Methyl-2-phenylhexaphenone.—Oxalyl chloride (12.7 g, 0.10 mol) was added to a solution of 2-phenyl-2-methylhexanoic acid in 50 ml of dry benzene and refluxed for 2 hr. The excess oxalyl chloride was distilled at atmospheric pressure, during which time portions of dry benzene were added to the flask until the temperature of the distillate reached 78°. The acid chloride was not purified further but rather was cooled in an ice bath and treated drop by drop with an ethereal solution of phenylmagnesium bromide prepared from 9.4 g (0.060 mol) of bromobenzene, 1.5 g (0.060 g-atom) of magnesium turnings, and 70 ml of anhydrous ether.

The Gilman test for Grignards was positive after 10 min at room temperature. The solution after refluxing for 15 min gave a positive Gilman test.

The ether was removed by distillation at atmospheric pressure, refluxed at 70° for 1 hr, and stirred overnight at room temperature. The mixture was then treated with ice followed by 100 ml of saturated ammonium chloride solution, and the organic phase was separated. The aqueous portion was extracted with ether. The ethereal portions were combined, washed with water, and dried over anhydrous magnesium sulfate, and the solvent was evaporated *in vacuo*. Distillation of the oily product gave 5.4 g of 2-methyl-2-phenylhexaphenone, bp 130–132° (0.1 mm) [lit.[14] bp 150–152° (0.5 mm)], $n^{20}D$ 1.5578.

The 2-methyl-2-phenylhexaphenone oxime was prepared by a literature procedure[13] and crystallized from ethanol–water, mp 72–76°. Three recrystallizations from dilute ethanol gave 0.488 g of 2-methyl-2-phenylhexaphenone oxime, mp 128–129°.

Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.97. Found: C, 81.00; H, 8.23; N, 4.83.

The 2,4-dinitrophenylhydrazone of 2-methyl-2-phenylhexaphenone was prepared by the procedure described by Schriner, Fuson, and Curtin[13] and after three recrystallizations from dilute ethanol had mp 155–157°.

Anal. Calcd for $C_{24}H_{26}N_4O_4$: C, 71.62; H, 6.51; N, 13.91. Found: C, 71.42; H, 6.53; N, 14.16.

The 2-acetamido-2-phenylhexane, mp 110–111°, and the 2-benzamido-2-phenylhexane, mp 146–147°, were prepared as previously described.[6]

Schmidt Reactions of Ketones.—Essentially the same procedure as described for the Schmidt reaction of acids[6] was used for the attempted rearrangement of 2-methyl-2-phenylhexaphenone and 3-phenyl-3-methylheptanone-2.

2-Methyl-2-phenylhexaphenone.—Sodium azide (0.65 g, 0.01 mol) was added to 2.67 g (0.01 mol) of 2-methyl-2-phenylhexaphenone in 50 g of polyphosphoric acid at 50° and stirred for 8 hr. The flask was filled with crushed ice. The cold aqueous mixture was extracted three times with 50-ml portions of methylene chloride, which was subsequently washed with water and dried over anhydrous magnesium sulfate and the solvent was evaporated at reduced pressure. The residual oil was diluted with ether to give 240 mg of benzamide, mp 124° (lit.[13,14] mp 128°), identified by comparison of the infrared and mixture melting point with those of an authentic sample. The aqueous polyphosphoric acid was basified with solid sodium hydroxide and ice maintaining a temperature below 25° and was extracted with three 50-ml portions of methylene chloride. The methylene chloride was washed with water and dried over anhydrous magnesium sulfate, and the solvent was removed at reduced pressure. Dilution with ether gave an additional 244 mg of benzamide. The ethereal mother liquors were examined by vpc (Silicone Gum Nitrile) analysis indicating four components.

The first component had a retention time of 3.2 min (7.76%) and was identified as *trans*-2-phenyl-2-hexene by its retention time.

The second component had a retention of time 3.8 min (24.3%) and was identified as aniline by isolation and derivatization to aniline hydrochloride.

The third component had a retention time of 5.8 min (58.0%) and was identified as 2-methyl-2-phenylhexaphenone by peak enhancement and comparison of its complete infrared spectrum with the spectrum of an authentic sample.

The fourth component had retention times of 8.1, 8.3, and 9.1 min (5.0% total) and was identified as polymeric material by retention time and infrared comparison with a sample as previously described.[6]

3-Phenyl-3-methylheptanone-2.—A mixture of 1.63 g (0.008 mol) of 3-phenyl-3-methylheptanone-2 in 38 g of polyphosphoric acid at 50° was treated with 0.560 g (0.008 mol) of sodium azide as previously described for 8 hr. Vpc (silicone gum nitrile) analysis showed five components.

The **first component** had a retention time of 1.2 min (29.3%) and was identified as hexanone-2 by its retention time.

The **second component** had a retention time of 3.2 min (8.3%) and was identified as *trans*-2-phenyl-2-hexene by its retention time.

The **third component** had a retention time of 3.8 min (40.8%) and was identified as aniline by its retention time and peak enhancement.

The **fourth component** had a retention time of 6.2 min (24.7%) and was identified as 3-phenyl-3-methylheptanone-2 by peak enhancement and comparison of its complete infrared spectrum with the spectrum of an authentic sample.

The **fifth component** had retention times of 8.1, 8.3, and 9.1 min (26.0% total) and was identified as polymeric products based on its retention time.

Without Sodium Azide.—When each of the ketones above was heated at 50° in polyphosphoric acid for 8 hr, the ketones were recovered unchanged in almost quantitative amounts.

Registry No.—3-Phenyl-3-methylheptanone dinitrophenylhydrazone, 36789-56-7; 2-methyl-2-phenylhexaphenone dinitrophenylhydrazone, 36789-57-8.

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[13] R. L. Schriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," Wiley, New York, N. Y., 1956, p 316.

[14] J. B. Conant and G. H. Carlson, *J. Amer. Chem. Soc.*, **54**, 4048 (1932).