Beckmann Rearrangements in Alicyclic Systems. IV. 2,2-Disubstituted 1-Indanone Oximes and Related Homologs[1,2]

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The Beckmann rearrangement of a series of 2,2-disubstituted 1-indanone, tetralone, and benzosuberone oximes using polyphosphoric acid as the catalyst and solvent is reported. In each of the rearrangements studied almost quantitative yields of the lactam expected from the normal course of rearrangement was obtained. The structure of the lactams was established by hydrolysis to the amino acid followed by coupling the diazotized amino acid with β-naphthol. In each case, the lactams formed were the result of phenyl migration despite the steric hindrance imparted by the substituents on the α-carbon. These results are contrasted with observations previously reported for simple spiro and geminally disubstituted ketoximes on rearrangement in this medium.

The Beckmann rearrangement of a number of simple spiroketoximes,[3] 2,2-dimethyl-,[4] and 2,2-diphenyl-[5] cycloalkanone oximes has recently been reported. In all of these systems, the configuration of the oximino hydroxyl group was clearly *anti* to the bulky α-disubstituted carbon atom. As a result, all of these reactions proceeded initially *via* the fragmentation route[6] rather than by direct rearrangement. The products isolated in these reactions were shown to arise from further hydration or cyclization reactions of the unsaturated nitrile intermediates in the solvent medium. The most interesting of the catalysts used was polyphosphoric acid, supposedly a catalyst and solvent system which suppresses abnormal rearrangements.[7] For example, using polyphosphoric acid 2,2-diphenylcyclohexanone oxime rearranged to 2-benzhydrylidenecyclopentanone imine which on hydrolysis gave the corresponding α,β-unsaturated ketone.[5]

In view of these data, it was of further interest to contrast the behavior of a series of cyclic compounds in which the oximino group was flanked on one side by the fully substituted α-carbon and on the other side by an aromatic nucleus. These systems are cyclic analogs of pivalophenone oxime which has been shown to yield three different products on rearrangement[8,9]; Hydrogen chloride in acetic acid gives pivanilide, benzenesulfonyl chloride in alkali yields *t*-butylbenzamide and phosphorus pentachloride cleaves the molecule to benzonitrile. Complications arise, however, by geometrical isomerization of some oximes in either acid or base media.[10,11] Brown and co-workers[9] have explained these results by postulating that a preliminary isomerization of the oxime is likely in the reaction catalyzed by hydrogen chloride, while the very rapid dissociation of the oxime chlorophosphate in phosphorus pentachloride reactions causes cleavage to benzonitrile. It should be noted that alternative explanations of this phenomena are possible which account for the observed products.

Recently, Smith[12] has reported that polyphosphoric acid does not isomerize oximes readily. Therefore, it would be expected that in the systems under study the configuration of the oxime will determine the course of the rearrangement. It could also be concluded that polyphosphoric acid would behave as a fragmentation catalyst in a fashion similar to phosphorus pentachloride on the basis of our previous studies.[3–5]

Preliminary examination of molecular models[13] of 2,2-disubstituted 1-indanones indicated that the oxime having the hydroxyl group *anti* to the phenyl ring would be most likely and therefore direct rearrangement with phenyl migration would be the favored reaction course. As will be developed later, this configurational prediction is not clear in the homologous tetralone and benzosuberone systems. In addition, if normal rearrangement to the lactams (from either configuration) could be successfully accomplished, the resulting compounds would be of interest as potential physiologically active compounds after reduction to the corresponding amines. These structural systems are examples of the spirotetrahydroquinoline or isoquinoline systems and structural analogs of demethylhexahydroapoerysodine.

In light of these interests, our rearrangement studies were extended to alicyclic systems containing a fused aromatic ring, namely, 2,2-disubstituted

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(2) This study was presented, in part, at the 136th National American Chemical Society Meeting, Atlantic City, New Jersey, 1959.

(3) (a) R. K. Hill and R. T. Conley, *Chem. Ind.* (London), 1314 (1956); (b) R. K. Hill and R. T. Conley, *J. Am. Chem. Soc.*, **82**, 645 (1960); (c) R. T. Conley and M. C. Annis, *J. Org. Chem.*, **27**, 1961 (1962).

(4) R. T. Conley and B. E. Nowak, *ibid.*, in press.

(5) R. T. Conley and B. E. Nowak, *ibid.*, **27**, 1965 (1962).

(6) For an excellent review see: R. K. Hill, *ibid.*, **27**, 29 (1962).

(7) E. C. Horning, V. L. Stromberg, and H. A. Lloyd, *J. Am. Chem. Soc.*, **74**, 5153 (1952).

(8) O. Wallach, *Ann.*, **259**, 309 (1890).

(9) R. F. Brown, N. M. van Gulick, and G. H. Schmidt, *J. Am. Chem. Soc.*, **77**, 1094 (1955).

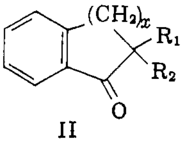
(10) P. W. Neber, K. Hartung, and W. Ruopp, *Ber.*, **58**, 1234 (1925).

(11) R. S. Montgomery and G. Dougherty, *J. Org. Chem.*, **17**, 823 (1952).

(12) N. H. P. Smith, *J. Chem. Soc.*, 4209 (1961).

(13) Dreiding models and Stuart-Briegleb models were found very useful in the examination of conformational interactions in these systems, particularly, in the estimation of the relative energy differences of the *syn*- and *anti*-oximes.

TABLE I

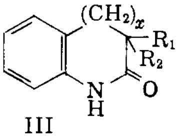


II

		Ketone				Oxime derivative		Calcd., %			Found, %		
No.	x	R₁	R₂	B.p., °C./mm.	M.p., °C.	Formula, mol. wt.	M.p., °C.	C	H	N	C	H	N
IIa	1	—CH_3	—CH_3	104–105/12.5[a]	44–45[h]	$C_{11}H_{13}NO$ (175.22)	116.5–117.5[j]	75.40	7.48	7.99	75.42	7.51	8.03
IIb	1	—$(CH_2)_4$—		106/1.6[b] 140/98	...	$C_{13}H_{15}NO$ (201.26)	134–135[k]	77.58	7.51	6.96	77.55	7.55	7.23
IIc	1	—$(CH_2)_5$—		103/0.8[c]	58–59[i]	$C_{14}H_{17}NO$ (215.29)	186.5–187[l]	78.10	7.96	6.51	78.12	7.96	6.68
IId	2	—CH_3	—CH_3	150/5.0[d]	...	$C_{12}H_{15}NO$ (189.25)	132–132.5[m]	76.15	7.99	7.40	76.29	8.05	7.51
IIe	2	—$(CH_2)_5$—		116/0.8[e]	...	$C_{15}H_{19}NO$ (229.31)	160.5–161[n]	78.56	8.35	6.11	78.75	8.49	6.05
IIf	3	—CH_3	—CH_3	125/1.1[f]	...	$C_{13}H_{17}NO$ (203.27)	137.5–138[o]	76.81	8.43	6.89	76.99	8.57	6.80
IIg	3	—$(CH_2)_4$—		118/0.9[g]	...	$C_{15}H_{19}NO$	123–124.5[p]	78.56	8.35	6.11	78.63	8.43	6.00

[a] Ref. 14[b] reports b.p. 95°/0.5 mm. [b] Ref. 14[b] reports b.p. 146°/2 mm. [c] Ref. 14[b] reports b.p. 146°/1 mm. [d] Ref. 14[b] reports b.p. 106°/0.5 mm. [e] Ref. 14[b] reports b.p. 140–143°/0.5 mm. [f] P. Ramart-Lucas and J. Hock, *Compt. rend.*, **201**, 1387 (1935) report b.p. 140°/16 mm. [g] New compound. *Anal.* Calcd.: C, 84.07; H, 8.47. Found: C, 84.01; H, 8.53. [h] Ref. 14[b] reports m.p. 46–47°. [i] M. Mousseron, R. Jacquier, and H. Christol, *Compt. rend.*, **243**, 1532 (1956) report m.p. 58°. [j] E. Rothstein, *J. Chem. Soc.*, 1459 (1951), reports m.p. 115°. [k] Ref. 14[b] reports m.p. 134–135°. [l] Ref. 14[b] reports m.p. 187°. [m] Ref. 14[b] reports m.p. 132°. [n] Ref. 14[a] reports m.p. 160–161°. [o] Ref. *f* reports m.p. 139°. [p] New compound.

TABLE II



III

Compound no.	x	R₁	R₂	M.p., °C.	Yield, %	Formula, mol. wt.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIIa	1	—CH_3	—CH_3	49–50	96.5	$C_{11}H_{13}NO$ (175.22)	75.40	7.48	7.99	75.46	7.56	8.12
IIIb	1	—$(CH_2)_4$—		80.5–81.0	97.5	$C_{13}H_{15}NO$ (201.26)	77.58	7.51	6.96	77.40	7.39	7.02
IIIc	1	—$(CH_2)_5$—		97–98.5	95.0	$C_{14}H_{17}NO$ (215.29)	78.10	7.96	6.51	78.01	7.87	6.69
IIId	2	—CH_3	—CH_3	139–140	79.5	$C_{12}H_{15}NO$ (189.25)	76.15	7.99	7.40	76.30	7.87	7.39
IIIe	2	—$(CH_2)_5$—		182–183	82.4	$C_{15}H_{19}NO$ (229.31)	78.56	8.35	6.11	78.66	8.50	6.08
IIIf	3	—CH_3	—CH_3	192–192.5	97.5	$C_{13}H_{17}NO$ (203.28)	76.81	8.43	6.89	77.07	8.46	7.04
IIIg	3	—$(CH_2)_4$—		196.5–197	92.0	$C_{15}H_{19}NO$ (229.31)	78.56	8.35	6.11	78.69	8.33	6.23

1-indanone, tetralone and benzosuberone oximes. The compounds investigated are summarized in Table I.

The syntheses of the ketones used in this study were carried out by the elegant route described by Mousseron, Jacquier, and Christol.[14] For example, 1-indanone (I) reacted with tetramethylene dibromide or methyl iodide in the presence of potassium *t*-butoxide. After a short reflux period, the products were isolated and purified to yield 2,2-tetramethylene-1-indanone (IIb) or 2,2-dimethyl-1-indanone (IIa) as shown in Figure 1. All oximations were carried out by the hydroxylamine hydrochloride in ethanol–pyridine solution procedure.[15]

The Beckmann rearrangement of each oxime in polyphosphoric acid (fifteen to twenty fold excess) was carried out at 125–130° for ten minutes to give in every case high yields of a single lactam (Figure 2). The physical constants and yields of these products are summarized in Table II. Typical procedures common to all rearrangements reported here are given in the experimental section.

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(14) (a) M. Mousseron, R. Jacquier, and H. Christol, *Compt. rend.*, **239**, 1805 (1954); (b) M. Mousseron, R. Jacquier, and H. Christol, *Bull. soc. Chim. France*, 346 (1957).

(15) W. E. Bachmann and M. X. Barton, *J. Org. Chem.*, **3**, 307 (1938).

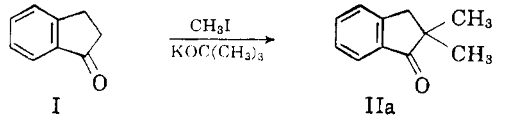

Figure 1

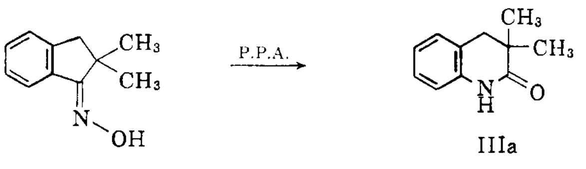

Figure 2

The structure of each lactam was established unequivocally by hydrolysis in 30% sulfuric acid to the amine hydrogen sulfate. The hydrolysis solution was used directly for diazotization with sodium nitrite. To the resulting diazonium salt β-naphthol in sodium hydroxide was slowly added. In each case a dark red, insoluble dye was formed. Since only the isomer with the amine attached to the aromatic nucleus would react in the coupling reaction with β-naphthol, the position of the amino group and, therefore, the structure lactam was established with certainty.

Further confirmation of the aromatic amine moiety was obtained by examination of the amino acid, from hydrolysis of the lactams in 30 % sulfuric acid, in acid and base solution in the ultraviolet region. A hypsochromic shift of over 30 mμ was observed in the position of the ϵ-band absorption maximum. This shift is comparable to that reported by Doub and Vandenbelt[16] for aniline when compared as the cation and as free amine. No comparable shift is noted for substituted benzoic acids.

All of the lactams produced were purified by sublimation at reduced pressure. In the case of the rearrangement product mixture from 2,2-dimethyl-1-tetralone oxime, an appreciable residue remained in the sublimator as a black tarry mass. Infrared examination of this residue indicated the presence of a small amount of nitrile as evidenced by a weak absorption band at 4.45 μ in carbon tetrachloride solution. In this case some fragmentation of the oxime by cleavage of the disubstituted α-carbon–oximino carbon bond must have occurred. Examination of the reaction mixtures for ketonic products using 2,4-dinitrophenylhydrazine reagent failed to indicate the presence of α,β-unsaturated ketones analogous to those observed in previous studies.[3–5] These data indicate that in all cases, the oximino–hydroxyl group must have rearranged from an anticonfiguration with respect to the aromatic ring. As cited earlier for the rearrangements of the indanone series this is quite consistent and readily predictable since the oximino hydroxyl can be sterically situated between the geminal substituents on the α-carbon. However, in the tetralone and benzosuberone cases, this situation is not sterically possible. In the case of 2,2-dimethyl-1-tetralone oxime considerable crowding of the oximino hydroxyl in either configuration apparently exists. One of the methyl groups on the α-carbon lies in the plane of the oximino group. Also in these configurations a strong 1,3-methyl–hydrogen interaction is apparent between the remaining pseudoaxial methyl group and pseudoaxial hydrogen atom on carbon-4. Similar conformational arguments indicate that the oximino group is considerably puckered in the benzosuberone cases and distorted from coplanarity with the aromatic ring. In these cases, it is doubtful that the oximino group has a preferred configuration. The dissociation of the oximino hydroxyl during rearrangement would be expected to release a considerable amount of strain.

On the basis of these arguments, it would be expected that steric control due to oxime configuration would not be favored in the tetralone and benzosuberone systems. Rather since the dissociation of the oximino hydroxyl by either protonation or scission of the N—O bond of the intermediate oxime–polyphosphate ester would give a nonstereoselective positively charged nitrogen ion, group migration would be controlled as in analogous carbon–carbon rearrangement systems[17] by migratory aptitude due primarily to transition state stabilization. Since rearrangement of the phenyl group may be enhanced through participation of the electron donating ring to form a stabilized bridged ion,[18] it can be proposed that the rearrangement proceeds through the steps indicated in Figure 3. These postulates agree with the observation of some cleavage by the fragmentation route in the tetralone series to nitrile due to only partial stabilization of the bridged ion by phenyl participation. In the benzosuberone oxime rearrangements, this situation is not a limiting factor, since more complete participation is possible and therefore only a single lactam is observed. Fragmentation products, therefore, are present in only very small quantities if at all. Further intensive investigation is in progress to attempt to confirm these postulations.

It should be pointed out that these proposals offer a reasonable alternative postulation[19] for the abnormal behavior of pivalophenone type oximes and their cyclic analogs. The effect of the reaction medium on the stability of the possible transition

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(16) L. Doub and J. M. Vandenbelt, *J. Am. Chem. Soc.*, **69**, 2714 (1947).

(17) For example, see D. J. Cram, "Steric Effects in Organic Chemistry," M. S. Newman, ed., John Wiley & Sons, Inc., New York, N.Y., 1956, Chap. 5.

(18) For review and references see: L. G. Donaruma and W. Z. Heldt, *Org. Reactions*, 1 (1960).

(19) NOTE ADDED IN PROOF: Since the submission of this manuscript, additional experimental evidence for a nonstereoselective positively charged nitrogen ion intermediate in similar hindered oxime rearrangements has been reported in preliminary form by Lansbury and Colson, Abstracts of Papers, 142nd National American Chemical Society Meeting, p. 12-Q.

states may well govern the course of rearrangement and/or fragmentation of hindered oximes. These postulates are also consistent extensions of existing thoughts on the factors governing both carbon-nitrogen and carbon-carbon rearrangements.

Experimental

Since all preparation and rearrangements were carried out using essentially the same methods, only typical experiments are reported here. All melting points were taken using the capillary method and are uncorrected. The infrared spectra used for functional group identification were recorded using a Baird, Model AB-2, or a Beckman IR-5 recording spectrophotometer with sodium chloride optics. The samples were examined in dilute carbon tetrachloride solution and/or potassium bromide discs. The ultraviolet spectra were obtained using a Beckman DK-2A recording spectrophotometer in aqueous acid or base solutions as indicated. The purity of all ketones was checked after distillation by vapor chromatography using a Perkin-Elmer, Model 154-C, vapor fractometer equipped with a Perkin-Elmer R-column (Ucon polyglycol LB-550-X). Solid ketones were chromatographed as solutions in chloroform.

2,2-Pentamethylene-1-indanone.—Using a modification of the procedure described by Mousseron, Jacquier, and Christol,[14] 2,2-pentamethylene-1-indanone was prepared as follows:

To a freshly prepared benzene solution (300 ml.) of potassium *t*-butoxide (from 0.5 g.-atom of potassium metal) 25 g. (0.189 mole) of 1-indanone was added. After several minutes, 40.9 g. (0.189 mole) of 1,4-dibromobutane was added slowly to the purple solution. After the addition was complete, the reaction mixture was heated at reflux for 5 hr. The reaction mixture was poured over a slurry of 300 g. of crushed ice and 75 ml. of concentrated hydrochloric acid. The organic layer was separated and the remaining aqueous acid solution extracted three times with 300-ml. portions of diethyl ether. The organic layer and ether extracts were combined, washed with 40 ml. of 5% sodium carbonate followed by 40 ml. of water. The ethereal solution was dried over anhydrous sodium sulfate, filtered, and evaporated. The residual oil was fractionated through an 8-inch, closely spaced Vigreux column to yield 14.1 g. (40%) of 2,2-pentamethylene-1-indanone, b.p. 140°/9.8 mm. (lit. 14b b.p. 146°/2 mm.). The infrared spectrum (carbon tetrachloride) showed an intense C=O band at 5.93 μ.

The 2,4-dinitrophenylhydrazone was prepared using the sulfuric acid-ethanol procedure. After two recrystallizations from chloroform-methanol, a red crystalline derivative, m.p. 206.5-208° dec., was obtained, (lit. 14[b] m.p. 208°).

Anal. Calcd. for $C_{19}H_{18}N_4O_4$: N, 15.29. Found: N, 15.00.

The oxime was prepared using the method described by Bachmann and Barton.[15] After two recrystallizations from ethanol, 2,2-pentamethylene-1-indanone oxime was obtained as a white crystalline solid, m.p. 134-135°, (Lit.,[14b] m.p. 134-135°C.).

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.55; H, 7.55; N, 7.23.

Polyphosphoric Acid Rearrangement.—A mixture of 2.00 g. of 2,2-pentamethylene-1-indanone oxime and 35 g. of polyphosphoric acid was heated slowly in an oil bath. At a temperature of 115°, the temperature of the mixture rose sharply to 128°. After 10 min. at 125-130°. the mixture was allowed to cool. The contents of the reaction vessel were hydrolyzed in a mixture of 300 g. of crushed ice and 100 ml. of 25% sodium hydroxide. The aqueous mixture, containing a white solid, was extracted three times with 100-ml. portions of chloroform. The chloroform extracts were combined, dried over anhydrous magnesium sulfate, filtered, and evaporated to yield 1.95 g. (97.5%) of crude white 3,3-tetramethylene hydrocarbostyril, m.p. 79-80.5°. The solid was purified by sublimation at 66°/0.05 mm. to give 1.94 g. of white needles, m.p. 80.5-81.0°.

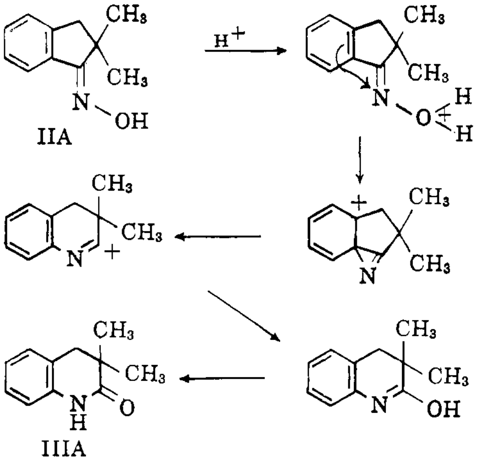

Figure 3

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.40; H, 7.39; N, 7.02.

The infrared spectrum (carbon tetrachloride) indicated a single sharp band at 2.95 mμ and an Amide I band at 6.15 mμ. The residue in the sublimator (0.01 g.) was examined spectrally. The spectrum was almost identical to that of the sublimate. No ketonic carbonyl or nitrile was observable in the spectrum of the residue.

In a second experiment, the total crude product from the chloroform extracts was tested with 2,4-dinitrophenylhydrazine reagent. This test failed to indicate the presence of ketonic products.

Hydrolysis, Diazotization, and β-Naphthol Coupling.—A mixture of 0.20 g. of 3,3-tetramethylene hydrocarbostyril and 10 ml. of 30% sulfuric acid was heated at reflux for 4 hr. On cooling, 20 ml. of water was added. The solution (3 ml.) was cooled in an ice bath, and treated with a stoichiometric amount of sodium nitrite in 25 ml. of water. On addition of 1 g. of β-naphthol in 10 ml. of 10% sodium hydroxide a dark red precipitate formed. After filtration and air drying, the red amorphous solid was recrystallized from a small amount of benzene.

Anal. Calcd. for $C_{23}H_{22}N_2O_3$: N, 7.05. Found: N, 6.80.

In a second experiment the solution was chilled after reflux to yield a solid precipitate which was dried at 40° in a vacuum oven. A 10-mg. sample of the dry solid was dissolved in 100 ml. of concentrated sulfuric acid and another 10 mg. in 100 ml. of 1 *N* potassium hydroxide. After a one-hundred fold dilution of these solutions, the ultraviolet spectra were determined, $\lambda_{\max_{H_2SO_4}}$ 253 mμ, $\epsilon_{\max}$ 250; $\lambda_{\max_{KOH}}$ 286.5 mμ, $\epsilon_{\max}$ 1,450.

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