# Reaction of Nitrenes with Strained Olefins. Preparation and Reactions of Some 6-Azabicyclo[3.1.0]hexanes



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A number of examples of the 6-azabicyclo[3.1.0]hexane ring system have been prepared by the oxidation of *N*-aminophthalimide or 3-amino-2-methyl-4-quinazolone with lead tetraacetate in the presence of variously substituted cyclopentenes.

Thus, 6-phthalimidyl-6-azabicyclo[3.1.0]hexane, dimethyl-6-phthalimidyl-6-azabicyclo[3.1.0]-hexane-1,5-dicarboxylate, 2,3-benzo-6-phthalimidyl-6-azabicyclo[3.1.0]hexane and *N*-3-(2-methyl-4-quinazolyl)-6-azabicyclo[3.1.0]hexane were prepared for the first time. All of the new compounds were found to be stable in refluxing carbon tetrachloride and chlorobenzene. Refluxing 6-phthalimidyl-6-azabicyclo[3.1.0]hexane in acetic acid for 24 hours resulted in quantitative rearrangement to a phthalohydrazide, **8**.

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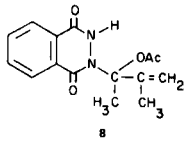
Recent interest in the generation and reactions of nitrenes has grown rapidly, as evidenced by the number of reviews on the topic which have appeared in the last few years (2). Many of these focus to some extent on the growing controversy over whether the nitrene intermediate is actually produced under various reaction conditions (2). Our interest has centered on the presumed production of the *N*-nitrene intermediate or diazene, **1** (3). Some success has been achieved in the rationalization of the

1

products formed in a number of reactions using **1** as a postulated intermediate (4). Oxidation of a primary amino group to the nitrene level has been reported to be particularly successful with hydrazine derivatives to give "aminonitrenes" **1** (3). If the oxidation is carried out in the presence of suitable olefins, aziridines are formed (5). The sequence of events between the time the reactants are brought together and the products are isolated is a matter of conjecture. The question as to whether or not *N*-nitrenes are involved in these reactions is still largely unresolved (6). It has been pointed out that while such reactions may well involve the formation of nitrenes, for most reactions this has not been shown (7) and kinetic studies, such as those carried out by Walker and Waters (8), need to be performed before the nechanism of these oxidations can be settled (9).



8

The intervention of a nitrene intermediate is rendered highly probable by generating the species by two or more independent routes and by showing that the same product or product mixture results (10). This technique is exemplified in the area of *N*-nitrenes by the elegant work of Jones (11). Unfortunately, this work is not very extensive. Thus, while there appears to be no direct evidence that nitrenes are involved in the reaction of lead tetraacetate with *N*-aminophthalimide, for example, the nitrene mechanism is a good working hypothesis (12), and the latest work shows that the reaction may be occurring, at least in part, *via* a nitrene mechanism (12).

When we initiated our research we thought it would be of interest to show the synthetic utility of these intermediates regardless of their exact nature. We also hoped to throw some light on the question of the nature of the intermediate. Rees has postulated that *N*-nitrenes are nucleophilic. This hypothesis is supported by the high yields of aziridines obtained when *N*-amino compounds are oxidized in the presence of electrophilic olefins. Although Rees and co-workers used a number of olefins bearing electronegative substituents, cyclohexane was the only strained compound employed. This is the report of the reaction of two *N*-amino compounds with various strained olefins in an attempt to find a useful synthetic route to the bicyclo[3.1.0]hexyl ring system.

There appears to be only two reported examples of the use of a "nitrene" to prepare this heterobicyclic system. Thus, Mayer and co-workers have obtained the expected aziridine (an *N*-substituted derivative of the parent system) from the reaction of 4-amino-3,5-diphenyl-1,2,4-triazole with cyclopentene and lead tetraacetate (13). While our work was in progress, Anderson and Fagerburg reported the synthesis of *N*-phthalimidyl-6-azabicyclo[3.1.0]hexane (14).

Hoesch and Dreiding have reported the synthesis of an unsaturated derivative of the system, *i.e.*, *N*-phthalimidyl-6-azabicyclo[3.1.0]hex-3-ene by the addition of "phthalimidonitrene" to cyclopentadiene (15).

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Results and Discussion.

Table I gives the products and isolated yields of the new azabicyclics prepared in this study. Yield comparisons indicate that the intermediate, whatever its exact nature, does have some nucleophilic character. The only product isolated from the addition of lead tetraacetate to a mixture of 3-amino-2-methyl-4-quinazolone and dimethylcyclopentene-1,2-dicarboxylate was the deaminated quinazolone, *i.e.*, 2-methyl-4-quinazolone. Since this compound was isolated in only 31-37% yields, the reaction is under further investigation. A similar result was obtained in the lead tetraacetate catalyzed reaction of 3-amino-2-methyl-4-quinazolone with dimethylcyclobutene-1,2-dicarboxylate (16). Reaction of *N*-aminophthalimide with indole in the presence of lead tetraacetate in dichloromethane solvent led to an intractable, black reaction mixture which was not investigated further.

One of the reasons for synthesizing the compounds described in this communication was to study their reactions. All of the new compounds reported are remarkably thermally stable. Each was reproducably recovered to the extent of approximately 100% after refluxing for 24 hours in carbon tetrachloride and in chlorobenzene (b.p. 132°).

Reflux of 6-phthalimidyl-6-azabicyclo[3.1.0]hexane **2** in acetic acid for 24 hours produced a compound assigned structure **8** in quantitative yield. The assignment was based on spectral and analytical data (see Experimental). The phthalimide to phthalohydrazide (**2**→**8**) rearrangement is well-documented (17), though such reactions generally take place in basic solution. The rearrangement of the carbon skeleton is more difficult to explain. This compound, as well as the acid-catalyzed rearrangement products of other 6-azabicyclo[3.1.0]-hexanes, is currently under investigation in our laboratories.

## EXPERIMENTAL

Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. Ir spectra were recorded on a Perkin Elmer Model 267 or 237B grating infrared spectrophotometer. Nmr spectra (in deuterochloroform with tetramethylsilane as internal standard) were measured on a Varian T-60 or T-60A spectrometer. The elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., or by Integral Microanalytical Laboratories, Inc., Raleigh, N. C.

The lead tetraacetate was obtained from G. Frederic Smith Chemical Co. It was not recrystallized but the acetic acid was removed by vacuum to give white, powdery material before use. The dichloromethane was washed with concentrated sulfuric acid and 10% potassium hydroxide, stored over solid sodium hydroxide overnight and distilled. It was stored over molecular sieves in brown bottles. The carbon tetrachloride and chlorobenzene were reagent grade and were used without further purification.

The *N*-aminophthalimide was prepared as described by Drew and Hatt (17b).

3-Amino-2-methyl-4-quinazolone was prepared as described by Rees, *et. al.*, (6c). Dimethylcyclopentene-1,5-dicarboxylate was prepared as described by McDonald and Reitz (18).

Preparation of Aziridines: General Procedure.

To a solution of 0.0125 mole of the *N*-amino compound and 0.0625 mole of the olefin in dry dichloromethane (40 ml.) was added 0.0125 mole lead tetraacetate over a period of 12 minutes in the dark. After stirring for an additional 15 minutes the reaction mixture was filtered and the solid washed with additional dichloromethane.

The combined layers were washed with 1% sodium hydroxide and water, dried over anhydrous magnesium sulfate and then evaporated to dryness. The yellow solid which resulted was recrystallized according to the procedure indicated for each aziridine.

The following aziridines were prepared in this way:

6-Phthalimidyl-6-azabicyclo[3.1.0]hexane (**2**).

This compound was prepared from *N*-aminophthalimide and cyclopentene. The yellow crude of product was mixed with boiling water and then recrystallized from ethanol-water to yield 0.52 g. (18% yield) of **2** as yellow needles, m.p. 128.5-129°. The aziridine showed ir (nujol): 702, 710, 875, 1130, 1705 $cm^{-1}$; nmr: δ 7.70 (s, 4H), 3.18 (s, 2H) and a multiplet with centers at 1.68 and 2.31 (6H); ms: *m/e* 228 ($M^+$).

*Anal.* Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.23; H, 5.13; N, 12.08.

Dimethyl-6-phthalimidyl-6-azabicyclo[3.1.0]hexane-1,5-dicarboxylate (**3**).

This compound was prepared from *N*-aminophthalimide and dimethylcyclopentene-1,5-dicarboxylate. The above procedure yielded a yellow solid and an oil. Unreacted dimethylcyclopentene-1,5-dicarboxylate was removed by vacuum distillation to yellow crude material which was recrystallized in absolute ethanol to yield 1.13 g. (28% yield) of **3** as yellow needles, m.p. 156-157°. The aziridine showed ir (nujol): 875, 1125, 1725, 1760 $cm^{-1}$; nmr: δ 7.85 (s, 4H), 3.87 (s, 6H) and a multiplet with centers at 1.81 and 2.75 (6H); ms: *m/e* 344 ($M^+$).

*Anal.* Calcd. for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.14. Found: C, 59.37; H, 4.63; N, 8.21.

2,3-Benzo-6-phthalimidyl-6-azabicyclo[3.1.0]hexane (**4**).

This compound was prepared from *N*-aminophthalimide and indene. The above procedure yielded a yellow solid and an oil. Completely solidified material was obtained by placing the material in a freezer overnight. Recrystallization from acetone-water produced 1.42 g. (41% yield) of **4**, a yellow solid, m.p. 187-188°. The aziridine showed ir (nujol): 700, 750, 1700, 1760 $cm^{-1}$; nmr: δ 7.7 (m, 4H), 7.2 (m, 4H), 4.2 (d), 3.7 (m) and 3.3 (m) (integral 4); ms: *m/e* 276 ($M^+$).

*Anal.* Calcd. for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 74.03; H, 4.50; N, 9.90.

*N*-3-(2-methyl-4-quinazolyl)-6-azabicyclo[3.1.0]hexane (**5**).

This compound was prepared from 2-methyl-3-amino-4-quinazolone and cyclopentene. The yellow-orange solid was dissolved in absolute ethanol. This was removed on a rotary evaporator to leave yellow-orange crude material which was dried under vacuum but could not be recrystallized. Yields ranged from 28.5 to 41%, m.p. 122-124°. The aziridine showed ir (nujol): 760, 1165,

1280, 1580, 1670 $cm^{-1}$; nmr: multiplet with centers at δ 8.18 and 7.58 (4H), 3.18 (s, 2H), 2.70 (s, 3H), multiplet with centers at 2.28 and 1.73 (6H); ms: *m/e* 241 ($M^+$).

*Anal.* Calcd. for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41. Found: C, 69.46; H, 6.40; N, 17.12.

Reaction of 2-Methyl-3-amino-4-quinazolone and Dimethylcyclopentene-1,5-dicarboxylate.

The reaction of 2-methyl-3-amino-4-quinazolone and dimethylcyclopentene-1,5-dicarboxylate by the above procedure yielded a solid and an oil. 7.08 g. unreacted dimethylcyclopentene-1,5-dicarboxylate was recovered by vacuum distillation leaving a solid recrystallized in benzene. White crystals of 2-methyl-4-quinazolone, m.p. 238-239° (0.74 g, 37.4% yield) were collected. The nmr and ir were identical with authentic 2-methyl-4-quinazolone.

Determination of Thermal Stability of Aziridines: General Procedure.

A solution of about 0.1 g. of weighed aziridine was refluxed for 24 hours in 10 ml. of carbon tetrachloride or chlorobenzene. The solvent was removed *via* a rotary evaporator and the residue dried. In all cases about 0.1 g. of material with m.p. and ir spectrum identical with that of starting material was obtained.

Reaction of 6-Phthalimidyl-6-azabicyclo[3.1.0]hexane (**2**) with Acetic Acid.

1.00 g. of the aziridine was refluxed in 30 ml. of glacial acetic acid for 24 hours. After this time, the reaction mixture was diluted with water and washed with ether. The ether was washed with saturated bicarbonate until carbon dioxide evolution ceased. It was then washed with brine and dried over anhydrous magnesium sulfate. The magnesium sulfate was filtered and the ether removed on a rotary evaporator to yield a slightly yellow oil, which solifidied to a white solid after sitting in a freezer for two days. Recrystallization from ethanol produced white crystals, (**8**) m.p. 67-68°; ir (nujol): 710, 1725, 3270, 3320 (w) $cm^{-1}$; nmr: δ (7.8, m, 4H), broad multiplets centered at δ 5.0 and 4.75 (2H), 3.7 (broad s, 1H), broad multiplet centered at δ 1.8 (9H). This multiplet appears to contain two sharp singlets; ms: *m/e* 228 ($M^+$ - HOAc).

*Anal.* Calcd. for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.56; H, 5.77; N, 9.64.

Acknowledgement.

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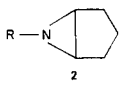
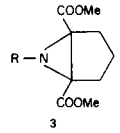
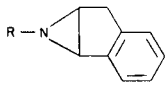
Table I

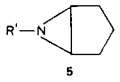

| Aziridine | Yield, % (a) |
|---|---|
| 2 | 18, 49 (b,c) |
| 3 | 28 |
| 4 | 41 |
| 5 | 35 |
| 6 | 0 |
| 7 | 41 (d) |

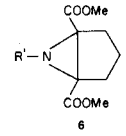
(a) Isolated yields.
(b) Reference 14b.
(c) Before recrystallization.
(d) Reference 5c.

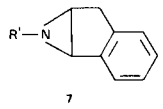


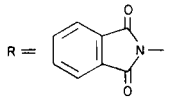



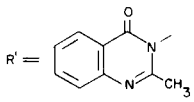

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