The Reductive Metalation of 9-Phenylacridine

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The reductive metalation of 9-phenylacridine by sodium to a dianion is described and the reactions of the dianion with electrophiles investigated. Reactions of the dianion with methanol, dimethyl sulfate, $X(CH_2)_nX$ (n = 2,3,4, X = Cl, Br), and methyl chloroformate were studied. Reactions occurred exclusively at the 9 and 10 positions forming 9,10-dihydro-9-phenylacridine derivatives. Of particular interest was the fact that the dianion was dialkylated with 1,2-dichloroethane but monoalkylated at the 9-position with 1,3-dichloropropane and 1,4-dichlorobutane. These results are compared to those obtained with dianions derived from other heterocyclic systems and analyzed using Baldwin's Rules for Ring Closure.

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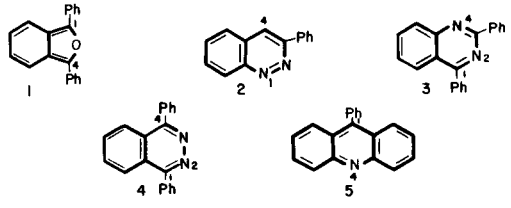
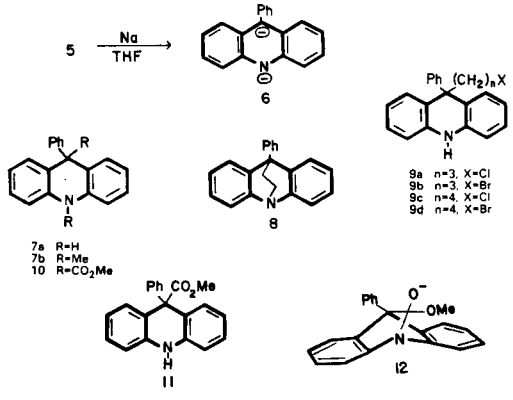
Recently, we have investigated the reductive metalation of various heterocyclic systems by alkali metals [1-4]. Each system investigated involved a two electron reduction to form a monomeric dianion and the chemical behavior of this dianion was evaluated by protonation, alkylation with methyl iodide, alkylation with $X(CH_2)_nX$ (n = 2,3,4; X = Cl, Br), and acylation with methyl chloroformate.



From this study it was apparent that the dianions derived from **1**, **2**, **3** and **4** behaved as "1,4-dianions" on protonation [5], methylation and alkylation with 1,2-dichloroethane. However, a divergence of behavior arose when 1,3-dichloropropane or 1,4-dichlorobutane was used. Bridging (1,4-dialkylation) occurred with **1**, 1,2-alkylation occurred with **3** and **4** but monoalkylation producing a chlorotri- (or tetra-) methylene group resulted with **2**. This varying behaviour of heterocyclic dianions prompted further investigation. All dianions (except that derived from **1**) can be considered to be highly delocalized after the first alkylation step when dihaloalkanes are used. Subsequent reaction would depend on the nucleophilicity of the derived monoanion or (as suggested) the stereochemical restrictions of the second alkylation.

Consequently, 9-phenylacridine **5** was selected for examination. The dianion derived from **5** should approximate a combination of a triphenylmethyl anion and a diphenylamino anion.

As expected, the dianion **6** formed readily in tetrahydrofuran when **5** was agitated with sodium for several hours. The reactivity of this dianion was assessed by protonation (water) and methylation (methyl iodide) forming 9,10-dihydro-9-phenylacridine **7a** and 9,10-dihydro-9,10-dimethyl-9-phenylacridine **7b**, respectively.



Scheme 1. Reactions of the 9-Phenylacridine Dianion.

When the dichloroalkanes were used as alkylating agents, the pattern previously described for **2** emerged. Thus 1,2-dichloroethane provided the 9,10-ethano-bridged derivative **8** while 1,3-dichloropropane and 1,4-dichlorobutane produced the monoalkylation products **9a** and **9c**. Attempts to force bridging by using the more reactive dibromo analogs of these last two dihalides resulted in extensive regeneration of starting material, **5**. No doubt on changing the leaving group from Cl to Br, electron transfer from the dianion **6** to the dibromo compound became predominant and **5** was produced.

One additional aspect involving the acylation of **6** with methyl chloroformate was examined. In earlier work [6] involving the acylation of the benzophenone anil dianion, it had been noted that (at −70°) acylation occurred on the carbon but on warming the resulting monoanion above 0° C--N migration of the acyl group occurred. In the present instance, using two or more equivalents of methyl chloroformate gave 9,10-dicarbomethoxy-9,10-dihydro-9-phenylacridine, **10**. When one equivalent of the acylating reagent was used, only 9-carbomethoxy-9,10-dihydro-9-phenylacridine was obtained both at −70° and above 0°. No migration of the carbomethoxy group was observed.

Discussion.

It is instructive to examine the reactions discussed in this paper in the light of Baldwin's rules for ring closure [7]. Exo-Tet ring closures forming ring sizes 3 through 7 inclusive are allowed. Reaction of the isobenzofuran dianion (from **1**) with the dichloroalkanes used fits this rule provided the ether oxygen is counted as part of the newly formed ring and not the benzo ring. Also fitting the rule are the successful bridging reactions observed with 1,2-dichloroethane and the dianions of **2, 3, 4** and **5**.

1,4-Dichlorobutane does not form bridged alkylation products with the dianions of **2, 3, 4** and **5** since an 8-membered ring would be formed. Instead, with the dianions of **3** and **4** alkylation occurs 1,2 forming a 6-membered ring and with the dianions of **2** and **5** monoalkylation occurs leaving a 4-chlorotetramethylene substituent.

The exceptional situation is the lack of 1,4-dialkylation (bridging) with 1,3-dichloropropane in the case of the dianions of **2** and **5** since this would appear feasible under Baldwin's rules. The explanation advanced earlier [2] appears applicable here.

The 3-chlorotrimethylene group in order to complete the bridging must assume a conformation in which the leaving chloride group eclipses a proton of the adjacent methylene group. Given the higher energy of activation that this would require, the formation of a bridge is discouraged and only monoalkylation is observed.

Insofar as the acylation is concerned, it was of interest to see if 1,4-migration (*i.e.* C--N migration of the carbomethoxy group would occur in the mono-anion of **11** formed after the mono-acylation of the dianion of **5**. Since it did not, this suggests that a bridged intermediate **12** (analogous to that suggested [6] for the C-N migration observed in the study with this C--N migration observed in the study with benzophenone anil dianion) does not form. Perhaps the presence of the two benzo rings renders the geometry of the intermediate **12** too difficult to attain and migration does not form.

EXPERIMENTAL

Melting points were determined in open capillary tubes using a Mel-Temp apparatus, and are uncorrected. Column chromatography was effected by the method of Still [8] on 230-400 mesh Silica gel 60 (E. Merck), using as eluant a 20:80 mixture of ethyl acetate and 30-60 petroleum ether. The ^{1}H nmr spectra were recorded on a Bruker WP-80 spectrometer. Chemical shifts are reported in ppm downfield from the internal reference tetramethylsilane. A Beckman Acculab 10 spectrophotometer was used to obtain ir spectra and mass spectra (ms) were obtained on a Hitachi model RMV-6E mass spectrometer. Chemical analyses were performed by MHW Laboratories, Phoenix, Arizona.

Tetrahydrofuran was distilled from lithium aluminum hydride and stored over sodium with benzophenone ketyl as an indicator. From this it was distilled immediately prior to use.

9-Phenylacridine, **5**, was prepared according to a literature procedure [9], mp 185-187°. Its reaction with sodium was measured in the usual manner [1] and the deep blue dianion was rapidly formed. Normally 1.25 g (5 mmoles) of **5**, 100 ml of tetrahydrofuran and excess sodium was used. The reductive metalation was complete after 4-6 hours. After separation of the tetrahydrofuran solution from the excess sodium, addition of the electrophilic reagent was effected at an initial reaction temperature of −70°. Allowing the reaction mixture to warm to 20° completed the reaction as indicated by the disappearance of the blue colour of the dianion.

The solution was then treated with excess methanol followed by 30 ml of water. The product was isolated by extraction with diethyl ether, drying the extract (magnesium sulfate) and concentrating the extract *in vacuo*.

Details of the preparation of specific compounds are described below.

9,10-Dihydro-9-phenylacridine, **7a**.

The dianion **6**, was prepared as previously described from **5** (1.27 g, 5 mmoles). Quenching with methanol (50 mmoles) afforded, after recrystallization from ethanol, 0.82 g (64%) of **7a**, mp 172-173°, (reported [10] mp 172-173°); ir (nujol): 3380 (NH), 1595, 1570, 1300, 745 cm^{-1}; nmr (deuteriochloroform): δ 5.3 (s, 1H), 6.1 (broad s, 1H, exchanges with deuterium oxide), 6.7-7.4 (m, 13H).

9,10-Dihydro-9,10-dimethyl-9-phenylacridine, **7b**.

The dianion, **6**, prepared from **5**, (1.27 g, 5.0 mmoles), was treated with 1 ml (20 mmoles) of dimethyl sulfate. The crude reaction product (1.12 g) was recrystallized from ethanol giving 0.87 g (61%) of **7b**, mp 180-181°; ir (nujol): 1580, 1460, 1340, 1260, 750 cm^{-1}; nmr (deuteriochloroform): δ 1.90 (s, 3H), 3.42 (s, 3H), 6.8-7.4 (m, 13H).

Anal. Calcd. for $C_{21}H_{19}N$: C, 88.38; H, 6.7; N, 4.91. Found: C, 88.10; H, 6.73; N, 4.94.

9,10-Ethano-9,10-dihydro-9-phenylacridine, **8**.

The dianion prepared from **5** (1.27 g, 5 mmoles) was treated with 1,2-dichloroethane (0.4 ml, 5 mmoles). Recrystallization from ethanol yielded 0.61 g (71%) of two-carbon-bridged adduct, **8**, mp 225-227°; ir (nujol): 1185, 1010, 800, 765, 710 cm^{-1}; nmr (deuteriochloroform): δ AA'XX' system, peaks at 2.2-2.5 (m, 2H), and 3.13-3.4 (m, 2H), 6.8-7.8 (m, 13H).

Anal. Calcd. for $C_{21}H_{17}N$: C, 89.01; H, 6.0; N, 4.94. Found: C, 88.88; H, 6.15; N, 4.78.

When 1,2-dibromoethane was used as the alkylating agent, only starting material was recovered, (mp 184-185°).

9-(3-Chloropropyl)-910-dihydro-9-phenylacridine, **9a**.

The dianion, **6**, prepared from **5**, (1.50 g, 5.9 mmoles), was treated with 1,3-dichloropropane (0.56 g, 5.9 mmoles). The resulting yellow oil was crystallized from 30-60 petroleum ether and recrystallized from ethanol to yield 0.71 g (36%) of **9a**, mp 140-142°; ir (nujol): 3420 (N-H), 1610, 1380, 1260, 750 cm^{-1}; nmr (deuteriochloroform): δ AA'MM'XX' systems; peaks at 2.4-2.8 (m, 2H), 2.2-2.5 (m, 2H), and 3.2-3.5 (t, 2H, 6.1 (broad s, 1H, exchanges with deuterium oxide), 6.5-7.5 (m, 13H); ms: 333 (M$^+$, 9), 297 (8), 296 (32), 257 (54), 256 (100), 255 (40), 254 (34).

Anal. Calcd. for $C_{22}H_{20}ClN$: C, 79.15; H, 6.04; N, 4.2. Found: C, 79.35; H, 6.25; N, 4.17.

9-(3-Bromopropyl)-9,10-dihydro-9-phenylacridine, **9b**.

The dianion **6**, prepared from **5** (1.50 g, 5.9 mmoles) was treated with 1,3-dibromopropane (0.6 ml, 6.9 mmoles). The product could not be crystallized. Its nmr spectrum showed it to be a complex mixture. After purification by chromatography the monoalkylated adduct **9b** was obtained, 0.51 g, (26%), mp 158-162°. The nmr and ir spectra were essentially identical to those of **9a**.

9-(4-Chlorobutyl)-9,10-dihydro-9-phenylacridine, **9c**.

The dianion, **6**, prepared from **5**, (1.80 g, 3.1 mmoles), was treated with 1,4-dichlorobutane (0.37 ml, 3.1 mmoles). The yellow oil which resulted was purified by chromatography, and recrystallized from ethanol to yield 0.4 g (37%) of **9c**, mp 103-104°; ir (nujol): 3160 (N-H), 1600, 1565, 1315, 735 cm^{-1}; nmr (deuteriochloroform): δ 1.0-2.4 (m, 6H), 3.4-3.9 (m, 2H), 6.2-6.4 (broad s, 1H, exchanges with deuterium oxide), 6.6-7.9 (m, 13H).

Anal. Calcd. for $C_{23}H_{22}ClN$: C, 79.40; H, 6.38; N, 4.03. Found: C, 79.28; H, 6.30; N, 3.97.

9-(4-Bromobutyl)-9,10-dihydro-9-phenylacridine, **9d**.

The dianion **6** prepared from **5** (0.80 g, 3.1 mmoles) was treated with 1,4-dibromobutane (0.34 ml, 3.1 mmoles). The nmr of the resulting yellow oil showed it to be a complex mixture. It was purified by chromatography to yield 0.2 g (18%) of **9d**, mp 149-151°.

The nmr and ir spectra were essentially identical to those of **9c**.

9-Carbomethoxy-9,10-dihydro-9-phenylacridine, **11**.

The dianion, **6** prepared from **5**, (2.00 g, 7.8 mmoles) was treated with methyl chloroformate (0.60 ml, 7.8 mmoles) at 25°. The product (2.02 g) was heavily contaminated with the dihydro adduct **7a**. The yield of **11**, calculated from the nmr an integration ratios, was 1.59 g (67%). Two recrystallizations from ethanol provided an analtyical sample, mp 179-181°; ir (nujol): 3375 (N-H), 1740, 1605, 1325, 1215, 1010, 755 cm^{-1}; nmr (deuteriochloroform): δ 3.70 (s, 3H), 6.3 (s, 1H, exchanges with deuterium oxide), 6.6-7.3 (m, 13H); ms: 315 (M^+, 4), 257 (30), 256 (100), 254 (16), 180 (18), 129 (5), 128 (10), 127 (8).

Anal. Calcd. for $C_{21}H_{17}NO_2$: C, 80.14; H, 5.43; N, 4.44. Found: C, 80.04; H, 5.44; N, 4.46.

Note: The same products were obtained when the reaction temperature was maintained at −78° throughout.

9,10-Dicarbomethoxy-9,10-dihydro-9-phenylacridine, **10**.

The dianion **6** prepared from **5** (2.00 g, 7.8 mmoles) was treated with methyl chloroformate (1.5 ml, 19 mmoles). Recrystallization from ethanol afforded 1.89 g (65%) of **10**, mp 153-155°; ir (nujol): 1720, 1320, 1265, 1220, 1050, 755 cm^{-1}; nmr (deuteriochloroform): δ 3.6 (s, 3H), 3.8 (3H), 6.9-7.8 (m, 13H); ms: 373 (M^+, 2), 315 (26), 314 (100), 271 (6), 270 (27), 256 (5), 255 (18), 254 (26).

Anal. Calcd. for $C_{23}H_{19}NO_4$: C, 73.98; H, 5.13; N, 3.75. Found: C, 74.11; H, 5.38; N, 3.71.

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