Reaction of N-Diazoacetyl-Δ^3-piperideines: Formation of 1-Azabicyclo[4.2.0]-3-(and 4)-octen-8-ones (1-Carba-Δ^1(and Δ^2)-cephems)[1a,b,†]

Vlasios Georgian* and William H. Koster[1c]
Department of Chemistry, Tufts University
Medford, Massachusetts 02155 U.S.A.

The formation of 1-azabicyclo[4.2.0]-3-(and 4)-octen-8-ones from N-diazoacetyl-Δ^3piperideine is discussed.

In connection with our work on the synthesis of Cinchona alkaloid analogs, the obtention of the bridged 2-quinuclidone 3 appeared to be an attractive intermediate synthetic target. As an intermediate 3 was attractive since the steric requirements of the 2-quinuclidone ring system thwart amide resonance, thereby increasing the reactivity of the carbonyl group relative to that of a normal amide and thus forming a potential site for further modifications.[2]

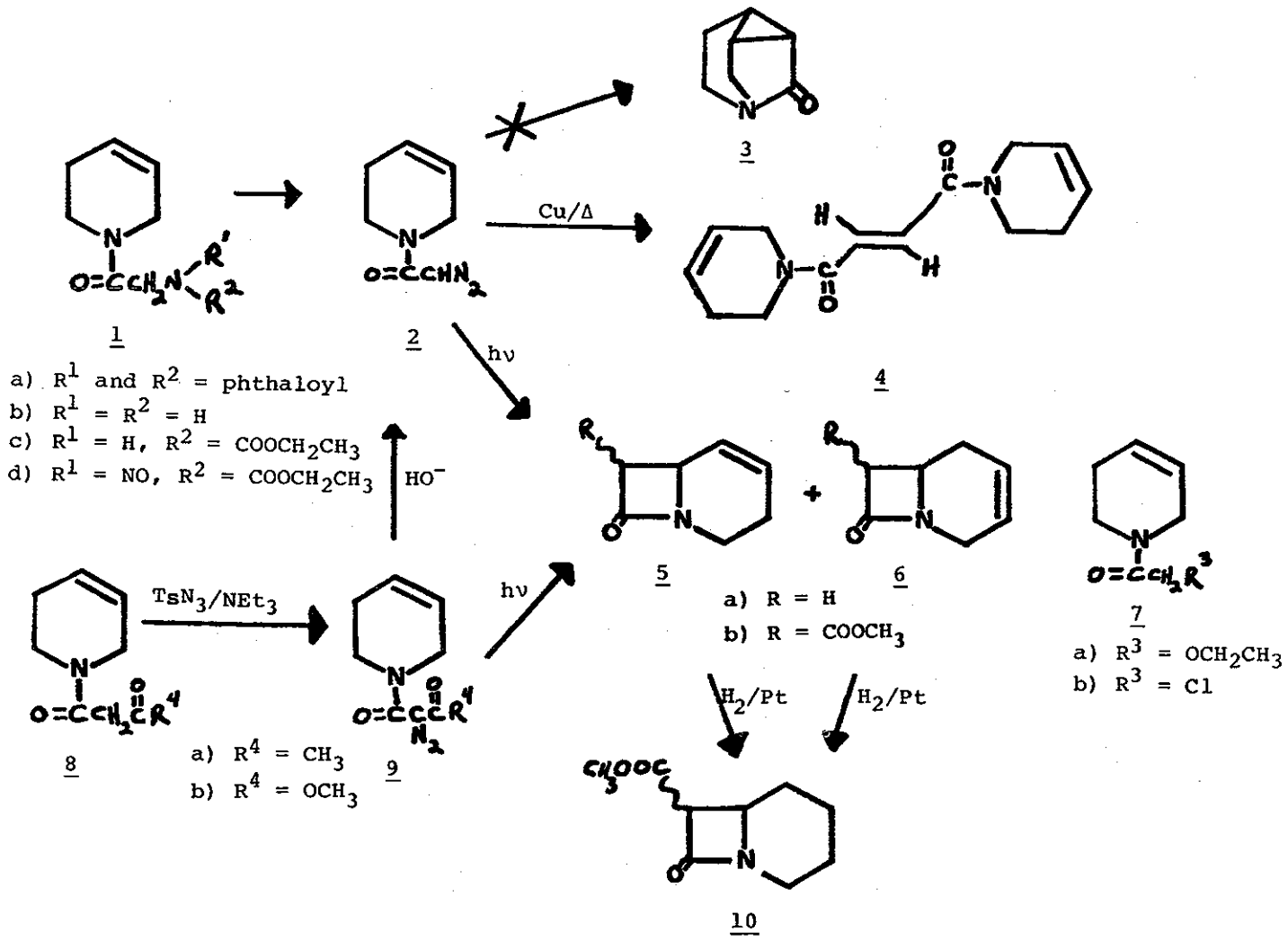
The observation that carbonylcarbenoids react intramolecularly with double bonds to form tricyclic structures[3] prompted us to investigate the thermolytic and photolytic decomposition of N-diazoacetyl-Δ^3-piperideine 2 to carbenoid and carbene intermediates in the hope that the desired bridged quinuclidine structure 3 would result.[4] In the event, copper catalyzed thermolysis yielded dicarboxamidoethylenes,[5] while photolysis gave fused β-lactams[6] and products resulting from the reaction of the carbene with solvent. Transannular addition to the double bond in 2 to form 3 did not occur, but an alternate route to C-substituted 5-azatricyclo-

[3.2.1.$0^{2,7}$]octanes (bridged quinuclidines) has been found and will be discussed in subsequent communications.

N-Diazoacetyl-Δ^3-piperideine (2) was prepared by two routes. In the first method N-phthalimidoacetyl chloride was coupled with Δ^3-piperideine yielding amide 1a; treatment with hydrazine gave glycyl-Δ^3-piperideine (1b), followed by acylation with ethyl chloroformate to form urethane 1c, and nitrosation yielded 1d, which upon treatment with aqueous base gave 2 as a yellow oil; ir(CCl_4) 2100 (C=N_2), 1620 cm^{-1}(amide C=O); PMR(CCl_4,δ) 2.13 (m,2H 5-H) 3.43 (t, J = 5.5Hz,2H,2-H), 3.80 (m,2H,6-H), 5.35 (s,1H,CHN_2), 5.67 (m,2H,HC=CH); UV(cyclohexane) λ_{max} = 248nm(ε= 19,300). An alternate scheme involved the reaction of diketene with Δ^3-piperideine to give 8a, followed by diazo exchange with p-toluenesulfonyl azide to form 9a,[7] which yielded 2 after deacetylation with hydroxide.[8]

Thermolytic decomposition of 2 with copper bronze in refluxing (13 hr.) cyclohexane (c = 2%W/V) (conditions favoring intramolecular additions)[3] followed by chromatography led to the isolation of fumaramide 4 (ca. 50% yield) having a vinyl signal at 7.36ppm. The PMR spectrum of the reaction mixture indicated that the isomeric maleamide, having a singlet at 6.24ppm constituted 5-10% of the total dimerization product.

Irradiation of diazo compound 2 in a 1:1 mixture of cyclohexane:ether (c<1% W/V) for 3 h using a 450 watt Hanovia UV lamp with a Pyrex filter formed a mixture of products separated on silica gel. Two components were β-lactams, ir(neat) 1750cm^{-1} (β-lactam C=O), and a third product isolated was ether 7a. The structures of the


1
a) R1 and R2 = phthaloyl
b) R1 = R2 = H
c) R1 = H, R2 = COOCH2CH3
d) R1 = NO, R2 = COOCH2CH3
2
3
4
Cu/Δ
hν
HO⁻
TsN3/NEt3
8
a) R4 = CH3
b) R4 = OCH3
9
5
6
a) R = H
b) R = COOCH3
7
a) R3 = OCH2CH3
b) R3 = Cl
H2/Pt
H2/Pt
10

isomeric β-lactams were established by PMR. A doublet of doublets was observed for both the C-7 cis and trans protons of the less polar (on silica gel) isomer 1-azabicyclo[4.2.0]-4-octen-8-one(5a) (1-carba-Δ^1-cephem). The trans C-7 proton (J_{gem} = 14.5 Hz, J_{trans} = 2.5Hz) at 2.49ppm and the cis C-7 proton (J_{gem} = 14.5Hz, J_{cis} = 5.5Hz) at 3.14ppm had characteristic coupling constants.[9] Similarly, the more polar isomer 1-azabicyclo[4.2.0]-3-octen-8-one(6a) (1-carba-Δ^2-cephem) also had a doublet of doublets for the trans C-7 proton (J_{gem} = 14Hz, J_{trans} = 1.5 Hz) at 2.43 ppm, but the cis C-7 proton at 3.10 ppm was split further by long-range W coupling (J_{gem} = 14Hz, $J_{6,7\ cis}$ = 4.5Hz, $J_{5,7cis}$ = 1.5 Hz),[10] which is not possible for the 4,5 dehydro isomer 5a. Complex resonances for the vinyl protons of the allylic insertion product 5a produce an unsymmetrical multiplet consisting of three lines whose center of mass is located at 5.87 ppm. The 3,4 dehydro isomer 6a has a symmetric multiplet at 5.24 ppm whose line shape is characteristic of Δ^3-piperideines.[11] The ether insertion product 7a, ir (neat) 1640 cm^{-1}; PMR(CCl_4, δ) 1.18 (t,J = 7Hz,3H,CH_3), 3.48 (q,J = 7Hz,2H,OCH_2), 3.99 (m, 4H, $COCH_2O$ and 2-H); M^+, m/e 169($C_9H_{15}NO_2$ 169) was formed in a ca. 1:1 ratio with intramolecular insertion products 5a and 6a.

To circumvent the formation of ether 7a, the photolytic decomposition of 2 was conducted in carbon tetrachloride. Analysis of the reaction mixture by vpc showed that β-lactams 5a and 6a were formed in a 2:1 ratio, while a third product 7b(∿35%), ir(neat) 1650 cm^{-1}(amide C=O); M^+,m/e 159($C_7H_{10}NOCl$ = 159) was isolated which was identified as N-chloroacetylpiperideine. The formation of 7a and 7b was unexpected since it has been shown that acyclic

α-diazo amides react to form β- and γ-lactams with a total lack of intramolecular insertion products in aprotic solvents.[12] In this mode of decomposition of 2 none of the desired γ-lactam 3 was obtained since planar amide resonance undoubtedly holds the carbene in a configuration sterically unfavorable for reaction with the double bond. Without the availability of this pathway, inter- and intramolecular carbene insertion become competitive.

Bicyclic β-lactams 7-methoxycarbonyl-1-azabicyclo[4.2.0]-4-octen-8-one(7-methoxycarbonyl-1-carba-Δ^1-cephem)(5b) and 7-methoxycarbonyl-1-azabicyclo[4.2.0]-3-octen-8-one (7-methoxycarbonyl-1-carba-Δ^2-cephem)(6b) were prepared by allowing Δ^3-piperideine to react with methoxycarbonylacetyl chloride, followed by diazo exchange to give 9b, ir(CCl_4) 2125 (C=N_2), 1725(ester C=O), 1630cm^{-1}(amide C=O). An ethereal solution of 9b was irradiated as above for 4.5 h. After chromatography on silica gel, two fractions were obtained containing β-lactams 5b and 6b; ir(neat) 1775(β-lactam C=O), 1740cm^{-1} (ester C=O); M^+, m/e 181 ($C_9H_{11}NO_3$ = 181). Assignment of the regioisomeric structures was made by PMR since the resonance characteristics of the vinyl proton multiplets for 5b (5.92ppm) and 6b (5.74ppm) were similar to the multiplets of the unsubstituted analogs, 5a and 6a respectively. Again the less polar fraction contained the allylic insertion products 5b and the more polar fraction consisted of isomers 6b. The relative amounts of the cis and trans isomers in each case were not ascertained. Further proof that these compounds were isomeric at the double bond was demonstrated by catalytic reduction (PtO_2). In both cases one equivalent of hydrogen was taken up rapidly to

give 7-methoxycarbonyl-1-azabicyclo[4.2.0]octan-8-one (7-methoxycarbonyl-1-carbacepham)(10), ir(neat) 1755(β-lactam C=O), 1735cm^{-1} (ester C=O).

Though the desired azatricyclooctane 3 did not form under the conditions described, we have demonstrated that unsaturated bicyclic β-lactams 4 and 5, i.e. 1-carbacephems, in the same oxidation state as the naturally occurring cephalosporins, can be formed directly.

References

† Dedicated to Professor R. B. Woodward for his sixtieth birthday.

1a) W. H. Koster, Doctoral Dissertation, Tufts University, Medford, Mass., (1972).

1b) For introduction of this system of nomenclature for fused beta-lactams, see L.D. Cama, B.G. Christiansen, J. Amer.Chem.Soc. 96, 7582, (1974), and R.N. Guthikonda, L.D. Cama, B.G. Christiansen, ibid., 96, 7584 (1974).

1c) Present address: The Squibb Institute for Medical Research, Princeton, N.J. 08540.

2) E.I. Levkoeva, E.S. Nikitskaya, and L.N. Yakhontov, Khim. Geterotsikl Soedin, 7, 378(1971) C.A. 76, 14303g, (1972).

3) D.J. Beames and L.N. Mander, Chem. Commun., 498 (1969). For a review of many references to such a reaction, see W. Kirmse, "Carbene Chemistry" Academic Press, New York, N.Y., 2nd ed. (1971)p338.

4) Although it might have been foreseen that the amide resonance in 2(carbenoid form) would keep the carbonylcarbene chain from approaching the double bond, it could be argued that any stabilization of the carbenoid site by the carbonyl group would lead to a diminished conjugation of the carbonyl and nitrogen and thus permit a higher energy species to assume the proper conformation necessary to intramolecular cycloaddition to structure 3.

5) W. Kirmse, "Carbene Chemistry", Academic Press, New York, N.Y., (1964) p.131 and ibid. 2nd ed.(1971)p.337 for references to other examples.

6) G. Lowe, Chem. Ind., 459(1975). For other cases intramolecular insertions with α-diazoamides see: E.J. Corey and A.M. Felix, J. Amer. Chem. Soc., 87, 2518 (1965) and R.R. Rando, Ph.D. Dissertation, Yale University, New Haven, Conn. (1967).

7) M. Regitz, Angew. Chem. Internat. Ed., 6, 733 (1967).

8) M. Regitz, J. Hocker, and A. Liedhegener, Org. Prep. and Proc., 1, 99 (1969).

9) H.B. Kagan, J.J. Basselier, and J.L. Luche, Tetrahedron Lett., 941 (1964); K.D. Banow and T. M. Spotswood, ibid, 3325 (1965).

10) R. Moll, Z. Naturforsch, 21B, 297 (1966); D.M. Brunwin, G. Lowe, and J. Parker, Chem. Commun., 865 (1971).

11) J.N. Shoolery, Disc Farad. Soc. 34, 104 (1962).

12) R.R. Rando, J. Amer. Chem. Soc., 92, 6706 (1970).

Received, 28th November, 1977