Unexpected *gem*-Dimethyl–Carbonyl Rearrangement during Nitration of 6,6-Dimethyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one

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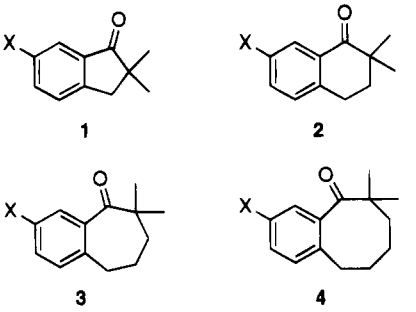
Received August 22, 1994

The development of fluorine-18 (β^+, half life = 110 min) labeled radiopharmaceuticals for positron emission tomographic (PET) imaging requires rapid synthetic methods for the incorporation of the label directly onto the pharmaceutical skeleton or suitable precursors from which the desired radiotracer can be derived. There are several known methods for the incorporation of [^{18}F]-fluoride ion onto activated aromatic rings, the most widely utilized being the fluoro-for-nitro exchange on *ortho*- or *para*-nitro-substituted benzaldehydes and acetophenones.[1] Recently, we discovered the ability to incorporate [^{18}F]fluoride ion into nitro-substituted aromatic ketones having the nitro group *meta*-disposed to the ring-activating carbonyl.[2] In order to explore the applicability of this labeling scheme to pharmaceutically useful fused ring systems, we synthesized a series of *m*-nitro-α,α-dimethylbenzocyclo[n]ones **1b**–**4b** (Chart 1) via standard alkylation and nitration methodology. We now report an unexpected *gem*-dimethyl–carbonyl rearrangement which occurred during the nitration reaction of 6,6-dimethyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene-5-one (6,6-dimethylbenzosuberone) (**3a**).

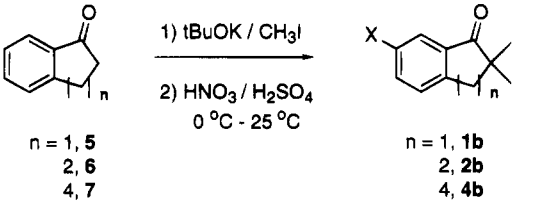
The general synthetic route followed for the production of the five-, six-, and eight-membered ring *m*-nitro-α,α-dimethylbenzocyclo[n]ones **1b**, **2b**, and **4b**, respectively, is shown in Scheme 1. The *gem*-dimethyl derivatives were obtained in 74–94% yield by treatment of the readily available benzocyclo[n]ones **5**–**7**[3] with potassium *tert*-butoxide in ether, followed by quenching of the enolate with excess iodomethane.[4] The dimethylated compounds were then dissolved in concentrated sulfuric acid, treated with a concentrated sulfuric–nitric acid mixture (1.5/1.0, v/v) at 0 °C, allowed to warm to room temperature, and then quenched. The nitro compounds were extracted and purified by flash chromatography affording **1b**[5], **2b**, and **4b** in 61–72% yield. However, similar treatment of the seven-membered ring *gem*-dimethyl ketone **3a** (Scheme 2), produced from benzosuberone (**8**),[3,6] yielded the unexpected rearranged product **9**, in which the *gem*-dimethyl and carbonyl groups interchanged positions, in 72% yield.[7] The structure of **9** was confirmed by X-ray crystallography. The unrear-

Chart 1

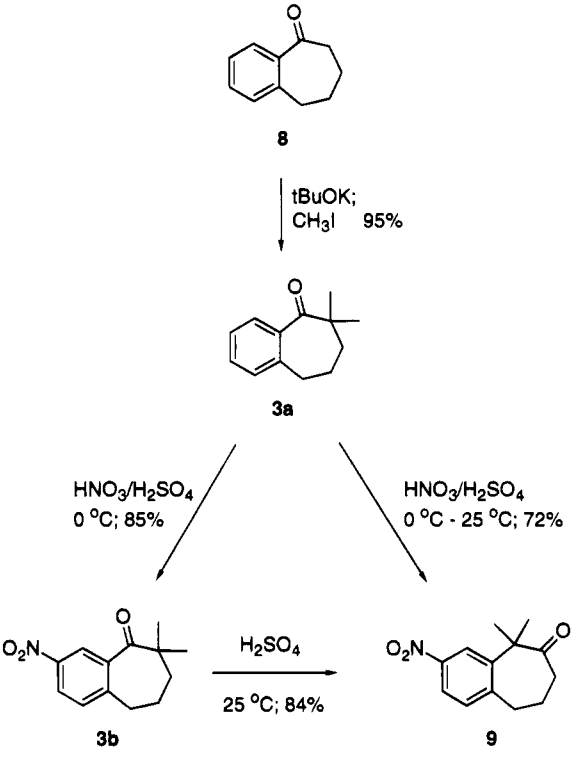


a: X = H
b: X = NO_2

Scheme 1



Scheme 2



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(1) (a) Attina, M; Cacace, F; Wolf, A. P. *J. Labelled Cmpds. Radiopharm.* **1983**, *20*, 501. (b) Kilbourn, M. R.; Welch, M. J.; Dence, C. S; Tewson, T. J.; Saji, H.; Maeda, M. *Int. J. Appl. Radiat. Isot.* **1984**, *35*, 591. (c) Hwang, D.-R.; Lang, L.; Moerlein, S.; Dence, C.; Welch, M. J. 194th Annual Meeting of the American Chemical Society, New Orleans, 1987, Abstract NUCL-119. (d) Ding, Y-S; Shiue, C-Y; Fowler, J. S.; Wolf A. P.; Plenevaux, A. *J. Fluorine Chem.* **1990**, *48*, 189. (e) Banks, W. R.; Hwang, D.-R. *Int. J. Appl. Rad. Isot.* **1994**, *45*, 599.

(2) VanBrocklin, H. F.; Enas, J. D.; Garcia, J. G.; Hanrahan, S. M. *J. Labelled Cmpds. Radiopharm.* **1994**, *35*, 169.

(3) Ketones **5**, **6**, and **8** are available from Aldrich. Ketone **7** was prepared by a known procedure: Suzuki, M.; Hart, H.; Dunkelblum, E.; Li, W. *J. Am. Chem. Soc.* **1977**, *99*, 5083.

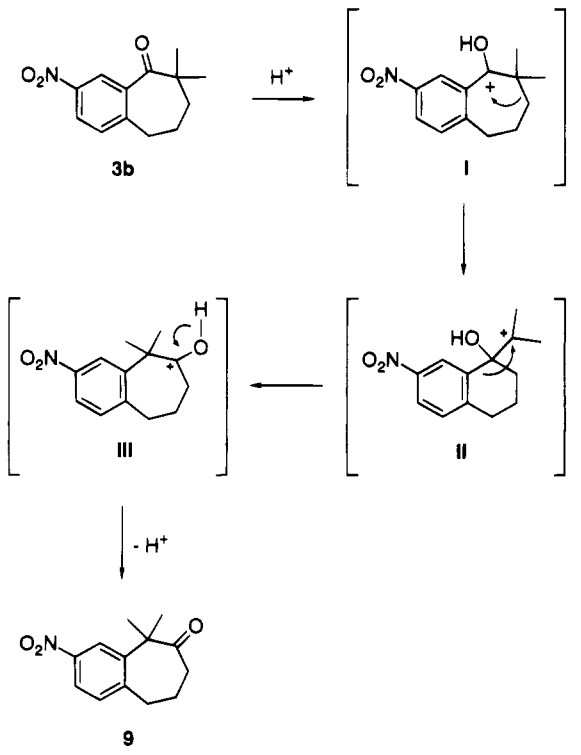
(4) (a) Edwards, H. N.; Wycpalek, A. F.; Corbin, N. C.; McChesney, J. D. *J. Chem. Soc. Synth. Commun.* **1978**, *8*, 563. (b) Lemmen, P.; Lenoir, D. *Chem. Ber.* **1984**, *117*, 2300.

(5) Enas, J. D., Garcia, J. G., Mathis, C. A., Gerdes, J. M. *J. Fluorine Chem.* **1993**, *63*, 233.

(6) A procedure involving formation of the enolate of **8** with sodium amide in refluxing toluene afforded only a 58% yield of **3a**: Dunkelblum, E.; Hart, H.; Suzuki, M. *J. Am. Chem. Soc.* **1977**, *99*, 5074.

0022-3263/94/1959-8299$04.50/0

Scheme 3



ranged nitro ketone **3b** was isolated only upon quenching the nitration reaction at 0 °C instead of room temperature.

While acid-promoted rearrangements of oxime (Beckmann) and Wittig derivatives of various benzosuberones are known,[10] this appears to be the first example of a *gem*-dimethyl–carbonyl rearrangement of the parent ketone. The presence of the nitro moiety is essential for rearrangement to occur[11] as evidenced by the fact that **3b** rearranges to **9** in 84% yield upon dissolution and stirring in concentrated sulfuric acid at room temperature (Scheme 2), while unsubstituted dimethyl ketone **3a** remains unaffected under these same conditions. Likewise, acid media must be present, as the thermally induced rearrangement does not occur when nitro ketone **3b** is heated to reflux in toluene for 24 h in the absence of sulfuric acid.

A possible mechanism for the acid-promoted rearrangement of **3b** to **9** is given in Scheme 3. Protonation of the carbonyl group (under extremely acidic conditions) is followed by migration of the C(*gem*-dimethyl)–C(CH_2) bond to produce the ring contracted stabilized tertiary carbocation **II**. Ring expansion[12] by pseudopinacol migration of the nitrophenyl ring affords the rearranged carbocation **III**. Finally, proton abstraction from **III** yields the *gem*-dimethyl ketone **9**.[13] On the basis of this mechanism, the purpose of the strongly electron-withdrawing nitro moiety may be to facilitate phenyl migration (**II**–**III**) through inductive stabilization of the developing negative charge on the phenyl ring. However, as to why the ring contraction–expansion would be achievable only by the seven-membered ring nitro-substituted benzocyclo[n]one **3b** and not by the five-, six-, and eight-membered ring ketones **1b**, **2b**, and **4b** (even upon heating in acid) is unclear and warrants further investigation.[14]

In summary, classical nitration of 6,6-Dimethyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (**3a**) at 0–25 °C affords an unexpected rearranged product **9** instead of **3b**. Of the four nitro-substituted benzocyclo[n]ones **1b**–**4b**, only the seven-membered ring ketone **3b** undergoes this rearrangement in concentrated sulfuric acid medium. Both the nitro group and room temperature are necessary for this rearrangement to occur. Further studies will be necessary to confirm the rearrangement mechanism. We expect that this rearrangement reaction will be useful in a number of applications in medicinal and radiopharmaceutical chemistry.

Experimental Section

General. The general experimental methods used in this work have been previously reported.[5] *gem*-Dimethyl ketones **1a**–**4a** were produced in 74–94% yield from ketones **5**–**8** following a known procedure.[4b]

Nitration of *gem*-Dimethylbenzocyclo[n]ones 1a–4a. The known benzocyclo[n]ones **1a**,[4b] **2a**,[15] **3a**,[6] or **4a**,[3] were nitrated according to a published procedure[16] to afford, after flash chromatography (CH_2Cl_2 as eluent) or recrystallization, nitroketones **1b**[5]–**4b** in 61–85% yields. The same products were obtained by quenching the reaction after 2 h stirring at rt except for benzocyclo[n]one **3a** which gave rearranged ketone **9** (72%).

Rearrangement of 6,6-Dimethyl-3-nitro-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (3b) in Sulfuric Acid. Nitro ketone **3b** (5.1 g, 22 mmol) was dissolved in concentrated sulfuric acid (28 mL) at rt and stirred for 2 h. The reaction mixture was then poured onto ice. After neutralization with a 10% sodium bicarbonate solution, the mixture was extracted with dichloromethane. The combined organic layers were washed with water and brine, dried over magnesium sulfate, filtered, and concentrated to a dark amber residue. Flash chromatography (CH_2Cl_2) and recrystallization afforded the rearranged ketone **9** (4.3 g, 84%) as a transparent solid.

Attempted Rearrangement of Nitro Ketones 1b, 2b, and 4b in Sulfuric Acid. The nitro ketones **1b**, **2b**, and **4b** (22 mmol) were each dissolved in concentrated sulfuric acid (28 mL) and allowed to stir for 2 h at each of the following temperatures: 25, 45, 85, 105, and 120 °C. Workup of the reaction

(7) The nitration of **1a**, **2a**, and **4a** and the nitration-rearrangement of **3a** proceeded only under the strongly acidic conditions of concentrated sulfuric–nitric acid mixture. Reaction of these same substrates with (a) nitric–acetic acid mixture in acetic anhydride[8] or (b) copper nitrate in acetic anhydride[9] yielded only starting material.

(8) Buckles, R. E.; Bellis, M. P. *Organic Syntheses;* Wiley: New York, 1963; Collect. Vol. IV, p 722.

(9) Kapur, S.; Mathur, N. C.; McManus, K.; Pincock, A. L.; Pincock, J. A. *Can. J. Chem.* **1988**, *66*, 2888.

(10) (a) Conley, R. T.; Frainier, L. J. *J. Org. Chem.* **1962**, *27*, 3844. (b) Hino, K.; Yasutaka, N.; Uno, H. *Chem. Pharm. Bull.* **1988**, *36* (2), 2386. (c) Taylor, E. C.; Chiang, C-S. *Tetrahedron Lett.* **1977**, 1827.

(11) While a complete investigation of the effect of electron-withdrawing and electron-donating aryl substituents on the rearrangement reaction remains for future work, similar rearrangement also occurs with the *m*-amino derivative of **3a** (X = NH_2, Chart 1) presumably via the ammonium (X = $^+NH_3$) intermediate: unpublished observations.

(12) (a) Laboureur, J. L.; Krief, A. *Tetrahedron Lett.* **1984**, *25*, 2713. (b) Krief, A.; Laboureur, J. L. *J. Chem. Soc., Chem. Commun.* **1986**, 702. (c) Paquette, L. A.; Peterson, J. R.; Ross, R. J. *J. Org. Chem.* **1985**, *50*, 5200.

(13) Other syntheses of 6H-benzocyclohepten-6-ones related to **9** by ring expansion methodology: (a) El-Hossini, M. S.; McCullough, K. J.; McKay, R.; Proctor, G. R. *Tetrahedron Lett.* **1986**, *27*, 3783. (b) McKay, R.; Proctor, G. R.; Scopes, D. I. C.; Sneddon, A. H. *J. Chem. Res. (S)* **1989**, 269. (c) Khalaf, A. I.; Proctor, G. R.; Suckling, C. L.; Bence, L. H.; Irvine, J. I.; Stimson, W. H. *J. Chem. Soc. Perkin Trans. 1* **1992**, 1475.

(14) Peculiarities in the behavior of benzosuberones in acidic media are known, see: Amit, B.; Hassner, A. *Synthesis* **1978**, 932. These authors report anomalous behavior of the oxime of **3a** under Beckmann rearrangement conditions, in which ring contraction to a tetralin occurs, compared to the oximes of **1a** and **2a** which do not contract. In the present study, the anomalous behavior of **3b** may be dictated by an interplay of electronic and conformational factors.

(15) Burdon, M. G.; Moffatt, J. G. *J. Am. Chem. Soc.* **1966**, *88*, 5855.

(16) Ohkata, K.; Akiyama, M.; Wada, K.; Shun, S.; Toda, Y.; Hanafusa, T. *J. Org. Chem.* **1984**, *49*, 2517.

mixtures as above afforded either the starting material or decomposition products.

2,2-Dimethyl-7-nitro-1,2,3,4-tetrahydronaphthalen-1-one (2b): mp 101–102 °C; ^{1}H-NMR δ 8.84 (d, 1H, J = 2.4 Hz), 8.24 (d, 1H, J = 8.4 Hz), 7.40 (d, 1H, J = 8.4 Hz), 3.07 (t, 2H, J = 6.3 Hz), 2.01 (t, 2H, J = 6.3 Hz), 1.22 (s, 6H); ^{13}C-NMR δ 200.55, 149.97, 147.05, 132.24, 130.15, 126.68, 123.16, 41.53, 35.70, 25.80, 23.95; IR 1688 cm^{-1}. Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.40; H, 5.85; N, 6.36.

6,6-Dimethyl-3-nitro-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (3b): ^{1}H NMR δ 8.18 (dd, 1H, J = 8.2, 2.4 Hz), 8.11 (d, 1H, J = 2.4 Hz), 7.29 (d, 1H, J = 8.2 Hz), 2.86 (t, 2H, J = 6.8 Hz), 1.95 (quint, 2H, J = 6.8 Hz), 1.69 (t, 2H, J = 6.8 Hz), 1.19 (s, 6H); ^{13}C-NMR δ 212.2, 146.9, 144.7, 142.3, 129.8, 125.3, 122.4, 46.2, 37.4, 33.1, 25.6, 22.7; IR 1689 cm^{-1}; HRMS m/z 233.1030 (calcd for $C_{13}H_{15}NO_3$ 233.1059); LRMS m/z 233 (M$^+$), 215 (16), 69 (base), 41 (28).

6,6-Dimethyl-3-nitro-7,8,9,10-tetrahydro-5*H*-benzocycloocten-5-one (4b): ^{1}H-NMR δ 8.12 (d, 1H, J = 8.4 Hz), 7.86 (s, 1H), 7.32 (d, 1H, J = 8.4 Hz), 2.89 (m, 2H), 1.75 (m, 2H), 1.67 (m, 4H), 1.22 (s, 6H); ^{13}C-NMR δ 214.06, 146.58, 140.29, 130.58, 130.04, 123.18, 122.09, 48.46, 37.26, 33.72, 26.47, 25.02, 24.39; IR 1693 cm^{-1}; HRMS m/z 247.1235 (calcd for $C_{14}H_{17}NO_3$ 247.1200); LRMS m/z 247 (M$^+$), 229 (58), 165 (56), 69 (base), 55 (47).

5,5-Dimethyl-3-nitro-6,7,8,9-tetrahydro-6*H*-benzocyclohepten-6-one (9): mp 135–136 °C; ^{1}H NMR δ 8.26 (d, 1H, J = 2.8 Hz), 8.08 (dd, 1H, J = 8.0, 2.8 Hz), 7.29 (d, 1H, 8.0 Hz), 2.81-(t, 2H, J = 7.1 Hz), 2.48 (t, 2H, J = 7.1 Hz), 2.03 (quint, 2H, J = 7.1 Hz), 1.47 (s, 6H); ^{13}C-NMR: 215.1, 147.4, 146.0, 145.1, 130.9, 122.5, 120.8, 53.3, 36.0, 31.5, 26.3, 25.7; IR 1712 cm^{-1}. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.62; N, 6.00. Found: C, 66.99; H, 6.62; N, 5.88.

Acknowledgment. Thanks are due to Prof. Mark L. McLaughlin, Adam Matzger, Prof. John Katzenellenbogen, Dr. James P. O'Neil, Mr. Steven Hanrahan, and Dr. Alexander T. Shulgin for helpful discussions. This work was supported by the Director, Office of Energy Research, Medical Applications and Biophysical Research Division of the U.S. Department of Energy under contract No. DE-AC03-73SF00098.

Supplementary Material Available: ^{1}H-NMR spectra of compounds **3b** and **4b** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information. Atomic coordinates, bond lengths and angles, thermal parameters, and structure factors for compound **9** have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, upon request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.