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(6) Except for **5h** and **5l**, which developed inhomogeneity of color as decomposition proceeded.

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Dipole Stabilized Carbanions: *N*-Methyl Carboxamides

Peter Beak,* Gaylen R. Brubaker, and Robert F. Farney

Contribution from the Roger Adams Laboratory, University of Illinois, Urbana, Illinois 61801.

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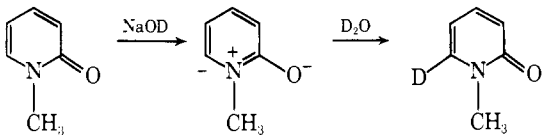
Abstract: The mechanism of the reaction of *N,N*-dimethylbenzamide (**1**) with lithium 2,2,6,6-tetramethylpiperidide to give *N*-methyl-*N*-phenacylbenzamide (**2**) has been investigated by a double labeling experiment. The labeling results are consistent with the initial formation of a formally dipole stabilized carbanion which is subsequently benzoylated by **1**. A mechanism involving a homoenolate anion intermediate which undergoes ring opening prior to benzoylation is ruled out by the same evidence. Related conversions of *N*-methyl-*N*-phenylbenzamide (**5**) to 2-anilinoacetophenone (**6**) and *N*-phenyl-*N*-phenacylbenzamide (**7**) and of *N*-methyl-3,3-diphenyl-2-piperidone (**8**) to *N*-methyl-*N*-(4,4-diphenylbutyl)-2-(3,3-diphenyl-2-piperidon-1-yl)acetamide (**9**) are reported. Circumstantial evidence is presented which suggests that these reactions involve the *N*-methyl syn to the carbonyl oxygen and are lithium dependent. The reaction of *N,N*-diethylbenzamide (**15**) with lithium 2,2,6,6-tetramethylpiperidide gives *o*-benzoyl-*N,N*-diethylbenzamide (**16**) due to metalation of the ortho carbon.

Carbanionic species bearing a formal negative charge adjacent to a heteroatom have recently been found to be exceedingly useful synthetically; such species have been considered theoretically interesting for some time.[1-15] A demonstration that mesomeric dipole stabilization can be important in the direct formation of a formal α-nitrogen carbanion was provided some years ago by our report of C-6 hydrogen-deuterium exchange of some pyridones in basic deuterium oxide at 100°.[2] The case is illustrated for *N*-methyl-2-pyridone.



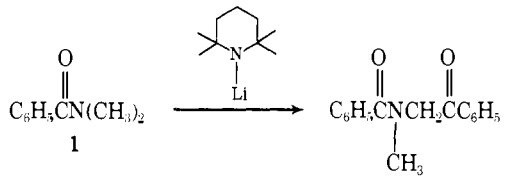
In recent years a number of α-nitrogen carbanions have been reported which could be dipole stabilized, although other effects may be important in various cases.[3] Specifically, an intermediate or product can be envisioned for which at least one canonical form has a positive charge on a nitrogen adjacent to the carbon bearing the negative charge in the hydrogen-deuterium exchanges[2-8] and/or metalations[3,8-14] of carboxamides,[2,4] a vinylogous carboxamide,[2] a vinylogous carbox-sulfoxamide,[7] isonitriles,[9] imidates which are part of azaheteroaromatic systems,[6,11] phosphoramides,[5,10] isothiocyanates,[12] azoxy compounds,[13] nitrosoamines,[3,8] and azine 1-oxides.[5,14] Such stabilization may also be important for some

heterocarbenes.[16] Of the cases studied to date the nitrosoamines[3,8] and the isonitriles[9] appear to have the greatest synthetic utility.

The present paper provides evidence for the formation of α-nitrogen carbanions from *N*-methyl carboxamides and describes reactions of synthetic and mechanistic significance.

Results

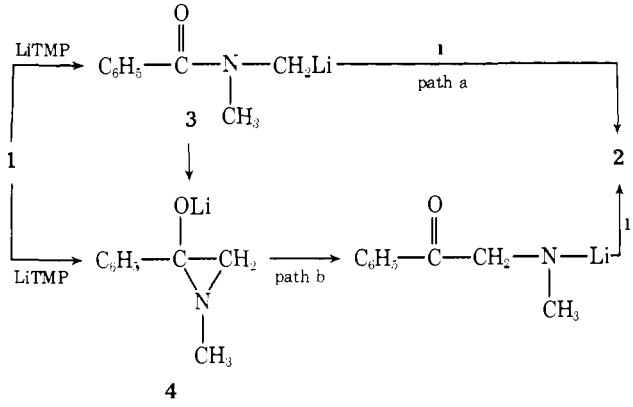
The reaction of *N,N*-dimethylbenzamide (**1**) with 1 equiv of lithium 2,2,6,6-tetramethylpiperidide[17] in tetrahydrofuran for 30 min at ambient temperature gives *N*-methyl-*N*-phenacylbenzamide (**2**) in 53% yield (69% conversion).[18] The



product was identified not only by its spectral and analytical properties, but also by comparison with authentic material prepared by aqueous hydrolysis of 2,4-diphenyl-*N*-methyloxazolium tosylate.[19] The use of lithium 2,2,6,6-tetramethylpiperidide (LiTMP), noted to be an exceptionally useful nonnucleophilic strong base by Olofson and Dougherty,[17] is dictated by the necessity of precluding nucleophilic addition to the carbonyl of **1**.

While the conversion of **1** to **2** can be readily rationalized to proceed via benzoylation of the formally dipole stabilized carbanion **3** (path a Scheme I) by **1**, a pathway involving the

Scheme I



homoenolate species **4**, which could ring open to give a lithium amide prior to benzoylation by **1**, is also plausible (path b, Scheme I).[20] The possible intermediate **4** could be formed either directly from **1** or via **3**. The difference in the paths is illustrated in Schemes II and III for reaction of an equimolar

Scheme II

Path a

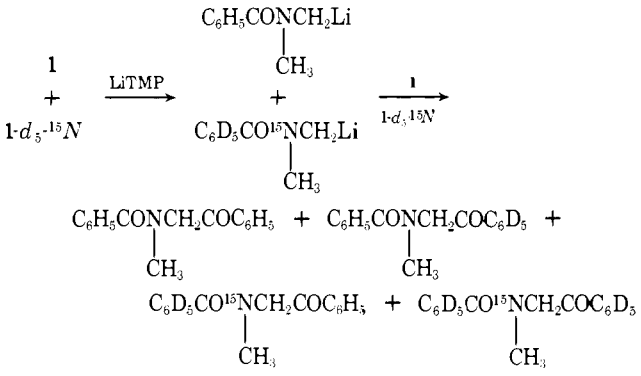


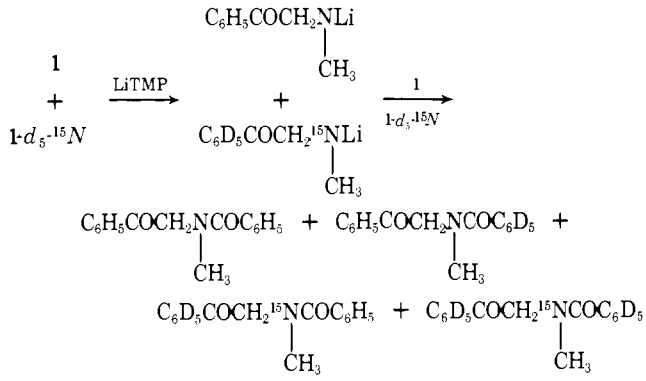
Table I. Mass Spectral Analysis of **3** from the Reaction of Equimolar **1** and **1**-d_5-^{15}N with LiTMP

	m/e (relative intensity)[a]		
Fragment ions	Pathway a	Pathway b	Observed[b]
$C_9H_{10}NO$	148 (100)	148 (100)	148 (100)
$C_9H_{10}{}^{15}NO$		149 (100)	149 (15)[c]
$C_9H_5D_5NO$		153 (100)	153 (15)[c]
$C_9H_5D_5{}^{15}NO$	154 (100)	154 (100)	154 (80)

[a] Intensity assigned for comparison of peaks at *m/e* 148–154 due to loss of benzoyl only. The intensity of the peak in the spectrum of unlabeled material is 148 (27), 149 (3), 153 (6) 154 (1). The high-resolution spectrum corrects for other contributions to the diagnostic peaks. [b] Low resolution spectrum. [c] High-resolution mass spectrometry shows *m/e* 149 and 153 have less than one-third the assigned isotopic composition.

Scheme III

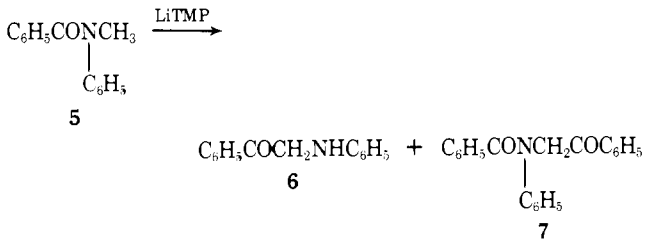
Path b



mixture of **1** and **1**-d_5-^{15}N to give different mixtures of isotopically substituted **2**. If path a is operative the relative position of the labels in the doubly labeled product is the same as in the reactant, i.e., the C_6D_5 and ^{15}N isotopes are bonded to the same carbonyl group. On the other hand, if path b is followed the isotopes are redistributed by the ring opening of the homoenolate; i.e. the C_6D_5 and ^{15}N in the doubly labeled product are separated by a carbonyl and methylene group. Since the mass spectrum of independently synthesized *N*-methyl-*N*-phenacylbenzamide-d_5 shows that the loss of the benzoyl group from the methylene accounts for greater than 95% of the fragment at *m/e* 148 in the mass spectrum of **2**, this tool can be used for product analysis. The quantitative results expected in the mass spectrum for reaction of an equimolar mixture of **1** and **1**-d_5-^{15}N by each pathway in Scheme I are compared with the results actually observed in Table I. For pathway a, fragment peaks due to the loss of the benzoyl group are expected to be of equal intensity and located at *m/e* 148 and 154. If pathway b is operative, fragments of equal intensity would be expected at *m/e* 148, 149, 153, and 154. While the results in the third column of the Table do show fragments at all four masses, those at 149 and 153 are of much lower intensity than the 148 and 154 peaks. In fact, high resolution analysis of these peaks shows that while the nominal 148 and 154 peaks do have the isotopic composition assigned in the Table, the 149 and 153 peaks contain less than one-third the fragments with the isotopic composition required by pathway b. Accordingly the process outlined in Scheme I as pathway a, reaction via the formally dipole stabilized carbanion **3**, accounts for more than 90% of the reaction. This appears to be the first report of for-

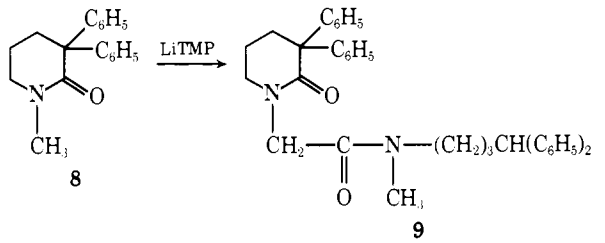
mation of such a formal anion activated only by a carboxamide without additional stabilization provided by unsaturation.[2,4]

The reaction of *N*-methyl-*N*-phenylbenzamide (**5**) with LiTMP does not give any detectable product after 45 min. However if the reaction is allowed to proceed 5 h, 2-anilinoacetophenone (**6**) and *N*-phenyl-*N*-phenacylbenzamide (**7**)

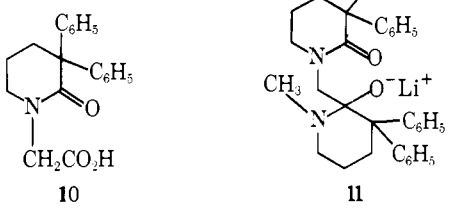


are formed to the extent of 26 and 16%, respectively. Control experiments establish that the conversion of **7** to **6** does not occur on workup, and, if **7** is allowed to react with LiTMP and lithium *N*-methylanilide for 5 h, NMR analysis of the products shows 43% **5**, 5% **6**, and 16% **7** to be present. It is likely that the low yields are due to the instability of **6** and **7** to the reaction conditions and that **6** results from debenzoylation of **7** during the reaction and not from intramolecular rearrangement of **5**.

In order to test the hypothesis that proton removal can occur syn to the carbonyl, *N*-methyl-3,3-diphenyl-2-piperidone (**8**) was prepared and its reaction with LiTMP investigated. After a reaction time of 30 min the product **9** is obtained in 52% yield.



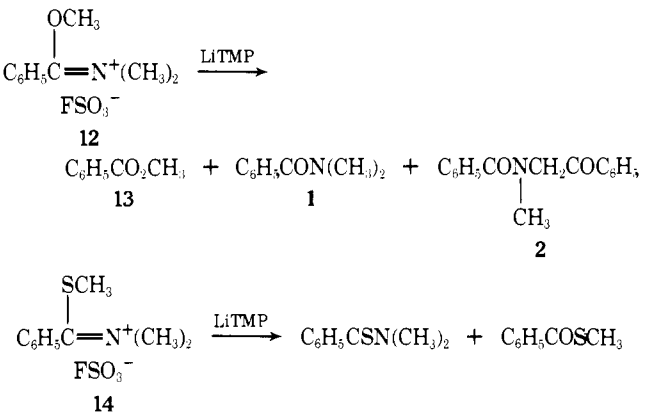
The structure of this material is established by its spectral and analytical properties and by acidic hydrolysis to give the acid **10** identical with an independently synthesized sample. The basic material from the hydrolysis of **9** was tentatively identified as *N*-(4,4-diphenylbutyl)-*N*-methylamine. Apparently **9** arises from ring opening of the intermediate **11** by carbon-



carbon bond cleavage to give a benzhydryl anion. The reactivity of **8** establishes that proton removal can occur from the *N*-methyl syn to the carbonyl oxygen of the amide. While this result does not establish which methyl is involved in the reaction of **1**, **1** and **8** do react at comparable rates and it appears reasonable to suggest that the syn methyl is involved for **1** also.

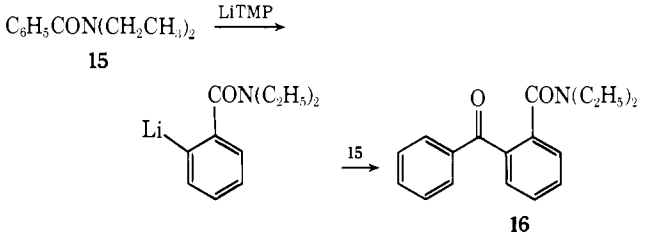
When the reaction of **1** and LiTMP was carried out in the presence of dicyclohexyl-18-crown-6 ether,[21] the formation of **2** could not be observed even with a reaction time of 12 h. Isolation of the products showed only **1** and the crown ether to be present by NMR. In further experiments the reaction of **1** and LiTMP was carried out in tetrahydrofuran-d_8, with and without added crown ether, and the course of the reaction was followed by NMR. The reaction which did not contain crown ether showed the disappearance of **1** and the appearance of peaks readily ascribable to the anion of **2**. By contrast, the reaction in the presence of the crown ether showed no decrease in the signals of **1** and no formation of product. Product isolation also showed that **2** was formed in the former but not in the latter reaction. The inhibitory effect of dicyclohexyl-18-crown-6 ether on the reaction is provisionally ascribed to its binding of lithium such that this cation is not available for complexation with the amide, a process which apparently provides activation for proton removal from the methyl bonded to the amide nitrogen.

Two efforts have been made to take advantage of this apparent need for complexation of the amide group. Because of the expectation that aluminum would complex strongly to the carbonyl oxygen, a reaction of **1** and diethylaluminum 2,2,6,6-tetramethylpiperidide was carried out.[22] However, only **1** could be recovered from these experiments, although the recovery was only 40%, and no other products were detectable by TLC or NMR. In a different approach the reaction of **12** with LiTMP was investigated and found to give, after hydrolysis, 13% **2**, 30% **1**, and 57% methyl benzoate (**13**). However, an independent experiment showed that only **13** is produced on hydrolysis of **12**, suggesting that **1** is formed from **12** under the reaction conditions. In that case **1** could well be the precursor of **2**. That conclusion is supported by the fact that **14** gives both *N*,*N*-dimethylthiobenzamide and methyl



thiobenzoate on reaction with LiTMP and hydrolysis. It was determined the *N*,*N*-dimethylthiobenzamide does not react with LiTMP under these conditions.

The product of the reaction of *N*,*N*-diethylbenzamide (**15**) and LiTMP reveals a structural limitation on the formation of α-nitrogen carbanions under the present conditions. The reaction provides *o*-benzoyl-*N*,*N*-diethylbenzamide (**16**) in



57% yield and clearly results from the precedented[23] removal of an ortho proton followed by benzoylation. As previously noted, this result provides a novel route to *o*-benzoyl substitution as well as revealing the possibility for substitution of other electrophiles ortho to such functions.[23,24] In an effort to block the ortho positions from reaction and to inhibit nucleophilic addition to the carbonyl and thereby provide a trappable carbanion,[25] the reaction of 2,6-dichloro-*N*,*N*-dimethylbenzamide (**17**) with LiTMP at −78° followed by a deuterium oxide quench has been investigated. The product was identified as starting material containing predominantly one or two deuterium atoms in the ring. While the origin of the doubly deuterated material is interesting, the results again suggest that

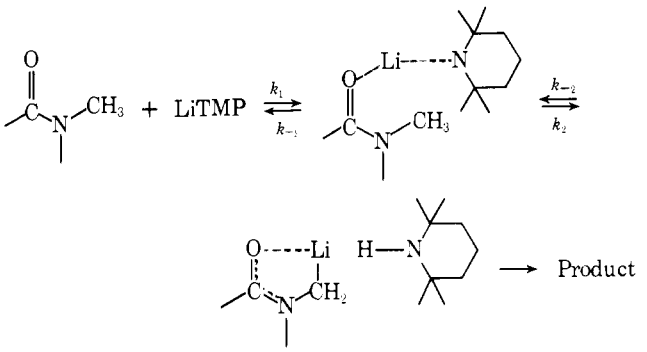
carbanion formation does not occur adjacent to the nitrogen.

Discussion

The conversions of **1** to **2**, **5** to **6** and **7**, and **8** to **9** suggest that *N*-methyl carboxamides which do not have hydrogens adjacent to the carbonyl group can be readily converted to α-amido- and α-amino ketones. Since α-aminoaryl ketones are logical precursors for β-aminoarylethanols (catecholamines) and β-aminoarylethanes (dopamines), compounds which exhibited a wide variety of physiological activities,[26] the reaction may be of specific synthetic use. However, our inability to obtain a metalated intermediate which could be trapped with a variety of electrophiles suggests that these reactions will be of less general synthetic value than metalations of isonitriles[9] and nitrosoamines.[3,8] The present study does provide some mechanistic insights which are relevant to further studies in this area.

The apparent lithium dependence of the conversion of **1** to **2** and the probable involvement of the syn methyl is incorporated in the mechanistic proposal of Scheme IV, which shows

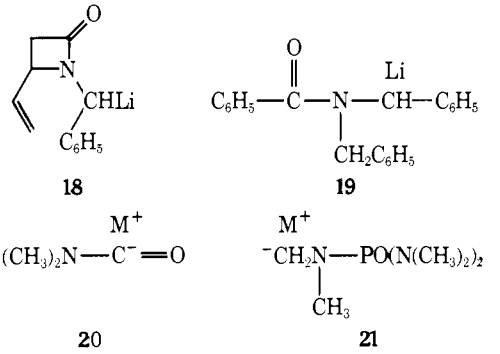
Scheme IV



the role that lithium could play in providing activation for removal of a proton from the carbon bonded to nitrogen. The formation of a lithium piperidide-amide complex could be replaced by a transition state, but formation of a complex is consistent with data in the literature which supports complexation between other amides and lithium ion.[27,28] While lithium dependence is clearly not required for the formation of all α-nitrogen carbanions from carboxamides,[2,4] its possible importance in other cases should be determined. For example, the involvement of lithium in the transition state for hydrogen abstraction from the α position of nitrosoamines could suppress the unfavorable electronic effect of adjacent negative charges which is otherwise introduced in the resonance contributor noted to be important in that reaction by Fraser and Whitfield.[8b]

The possible intermediacy of a lithium complexed species makes predictions about such formally dipole stabilized carbanions tenuous. Thus strongly electron-withdrawing groups which would probably stabilize the anionic intermediate might destabilize an essential lithium complex. For example, the greater barrier to rotation of *N,N*-dimethylthiobenzamide relative to *N,N*-dimethylbenzamide might be expected to provide a greater positive charge on the nitrogen of the former and a resultant greater inclination for loss of a proton from the *N*-methyl group. However *N,N*-dimethylthiobenzamide is inert to LiTMP,[29] while *N,N*-dimethylbenzamide reacts to give **2**. Possibly the appropriate lithium complex is not formed with the thioamide, or if formed does not have proper geometry for proton transfer to the piperidide. Similar uncertainties about complexing effects or geometries of complexes also make difficult interpretation of the reduced rate of reaction of **5** relative to **1**. We have made attempts to generate α-nitrogen carbanions from *N,N*-dimethylbenzenesulfonamide, *N,N*-dimethylpivalamide, *N*-nitro-*N*-methylbenzamide, *N*-methylphthalimide, *N,N,N,N*-tetramethylphthalamide, phenyl-*N*-methylthiobenzimidate, and tetramethylurea. In all except the first case intractable products were obtained.

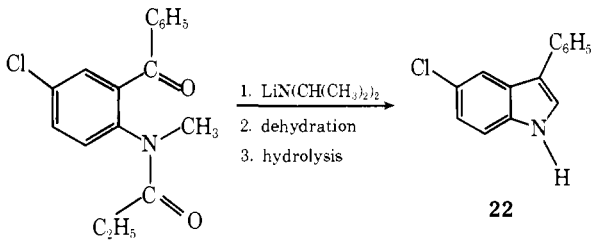
It should be noted that α-amido lithio carbanions are involved in a number of recently reported reactions. The [2,3] sigmatropic rearrangement of a β-lactam to a seven-membered lactam via **18**, and the trapping of the carbanion **19** from *N,N*-dibenzylbenzamide and **20** from formamides, may be in this category.[4,30] Analogously, the P-N cleavage of hexamethylphosphoric triamide upon reaction with alkyllithiums



18 **19**

20 **21**

may be initiated by formation of **21**.[5,10] Finally the recently reported conversion of 2-(*N*-methylbenzamido)-5-chlorobenzophenone to the indole **22** by reaction with lithium diisopropylamide followed by dehydration provides a case of intramolecular trapping of a formally dipole stabilized carbanion which may be of synthetic value.[31]



22

Experimental Section[32]

General. Solvents and starting materials from commercial sources were used without further purification unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl and stored under nitrogen. Methyl fluorosulfonate, carbon tetrachloride, dimethylformamide, and 1,2-dichloroethane were distilled from CaH_2. All reactions involving organolithium compounds, methyl fluorosulfonate, and salts thereof, were performed under dry nitrogen in oven-dried glassware. Thin layer chromatography was carried out on Brinkman GF-254 silica gel. The activity of the *n*-butyllithium (Matheson Coleman and Bell) and methyllithium (Alfa) was determined by titration with 1 M *sec*-butyl alcohol in benzene or xylene using 1,10-phenanthroline as indicator.[33] Dimethylamine hydrochloride-^{15}N (98% ^{15}N) obtained from Isomet Corp. was used without further purification.

***N,N*-Dimethylbenzamide**[34] **(1)**, ***N*-methyl-*N*-phenacylbenzamide**[19] **(2)**, ***N*-methyl-*N*-phenylbenzamide**[34a,35] **(5)**, ***N*-phenyl-*N*-phenacylbenzamide**[36] **(7)**, **2-anilinoacetophenone**[36,37] **(6)**, ***N,N*-diethylbenzamide**[38] **(15)**, **and *N,N*-dimethylthiobenzamide**[40] were prepared by published or conventional procedures. All compounds had NMR and ir spectral properties and elemental analyses consistent with the assigned structures.

***N,N*-Dimethylbenzamide-d_5-^{15}N (1-d_5-^{15}N).** Bromination of perdeuteriobenzene to give bromobenzene-d_5, followed by carboxylation of the Grignard derivative and treatment of the resultant acid with thionyl chloride, yielded benzoyl-d_5 chloride in approximately 40% yield: bp 196–197 °C (760 Torr) [lit.[11] 197.5 °C for C_7H_5OCl (760 Torr)].

Anal. Calcd for C_7D_5OCl: C, 57.74; D, 6.92; Cl, 24.35. Found: C, 57.75; D (as H), 6.86; Cl, 24.57.

To 414 mg (5.05 mmol) of dimethylamine-^{15}N hydrochloride in 10 ml of THF at −20 °C was added ethereal methyllithium (5.50 mmole). Most of the hydrochloride dissolved when the mixture was warmed to 0 °C. A second equivalent of methyllithium was added and the mixture was stirred 5 min at 10 °C. Upon addition of 790 mg (5.50 mmole) of benzoyl-d_5 chloride, a precipitate formed. The mixture was warmed to room temperature and after 30 min quenched with 1.5 ml of dilute HCl. The organic products were separated by extraction with diethyl ether, and the crude products were passed through 10 g of silica gel to give 750 mg of material. Two successive semimicro vacuum distillations gave a product which had one component identical in retention time with authentic *N,N*-dimethylbenzamide by GLC analysis on 2 ft × 0.25 in. 10% Poropak Q column (column temperature 195 °C). NMR (CCl_4) δ 3.00 (d, $J_{15}NCH$ = 1.3 Hz); mass spectrum (70 eV) *m/e* (relative intensity) 156 (3.5), 155 (32.4), 154 (6.9), 153 (43.0), 149 (0.0), 148 (0.0), 110 (100.0), 82 (57.9), 54 (19.4); mass spectrum of unlabeled, undeuterated *N,N*-dimethylbenzamide (70 eV) *m/e* (relative intensity) 156–152 (0.0), 151 (0.2), 150 (3.0), 149 (25.4), 148 (40.4), 105 (100.0), 77 (70.0), 51 (21.9).

***N*-Methyl-*N*-phenacylbenzamide-d_5** was prepared from aminoacetophenone hydrochloride and benzoyl-d_5 chloride according to a published procedure.[19] The material had melting point, NMR, and TLC characteristic of the assigned structure. In the low-resolution mass spectrum the ratio of peaks at *m/e* 148:153 was 3:100. In the high-resolution spectrum the ratio of *m/e* 148.0744:153.1058 was 4.2:100.0.

1-Methyl-3,3-diphenyl-2-piperidone (8) was prepared by treatment of 3,3-diphenyl-2-piperidone[42] with 1 equiv of NaH in dimethylformamide at 80 °C for 90 min, followed by cooling to 0 °C and addition of excess methyl iodide. Addition of $CHCl_3$ and repeated water washes gave **8** in 40% yield: mp 121–122 °C [lit.[42] mp 119–120 °C]; ir and NMR spectra are identical with published spectra.[43]

Anal. Calcd for $C_{18}H_{19}NO$: C, 81.48; H, 7.21; N, 5.27. Found: C, 81.42; H, 7.25; N, 5.24.

1-Carboxymethyl-3,3-diphenyl-2-piperidone (10). The procedure was the same as for **8** except that sodium 2-bromoacetate was the alkylation agent and the product was worked up extractively with diethyl ether for acidic material to give an oil, which was dissolved in *n*-chlorobutane. Cooling overnight resulted in the precipitation of 180 mg (18%) of **10**, mp 188–189 °C; NMR ($CDCl_3$) δ 10.90 (s, 1, COOH), 7.25 (s, 10, Ar), 4.13 (s, 2, NCH_2COOH), 3.4 (t, 2, CH_2N), 2.8–2.4 (m, 2, CH_2CPh_2), 2.0–1.6 (m, 2, $CH_2CH_2CH_2$); ir (KBr) 3070 (CH), 2960 (CH), 2660 (OH), 1753 (C=O acid), 1646 (C=O), 1620, (all broad), 1500, 1450, 1408, 1355, 1285, 1210, 1040, 974, 764, 706 cm^{-1}; mass spectrum (70 eV) *m/e* (relative intensity) 310 (24), 309 (100), 308 (29), 265 (18), 206 (63), 193 (23).

Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.19; N, 4.53. Found: C, 73.76; H, 6.46; N, 4.41.

***N,N,O*-Trimethylbenzimidatium Fluorosulfonate (12).** Treatment of 1.13 g (7.6 mmol) of **1** in 1,2-dichloroethane with 0.86 g (7.6 mmol) of methyl fluorosulfonate for 70 min, followed by the addition of CCl_4, gave a white crystalline precipitate. This material was washed with CCl_4 under nitrogen and dried under vacuum to yield 1.35 g (68%) of **17**, mp 100–102 °C; NMR (CD_3CN) δ 7.63 (s, 5, Ar), 3.90 (s, 3, OCH_3), 3.43 (s, 3, NCH_3), 3.13 (s, 3, NCH_3); ir (Nujol) 2950 (CH), 2924 (CH), 2857 (CH), 1667 (C=N), 1601, 1499, 1471, 1379, 1282, 1075, 980, 893, 782 cm^{-1}.

Anal. Calcd for $C_{10}H_{11}NO_4SF$: C, 45.62; H, 5.36; N, 5.33; S, 12.18. Found: C, 45.30; H, 5.27; N, 5.33; S, 12.30.

***N,N,O*-Trimethylthiobenzimidatium fluorosulfonate (14)** was prepared in 93% yield from *N,N*-dimethylthiobenzamide and methyl fluorosulfonate by the same procedure as reported above for **12**. The material **14** has mp 105–110 °C; NMR (Me_2SO-d_6) δ 7.6 (m, 5, Ar), 3.65 (s, 3, NCH_3), 3.3 (s, 3, NCH_3), 2.05 (s, 3, SCH_3); ir (Nujol) 2930 (CH), 2870 (CH), 1635 (C=N), 1601, 1460, 1380, 1270, 1160, 1070, 995, 975, 940, 880, 778 cm^{-1}.

Anal. Calcd for $C_{10}H_{11}NO_3S_2F$: C, 42.92; H, 5.05; N, 5.01; S, 22.96. Found: C, 42.63; H, 5.02; N, 4.85; S, 23.00.

***N,N*-Dimethyl-2,6-dichlorobenzamide (17).** A 4.19-g (20 mmol) portion of 2,6-dichlorobenzoyl chloride[44] was added to an ethereal solution of 1.0 g (20 mmol) of $LiN(CH_3)_2$ and excess dimethylamine at 0°. The solution was allowed to stir and warm to room temperature, the LiCl was removed by filtration, and the resulting solution was concentrated to a solid. Recrystallization from ethanol yielded 2.3 g (55%) of **17** as a yellow crystalline solid, mp 115–116 °C; NMR ($CDCl_3$) δ 7.23 (s, 3, Ar), 3.06 (s, 3, CH_3), 2.78 (s, 3, CH_3); ir (KBr) 3080 (CH), 2945 (CH), 1650 (C=O), 1600, 1580, 1565, 1505, 1435, 1405, 1275, 1205, 1130, 800, 765, 738 cm^{-1}; mass spectrum (70 eV) *m/e* (relative intensity) 219 (18), 217 (27), 184 (17), 182 (48), 177 (12), 175 (64), 173 (100), 147 (13), 145 (20).

Anal. Calcd for $C_9H_9NOCl_2$: C, 49.80; H, 4.14; N, 6.39; Cl, 32.37. Found: C, 49.67; H, 4.08; N, 6.69; Cl, 32.14.

General Procedure for the Reaction of an Amide with Lithium 2,2,6,6-Tetramethylpiperidide. *n*-Butyllithium (1 equiv) in hexane was added to a weighed sample of 2,2,6,6-tetramethylpiperidine in a few milliliters of THF to form the lithium salt (LiTMP). After the resulting solution was allowed to stir for a few minutes, either the amide (1 equiv) in THF was added, or THF was added followed by the solid amide. The reaction was quenched with 10% HCl, diethyl ether was added, and an extractive product isolation was carried out with washes of 10% HCl, 5% HCl, and water. The ether was dried (Na_2SO_4) and the solvent removed under vacuum.

Reaction of *N,N*-Dimethylbenzamide (1) with LiTMP. Reaction of 0.900 g of **1** for 30 min at ambient temperature and extractive workup provided 0.803 g of crude product. Analysis (TLC, EtOAc/CCl_4 eluent) indicated the presence of at least five components which were separated by column chromatography (100 g silica gel, EtOAc/CCl_4 eluent). The first three components eluted (10, 9, and 13 mg, respectively) were not investigated. The fifth component eluted was identified as unchanged starting material (206 mg, 23% yield).

The fourth component eluted was identified as *N*-methyl-*N*-phenacylbenzamide (405 mg, 53% yield based on stoichiometry requiring 2 mol of starting material to give 1 mol of product; 69% yield based on the amount of reacted starting material): mp 65–67 °C (lit.[19] 64–65 °C); mmp 65–66 °C; NMR ($CDCl_3$) δ 8.20–7.70 (m, 3, Ar), 7.70–7.20 (m, 7, Ar), 4.72 (s, 2, CH_2), 3.12 (s, 3, NCH_3); ir (solid film) 3040, 2910, 1700, 1635 (C=O), 1465, 1390, 1350, 1305, 1215, 1080, 1005, 923–910, 810 cm^{-1}; mass spectrum (70 eV) *m/e* (relative intensity) 255 (0.2), 254 (0.2), 254 (2), 253 (9), 210 (12), 209 (32), 181 (3), 155 (0), 154 (1), 153 (6), 152 (11), 151 (2), 150 (1), 149 (3), 148 (27), 134 (2), 106 (8), 105 (94), 78 (11), 77 (41), 51 (12), 50 (4), 44.5 (23), 44 (22), 28 (100). Comparison of **2** with *N*-methyl-*N*-phenacylbenzamide prepared by the method of Ott[19] showed the two materials identical in ir, NMR, melting point, and mixture melting point.

When the reaction of **1** was carried out under the same conditions as above but in the presence of 1 equiv of analytically pure dicyclohexyl-18-crown-6 ether,[21] no reaction occurred. Even after a reaction time of 12 h the usual workup gave only unreacted **1** and crown ether according to NMR.

Reaction of an Equimolar Mixture of *N,N*-Dimethylbenzamide and *N,N*-Dimethylbenzamide-d_5-^{15}N with LiTMP. High-Resolution Mass Spectrum Analysis of Isotopically Substituted *N*-Methyl-*N*-phenacylbenzamide. Unlabeled *N,N*-dimethylbenzamide (1.00 mmol) was thoroughly mixed with *N,N*-dimethylbenzamide-d_5-^{15}N (1.00 mmol) in 15 ml of THF. The mixture was slowly added to a vigorously stirred solution of 2.00 mmol of LiTMP in 20 ml of THF. After 15 min the charge was quenched with dilute HCl and, following extractive workup, *N*-methyl-*N*-phenacylbenzamide was isolated by column chromatography. Relative peak intensities in the low-resolution mass spectrum analysis of the isotopically substituted *N*-methyl-*N*-phenacylbenzamide are shown in Table I. The relative intensities of ions of *m/e* 148 and 154 obtained from the low-resolution spectrum analysis of unlabeled **3** is 1.00:0.03.

Reaction of *N*-Methyl-*N*-phenylbenzamide (5) with LiTMP. A 422-mg (2 mmol) sample of **5** was allowed to react with 1 equiv of LiTMP for 5 h. The solution was quenched with sufficient 10% HCl to neutralize the LiTMP and immediately added to an acetic acid/sodium acetate buffer. Extractive workup with separation into basic and neutral provided a crude basic product of 52 mg (12%) of **6** and 7 mg (3%) of *N*-methylaniline, by NMR. Crystallization and washing of this material with hexane yielded 28 mg of **6**, mp 92–93 °C with NMR and ir spectra identical with those of authentic material.

The neutral product consisted of 268 mg of a yellow oil. Elution from 27 g of silica gel with 30% ethyl acetate in hexane yielded first 115 mg (27%) of **5**, and then 16.5 mg (5%) of **7**, which had ir and mass spectra identical with those of authentic material.

Tests of the Stability of *N*-Phenyl-*N*-phenacylbenzamide (7) to Workup and Reaction Conditions. Two portions of a THF solution of **7** were mixed with equal volumes of 10% HCl and acetic acid/sodium

acetate buffer, respectively, and the mixture was allowed to stand for 1 h. The organic material of each was examined by TLC and NMR. Only starting material was detected.

A 369-mg (1.17 mmol) portion of **7** and 145-mg (1.33 mmol) portion of *N*-methylaniline were added to a THF solution containing 3.3 mmol of LiTMP. After allowing this solution to stir for 5 h, 10% HCl and acetic acid/sodium acetate buffer were added as above. The resulting solution was extracted with ether, washed with acetic acid/sodium acetate buffer, dried (Na_2SO_4), and analyzed by NMR (internal standard) to contain 60 mg (16%) of **7**, 26 mg (5%) of **6**, and 210 mg (43%) of **5**.

Reaction of 1-Methyl-3,3-diphenyl-2-piperidone (8) with LiTMP. A 667-mg (2.5 mmol) sample of **8** was added to 25 ml of THF solution containing 2.5 mmol LiTMP. After 30 min the reaction was worked up by extraction to yield 644 mg of a yellow oil. A 486-mg portion of that oil was eluted from 50 g of silica gel with 30% ethyl acetate in hexane to yield two components, 260 mg (52%) and 80 mg (16%), respectively, corrected for the total mass. The first material was recrystallized from ether–hexane to yield a white solid, mp 126–128 °C, that has been identified as *N*-methyl-*N*-(4,4-diphenylbutyl)-2-(3,3-diphenyl-2-piperidon-1-yl)acetamide(9): NMR ($CDCl_3$) δ 7.26 (s, 10, Ar), 7.23 (s, 10, Ar), 4.13 (s, 2, NCH_2CO), 3.9 (t, 1, CPh_2H), 3.9–3.7 (m, 4, CH_2CH_2N), 2.86 (s, 3, NCH_3), 2.8–2.5 (m, 2, endocyclic CH_2CPh_2), 2.3–1.2 (m, 6, endocyclic $CH_2CH_2CH_2$, $NCH_2CH_2CH_2Ph_2H$); ir (KBr) 3060 (CH), 3025 (CH), 2940 (CH), 2870 (CH), 1642 (C=O), 1495, 1450, 1405, 1348, 1280, 1205, 1186, 1165, 1042, 755, 701 cm^{-1}; mass spectrum (70 eV) *m/e* (relative intensity) 530 (38), 292 (77), 291 (100), 264 (11), 263 (10), 240 (11), 236 (13), 167 (38), 129 (24), 91 (36).

Anal. Calcd for $C_{36}H_{38}N_2O_4$: C, 81.48; H, 7.21; N, 5.27. Found: C, 81.26; H, 7.19; N, 5.24.

The other component has not been isolated in a pure form, but it gives a mass spectrum identical with that of 3,3-diphenyl-2-piperidone.

Hydrolysis of *N*-Methyl-*N*-(4,4-diphenylbutyl)-2-(3,3-diphenyl-2-piperidon-1-yl)acetamide (9). A 135-mg (0.25 mmol) sample of **9** was treated with 33% H_2SO_4 at 85° for 4 days. The solution was worked up extractively ($CHCl_3$) to yield acidic, basic, and neutral products. The acidic material was 45.5 mg (57%) of **10**, mp 120–125 °C, with ir and mass spectra identical with those of the authentic material. The neutral material was 27.2 mg (2) of impure starting material by ir spectra and TLC. The acid-soluble portion was 26.2 mg (43%) of material tentatively identified as *N*-(4,4-diphenylbutyl)-*N*-methylamine. The amine was precipitated from ether as the HCl salt, mp 157–159 °C: mass spectrum (70 eV) *m/e* (rel intensity) 239 (21), 165 (10), 59 (29), 44 (100); ir (KBr) 3065 (CH), 3030 (CH), 2950 (CH), 2780 (N^+H), 1680 (N^+H), 1495, 1090, 1032, 750, 705 cm^{-1}. Elemental analysis indicated that this material contained a small amount of noncombustible material; the analysis is outside the acceptable limits for carbon.

Anal. Calcd for $C_{17}H_{22}NCl$: C, 74.03; H, 8.04; N, 5.08. Found: C, 73.53; H, 8.01; N, 5.20.

Reaction of *N,N*-Diethylbenzamide (15) with LiTMP. A solution of 832 mg (5.6 mmol) of **15** in THF was allowed to react with 1 equiv of LiTMP for 45 min and then subjected to extractive workup. The resulting 640 mg of oil as chromatographed on 32 g of silica gel and eluted with 30% ethyl acetate in hexane to yield 452 mg (57%) of *o*-benzoyl-*N,N*-diethylbenzamide (**16**), mp 51–54 °C; spectral properties were identical with those obtained from authentic material. Also isolated was 71 mg (9%) of **15**.

Reaction of 2,6-Dichloro-*N,N*-dimethylbenzamide (17) with LiTMP and D_2O Quench. A 453-mg (2.1 mmol) sample of **17** was added to a THF solution of 16.6 mmol of LiTMP at −70°. After 10 min the reaction was quenched with 4 ml of D_2O and was allowed to warm to room temperature. Extractive workup yielded 383 mg of an oil that was chromatographed in 24 g of silica gel with 35% ethyl acetate in hexane to yield 170 mg (38%) of **17**, mp 115–116 °C. The NMR spectrum of this material is identical with that of starting material except that the aromatic region is only 50% of the theoretical area and is slightly broadened. Mass spectral data are consistent with the following deuterium incorporation in the ring: d_0 13%, d_1 44%, d_2 44 ± 6%.

Reaction of *N,N,O*-Trimethylbenzimidatium Fluorosulfonate (12) with LiTMP. A THF solution containing 5.36 mmol of LiTMP was added to a heterogeneous solution of 1.39 g (5.26 mmol) of **12** in THF. The mixture became homogeneous and deep red in color as it was allowed to stir for 2 h. The reaction was quenched with sufficient 10% HCl to neutralize the LiTMP and was immediately added to an acetic acid/sodium acetate buffer. Extractive workup was carried out to yield 0.80 g of an oil that was chromatographed from 100 g of silica gel. Elution with 33% ethyl acetate in hexane yielded 0.415 g (57%) of methyl benzoate, 0.245 g (30%) of *N,N*-dimethylbenzamide, and 0.06 g (13%) of *N*-methyl-*N*-phenacylbenzamide, identified by TLC and NMR.

A solution (20 ml) of acetic acid/sodium acetate buffer containing **12** was allowed to stir for 16 h. Extractive workup yielded a quantitative yield of methyl benzoate, by NMR and TLC.

Reaction of *N,N*-Dimethyl-*S*-methylthiobenzimidatium Fluorosulfonate (14) with LiTMP. A THF solution containing LiTMP was added to a heterogeneous solution of 346 mg (1.24 mmol, 1 equiv) of **14** in THF. The solution became dark brown and homogeneous with stirring, and was quenched and subjected to the normal extractive workup after 1 hr to provide 80 mg of oil. The NMR and TLC of this material were consistent with approximately equal amounts of methyl thiobenzoate and *N,N*-dimethylthiobenzamide as the major components. Further separation and identification were not performed.

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Zinc-Induced Reactions of Bromo Ketones. 6,7-Dihydrodibenzo- and 6,7-Dihydrodithieno[*a,c*]cyclooctene-5,8-diones and Their Dehydro Derivatives

E. Ghera,* Y. Gaoni,* and S. Shoua

Contribution from the Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel. *Received July 1, 1975*

Abstract: The synthesis of 6,7-dihydrodibenzo- and 6,7-dihydrodithieno[*a,c*]cyclooctene-5,8-diones (**4**–**7**) by the use of a novel zinc-induced cyclization of bis(bromoacyl)biphenyls and -bithienyls is reported. The synthesized compounds serve as precursors of the fully conjugated, dibenzo and dithieno analogues **8**, **9**, and **11** of cyclooctatetraenoquinone. The latter compounds were found to undergo some specific reactions: dibenzo[*a,c*]cyclooctene-5,8-dione (**8**) adds acetic anhydride by a 1,4-addition, whereas the corresponding 6,7-dimethyl derivative **9** rearranges in acidic conditions to fluorene, spiroannelated with a γ-lactone (**22**). The conformational preferences of the stereoisomeric *cis*- and *trans*-6,7-dihydro-6,7-dimethyldibenzo[*a,c*]cyclooctene-5,8-diones (**5** and **6**) have been investigated and their inversion barriers have been determined: the cis stereomer **5** has a higher energy barrier for inversion and is thermodynamically the more stable of the two isomers.

The synthetic importance of α-keto radicals, generated from ketones by the action of light,[1] peroxides,[2] or metallic ions[3] has been generally limited to addition reactions to unsaturated systems. Intermolecular dimerizations involving these radicals and leading to 1,4-diketones[4] have been found to be of rather limited synthetic value.[5] Moreover, the peroxide-initiated reactions of aliphatic 1,3- and 1,4-diketones did not afford cyclic diketones via a potential intramolecular coupling.[6] Recently it was found that aromatic α-ketomethylene radicals, generated by the action of zinc on bromo ketones, could undergo an intermolecular coupling.[7] This method was applied with advantage to the synthesis of six-membered cyclic diketones, by free-radical cyclizations involving two vicinal bromoacyl groupings attached to heterocyclic substrates.[8] The same approach has been extended now to further separated bromoacyl groupings, attached to aromatic or heteroaromatic substrates, thus providing a method for the synthesis of annelated medium-sized cyclic 1,4-diketones.

Results and Discussion

Treatment of 2,2′-bis(bromoacetyl)biphenyl (**1**) and of the 4,4′-bis(bromoacetyl)bithienyl (**3**) with zinc-copper couple in dimethyl sulfoxide (Me_2SO), in the presence of sodium iodide and sodium bicarbonate, resulted in an intramolecular coupling leading to the annelated cyclooctadienediones **4** and **7** in yields of ca. 50%. These cyclizations, although limited at present to aromatic or heteroaromatic diketones, appear to be the first reported intramolecular coupling reactions to involve α-ketomethylene groups and to lead to medium-sized cyclic 1,4-diketones.

The structure of **4** (and **7**) was established on the basis of spectral and chemical properties. The absence of methyl signals in the NMR spectrum of **4**, together with its elemental analysis, indicated a tricyclic diketone structure. The NMR spectrum showed one singlet for the cyclic methylene protons (at δ 2.82), unchanged down to −50°, and these data, associ-