[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE OHIO STATE UNIVERSITY]

Reaction of Unsymmetrical Cycloalkanones and Hydrazoic Acid; Synthesis of *d,l*-Lysine[1]

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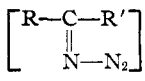
Reaction of 2-alkylcyclopentanones and 2-alkylcyclohexanones with hydrazoic and sulfuric acids at 3–7° results in migration of the 2-alkylmethylene group to yield 6-alkyl-2-piperidones (63–80%) and 7-alkyl-2-ketohexamethylenimines (58–87%), respectively. Reactions of 2-carbethoxycyclohexanone (D. W. Adamson, *J. Chem. Soc.*, 1564 (1939)) and 2-cyanocyclohexanone with hydrazoic and sulfuric acids result in migration of the electronegatively-substituted methylene groups with formation of 7-carbethoxy-2-ketohexamethylenimine (80%) and 7-cyano-2-ketohexamethylenimine (69.5%), respectively. A novel synthesis of *d,l*-lysine dihydrochloride (59.5%) from 2-cyanocyclohexanone and hydrazoic acid has been devised. Reaction of 2-chlorocyclohexanone results in migration of either the methylene or the chloromethylene group to yield, depending on experimental conditions, 3-chloro-2-ketohexamethylenimine (8.9–31.4%), adipamide (0–10.4%) and polymer (~80%, unidentified).

The Schmidt reaction[2] of ketones and hydrazoic acid results principally in formation of substituted amides and nitrogen (Equation 1).

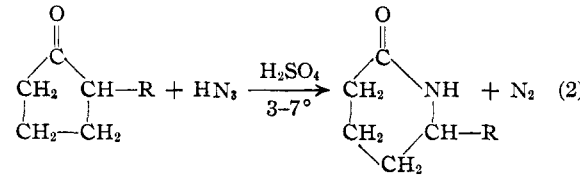
$$R\text{-}CO\text{-}R + HN_3 \longrightarrow R\text{-}CO\text{-}NH\text{-}R + N_2 \quad (1)$$

The mechanism of this acid-catalyzed reaction has been a subject of recent interest and it appears that the rearrangement involves the formation of a hydroxycarbonium ion followed by addition of hydrogen azide and subsequent electrophilic attack on nitrogen.[3] Smith, *et al.*,[3b,4a,4b] suggest that transmigration of a Beckmann-type intermediate



is a principal factor governing the course of rearrangement. In support of this postulate, it was found[4a,4b] that the direction of rearrangement in unsymmetrical diaryl and alkylaryl ketones is dependent on the steric environment of the carbonyl group and not on "migration aptitude" of groups.

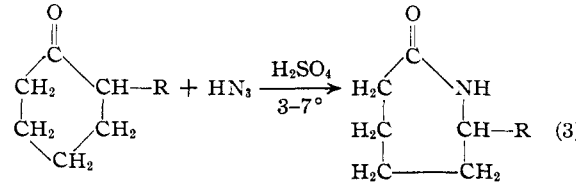
In synthesis of amino acids from hydrazoic acid and cycloalkanones (the latter substituted in the 2-position with electrophilic or nucleophilic groups of different sizes) it became possible to differentiate in non-aromatic systems between electronic effects in the migrating group and migration in an intermediate which might be affected by steric interaction of a neighboring group. In reaction with hydrazoic and sulfuric acids at 3–7°, cyclopentanones substituted in the 2-position with groups releasing electrons (*e.g.*, methyl, ethyl, propyl, isopropyl) gave the corresponding 6-alkyl-2-piperidones (Equation 2) in 45–75% yield (Table I); there was no evidence of formation of the isomeric 3-alkyl-2-piperidone. Since it was desirable to determine precisely the specificity of rearrangement, crude products from



(2)

each reaction were fractionally crystallized and non-crystallizable materials were chromatographed on alumina or silicic acid–Celite to separate any isomeric alkylpiperidones. The reliability of the chromatographic separations was demonstrated by separating mixtures of 2-piperidone and 2-keto-7-methylhexamethylenimine in 98 and 88% efficiency on alumina; using silicic acid–Celite as adsorbent, the homologs, 2-ketohexamethylenimine and 2-keto-7-methylhexamethylenimine, were separated in 90 and 86% yields. Analysis of the crude products from reactions of 2-alkylcyclopentanones and hydrazoic acid revealed that, at a minimum, they contained 82–94% of 6-alkyl-2-piperidone (Table I); the remaining products consisted primarily of amino acids, tetrazoles and initial materials.

Reactions of 2-alkylcyclohexanones (methyl, ethyl, propyl) with hydrazoic and sulfuric acids were studied to determine if the direction and specificity of migration in cyclohexanones is similar to that in cyclopentanones; von Braun and Heymons[5] report that 2-keto-7-methylhexamethylenimine is obtained in 45% yield from 2-methylcyclohexanone. In the present experiments, the only lactams obtained were 7-alkyl-2-ketohexamethylenimines, formed by migration of the 2-alkylmethylene group (60–87% yield, 74–92% recovery of single isomer, Table II, Equation 3). Since Beckmann rearrangement of oximes from 2-alkylcyclo-



(3)

pentanones and 2-alkycyclohexanones yields but one isomer,[6] identical with those obtained in this study, it appears that steric factors which influence

(1) Presented at the 117th Meeting of the American Chemical Society, Philadelphia, Pa., April 11, 1950. This is based on the thesis presented to the Graduate School of The Ohio State University by James C. Kirk in partial fulfillment of the requirements for the Ph.D. degree, December, 1949.

(2) H. Wolff, "The Schmidt Reaction," in R. Adams, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 307.

(3) (a) M. S. Newman and H. Gildenhorn, THIS JOURNAL, **70**, 317 (1948); (b) P. A. S. Smith, *ibid.*, **70**, 320 (1948); (c) P. A. S. Smith and D. M. Howell, 116th Meeting of the American Chemical Society, September 18, 1949.

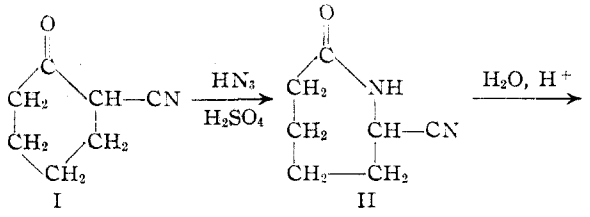
(4) (a) P. A. S. Smith and J. P. Horwitz, THIS JOURNAL, **72**, 3718 (1950); (b) P. A. S. Smith and B. Ashby, *ibid.*, **72**, 2503 (1950); *cf.* D. E. Pearson and C. M. Greer, *ibid.*, **71**, 1895 (1949); H. H. Szmant and V. V. McIntosh, *ibid.*, **72**, 4835 (1950); J. K. Sanford, F. T. Blair, J. Arroya and K. W. Sherk, *ibid.*, **67**, 1941 (1945).

(5) J. v. Braun and A. Heymons, *Ber.*, **63**, 502 (1930).

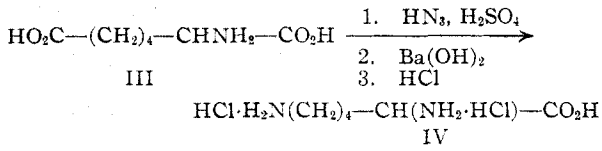
(6) (a) J. L. Hildebrand and M. T. Bogert, THIS JOURNAL, **58**, 650 (1936); (b) H. E. Ungnade and A. D. McLaren, *J. Org. Chem.*, **10**, 29 (1945); A. D. McLaren and G. Pitzl, THIS JOURNAL, **67**, 1625 (1945).

the formation of the *trans*-oximino-2-alkylcycloalkanones are being manifested in reactions of the analogous 2-alkylcycloalkanones with hydrazoic acid. Rate of reaction with hydrazoic acid[7] and yield of lactam are greater with 2-alkylcyclohexanones than with 2-alkylcyclopentanones; an analogous increase in yield has been observed in Beckmann rearrangement of oximes of these ketones.[6]

2-Carbethoxycyclopentanone and 2-carbethoxycyclohexanone (each substituted in the 2-position by a group which attracts electrons) react with hydrazoic acid and sulfuric acid to yield 2-amino-1,6-hexanedioic and 2-amino-1,7-heptanedioic acids[8] (80%), respectively, after hydrolysis. Rearrangement in these compounds involves migration of the electronegatively-substituted methylene group and is therefore identical in direction with that obtained with 2-alkylcycloalkanones. To determine the effect of a smaller electron-attracting group on the direction of rearrangement, 2-cyanocyclohexanone (I) was treated with hydrazoic and sulfuric acids. The direction of migration was identical with the previous examples and 7-cyano-2-ketohexamethylenimine (II) was obtained (69.5%). There was no evidence for the formation of the isomer, 3-cyano-2-ketohexamethylenimine. The structure of the cyanolactam (II) was established by hydrolysis to 2-amino-1,7-heptanedioic acid (III). These reactions were utilized for synthesis of *d,l*-lysine dihydrochloride (IV, 59.5%) from 2-cyanocyclohexanone and two equivalents of hydrogen azide, by the sequence

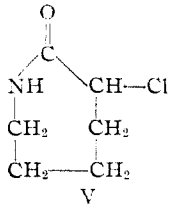


I II



III IV

Reaction of 2-chlorocyclohexanone with hydrazoic acid gave products resulting from migration of the chloromethylene group and the α-methylene group; the products depend on the conditions of the experiment. In sulfuric acid, reaction proceeds



V

with extensive evolution of hydrogen chloride and yields 3-chloro-2-ketohexamethylenimine (V, 8.9%) and an unidentified polymer[9] (>80%, possibly from 2-ketoazacyclohept-7-ene); in chloroform at 30° with moist hydrogen chloride as catalyst, the products are adipamide[10] (10.5%), 3-chloro 2-ketohexamethylenimine (26.4%) and polymer; in ethanol, at 40–45°, with concentrated sulfuric acid as catalyst, the yield of (V) is increased to 31.4%. 3-Chloro-2-ketohexamethylenimine was identified, after hydrolysis with hydrochloric acid, neutralization and benzoylation, as 6-benzoylamino-2-chlorohexanoic acid; amination and subsequent hydrolysis of this derivative yields *d,l*-lysine.[11]

It appears from this investigation that, in the transition state, interference from chlorine may be less than that from alkyl, cyano or carbethoxy groups,[12] and that specificity of reaction is dependent on temperature.[4b] The Beckmann rearrangement of unsymmetrical ketones becomes less specific at elevated temperature and yields almost equivalent amounts of isomeric products.[13] Although, in both the Beckmann and Schmidt reactions, little evidence has been obtained concerning the steric nature of intermediates as a function of temperature or solvent composition, it may be surmised that the lack of specificity during rearrangement of 2-chlorocyclohexanone at higher temperatures is related to rapid *syn–anti* isomerization processes.

Acknowledgment.—The authors wish to thank Dr. M. S. Newman for providing the stimulus for inception of certain phases of this investigation.

Experimental

Reagents.—2-Methylcyclopentanone,[14] 2-ethylcyclopentanone,[14] 2-propylcyclopentanone,[15] 2-isopropylcyclopentanone,[16,17] 2-methylcyclohexanone[18] and 2-ethylcyclohexanone[19] were prepared by hydrolysis and decarboxylation of the corresponding 2-alkyl-2-carbethoxycycloalkanone[20] with 47% sulfuric acid. 2-Chlorocyclohexanone was obtained by chlorination of cyclohexanone[21]; reaction of 2-chloro-

(7) These observations are in agreement with the predicted effects of i-strain on the rate of addition reactions of cyclic ketones, H. C. Brown, 118th Meeting of the American Chemical Society, Chicago, Illinois, August, 1950; *cf.* S. L. Friess, THIS JOURNAL, **71**, 2571 (1949); H. C. Brown, R. S. Fletcher and R. B. Johannesen, *ibid.*, **73**, 212 (1951).

(8) D. W. Adamson, *J. Chem. Soc.*, 1564 (1939); *cf.* K. V. Schmidt, *Frdl.*, **16**, 2862 (1931); *C. A.*, **21**, 3057 (1927).

(9) The rubber-like polymer is translucent, water-soluble, contains no chlorine, and evolves ammonia when heated with sodium hydroxide.

(10) Adipamide may have been produced by reaction of 2-ketoazacyclohept-7-ene or its hydrolysis products, *i.e.*, adipamide half-aldehyde, with hydrogen azide.

(11) A. Galat, THIS JOURNAL, **69**, 86 (1947).

(12) This is to be expected based on the order of size of groups.

(13) A. D. McLaren and R. E. Schachat, *J. Org. Chem.*, **14**, 254 (1949).

(14) F. H. Case and E. E. Reid, THIS JOURNAL, **50**, 3064 (1928), Van Rysselberge, *Bull. sci. acad. roy. Belg.*, [5] **11**, 171 (1921); (*C. A.*, **21**, 375 (1927)).

(15) G. Chiurdoglu, *Bull. soc. chim. Belg.*, **48**, 35 (1934).

(16) A. Kotz and P. Schuler, *Ann.*, **350**, 217 (1906).

(17) 2-Isopropylcyclopentanone forms a 2,4-dinitrophenylhydrazone which melts at 154.0–154.6°. *Anal.* Calcd. for $C_{14}H_{18}N_4O_4$: C, 54.89; H, 5.92; N, 18.29. Found: C, 55.12; H, 5.66; N, 18.43.

(18) M. S. Newman and H. M. Walborsky, THIS JOURNAL, **72**, 4296 (1950).

(19) L. Ruzicka and E. Peyer, *Helv. Chim. Acta*, **18**, 676 (1935).

(20) There is a great difference in the rates of hydrolysis and decarboxylation of 2-alkyl-2-carbethoxycyclopentanones and 2-alkyl-2-carbethoxycyclohexanones. 2-Carbethoxy-2-propylcyclopentanone and 2-carbethoxy-2-isopropylcyclopentanone react in 4–6 hours with hot 47% sulfuric acid to yield 2-propylcyclopentanone (63%) and 2-isopropylcyclopentanone (52.5%); whereas 2-carbethoxy-2-ethylcyclohexanone was refluxed with 47% sulfuric acid for 48 hours before 28% reaction was obtained. 2-Carbethoxy-2-propylcyclohexanone and 2-carbethoxy-2-isopropylcyclohexanone were practically unaffected (<5%) by refluxing 47% sulfuric acid in 48 hours.

(21) M. S. Newman, M. D. Farbmann and H. Hypsher, *Org. Syntheses*, **25**, 22 (1945).

TABLE I

REACTION OF 2-ALKYLCYCLOPENTANONES WITH HYDRAZOIC ACID

Cyclopentanone	Product, piperidone	M.p., °C.[a]	B.p., °C.	Mm.	Yield, % crude	Yield, % pure product	Pure product % of total product[b]
Cyclopentanone	Piperidone		145–146	18[c]		79.8[d]	
2-Methyl-	6-Methyl-2-[e,f,g]	87.5–88.0[e]	132–134	15[e]	71.5[h]	74.5[d], 58.8[h]	89,[d] 82[h]
2-Ethyl-	6-Ethyl-2-[i,j]	88.0–88.8[i]	145–150	15	86.5[h]	62.5,[d] 64.8[h]	83,[d] 85.6[h]
2-Propyl-	6-Propyl-2-[k,l]	91.4–92.6[k]	146–148	13	78.0[h]	61.1,[d] 67.4[h]	89.4,[d] 94[h]
2-Isopropyl-	6-Isopropyl-2-[m]	85.2–86.0	148–150	15	71.5[h]	45.5[d], 63.1[h]	78[d], 84.7[h]

[a] All melting points are corrected. [b] Based on recovery of single isomer from crude product. [c] O. Wallach, *Ann.*, **312**, 179 (1900), reports b.p. 137° (14 mm.). [d] Procedure 1. [e] J. G. Hildebrand and M. T. Bogert, THIS JOURNAL, **58**, 650 (1936) report m.p. 87.2–88.0°, b.p. 140–148° (28 mm.). [f] Hydrolyzed to 5-aminohexanoic acid, m.p. 166–167°. [g] *p*-Phenylphenacyl ester of deaminated acid, hexanoic acid, m.p. 64.2–65.4°; N. L. Drake and J. Bronitsky, THIS JOURNAL, **52**, 3715 (1930) report m.p. 65°. [h] Procedure 2b. [i] Ref. *e*, m.p. 88.5–89.6°. [j] *p*-Phenylphenacyl ester of deaminated amino acid, heptanoic acid, m.p. 60–61° (ref. *e*, m.p. 62°). [k] Ref. *e*, m.p. 91.5–92.4°. [l] *p*-Phenylphenacyl ester of deaminated acid, octanoic acid, m.p. 66–67° (ref. *e*, m.p. 67°). [m] New compound.

TABLE II

REACTION OF 2-SUBSTITUTED CYCLOHEXANONES WITH HYDRAZOIC ACID

Cyclohexanone	Product, hexamethylenimine	M.p., °C.[a]	Yield, % crude	Yield, % pure product	Pure product, % of total product[b]
2-Methyl-	2-Keto-7-methyl-[c,d,e]	90.5–91.5[c,f]	70[g], 95.5[h]	58.3,[g] 71[h]	74,[g] 74.5[h]
2-Ethyl-	7-Ethyl-2-keto-[i]	91.5–92.0	93[h]	78[h]	84[h]
2-Propyl-	2-Keto-7-methyl-[j]	98.6–99.2	96.5[k]	87[k]	91.5[k]
2-Cyano-	7-Cyano-2-keto-[i]	126.6–127.4		69.5	
2-Carbethoxy-	7-Carbethoxy-2-keto-[l]	97.2–98.0		80[l]	
2-Chloro-	3-Chloro-2-keto-[i]	97.2–98.0		8.9,[m] 26.4,[n] 31.4[o]	

[a] All melting points are corrected. [b] Based on recovery of single isomer from crude product. [c] O. Wallach, *Ann.*, **346**, 252 (1906) reports m.p. 90.5–91.5°. [d] Hydrolyzed to 6-aminoheptanoic acid; m.p. 200.2–201.4°; J. G. Hildebrand and M. T. Bogert, THIS JOURNAL, **58**, 650 (1936) report m.p. 196.0–197.5°. [e] *p*-Phenylphenacyl ester of deaminated amino-acid, heptanoic acid, m.p. 60.8–61.6°; N. L. Drake and J. Bronitsky, *ibid.*, **52** 3715 (1930) report m.p. 62°. [f] B.p. 155–160° (22 mm.). [g] Procedure 3. [h] Procedure 2a. [i] New compound. [j] A. D. McLaren and G. Pitzl, *ibid.*, **67**, 1625 (1945) report m.p. 100.5–101.5°. [k] Procedure 2b. [l] D. W. Adamson, *J. Chem. Soc.*, 1564 (1939); estimated yield. [m] Reaction catalyzed by sulfuric acid. [n] Catalyzed by hydrogen chloride; adipamide, m.p. 223–224° (from ethanol) was obtained in 10.5% yield; product identified by analysis and by hydrolysis to adipic acid. L. Henry, *Jahresber*, 1334 (1885), reports m.p. of adipamide as 220°. [o] Reaction catalyzed by sulfuric acid in ethanol at 40–45°.

cyclohexanone and potassium cyanide yielded 2-cyanocyclohexanone.[22] 2-Allylcyclohexanone[23] was hydrogenated over Raney nickel to yield 2-propylcyclohexanone.

2-Propylcyclohexanone.—2-Allylcyclohexanone (67 g., 0.48 mole) in absolute ethanol (150 ml.) was reduced with Raney nickel (3 g.) and hydrogen at 40 pounds per square inch. After hydrogen (0.48 mole) had been absorbed, the catalyst was filtered and solvent was removed by distillation at atmospheric pressure. The residue was dissolved in ether (150 ml.) and stirred with an aqueous solution of sodium hydroxide (1%) and potassium permanganate (1%) to remove 2-allylcyclohexanone. The permanganate solutions were extracted with ether. The ether extracts were combined, washed with water, and dried over sodium sulfate. Distillation of the product, after removal of ether, yielded 2-propylcyclohexanone (54 g., 79.5%); b.p. 96–7° (25 mm.); $n^{20.7}$D 1.4532; lit. n^{14}D 1.4555.[23]

Technique.—The reactions of 2-alkylcycloalkanones with hydrazoic acid were conducted under conditions in which experimental variables (temperature, order and rate of addition, etc.) were kept at a minimum. In experiments in which the products were separated by chromatographic techniques, the ketones were used in one-hundredth molar quantities; if the products were separated by distillation, the reactions were conducted with one-tenth mole of ketone. Hydrazoic acid was used in 11.5% excess. With cyclopentanone as reference ketone, the procedures gave reproducible yields of 2-piperidone of 79.5 ± 2%. The formation of tetrazoles was minimized by adding dilute hydrazoic acid (a standardized solution in chloroform) dropwise to a rapidly stirred mixture of ketone and catalyst in excess chloroform. The extent of reaction was followed by the volume of nitrogen liberated. In many experiments the reaction mixture was neutralized with aqueous sodium hydroxide at temperatures below 10° and then extracted with chloroform; however, the reactions were best stopped by quenching the mixtures on ice and then rapidly extracting the cold aqueous layer many times with large volumes of chloroform.

Separation and purification of product, after solvent had been removed under vacuum and the yield of crude material had been determined, was made by at least two of three procedures: (1) distillation of crude product in vacuum and recrystallization of the purified product, (2) recrystallization of crude product and subsequent chromatography of an aliquot of all mother liquors, and (3) chromatography of an aliquot of the total crude product. *Procedure 1* was used to determine initial information concerning the nature of the rearrangement of individual ketones and to prepare large quantities of products; the efficiency of this procedure as a separation method was less than that of the subsequent chromatographic procedure. *Procedure 2* gave the highest efficiency and greatest reproducibility. In this method, crude product was recrystallized from petroleum ether (30–60°) and weighed. An aliquot of the mother liquors was chromatographed on alumina (*Procedure 2a*) or silicic acid–Celite 535[24] (*Procedure 2b*), developed with ethyl or tertiary butyl alcohol, streaked with alkaline potassium permanganate and eluted with ethanol (15%)–petroleum ether. The product crystallized from the eluate after solvent was evaporated; micro recrystallization of the adsorbate was occasionally necessary to obtain a pure product. *Procedure 3* was used with efficiency and rapidity in many experiments; however, the results were not as reproducible as those from Procedure 2.

The yield of lactam (Tables I and II), calculated by two methods, was based on (1) crude product and (2) purified product; the separation efficiency (minimum single isomer percentage) was based on recovery of pure product from crude product. Typical procedures for the reactions of 2-alkylcycloalkanones with hydrazoic acid and the subsequent separation methods are described in following experimental sections.

(22) R. E. Meyer, *Helv. Chem. Acta*, **16**, 1291 (1933).

(23) R. Cornubert and A. Maurel, *Bull. soc. chim.*, [4] **49**, 1498, 1506 (1931).

(24) Silicic acid (C.P.) was obtained from Colemen and Bell Co., Norwood, Ohio; Celite 535 is manufactured by Johns-Manville Co., New York, N. Y.

Chromatographic Separation of 2-Keto-7-methylhexamethylenimine and Piperidone on Alumina.—A mixture of 2-keto-7-methylhexamethylenimine (50 mg.) and piperidone (50 mg.) dissolved in 30–60° petroleum ether (25 ml.) was chromatographed on a column of activated alumina (35 × 200 mm.) using 2% absolute ethanol in 30–60° petroleum ether (500 ml.) as developer. The column was extruded and streaked with alkaline potassium permanganate solution (0.7% potassium permanganate in 5% sodium hydroxide); adsorbate was located near the bottom of the column. Elution of this zone with 15% absolute ethanol in 30–60° petroleum ether (200 ml.) gave 2-keto-7-methylhexamethylenimine (49 mg., 98% recovery), m.p. 90–91°; lit.[25] 90–91°, after removal of solvents. Elution of the remainder of the column gave no residue after evaporation of the solvents. Evaporation of the developing solution gave piperidone (44 mg., 88% recovery).

The alumina adsorbent was Alcoa 200-mesh which had been ground in a ball mill to a very fine powder and activated by heating for 5 hours at 400°. The alumina was kept in stoppered flasks stored over phosphoric anhydride. In packing the column, it was necessary to make all transfers in an anhydrous atmosphere; if the alumina became hydrated, the chromatographic separations were not reproducible. The petroleum ether was washed with 100% sulfuric acid and water, dried over calcium chloride, filtered through a column of activated alumina and redistilled. In many cases, development of the adsorbate with ethanol–petroleum ether led to esterification of the lactam; this could be avoided usually by using *t*-butyl alcohol (4%) in petroleum ether as developer.

Chromatographic Separation of 2-Ketohexamethylenimine and 2-Keto-7-Methylhexamethylenimine on Silicic Acid–Celite.—A mixture of 2-ketohexamethylenimine (50 mg.) and 2-keto-7-methylhexamethylenimine (50 mg.) was dissolved in C. p. benzene (25 ml.) and chromatographed on a column (55 × 200 mm.) of silicic acid–Celite (3:1 by volume; the adsorbent was washed with absolute methanol and dried for 4 hours at 400°). The column was developed with 2% absolute methanol in C. p. benzene (500 ml.), extruded, and streaked with alkaline potassium permanganate solution. Adsorbate zones were located near the top and bottom of the column. Elution of the top zone with absolute methanol (200 ml.) gave 2-ketohexamethylenimine (45 mg., 90% recovery) after removal of solvent; m.p. 67–68°, lit.[26] 67–68°; mixed m.p., no depression. Elution of the bottom zone with absolute methanol (200 ml.) and evaporation of solvents yielded 2-keto-7-methylhexamethylenimine (43 mg., 86% recovery); m.p. 90–91°, lit.[25] 90–91°; no depression by an authentic sample.

Reaction of 2-Isopropylcyclopentanone with Hydrazoic Acid (Procedure 2b).—Hydrazoic acid (0.495 g., 0.01 mole) in chloroform (12 ml.) was added, dropwise, in two hours to a stirred mixture of 2-isopropylcyclopentanone (1.26 g., 0.01 mole), concentrated sulfuric acid (4 ml.) and chloroform (10 ml.) at 3–7°. After addition was completed, the mixture was stirred for one hour, then poured on ice. The phases were separated and the aqueous layer was extracted with chloroform (ten 30-ml. portions). The chloroform extract was washed with 10% potassium carbonate solution, washed with water, and dried over sodium sulfate. After chloroform had been removed at reduced pressure, crude lactam (1.01 g., 71.5%) crystallized; recrystallization of the crude product from 30–60° petroleum ether gave 6-isopropyl-2-piperidone (0.79 g.); m.p. 85.2–86°; white needles.

Most of the petroleum ether was distilled from the mother liquor of recrystallization and the residue was diluted to a volume of 25 ml. One-half of this solution was chromatographed on silicic acid–Celite using 2% absolute ethanol in benzene (500 ml.) as developer. Adsorbate was located in a narrow zone near the middle of the column. Elution of this zone with 15% absolute ethanol (200 ml.) in 30–60° petroleum ether gave **6-isopropyl-2-piperidone** (0.10 g.), m.p. 85–86°. Total yield, 0.89 g. (63.1%); thus 84.7% of the total product was 6-isopropyl-2-piperidone.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.98; H, 10.71; N, 9.93. Found: C, 68.64; H, 10.68; N, 10.16.

Reaction of 2-Ethylcyclopentanone with Hydrazoic Acid (Procedure 3).—2-Ethylcyclopentanone (1.12 g., 0.01 mole) reacted with hydrazoic acid at 3–7° by the procedure described for 2-isopropylcyclopentanone. The crude product (1.11 g., 86.5%) was diluted to a volume of 50 ml. with benzene. A 5-ml. aliquot was chromatographed on silicic acid–Celite. After elution and evaporation of the solvents, as described in previous separations, the top portion of the column gave white crystals of 6-ethyl-2-piperidone (0.095 g., 64.8%); m.p. 88.0–88.9°, lit.[6a] m.p. 88.5–89.6°. The recovery of 6-ethyl-2-piperidone from the crude reaction product was 85.6%.

(**Procedure 1**).—Procedure 3 was repeated using tenfold quantities of reagents. The stirred reaction mixture was neutralized below 10° with 30% sodium hydroxide. Water was added, the layers were separated, and the aqueous layer was continuously extracted with chloroform for five hours. After the chloroform extracts were combined, dried over sodium sulfate, and distilled, vacuum distillation of the residue yielded: Fraction 1, 0.5 g., b.p. up to 145° (15 mm.); Fraction 2, 7.6 g., b.p. 145–150° (15 mm.); residue 1.6 g. Fraction 2 solidified in the receiver and was identified as 6-ethyl-2-piperidone (62.5%); m.p. 88–89°; thus 83% of the total reaction product is 6-ethyl-2-piperidone.

Proof of Structure of Alkyl Lactams.—6-Alkyl-2-piperidones and 7-alkyl-2-ketohexamethylenimines were hydrolyzed to the corresponding 5- and 6-aminoalkanoic acids in 80–95% yield (Tables I and II). The typical procedure developed for the hydrolysis is: 7-ethyl-2-ketohexamethylenimine (4 g.) was refluxed for 8 hours with 47% sulfuric acid (15 ml.). The solution was almost neutralized with hot, saturated barium hydroxide solution and then centrifuged. The supernatant liquor was decanted and evaporated in vacuum on a steam-bath until crystallization began. The yield of white crystalline 6-aminoöctanoic acid (3.96 g.) is 87.5%; m.p. 191–192°. When heated above its melting point, the amino acid loses water to regenerate the original lactam; m.p. 91.5–92°. **The picrate**, prepared by heating a solution of 6-aminoöctanoic acid with an alcoholic solution of picric acid, melts at 157.5–158.6°.

Anal. Calcd. for $C_{14}H_{20}O_9N_4$: C, 43.30; H, 5.19; N, 14.43. Found: C, 43.56; H, 5.23; N, 14.60.

Hydrolysis of 6-ethyl-2-piperidone, 6-propyl-2-piperidone and 6-isopropyl-2-piperidone gave amino acids which are difficult to crystallize. These amino acids were deaminated to the corresponding alkanoic acids and then converted into their *p*-phenylphenacyl esters. The procedure developed, a modification of that by Kwisda,[27] was as follows: amino acid (3 g.) was heated in a sealed tube with 96% hydriodic acid (10 ml., sp. gr. 1.94) and red phosphorus (0.5 g.) for 12 hours at 200°. The mixture was diluted with water (35 ml.); the iodine was reduced with sulfur dioxide. The organic acid was extracted from the aqueous solution with ether. The ether extracts were combined, washed with water, dried over sodium sulfate, and evaporated. *p*-Phenylphenacyl esters (Tables I and II) were obtained by refluxing the acids with *p*-phenylphenacyl bromide.[28]

Reaction of 2-Cyanocyclohexanone with Hydrazoic Acid.—A mixture of 2-cyanocyclohexanone (12.3 g., 0.1 mole) and hydrazoic acid (4.95 g., 0.115 mole) in chloroform (77 ml.) was added, dropwise, to a stirred mixture of concentrated sulfuric acid (20 ml.) and chloroform (60 ml.) at 3–7°. The volume of nitrogen evolved was 2210 ml. (98.7% of theory, corrected). The mixture was poured on ice, the phases were separated, and the aqueous layer was extracted with chloroform. The chloroform solutions were combined, washed with 10% potassium carbonate solution, and dried over sodium sulfate. Solvent was removed at atmospheric pressure. The yellow residue which crystallized was recrystallized from a mixture of benzene and petroleum ether to give white needles of **7-cyano-2-ketohexamethylenimine** (9.42 g., 69.5%); m.p. 126.6–127.4°.

Anal. Calcd. for $C_8H_{10}ON_2$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.78; H, 7.06; N, 20.23.

The structure of 7-cyano-2-ketohexamethylenimine was established by hydrolysis to 2-amino-1,7-heptanedioic acid. 7-Cyano-2-ketohexamethylenimine (1.38 g.) was refluxed with 47% sulfuric acid for 12 hours. The solution was diluted with water (15 ml.) and almost neutralized with hot, saturated barium hydroxide solution. The mixture was centrifuged and the decantate was evaporated to dryness

(25) O. Wallach, *Ann.*, **346**, 252 (1906).

(26) O. Wallach, *ibid.*, **312**, 187 (1900); **343**, 43 (1905).

(27) A. Kwisda, *Monatsh.*, **12**, 419 (1891).

(28) N. L. Drake and J. Bronitsky, THIS JOURNAL, **52**, 3715 (1930).

under vacuum to yield white crystals of **2-amino-1,7-heptanedioic acid** (0.51 g., 29.2%); m.p. 220–222°, lit.[29] 225°. The product gave a characteristic red color with ferric chloride solution and liberated ammonia when heated with soda lime.

***d,l*-Lysine Dihydrochloride.**—A mixture of 2-cyanocyclohexanone (12.3 g., 0.1 mole) and hydrazoic acid (4.95 g., 0.115 mole) in chloroform (110 ml.) was added dropwise, in two hours, to a stirred mixture of concentrated sulfuric acid (20 ml.) and chloroform (60 ml.) at 3–7°. After addition was complete, the solution was stirred for two hours at room temperature, then slowly poured on cracked ice. The layers were separated and the chloroform layer was washed twice with 50 ml. of water. The aqueous solutions were combined, refluxed for three hours, then evaporated to a thick sirup under vacuum on a steam-bath. Hydrazoic acid (4.95 g., 0.115 mole) in chloroform (110 ml.) was added. Sulfur trioxide (*ca.* 25 g.) was distilled into the stirred solution at 40–45° until gas was evolved steadily. After evolution of gas had ceased, the mixture was stirred overnight at room temperature.

The layers were separated and the aqueous layer was almost neutralized with hot, saturated barium hydroxide solution. The mixture was centrifuged and the decantate was decolorized with activated charcoal. After adding concentrated hydrochloric acid (100 ml.) to the solution, it was evaporated to a thick sirup under vacuum on a steam-bath. The sirup was dissolved in a minimum amount of hot absolute alcohol and then cooled; ether was added in small amounts with stirring and cooling until the total volume was approximately five times that of the alcohol added. *d,l*-Lysine dihydrochloride precipitated as white crystals; the product was filtered and dried in vacuum; yield 13.0 g. (59.5%); m.p. 195–197°, lit.,[8] 187–189°. A second experiment gave a yield of 58.5%.

d,l-Lysine dipicrate (90%) was prepared from aqueous *d,l*-lysine dihydrochloride and picric acid, m.p. 183–185°, lit.,[8] m.p. 184–187°.

Anal. Calcd. for $C_{18}H_{20}N_8O_{16}$: C, 35.73; H, 3.33; N, 18.52. Found: C, 35.67; H, 3.51; N, 18.61.

(29) W. Dieckmann, *Ber.*, **38**, 1654 (1905).

Reaction of 2-Chlorocyclohexanone and Hydrazoic Acid.—A mixture of 2-chlorocyclohexanone (13.2 g., 0.1 mole) and hydrazoic acid (4.95 g., 0.115 mole) in chloroform (120 ml.) was added dropwise with stirring to a mixture of concentrated sulfuric acid (35 ml.) and absolute ethanol (100 ml.) at 40–45°. The mixture was stirred for one hour after addition of reactants, then cooled in an ice–salt mixture and neutralized with 40% sodium hydroxide at temperatures below 10°. Sodium sulfate that precipitated was filtered and washed with chloroform. The aqueous product was separated and extracted with chloroform. The chloroform extracts were combined, washed with 10% sodium carbonate solution, dried over sodium sulfate, and distilled under vacuum to yield, after removal of chloroform: Fraction 1, 2-chlorocyclohexanone, 4.66 g., b.p. 90–95° (15 mm.); Fraction 2, 0.29 g., b.p. 95–180° (15 mm.); Fraction 3, 3.05 g., b.p. 180–185° (15 mm.); residue, 1.8 g. Fraction 3 solidified to a white solid upon cooling and was identified as **3-chloro-2-ketohexamethylenimine** (31.4%); m.p. 97–98° (from 30–60° petroleum ether). Evaporation of the aqueous extract under vacuum yielded an elastic polymer.

Anal. Calcd. for $C_6H_{10}OClN$: C, 48.82; H, 6.83; N, 9.49. Found: C, 48.68; H, 6.82; N, 9.52.

6-Benzoylamino-2-chlorohexanoic Acid.—3-Chloro-2-ketohexamethylenimine (0.9 g., 0.0065 mole) was refluxed for 12 hours with concentrated hydrochloric acid (10 ml.). The solution was made basic with sodium hydroxide and cooled; benzoyl chloride (1 g.) was added with stirring and cooling. The mixture was stirred for 15 minutes at 0°, then acidified with dilute hydrochloric acid. The oil which separated was crystallized from water to give **6-benzoylamino-2-chlorohexanoic acid** (1.10 g., 66%); m.p. 137.5–138.5°, no depression by an authentic sample, m.p. 137.8–138.8.[30]

Anal. Calcd. for $C_{13}H_{16}O_3NCl$: C, 57.89; H, 5.98; N, 5.19. Found: C, 58.23; H, 5.76; N, 5.34.

(30) Reference 11 reports that 6-benzoylamino-2-chlorohexanoic acid melts at 145–147°; an authentic sample obtained from Dr. Galat melted at 137.8–138.8° and is identical with the product obtained in this research.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF MISSOURI]

The Alkylation of Phenol with Ethyl 6-Bromosorbate[1]

BY HERBERT E. UNGNADE[2] AND THOMAS R. HOPKINS

Ethyl 6-bromosorbate reacts with phenol to give ethyl 4-phenoxysorbate or ethyl 4-(*o*-hydroxyphenyl)-sorbate, depending on the conditions. Evidence for the assigned structures has been presented.

Only one previous attempt has been reported to prepare an allyl phenyl ether in which the allylic double bond is part of a conjugated system, namely, the reaction of phenol with sorbyl chloride. The usual method of preparation failed in this case and the product of a modified procedure proved to be *o*-sorbylphenol rather than the expected ether.[3]

In view of the difficulties involved in the preparation of sorbyl halides, the present investigation was undertaken with the more accessible ethyl 6-bromosorbate.

Bromination of ethyl sorbate with N-bromosuccinimide in benzene has given ethyl 6-bromosorbate (I) in 40–50% yield. Its structure is based on the ultraviolet absorption spectrum, the addition of maleic anhydride and the isolation of glyoxal from the ozonization products. The ester (I) reacts with phenol and potassium carbonate in methyl ethyl ketone to give a liquid phenoxy ester (II) which is unchanged by heating at 230–250°. It yields an adduct with maleic anhydride, absorbs at 255 mμ (log ε 4.2)[4] and gives acetaldehyde as the only volatile product from ozonization and reductive hydrolysis. It is therefore regarded as a substituted sorbic ester. The corresponding acid (III) is smoothly decarboxylated. The structure of the decarboxylation product (IV) has been established as 3-phenoxy-1,3-pentadiene by isolation of approximately equal amounts of acetaldehyde and formaldehyde from its ozonization products. The structure of the phenyl ether (II) is assigned on the basis of the reaction sequence (II) → (IV) and the formation of acetaldehyde in the ozonization of (II), but the possibility remains that the ester (II) actually has the phenoxy group on the beta carbon.[5]

(1) From the Master's thesis of T. R. Hopkins.

(2) Chemistry Department, New Mexico Highlands University, Las Vegas, N. Mex.

(3) Reichstein and Trivelli, *Helv. Chim. Acta*, **16**, 969 (1933).

(4) The phenoxy group evidently does not exert a measurable bathochromic effect in this case.

(5) As long as the point of attachment of the phenoxy group is not definitely established.