THE SYNTHESIS AND DIAZOTIZATION OF SOME KETONE HYDRAZONES[1]

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ABSTRACT

Hydrazones have been synthesized in this study both from a variety of bicyclic ketones and from ketones containing either the 1-naphthyl or 2-naphthyl group. Three of these hydrazones, those derived from 1-acetonaphthone, 2-acetonaphthone, and benzosuberone, have not been reported previously in the literature. All of the hydrazones were allowed to rearrange in a diazotizing medium to produce amide products. One of these, 4,5-benzo-ω-heptanolactam, has never been reported in the literature.

From the results of this research, it is possible to reaffirm some general conclusions concerning the utility and scope of the hydrazone diazotization-rearrangement. Among these are the facts that the reaction generally functions well only if at least one aromatic ring is present and that it is stereospecific with migration of the group *anti* to the NH_2 group of the original hydrazone. Thus, the assignment of hydrazone isomer configuration appears to be possible on the basis of the identity of the given amide product. Such assignments have been made for the compounds studied here. Some postulations concerning the steric requirements for hydrazone formation with the aromatic bicyclic ketones have also been made.
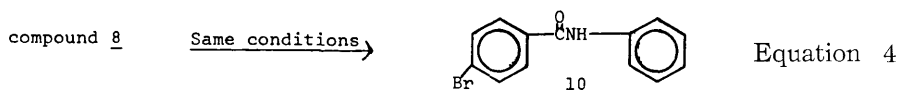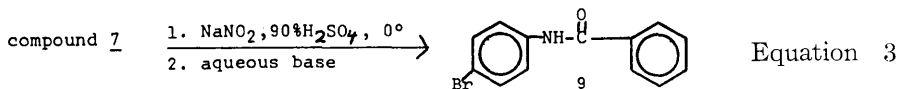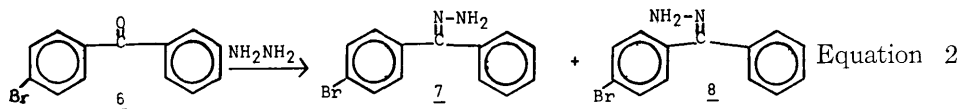
INTRODUCTION

The rearrangement of ketone hydrazones in a diazotizing medium to produce amides was first reported by Pearson and Greer (1949). Equation 1 illustrates this reaction with benzophenone hydrazone (1) which gives benzanilide (5) as the final product. (In this paper, the underlined number, 1, refers to the structural formula which has beneath it that same underlined number. This type of referral follows throughout the paper for structures 2 through 26. The names of less common compounds are also included beneath the structure.)
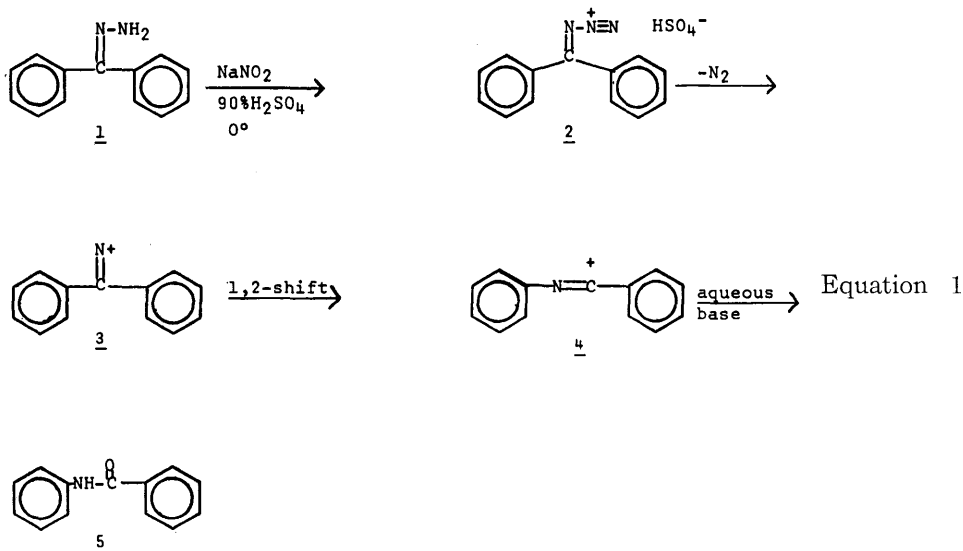
Further studies were made by Carter (1952) and by Pearson, Carter, and Greer (1953). These experiments revealed that the diazotization-rearrangement was generally applicable to ketone hydrazones. They postulated that the mech-

anism of the process was probably similar to that of the Beckmann rearrangement of ketone oximes. When an unsymmetrical ketone, such as 4-bromobenzophene (6), was employed in reaction with aqueous hydrazine (Equation 2), the two geometric isomers 7 and 8 were isolated. When each of these was rearranged in a separate diazotizing reaction medium, isomeric benzanilide products (9 and 10) resulted, as illustrated by Equations 3 and 4. Pearson, Carter, and Greer (1953)

$$\text{(6)} + NH_2NH_2 \longrightarrow \text{(7)} + \text{(8)} \qquad \text{Equation 2}$$

$$\text{compound } \underline{7} \xrightarrow[\text{2. aqueous base}]{\text{1. } NaNO_2, 90\% H_2SO_4, 0°} \text{(9)} \qquad \text{Equation 3}$$

$$\text{compound } \underline{8} \xrightarrow{\text{Same conditions}} \text{(10)} \qquad \text{Equation 4}$$

assumed that the group opposite (*anti*) to the departing nitrogen migrated according to the established precedents for rearrangements of this type, although they made no extensive mechanistic study of the process. A complete summary of related rearrangements prepared by Smith (1963) generally supports this viewpoint.

The diazotization of ketone hydrazones had received little attention since the publication of the original reports until recently, when a comprehensive kinetic-mechanistic study of the process was made by Fishel and Hawbecker (1968). By using a combination of product-ratio studies, stereochemical considerations, kinetic data, and structural determinations of the reaction intermediates via nuclear magnetic resonance spectrometry, these researchers were able to define several important points concerning the mechanism and limits of hydrazone diazotization. They confirmed the earlier finding of Pearson, Carter, and Greer (1953) regarding the fact that separate hydrazone isomers rearrange under diazotizing conditions to isomeric amides exclusively by *anti* migration, and they applied the reaction to a variety of additional benzophenone hydrazones. The reaction rates were found to be first order in hydrazone, and nitrogen loss was simultaneous with rearrangement. Because only intermediates 2 and 4 (but *never* 3) could be detected in the nuclear magnetic resonance (nmr) studies, the case for an anti-group migration with simultaneous nitrogen loss appeared to be firmly established. The conversion of ketone hydrazones to the corresponding amide products usually occurs in high yields (85-95%), with the different benzophenone hydrazones which resulted in this rearrangement being published recently as an undergraduate organic laboratory experiment (Hawbecker, 1970).

The purpose of the present research was to expand the scope of the hydrazone diazotization-rearrangement and to apply it to unique ketone hydrazones. Virtually all of the compounds employed in the study have at least one aromatic ring present, because it has been demonstrated (Pearson, Carter, and Greer, 1953; Fishel and Hawbecker, 1968) that the reaction often functions poorly when aryl groups are absent. As part of some other reaction mechanism studies (Lansbury, Colson, and Mancuso, 1964; Lansbury and Mancuso, 1966) it has been reported that the reaction is applicable to the hydrazones of certain aromatic bicyclic ketone systems. In the present research, our goal was to define more carefully the applicability of this reaction, employing hydrazones derived from aromatic bicyclic ketones, and to expand its use to ketone hydrazones containing

the naphthalene ring system. Preliminary reports of this research have been made by Gladon and Hawbecker (1969) and by Nordeen and Hawbecker (1970).

METHODS AND MATERIALS

Melting points were taken with a Thomas-Hoover melting-point apparatus and are uncorrected. The infrared spectra were determined on a Perkin-Elmer Model 237 B. Microanalyses were performed by Crobaugh Laboratories (3800 Perkins Avenue, Cleveland, Ohio 44114).

The 64% aqueous hydrazine, amyl nitrite, cyclopentanone, cyclohexanone, 1-indanone, 1-tetralone, 9-anthrone, 1-acetonaphthone, 2-acetonaphthone, and 2-benzonaphthone were obtained from Eastman Organic Chemicals (Rochester, New York). The 1-benzonaphthone was obtained from Pfaltz and Bauer, Inc. (Flushing, New York). The 9-fluorenone was purchased from Matheson Coleman and Bell (Norwood, Ohio). Benzosuberone and dibenzosuberone were obtained from Research Organic/Inorganic Chemical Corporation (Sun Valley, California). The sodium nitrite (Baker Analyzed Reagent) was purchased from the J. T. Baker Chemical Company (Phillipsburg, New Jersey).

PREPARATION OF HYDRAZONES

One equivalent of a given parent ketone and 1.5 equivalents of hydrazine (in the form of a 64% aqueous solution) were dissolved in the minimum amount of anhydrous ethanol required to effect solution. The alcoholic solutions were then refluxed for 10 to 12 hours to produce the desired hydrazones. After refluxing, the solutions were concentrated and cooled to produce the hydrazone precipitate. The solid hydrazones were recrystallized from anhydrous ethanol or high-boiling petroleum ether, while those which were oils at room temperature were vacuum distilled. This general method was used for the preparation of all the hydrazones listed in Table 1.

HYDRAZONE DIAZOTIZATION-REARRANGEMENT

The diazotization-rearrangement of each hydrazone was accomplished by the following reaction procedure. Into a 125 ml Erlenmeyer flask was placed 10–12 ml of 90% sulfuric acid. This was cooled with stirring (via a magnetic stirring bar) to 0°C. Sodium nitrite (0.8g) was added cautiously in a manner that allowed the temperature to be maintained below 8–10°C. Then one gram of the appropriate hydrazone was added with continued cooling and stirring. Again the temperature was maintained below 10°C. After the reaction had subsided (considerable foaming occurred in some cases), the solution was poured over a mixture composed of ice and 15 ml of concentrated aqueous ammonia. The solid product was then filtered, washed, air-dried, and recrystallized from either anhydrous ethanol or high-boiling petroleum ether. The properties of these products (the amides) are listed in Table 2.

PREPARATION OF AMIDES

An adaptation of the method presented by Shriner, Fuson, and Curtin (1964) was employed. A suspension of 0.027 moles of the amine portion of the proposed product was prepared in 25 ml of 10% aqueous sodium hydroxide using a 100-ml boiling flask as the container. The flask was placed on a magnetic stirrer and 0.03 moles of the appropriate acyl halide was added. The flask was stoppered and the contents were stirred very vigorously for 10 minutes or until a solid product formed. The products were recovered by filtration and recrystallized from absolute ethanol. The amides prepared by this method were used in identifying the amide products from the rearrangement of hydrazones derived from the acyl naphthalenes.

RESULTS

A summation of the hydrazones which have been prepared may be found in Table 1 and the results of the diazotization-rearrangement process for these compounds are listed in Table 2. Only hydrazones with at least one aromatic ring present rearranged readily. Diazotizations of both cyclopentanone hydrazone and cyclohexanone hydrazone were attempted many times, with the result always being hydrolysis to the original ketone. In no instance could any amide product (a lactam) be isolated. Alternate solvent systems employed for this study were 10% acetic acid-90% H_2SO_4, 10% diethyl ether-90% H_2SO_4, polyphosphoric acid,

TABLE 1

Preparation of ketone hydrazones

Parent Ketone	% Yield	mp°C
cyclopentanone	83.8	63 (b_p/2 mm Hg)[a]
cyclohexanone	75.9	60.5 (b_p/1.25 mm Hg)[b]
1-indanone	94.1	84–86[c]
1-tetralone	92.3	36–37[d]
benzosuberone	71.0	72–75[e]
9-fluorenone	74.5	148–149[f]
9-anthrone	——	——
dibenzosuberone	——	——
1-acetonaphthone	99.0	95–96[g]
2-acetonaphthone	99.0	114–116[h]
1-benzonaphthone	70.0	oil[i]
2-benzonaphthone	90.0	139–141[j]

[a]Doering and DePuy (1953) report 45°/1mm Hg.

[b]Newkome and Fishel (1966) report 55.6°/1mm Hg.

[c]Josephy and Radt (1945) report 84–86°.

[d]Newkome and Fishel (1966) report 38°.

[e]Not previously reported in literature. Analysis-Calcd. for $C_{11}H_{14}N_2$: C, 75.85; H, 8.05; N, 16.08. Found: C, 75.32; H, 8.38; N, 16.05.

[f]Pinck and Hilbert (1946) report 149°.

[g]Not previously reported in literature. Analysis-Calcd. for $C_{12}H_{12}N_2$; C, 78.20; H, 6.52; N, 15.20. Found: C, 78.39; H, 6.86; N, 14.28.

[h]Not previously reported in literature. Analysis-Calcd. for $C_{12}H_{12}N_2$: C, 78.20; H, 6.52; N, 15.20. Found: C, 78.89; H, 6.71; N, 14.47.

[i]Reimlinger, *et al.* (1964) report 86°. However, rearrangement produced the correct amide product in 80% yield.

[j]Reimlinger, *et al.* (1964) report 144°.

100% H_2SO_4, and glacial acetic acid. At least two separate attempts were made for each solvent system to employ amyl nitrite rather than sodium nitrite as the source of the diazotizing species, but this likewise failed to accomplish the rearrangement. Pearson, Carter, and Greer (1953) also reported difficulty with hydrolysis when they attempted the reaction with cyclohexanone hydrazone.

The present research also has demonstrated rather conclusively that the diazotization-rearrangement of hydrazones is indeed steresospecific in a variety of chemical systems. The ketones 1-indanone, 1-tetralone, 1-acetonaphthone, 2-acetonaphthone, 1-benzonaphthone, and 2-benzonaphthone are all unsymmetrical. Therefore they possess the structural arrangement necessary to produce a pair of geometric isomeric hydrazones. Although many attempts were made to isolate two hydrazone isomers of each of the indicated ketones, only a single isomer could be recovered in each case. Once a given hydrazone had been purified, it

rearranged in high yield (Table 2), in virtually every example studied, to produce an amide product which could be readily identified by comparison with literature values or with authentic amides. The rearranged products derived from the bicyclic ketone hydrazones produced lactam structures consistent in physical properties to those reported in Table 2. The infrared spectra also were consistent with the lactam structure, showing bands in both the 3200 cm^{-1} and 1650–1750 cm^{-1} regions.

TABLE 2
Diazotization—Rearrangement of ketone hydrazones

Parent Ketone	Amide Product	% Conversion	mp°C
cyclopentanone	hydrolysis to parent ketone	—	—
cyclohexanone	hydrolysis to parent ketone	—	—
1-indanone	3,4-dihydrocarbostyril	55	161–163[a]
1-tetralone	3,4-dihydrohomocarbostyril	75	139–141[b]
benzosuberone	4,5-benzo-ω-heptanolactam	87	153–155[c]
9-fluorenone	phenanthridone	80	283–284[d]
1-acetonaphthone	N-1-naphthylacetamide	80	152–154[e]
2-acetonaphthone	N-2-naphthylacetamide	97	128–130[f]
1-benzonaphthone	N-1-naphthylbenzamide	80	158–160[g]
2-benzonaphthone	N-2-naphthylbenzamide	85	140–143[h]

[a]Lansbury and Mancuso (1966) report 163°.
[b]Lansbury and Mancuso (1966) report 141°.
[c]Not previously reported in literature. Analysis-Calcd. for $C_{11}H_{13}NO$: C, 74.44; H, 7.43; N, 8.00. Found: C, 75.39; H, 7.52; N, 7.92.
[d]Badger, *et al.* (1951) report 287°.
[e]Conley (1958) reports 158°.
[f]Conley (1958) reports 132°.
[g]Betti and Becciolini (1915) report 159–160°.
[h]Huisgen (1949) reports 159°. However a mixed melting point with N-2-naphthylbenzamide was undepressed while a mixed melting point with 2-naphthanilide was depressed.

DISCUSSION

The findings of Pearson and Greer (1949) and of Fishel and Hawbecker (1968) concerning the probable mechanistic path for hydrazone diazotization-rearrangement (see Equation 1) generally led to the postulation that aromatic systems are necessary to stabilize the various intermediates (structures **2** and **4**) formed during the multi-step process. The present studies seem to establish without question the ineffectiveness of the reaction with non-aromatic systems. The reaction intermediates produced from the series of ketone hydrazones containing the napththyl groups can, of course, be stablized by resonance, and these compounds indeed undergo the rearrangement with facility. This would seem to give additional evidence of the importance of such stabilization in most rearrangements of diazotized hydrazones.

The product derived from benzosuberone hydrazone (**15**) has not been reported in the literature. However, the elemental analysis plus the infrared spectrum confirmed the structure indicated below for 4,5-benzo-ω-heptanolactam (**16**). The benzosuberone hydrazone itself is a new compound, as confirmed by similar analyses, and by the fact that it does rearrange in the diazotizing medium. This particular hydrazone does not fit the structural pattern of the hydrazones which rearrange most readily in the diazotizing solutions. The aromatic ring is not in a position to stabilize the reaction intermediate by resonance. Evidently other factors are important in the reaction of this compound, but without further studies, definite reasons can not be given. One can only postulate that the competitive

hydrolysis is somehow (perhaps by a transannular interference of the benzene ring) less favorable than rearrangement, so that the rearrangement does occur in high yield.

The general validity of assigning hydrazone stereochemistry on the basis of the structure of the rearrangement product has already been demonstrated by Fishel and Hawbecker (1968) with several different examples. It would seem that this type of assignment ought to be valid in the present research, and thus, structural assignments for the bicyclic ketone hydrazones are indicated below via indicated conversions (Equations 5–8).
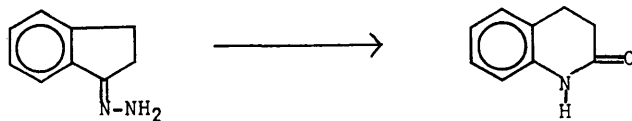
Equation 5

11

1-indanone hydrazone

12

3,4-dihydrocarbostyril
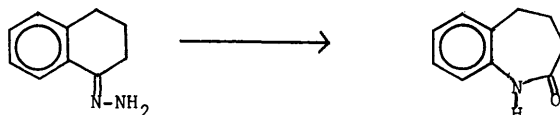
Equation 6

13

1-tetralone hydrazone

14

3,4-dihydrohomocarbostyril
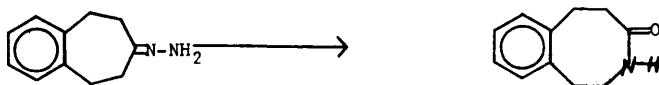
Equation 7

15

benzosuberone hydrazone

16

4,5-benzo-ω-heptanolactam
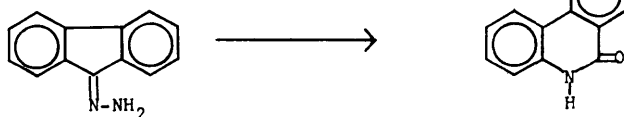
Equation 8

17

9-fluorenone hydrazone

18

phenanthridone

The products recovered from the rearrangement of hydrazones derived from the actyl naphthalenes were readily identified by comparison with literature values. In every case, both of the possible amide isomers have been reported in the literature, which greatly facilitated such comparison. Wherever there was any doubt, it was possible to confirm the identity of the product by mixed melting-point studies employing authentic amides. These could be readily prepared via a direct route employing appropriate amines and acyl halides. This is sometimes called the Schotten-Bauman reaction, and a procedure for this reaction may be found in many different organic laboratory manuals, with the method given by Shriner, Fuson, and Curtin (1964) being typical. The a-acetonaphthone hydrazone (**19**) and 2-acetonaphthone hydrazone (**21**) apparently have not been

previously reported in the literature, but the elemental analysis, spectral properties, physical characteristics, and the fact that each one undergoes diazotization-rearrangement strongly suggests that these are indeed the indicated hydrazones. Equations 9–12 indicate the structural arrangements of the various hydrazones derived from the acyl napthalenes, based upon the identities of the respective amide products.
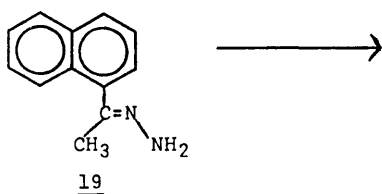
Equation 9

19
1 -acetonaphthone hydrazone

20
N-1-naphthylacetamide

Equation 10

21
2 -acetonaphthone hydrazone
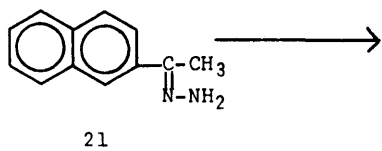
22
N-2-naphthylacetamide
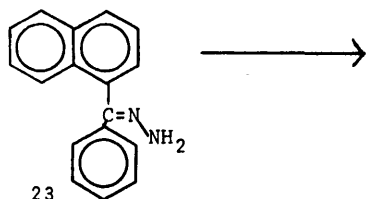
Equation 11

23
1 -benzonaphthone hydrazone

24
N-1-naphthylbenzamide
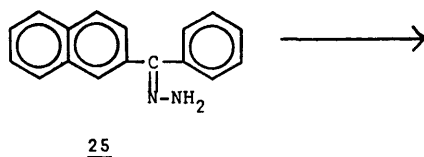
Equation 12

25
2 -benzonaphthone hydrazone

26
N-2-naphthylbenzamide

One other interesting observation can be made as a result of this research. As noted in Table 1, neither 9-anthrone nor dibenzosuberone would form a hydrazone, whereas the apparently similar compound, 9-fluorenone, readily reacted with hydrazine to produce the desired product. An examination of the molecular models (Fisher-Hirschfelder-Taylor type from Fisher Scientific Company) of 9-anthrone clearly revealed that the hydrogens on the benzene rings produce steric interference with the NH_2 of the hydrazone, so that this ketone did not react. The spatial requirements of the seven-membered central ring of dibenzosuberone aggravates this situation even more by tipping the benzene-ring hydrogens closer to the NH_2 of the hydrazone. In the case of 9-fluorenone, however, the spatial requirement of the five-member ring alleviates the steric crowding and the hydrazone product does indeed form. Examination of structures **17**,

27, and 28 clearly illustrates the steric situation as derived from the molecular models.

9-fluorenone hydrazone   9-anthrone hydrazone   dibenzosuberone
                                                   hydrazone

17   27   28   Last Diagram

CONCLUSION

In summation, the hydrazone diazotization-rearrangement process has been found to be applicable for hydrazones derived from a variety of unique parent ketones. The particular compounds examined in this research seemed to give further examples of the factors already cited in the literature as being typical of electron-deficient nitrogen rearrangements in general and of hydrazone diazotiza-tion-rearrangement in particular. The reaction generally works well only when at least one aromatic ring is present. In each case where a pure hydrazone can be isolated, the rearrangement occurs in relatively high yield, with exclusive migration of the group *anti* to the NH_2 of the hydrazone. Either sodium nitrite or amyl nitrite can be employed in sulfuric acid as the source of the diazotizing species, with about the same overall efficiency in either case.

ACKNOWLEDGMENTS

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