Novel Photoisomerization of 1-Acylindoles to 3-Acylindolenines: General Entry to the Total Synthesis of *Strychnos* and *Aspidosperma* Alkaloids

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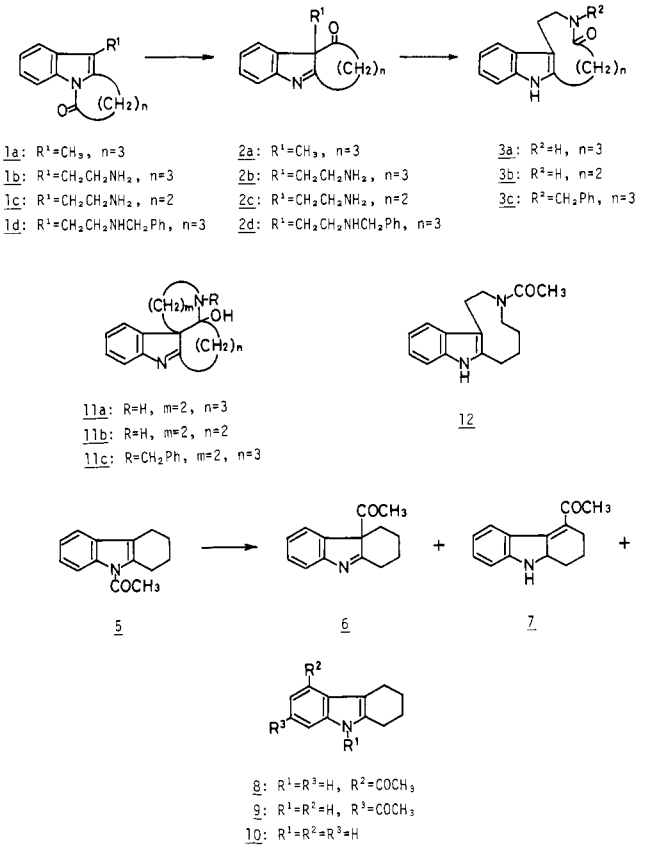
Received July 22, 1981

The photochemistry of the enamide system and its useful application have been well investigated;[1] simple enamides generally undergo a [1,3]-acyl radical shift to afford vinylogous amides [RN(COR^1)—CH=CHR^2 → RNH—CH=C(COR^1)R^2].[2] Meanwhile, photoisomerizations of 1-acylindoles of an enamide system have been described to merely provide 3-, 4-, and 6-acylindoles by the usual photo-Fries type of rearrangement.[3] In this communication, we report the novel photorearrangement synchronized with a conversion of 1-acylindoles **1a–d** to 3-acylindolenines **2a–d**, as depicted in Scheme I, which, with R^1 = $CH_2CH_2NHR^2$, n = 2,3, was followed by a simultaneous intramolecular ring enlargement to provide the nine- or eight-membered lactams **3a–c** in a one-pot reaction, establishing a versatile entry to the total synthesis of a diverse array of *Aspidosperma* and *Strychnos* alkaloids. The general synthetic scheme is demonstrated by formula 4 in Scheme II, with the dotted lines a or b and c.

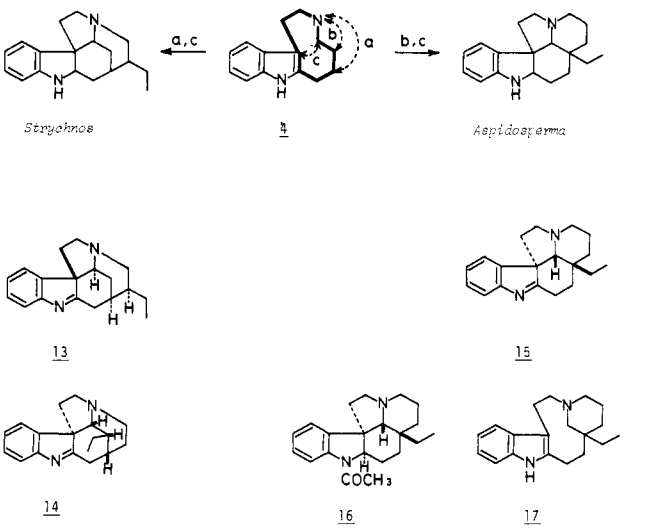
It was discovered by us that the photoisomerization of **5** wtih a 300-W high pressure mercury lamp afforded **6**[4,5] [RN(COR^1)—CH=CR^{2}R^3 → RN=CH—C(COR)R^{2}R^3], which is the so far unknown reactive species, together with **7**, **8**, and **9**, the products of the usual isomerization, in addition to the starting material **5** and **10**.[6,7] The remarkable reactivities of the novel product **6**, which is readily hydrolyzed at room temperature to give **10** and acetic acid,[4] attracted our attention to apply this reaction to the synthesis of natural products and other indole derivatives, since this compound **6** could be assumed to be hardly generated by any other method.

Due to these findings, compound **1a**[8,9] the acyl group of which is bound to the C-2 position at the other end and cannot be rearranged to the aromatic ring, was similarly irradiated to afford the carbazolenine **2a**[10] as a sole product, but only in 20% yield.

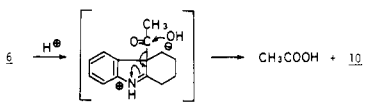
Scheme I



Scheme II

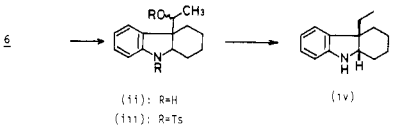


(1) Lenz, G. R. *Synthesis* **1978**, 489.
(2) Bertele, E.; Boos, H.; Dunitz, J. D.; Elsinger, F.; Eschenmoser, A.; Felner, I.; Gribi, H. P.; Gschwend, H.; Meyer, E. F.; Pesaro, M.; Scheffold, R. *Angew. Chem.* **1964**, *76*, 393. *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 490.
(3) Somei, M. Natsume, M. *Tetrahedron lett.* **1973**, 2451. Cf.: Carruthers, W.; Evans, N. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1523.
(4) Compound **6**: mp 66–68 °C; unstable pale yellow crystals; IR (Nujol) 1715, 1645 cm^{-1}; UV (EtOH) λ_{max} 260 nm; ^{1}H NMR (acetone-d_6) δ 1.63 (s, 3 H), 7.1–7.8 (m, 4 H); *m/e* 213 (M$^+$), 170 (M$^+$ – $COCH_3$). The formation of **10** and acetic acid by hydrolysis may be demonstrated by the following



i

pathway. Compound **6** was immediately reduced to ii with lithium aluminum hydride and tosylated to iii followed by reductive elimination of the tosyl groups with lithium aluminum hydride to iv, which was identified with the authentic sample.[5]



(5) Ban, Y.; Kinoshita, H.; Murakami, S.; Oishi, T. *Tetrahedron Lett.* **1971**, 3687.
(6) 4-Acetyl-1,2,3,9a-tetrahydrocarbazole (**7**): mp 156–158 °C; IR (Nujol) 3180, 1610 cm^{-1}; UV (EtOH) λ_{max} 245, 267, 307 nm; ^{1}H NMR ($CDCl_3$) δ 2.69 (s, 3 H), 3.27 (t, J = 7 Hz, 1 H), 4.8–5.3 (m, 3 H), 6.9–7.5 (m, 3 H), 9.1 (br 1 H). 5-Acetyl-1,2,3,4-tetrahydrocarbazole (**8**): mp 156–158 °C; IR (Nujol) 3270, 1650 cm^{-1}; UV (EtOH) λ_{max} 245, 360 nm; ^{1}H NMR (CD_3NO_2) δ 2.60 (s, 3 H), 7.04 (d–d, J = 8 and 8 Hz, 1 H), 7.42 (d–d, J = 8 and 1.5 Hz, 1 H), 7.48 (d–d, J = 8 and 1.5 Hz, 1 H). Compounds **8** was identified with the authentic sample which was synthesized from (*m*-carboxyphenyl)-hydrazine. 7-Acetyl-1,2,3,4-tetrahydrocarbazole (**9**): mp 210–211 °C (lit.[7] 206–208 °C); IR (Nujol) 3280, 1650 cm^{-1}; UV(EtOH) λ_{max} 233, 253, 302, 334 nm; ^{1}H NMR ($CDCl_3$) δ 2.60 (s, 3 H), 7.38 (d, J = 9 Hz, 1 H), 7.68 (d–d, J = 9 and 1.5 Hz, 1 H), 7.93 (d, J = 1.5 Hz, 1 H). Satisfactory elemental analyses were obtained on all new compounds.

(7) Plant, S. G.; Rogers, K. M. *J. Chem. Soc.* **1936**, 40.
(8) Compound **1a** was synthesized by the Fischer iodolization of methyl-4-oxoheptanoate[9] [mp 77–78 °C (lit.[10] 81 °C)].
(9) (a) Cason, J. *J. Am. Chem. Soc.* **1944** *66*, 46. (b) McKennis, H. *Ibid.* **1946** *68*, 832.

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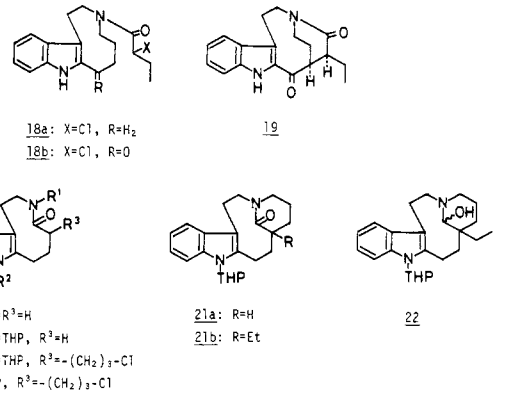
Chart I



18a: X=Cl, R=H_2
18b: X=Cl, R=O
19
20a: R^1=PhCO, R^2=R^3=H
20b: R^1=PhCO, R^2=THP, R^3=H
20c: R^1=PhCO, R^2=THP, R^3=$-(CH_2)_3-Cl$
20d: R^1=H, R^2=THP, R^3=$-(CH_2)_3-Cl$
21a: R=H
21b: R=Et
22

The indolenine **2a** was very unstable, which seemed to be the reason why the yield was actually exiguous.

To overcome this disadvantageous point, it was attempted to transform the photoproduct **2b**, possibly generated by irradiation of the substrate **1b** carrying a nucleophilic functional group (R = $CH_2CH_2NH_2$) in the molecule, immediately into the stable product **3a** by an intramolecular condensation leading to ring expansion; this was subsequently realized.

A solution of the amine **1b**[11,12] in methanol was irradiated for 18 h to furnish the nine-membered lactam **3a**[13] as a sole product in an excellent yield of 80%; the intermediate **2b** was not detected, and the reaction might be assumed to have proceeded through **2b** and **11a** to **3a**. In order to confirm the structure of the product **3a**, reduction of **3a** with lithium aluminum hyride, followed by acetylation, gave the amide **12** (mp 190–193 °C), which was identified with the authentic sample (mp 189–190 °C) on direct comparison.[14] Similarly, the reaction is effective with **1c** and **1d**, providing **3b** and **3c**, respectively, possibly through **2c–d** and **11b–c**.[15]

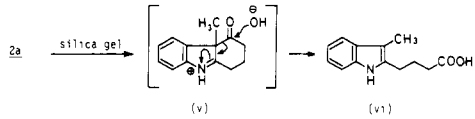
Although *Strychnos* and *Aspidosperma* alkaloids are biologically important and close relatives in indole alkaloid biosynthesis,[16] the synthesis of these alkaloids from a single common intermediate has not been reported previously. The nine-membered portion depicted by bold lines in formula **4**, whose lactam **3a** was obtained by one-pot synthesis through the present photoisomerization, constitutes the common part of the skeletons of the demonstrated alkaloids **13–17**.

The synthesis of *Strychnos* alkaloids such as (±)-tubifoline (**13**) and (±)-condyfoline (**14**)[17] was simply realized by conversion of **3a** to **18b**, since these alkaloids had been already synthesized by Harley-Mason from **18b**.[18] Thus, the lactam **3a** was reduced with lithium aluminum hydride and then acylated with α-chlorobutyryl chloride to **18a** (Chart I). Oxidation of **18a** with iodine pentoxide (I_2O_5) (80% aqueous THF, room temperature) provided **18b** in 65% yield.[19,20] Cyclization of **18b** (NaO-*t*Am, THF, reflux) provided **19** (mp 187-189 °C dec), which was identified with the authentic sample on direct comparison.[18] With regard to the stereo- and regioselective synthesis of *Aspidosperma* alkaloids (**15**,[21] **16**,[22] **17**[23]) from **3a**, attention was focused on the solution of the following problems: (1) selective protection and deprotection at N(a)H and N(b)H; (2) twofold alkylations at α carbon of the lactam carbonyl; (3) the C_3-bridge construction between N(b) and α carbon of the carbonyl; (4) the stereo- and regioselective transannular cyclization. These problems were solved in the following way. The lactam **3a** was treated with benzoyl chloride (Et_3N, THF, room temperature) to afford the imide **20a** (mp 162–163 °C) in 77% yield, which was reacted with an excess of dihydropyran[24] [camphorsulfonic acid (catalytic), CH_2Cl_2, room temperature, 8 h] to provide **20b** (mp 151–153 °C; 89%). The compound **20b** was treated with lithium diisopropylamide (THF–HMPA, −78 °C, 1 h), and then alkylated with 1-chloro-3-iodopropane to give **20c** in 71% yield as a diastereoisomeric mixture. Selective deprotection of **20c** (*n*-propylamine, CH_2Cl_2, room temperature, 1 h) furnished **20d** (mp 180–181 °C dec; 94%) on which only the benzoyl group was eliminated by aminolysis. Cyclization of **20d** [NaH (excess), KI, 18-crown-6 (catalytic), reflux, 1 h] gave the tetracyclic lactam **21a** in 92% yield,[25] which is an important intermediate for the synthesis of *Aspidosperma* alkaloids, by introduction of the C_2 unit at the α carbon of the lactam carbonyl.

Compound **21a** was lithiated [LDA, THF–HMPA (3:1), −78 °C, 1 h] and then alkylated (EtI, −60 °C, 45 min) to furnish the desired compound **21b**[26] in 84% yield. Thus, problems 1–3 were solved to give **21b** in six steps and in a high yield of 35% from **3a**.

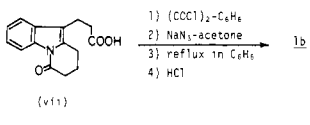
To our surprise, compound **21b** was reduced ($LiAlH_4$, THF, reflux, 1 h) and treated with acid (10%HCl–THF, room temperature, 1 h) to eliminate the tetrahydropyranyl group to give (±)-1,2-dehydroaspidospermidine (**15**)[21] in 48% yield. This al-

(10) Compound **2a**: pale yellow solid, hardly recrystallized. IR (Nujol) 1720, 1590 cm^{-1}; *m/e* 199 (M^+); ^1H NMR (CCl_4) δ 1.45 (s, 3 H). Compound **2a** was readily hydrolyzed to the carboxylic acid vi through v by silica gel chromatography.



The Fischer indolization of 2-methyl-1,3-cyclohexanedione was reported to give **1a** through a plausible intermediate v. (Cf.: Teuber, H.-J.; Cornelius, D.; Worbs, E. *Tetrahedron Lett.* **1964**, 331.)

(11) For the synthesis of the substrate **1b**, 4-oxoazelaic acid[12] was submitted to the Fischer indolization to give vii, which was converted to **1b** in 86% overall yield.



(12) von Pechmann, H.; Sidgwick, N. V. *Ber.* **1904**, *37*, 3816.

(13) Compound **3a** was obtained as a colorless amorphous solid, mp 120–121 °C; IR (Nujol) 3350, 1630 cm^{-1}; *m/e* 228 (M^+).

(14) Sakai, S.; Kubo, A.; Katsuura, K.; Mochinaga, K.; Ezaki, M. *Chem. Pharm. Bull. (Tokyo)* **1972** *20*, 76. Professor Sakai generously provided the authentic sample of **12**.

(15) The details will be published in full papers.

(16) Scott, A. I. *Acc. Chem. Res.* **1970**, *3*, 151.

(17) (a) Schumann, D.; Schmid, H. *Helv. Chim. Acta* **1963** *46*, 1996. (b) Kump, W. G.; Patel, M. B.; Rowson, J.; Schmid, H. *Ibid.* **1964**, *47*, 1497. (c) Wu, A.; Snieckus, V. *Tetrahedron Lett.* **1975** 2057.

(18) Dadson, B. A.; Harley-Mason, J.; Foster, G. H. *Chem. Commun.* **1968**, 1233. Dr. Harley-Mason kindly supplied the authentic sample of **19**.

(19) Compound **18b**: mp 200–201 °C; IR (Nujol) 3320, 1648, 1620 cm^{-1}; *m/e* 332 (M^+); ^1H NMR ($CDCl_3$) δ 0.29 (t, *J* = 7 Hz, 3 H), 9.3 (br s, 1 H). In this reaction, the other known oxidizing reagents[20] are not effective. This reagent (I_2O_5) was proved to be effective for the regioselective oxidation at the α-methylene carbon of the alkyl substituent at the 2-position of 2,3-dialkylindoles without any unfavored side reactions. The details will be published elsewhere.

(20) (a) Dolby, L. J.; Booth, D. L. *J. Am. Chem. Soc.* **1966** *88*, 1049. (b) Dolby, L. J.; Gribble, G. W. *J. Org. Chem.* **1967** *32*, 1391. (c) Hughes, B.; Suschitzky, H. *J. Chem. Soc.* **1965** 875. (d) Leete, E. *J. Am. Chem. Soc.* **1961**, *83*, 3645.

(21) (a) Biemann, K.; Spiteller, G. *J. Am. Chem. Soc.* **1962**, *84*, 4578. (b) Smith, G. F.; Wahid, M. A. *J. Chem. Soc.* **1963** 4002. (c) Klyne, W.; Swan, R. J.; Bycroft, B. W.; Schumann, D.; Schmid, H. *Helv. Chim. Acta* **1965** *48*, 443. (d) Giri, V. S.; Ali, E.; Pakrashi, S. C. *J. Heterocycl. Chem.* **1980**, *17*, 1133.

(22) (a) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872. (b) Kuehne, M. E.; Bayha, C. *Tetrahedron Lett.* **1966**, 1311. (c) Takano, S.; Hatakeyama, T.; Ogasawara, K. *J. Am. Chem. Soc.* **1976** *98*, 3022.

(23) (a) Kutney, J. P.; Abdurahman, N.; Le Quesne, P.; Piers, E.; Vlattas, I. *J. Am. Chem. Soc.* **1966** *88*, 3656. (b) *Ibid.* **1970**, *92*, 1727. (c) Harley-Mason, J.; Kaplan, M. *Chem. Commun.* **1967**, 915. (d) Cf.: Ziegler, F. E.; Zoretic, P. A. *Tetrahedron Lett.* **1968**, 2639. (e) Seki, K.; Ohnuma, T.; Ban, Y. *Ibid.* **1975**, 723.

(24) Takeda, T.; Mukaiyama, T. *Chem. Lett.* **1980**, 163.

(25) Compound **21a**: mp 196–198 °C dec; IR (Nujol) 1650 cm^{-1}; *m/e* 352 (M^+), 268 (M^+ − dihydropyran).

(26) Compound **21b**: mp 176–178 °C; IR (Nujol) 1630 cm^{-1}; *m/e* 380 (M^+), 296 (M^+ − dihydropyran); ^1H NMR ($CDCl_3$) δ 0.87 (t, *J* = 7 Hz, 3 H); 5.15 (d, *J* = 10 Hz, 1 H).

kaloid had not been readily isolated but chemically correlated from the natural quebrachamine (**17**) in a low yield on mild oxidation.[27] For establishment of the structure of the product **15**, it was reduced ($LiAlH_4$, THF, room temperature) and then acetylated to give (±)-1-acetylaspidospermidine (**16**) in 64% yield, which was identified with the authentic specimen synthesized by us through the other route.[23e] The reaction mechanism of this unexpected cyclization could be explained by presuming that the hydroxy group in the amino alcohol **22** generated by reduction of the lactam **21b** might be blocked by the nine-membered ring and thereby resistant to further reduction under mild conditions and would by treatment with acid give the iminium salt,[27] which may be readily cyclized to **15**. Therefore, **21b** was reduced under forcing conditions [$LiAlH_4$ (excess), dioxane, reflux, 4 h] and then treated with acid to furnish (±)-quebrachamine (**17**)[22,21a,28] in 45% yield. Thus, by controlling the reduction condition at the final stages, a variety of *Aspidosperma* alkaloids were produced through the regioselective formation of the iminium salt, thus answering problem 4. Studies along this approach are further in progress.

Acknowledgment. We thank Professor S. Sakai, Chiba University, Japan, and Dr. John Harley-Mason, Cambridge University, England, for the generous gifts of the authentic samples. This research was supported by a Grant-in-Aid for Special Project Research "Nitrogen Organic Resources" from the Ministry of Education, Science and Culture, Japan, which is gratefully acknowledged. We thank E. Ishigamori and S. Nomura for their technical cooperation.

(27) (a) Bycroft, B. W.; Schumann, D.; Patel, M. B.; Schmid, H. *Helv. Chim. Acta* **1964** *47*, 1147. (b) Camermen, A.; Camerman, N.; Kutney, J. P. Piers, E.; Trotter, J. *Tetrahedron Lett.* **1965**, 637.

(28) (a) Walls, F.; Collera, O.; Sandval, A. *Tetrahedron* **1958** *2*, 173. (b) Neuss, N. "Physical Data of Indole And Dihydroindole Alkaloids", 6th revised Ed.; Lilly Research Laboratories: Indianapolis, 1974; p 258.

Synthesis and Reactions of a Dimetallacyclohexene. Thermal Conversion to an *o*-Xylylene Complex and Phosphine-Induced Conversion to Free *o*-Xylylene and a New Reactive Dinuclear Cobalt Complex

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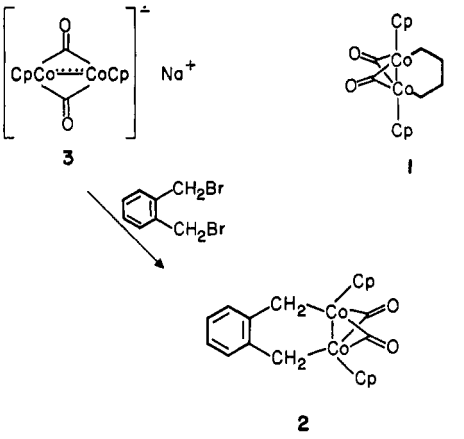
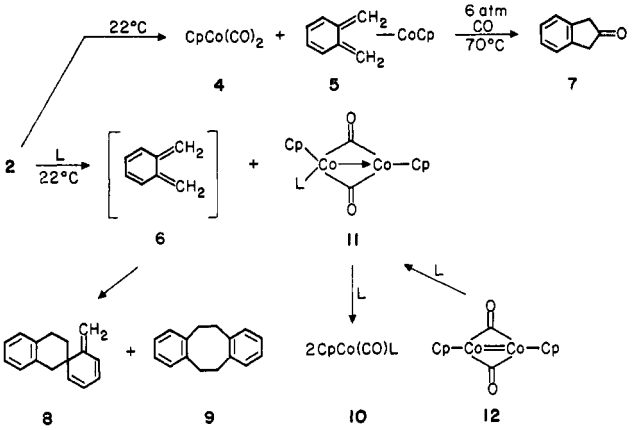
Received May 26, 1981

Saturated metallacycles containing two metals in the ring are proving to have a chemistry at least as rich and varied as that of their mononuclear predecessors. Several kinetically stable three-membered dimetallacycles have now been found and studied,[1] and results in at least one five-membered system suggest that in the cobalt series this ring size confers a similar degree of stability on a molecule.[2] However, saturated dinuclear metallacycles containing four[3] or six[4] atoms in the ring are exceedingly rare.

Scheme I



Scheme II



The larger metallacycles are of particular interest as models for possible dinuclear intermediates in reactions such as alkene and diene oligomerization; in addition, insertion of small unsaturated fragments (i.e., CO, C_2H_4) followed by reductive elimination could lead to new organic annulation procedures. Our attempts to prepare the six-membered cobalt system **1** (Cp = η_5-cyclopentadienyl) have been frustrated, apparently by facile β-elimination processes which can occur in such complexes.[5] In order to preclude this decomposition pathway, we sought to prepare the benzannulated analogue **2**. We now report (1) the successful synthesis of this complex, which is, to our knowledge, the first dimetallacyclohexene, (2) its thermal and ligand-induced decompositions, (3) cyclic ketone formation from a decomposition product of **2**, and (4) the detection and independent synthesis of an unstable dinuclear reaction intermediate which contains a dative metal–metal bond.

Synthesis of **2** was accomplished by analogy to the established procedure,[2] by addition of THF to a 1.5:1 mixture of α,α'-dibromo-*o*-xylene and radical anion **3** (Scheme I). After stirring for 5 min the solvent was removed and the residue chromatographed quickly on alumina II under air-free conditions, eluting

(1) See, for example: (a) Herrmann, W. A. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 800–812. (b) Herrmann, W. A.; Plank, J.; Riedel, D.; Ziegler, K.; Weidenhammer, K.; Guggolz, E.; Balbach, B. *J. Am. Chem. Soc.* **1981**, *103*, 63–75. (c) Hursthouse, M. B.; Jones, R. A.; Abdul Malik, A. M.; Wilkinson, G. *Ibid.* **1979**, *101*, 4128–4150. (d) Jones, R. A.; Wilkinson, G.; Galas, A. M. R.; Hursthouse, M. B.; Abdul Malik, K. M. *J. Chem. Soc., Dalton Trans.* **1980**, 1771–1778. (e) Dyke, A. F.; Knox, S. A. R.; Naish, P. J.; Orpen, A. G. *J. Chem. Soc., Chem. Commun.* **1980**, 237. (f) Halbert, R. T.; Leonowicz, M. E.; Maydonovitch, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 5101–5102. (g) Levisalles, J.; Rudler, H.; Dahan, F.; Jeanning, Y. *J. Organomet. Chem.* **1980**, *187*, 233–242. (h) Sumner, C. E., Jr.; Riley, P. E.; Davis, R. E.; Pettit, R. *J. Am. Chem. Soc.* **1980**, *102*, 1752–1754. (i) Theopold, K. H.; Bergman, R. G. *Ibid.* **1981**, *103*, 2489–2491.

(2) Theopold, K. H.; Bergman, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 5694–5695.

(3) There are a few examples of unsaturated four-membered dimetallacycles. See, e.g.: (a) Johnson, B. F. G.; Kelland, J. W.; Lewis, J.; Rehani, S. K. *J. Organomet. Chem.* **1976**, *113*, C42–C44. (b) Smart, L. E.; Browning, J.; Green, M.; Laguna, A.; Spencer, J. L.; Stone, F. G. A. *J. Chem. Soc., Dalton Trans.* **1977**, 1777–1785. (c) Rausch, M. D.; Gastinger, R. G.; Gardner, S. A.; Brown, R. K.; Wood, J. S. *J. Am. Chem. Soc.* **1977**, *99*, 7870–7876. (d) Dickson, R. S.; Mok, C.; Pain, G. *J. Organomet. Chem.* **1979**, *166*, 385–402. (e) Boag, N. M.; Green, M.; Stone, F. G. A. *J. Chem. Soc., Chem. Commun.* **1980**, 1281–1282.

(4) Known unsaturated six-membered dimetallacycles are mostly of the type formed by oligomerization of alkynes. See, for example, ref 3b and the following: (a) Knox, S. A. R.; Stansfield, R. F. D.; Stone, F. *J. Chem. Soc., Chem. Commun.* **1978**, 221–223. (b) Slater, S.; Muetterties, E. L. *Inorg. Chem.* **1981**, *20*, 946–947.

(5) Theopold, K. H.; Hersh, W. H.; Bergman, R. G. *Israel J. Chem.*, in press.

0002-7863/81/1503-6992$01.25/0