# Electrochemical Adamantylation of *N*-Heterocycles

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Electrochemically generated anion radicals of a number of nitrogen-heteroaromatic compounds react with 1-bromoadamantane to give adamantylated products. The major coupling product from quinolines results from substitution in the 2-position; if this position is blocked, adamantylation takes place in the carbocyclic ring. The coupling produces dihydrocompounds which may be oxidized during work-up. Besides quinolines, isoquinoline, phenanthridine, and *o*-phenanthroline have been reductively adamantylated.

Preparation of adamantylated heterocyclic compounds has been performed in fair yields either by condensation reactions with substrates possessing the adamantyl moiety [1] or by radical substitution.[2−4] The adamantyl radicals were obtained by silver ion catalyzed decarboxylation of adamantane-1-carboxylic acid in the presence of ammonium persulfate.

The electrochemical reductive alkylation [5] of aromatic hydrocarbons,[6] *N*-heteroaromatic compounds,[7−8] and activated olefins[9] in aprotic medium leads predominantly to monoalkylated dihydro compounds. For tertiary halides the reaction has been proposed [5] to occur between an alkyl radical and the substrate or its anion radical, whereas an $S_N2$-like attack of the radical anion on primary halides has been considered.[8]

1-Bromoadamantane (*1*), being a tertiary halide, might react in a similar way as the *t*-butyl halides in the electrochemical alkylation of various substrates.[5−7,9] Below is reported the results of an electrochemical adamantylation of isoquinoline (*2*), quinoline (*3*), 2-methoxyquinoline (*4*), 2-methyl- (*5*), 4-methyl-(*6*), and 6-methylquinoline (*7*), quinoline-3-carbonitrile (*8*), methyl quinoline-2-carboxylate (*9*), phenanthridine (*10*), and *o*-phenanthroline (*11*).

**10**          **11**
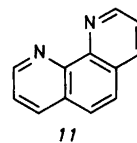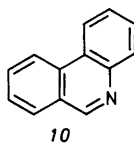
## RESULTS

*Cyclic voltammetry (CV).* CV at the hanging drop mercury electrode in *N,N*-dimethylformamide (DMF) containing 0.1 M tetrabutylammonium iodide (TBAI) of *2−8* gave one reversible peak; *9−11* gave, besides a reversible peak, one or two more peaks (Table 1). In most cases the anodic reoxidation peak had an irregular shape which suggested that some degree of adsorption was involved in the process.

*Table 1.* Peak potentials (*vs.* Ag/AgI, 0.1 M I⁻), enhancement factors R*, and $\Delta E$ (see text) for compounds *2−11*.

| Compound | $-E_p$/V | R* | $\Delta E$/V |
|---|---|---|---|
| *2* | 1.75 | 1.41 | 0.40 |
| *3* | 1.71 | 1.4 | 0.44 |
| *4* | 1.86 | 1.71 | 0.29 |
| *5* | 1.78 | 1.5 | 0.37 |
| *6* | 1.77 | 1.64 | 0.38 |
| *7* | 1.74 | 1.5 | 0.41 |
| *8* | 1.18 | 1.0 | 0.97 |
| *9* | 1.20 | 1.0 | 0.95 |
|  | 1.87 |  |  |
| *10* | 1.65 | 1.5 | 0.50 |
|  | 2.15 |  |  |
|  | 2.38 |  |  |
| *11* | 1.61 | 1.3 | 0.54 |
|  | 1.84 | 1.8 |  |
|  | 2.23 |  |  |

*Table 2.* Isolated yields of adamantylated products from the electrochemical adamantylation.

| Compound | Product | Yield/% | Compound | Product | Yield/% |
|----------|---------|---------|----------|---------|---------|
| 2 | 14 | 20 | 5 | 20 | 20 |
| 3 | 15 | 10 |   | 21 | 5 |
|   | 16 | 5 | 6 | 22 | 15 |
|   | 17 | 5 | 7 | 23 | 13 |
|   | 18 | 5 | 10 | 24 | 17 |
| 4 | 19 | 23 | 11 | 25 | 15 |
|   |   |   |   | 26 | 10 |

A plot of the polarographic half-wave potentials of *3−9* *vs.* Hammett $\sigma$ constants was linear which indicated a similar primary step in all cases. In Table 1 the half-wave potentials of *3−9* and the enhancement factors $R^*$ $(i_{p(1)}/i_{p(0)})$[5] obtained on addition of *1*, are listed together with the difference $\Delta E_p$ between the half-wave potentials of the substrate and that of *1*. From Table 1 is seen that the larger $\Delta E_{\frac{1}{2}}$ the smaller $R^*$, and that $R^* \sim 1$ for $\Delta E_{\frac{1}{2}} > 0.6$ V.

Addition of naphthalene (*12*) to *3* in the presence of *1* did not give a further enhancement of the current; rather, an insignificant decrease in the current was observed.

*Preparative electrolysis.* The reductive adamantylation of the heterocycles gave, besides the isolated major product, a number of minor products which were positional isomers of the major product or reduction or oxidation products of it. It was not possible to separate and characterize these minor products. In Table 2 are given the isolated yields of the major products; *8* and *9* are not included in Table 2 as no adamantylated products were obtained.

The yields of the isolated major product are moderate; several factors may be responsible for that. The product mixture is complex and losses occur during separation and purification; furthermore, some of the initially formed dihydro compounds are enamines which may be attacked by oxygen and form oxygen-containing products. Finally, dimerization and/or protonation of the initailly formed anion radicals may lower the yield of adamantylated products.
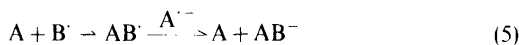
In a competition experiment *3* $(5 \times 10^{-2}$ M) and *12* $(2.5 \times 10^{-1}$ M) were electrolyzed in the presence of *1* $(10^{-1}$ M) at the reduction potential of *3*. No adamantylated derivatives of *12* were isolated.

## DISCUSSION

*General mechanism.* From CV it is evident that the primary step in the electrode reaction of *2−11* in aprotic media is the formation of the anion radical; these are formed at potentials where *1* is not reduced directly at the electrode. The anion radical may dimerize, accept a proton, or lose an electron to an electron acceptor such as *1*, whereby the substrate is regenerated.

In liquid ammonia the reaction between *3*·⁻ and butyl bromide has been suggested[8] to be an $S_N2$-like displacement of bromide by the anion radical. *1* is a bridgehead halide and as such incapable of reaction in a classical $S_N2$ reaction; an $S_N1$ reaction of *1*, which is very slow in aqueous solution,[10] would be even slower in DMF.

In the absence of a nucleophilic substitution reaction an electron transfer from the anion radical to *1*, followed by a fast cleavage of *1*·⁻ to bromide and adamantyl radical (*13*·) is a likely reaction. This is consistent with the enhancement factor $R^*$ being a function of $\Delta E_p$ and that no adamantylation takes place when $\Delta E_p > 0.6$ V. The reactions may thus be represented by eqns. (1)−(5), where A is the heterocyclic compound and BX is *1*. The adamantyl radical may then either accept an electron from A·⁻, couple

$$A + e^- \rightleftharpoons A^{\cdot-} \tag{1}$$

$$A^{\cdot-} + BX \rightleftharpoons A + BX^{\cdot-} \tag{2}$$

$$BX^{\cdot-} \rightarrow B^{\cdot} + X^- \tag{3}$$

$$A^{\cdot-} + B^{\cdot} \rightarrow AB^- \tag{4}$$

$$A + B^{\cdot} \rightarrow AB^{\cdot} \xrightarrow{A^{\cdot-}} A + AB^- \tag{5}$$

with A·⁻ (4) or with A (5), or abstract a hydrogen atom. Besides that the anion radical may dimerize or accept a proton.

The question whether eqn. (4) or (5) is the main path for the coupling reaction is still open, although (4) at present is considered most likely. The preference is mainly based on the product distribution to be discussed below, and it is also consistent with the results from the competition experiments.

The preparative competition experiment gave no adamantylated naphthalene; the presence of such compounds would have indicated eqn. (5) to be important, as the potential was held at a value where no naphthalene anion radical was formed. Methylation with methyl radicals produced from *t*-butyl-peroxide in neutral medium showed that in a competition experiment *2* and *3* were methylated 1.5, respectively 1.25, times faster than *12*. The corresponding competition factors have not been reported for adamantyl radicals in a neutral medium.

A reaction between *12* and *13*˙ would influence CV if the rate of the reaction could compete with that of the reaction between *3* and *13*˙; an increase in the limiting current would have resulted which was not observed.

*Product distribution.* Both adamantylation and *t*-butylation of *2* occur predominantly at C-6. Attack on *2* with methyl radicals produced from *t*-butylperoxide in neutral medium occurred at C-1; the yield of methylated product was low. Substitution at C-1 is in agreement with the atom localization[11] energy of isoquinoline.

Substitution with 1-adamantyl in the 1-position (and in the 4-, 5-, and 8-positions as well) would be subject to a certain steric hindrance, but the importance of that influence in the radical transition state is difficult to assess.

Adamantylation of protonated quinoline[3] favours position 2 *vs.* 4, 97:3; the same ratio is found in the 3,3-dimethylbicyclo[2.2.2]octan-1-ylation, whereas a ratio 65:35 is found in the 7,7-dimethylbicyclo-[2.2.1]heptan-1-ylation. This difference was discussed in terms of the nucleophilic properties of the radicals which are related to the steric strain within the radicals. In this connection it is also of interest that the steric interaction between the radical and the substrate in the transition state does not seem to be the deciding factor in determining the site of attack for the three bulky radicals mentioned.

The position of a coupling between *13*˙ and *2*˙⁻ would be determined by steric interactions, the charge density at a given ring-atom, and the ability to accommodate the negative charge of the resulting dihydroisoquinoline anion. The steric interaction is also here difficult to assess, but a certain discrimination against the positions 1, 4, 5 and 8 must be expected on steric grounds.

The proton hyperfine splitting constant in the ESR spectrum of an anion radical is generally taken as a measure of the unpaired-π-electron density at a given position; for *2*˙⁻ the value of the splitting constants at the different positions decrease in the following order: Position $8 > 1 > 4 > 5 > 6 \gg 3 > 7$.[12]

The negative charge of the initial product, the dihydroisoquinoline anion, would preferentially be localized on the most electronegative atom, the nitrogen. This can be obtained with substitution at positions 1, 3, 6 and 8. Substitution at C-3 would give an *o*-quinonoid product which is unfavourable. If positions 1 and 8 are less favoured due to steric interactions, it could be explained that 6 is a preferred point of attack; it has a reasonably high charge density, a negligible steric interaction in the transition state, and an intermediate anion with no *o*-quinonoid systems. It thus seems easier to explain the formation of the major product if reaction (4) and not reaction (5) is assumed to be responsible for the coupling.

If these arguments are applied to the quinolines, C-2 and C-7 are indicated as the most likely points of attack; C-2 turns out to be the preferred position for adamantylation, but if this position is blocked by a substituent, C-7 is attacked. The adamantylation of phenanthridine in the central ring would be expected from almost any model. 1,10-Phenanthroline is substituted α to nitrogen as expected; the second adamantylation takes place in the other hetero ring, but which species is involved in this second substitution is not obvious, neither why diadamantylated compounds rather than mono-adamantylated products are obtained in greatest yield.

The adamantylation of *N*-heterocycles by the silver-catalyzed oxidative decarboxylation of adamantane-1-carboxylic acid gives adamantylated products in $60-70\%$ yield.[3] The yields of the reductive electrochemical adamantylation using 1-bromoadamantane are somewhat lower and the product distribution is different; it is noteworthy that an appreciable part of the alkylation takes place in the carboxylic ring of isoquinoline and the quinolines.

In conclusion, the reductive adamantylation presents a method for the preparation of difficultly accessible adamantylated heterocyclic compounds

even if only moderate yields are isolated. The method could presumably be used to introduce other bridgehead systems into a number of compounds. The product distribution can be explained from a reaction between an anion radical and an adamantyl radical.

## EXPERIMENTAL

*General procedure for electrolysis and work-up.* The substrate (1 g) was reduced under nitrogen at the potential of its first polarographic wave in DMF containing 0.1 M tetrabutylammonium iodide (TBAI) or fluoroborate (TBABF$_4$) in the presence of 1-bromoadamantane (3 g) at a mercury pool electrode in a conventional H cell.[13] After completion of the electrolysis the DMF was removed *in vacuo* and the residue extracted several times with diethyl ether. The combined extracts were washed with water, dried (Na$_2$SO$_4$), and the ether removed by evaporation. The crude product was separated by column or preparative thin layer chromatography.

*Reduction of isoquinoline, 2 (n=2, 3).* The crude product (1.8 g) was separated by HPLC on an RP18 column with an 8:2 acetonitrile – water mixture as eluent. 6-(1-Adamantyl)-5,6-dihydroisoquinoline (*14*) was isolated in 20 % yield, m.p. 155 °C, $R_F$-value in TLC on silica 0.41 (benzene – ethyl acetate, 2:1). $^1$H NMR (CDCl$_3$): $\delta$ 1.3 – 1.4 (16 H, m), 2.8 (2 H, d), 5.56 (1 H, dd, J 10 and 2 Hz), 6.12 (1 H, dd, J 10 and 3.5 Hz), 7.06 (1 H, d, J 4.5 Hz), 7.75 – 8.3 (2 H, m). The component is suggested to be *14* on the basis of the close resemblance in the $^1$H NMR spectrum with that of 6-t-butyl-5,6-dihydroisoquinoline.[7] MS [IP 70 eV; m/e (%)]: 265 M$^+$ (43), 263 (68), 206 (68), 135 (100), 130 (36), 107 (21), 103 (8), 93 (46), 91 (20), 81 (24), 79 (51), 77 (28), 67 (24), 56 (30), 42 (21).

*Reduction of quinoline, 3 (n=3,7).* The crude product (2 g) was separated by column chromatography on silica with cyclohexane as eluent. The following compounds were isolated:

2-(1-Adamantyl)quinoline (*15*),[3] m.p. 88 – 90 °C (aqueous ethanol). Yield: 10 %. MS ([IP 70 eV; m/e (%)]: 263 M$^+$ (100), 220 (9), 206 (33), 194 (13), 180 (10), 135 (6), 128 (11), 101 (5), 91 (6), 81 (5), 79 (7), 77 (10).

7-(1-Adamantyl)-7,8-dihydroquinoline (*16*), m.p. 105 – 107 °C. Yield: 5 %. $R_F$: 0.49 (silica, benzene – ethyl acetate – methanol, 30:8:0.4). $^1$H NMR (CDCl$_3$): $\delta$ 1.4 – 2.3 (16 H, m), 3.01 (2 H, d, J 8.5 Hz); 6.06 (1 H, dd, J 10 and 3.8 Hz), 6.46 (1 H, dd, J 10 and 1.8 Hz), 7.00 (1 H, dd, J 7.5 and 4.8 Hz), 7.23 (1 H, dd, J 7.5 and 2 Hz), 8.26 (1 H, dd, J 4.8 and 2 Hz). MS ([IP 70 eV; m/e (%)]: M$^+$ 265 (9), 135

(100), 130 (40), 129 (46), 107 (8), 93 (22), 91 (6), 81 (9), 79 (27), 77 (13).

*x*-(1-Adamantyl)quinoline (*17*), m.p. 210 – 218 °C. Yield: 5 %. $R_F$ = 0.55 (silica, benzene – ethyl acetate, 12:5). MS [IP 70 eV; m/e (%)]: 263 M$^+$ (100), 220 (9), 206 (93), 180 (6), 157 (36), 135 (14), 128 (5), 101 (4), 93 (5), 79 (8), 77 (6).

*y*-(1-Adamantyl)quinoline (*18*), m.p. 118 °C. Yield: 5 %. $R_F$ = 0.40 (silica, benzene – ethyl acetate, 12:5). MS [IP 70 eV; m/e (%)]: 263 M$^+$ (97), 220 (20), 206 (100), 180 (12), 157 (7), 135 (12), 128 (5), 101 (5), 93 (7), 83 (10), 79 (10), 77 (15).

*Reduction of 2-methoxyquinoline, 4 (n=2,8).* The crude product (1.95 g) was separated by column chromatography on silica with cyclohexane as eluent and the main product purified by preparative TLC on silica with cyclohexane – ethyl acetate, 30:1, as eluent. 7-(1-Adamantyl)-7,8-dihydro-2-methoxyquinoline (*19*) was isolated in 23 % yield. Liquid, $R_F$ = 0.58 (silica, cyclohexane – ethyl acetate, 30:1). $^1$H NMR (CDCl$_3$): $\delta$ 1.15 – 2.15 (16 H, m), 2.79 (2 H, d), 3.75 (3 H, s), 5.81 (1 H, dd, J 10 and 3.5 Hz), 6.28 (1 H, dd, J 10 and 2 Hz), 6.45 (1 H, d, J 8 Hz), 7.13 (1 H, d, J 8 Hz). MS [IP 70 eV; m/e (%)]: 295 M$^+$ (15), 159 (18), 135 (100), 128 (7), 107 (5), 93 (13), 79 (15), 77 (5), 67 (6).

*Reduction of 2-methylquinoline. 5 (n=3,8).* The crude product was separated by column chromatography on silica with benzene as eluent. The following compounds were isolated:

7-(1-Adamantyl)-7,8-dihydro-2-methylquinoline (*20*). Yield: 20 %. M.p. 69 – 70 °C. $R_F$ = 0.64 (silica, cyclohexane – ethyl acetate, 2:1). $^1$H NMR (CDCl$_3$): $\delta$ 1.5 – 2.15 (16 H, m), 2.40 (3 H, s), 2.90 (2 H, d), 5.93 (1 H, dd, J 10 and 3 Hz), 6.35 (1 H, dd, J 10 and 2 Hz), 6.80 (1 H, d, J 7.5 Hz), 7.08 (1 H, d, J 7.5 Hz). MS [IP 70 eV; m/e (%)]: 279 M$^+$ (7), 143 (100), 135 (95), 128 (3), 107 (8), 93 (16), 91 (4), 79 (16), 67 (6).

The compound was suggested to be *20* on the basis of the close resemblance in the $^1$H NMR spectrum with that of the corresponding t-butyl derivative.[7]

*x*-(1-Adamantyl)-tetrahydro-2-methylquinoline (*21*), liquid, 5 % yield. $R_F$ = 0.85 (silica, cyclohexane – ethyl acetate, 2:1). MS [IP 70 eV; m/e (%)]: 281 M$^+$ (50), 266 (33), 146 (7), 135 (100), 130 (48), 118 (9), 107 (5), 93 (11), 91 (11), 81 (5), 79 (12), 77 (6), 67 (6).

*Reduction of 4-methylquinoline, 6 (n=2,0).* The crude product (1.9 g) was separated on silica with benzene as eluent. Product: 2-(1-Adamantyl)-4-methylquinoline (*22*), m.p. 117 °C. Yield: 15 %. $R_F$ = 86 (silica, benzene), $^1$H NMR (CDCl$_3$): $\delta$ 1.78 – 2.05 (15 H, 2s, br.), 2.61 (3H, s), 7.0 – 8.1 (5 H, m). MS [IP 70 eV; m/e (%)]: 277 M$^+$ (100), 262 (37), 234 (50), 220 (70), 208 (38), 194 (37), 170 (35), 142 (20), 135 (26), 128 (7), 115 (54), 91 (25), 79 (28), 77 (44), 67 (8).

*Reduction of 6-methylquinoline. 7* (*n* = 2,4). The crude product (1.8 g) was separated on preparative TLC on silica with benzene as eluent. Product: 2-(1-Adamantyl)-6-methylquinoline (*23*), m.p. 128 °C. Yield 13 %. $R_F$ = 0.74 (silica, benzene). $^1$H NMR (CDCl$_3$): $\delta$ 1.81 − 2.09 (15 H, 2s, br.), 2.50 (3 H, s), 7.25 − 7.93 (5 H, m). MS [IP 70 eV; *m/e* (%)]: 277 M$^+$ (100), 262 (45), 234 (67), 220 (72), 208 (67), 194 (64), 170 (67), 157 (67), 142 (61), 135 (13), 128 (9), 115 (50), 102 (17), 91 (28), 79 (25), 77 (33), 67 (17).

*Reduction of phenanthridine, 10.* The crude product (1.8 g) was separated by preparative GLC on silica with benzene as eluent. 9-(1-Adamantyl)-9,10-dihydrophenanthridine (*24*), m.p. 147 − 148 °C. Yield: 17 %. $R_F$ = 0.74 (silica, benzene). $^1$H NMR (CDCl$_3$): $\delta$ 1.48 − 1.88 (15 H, m), 3.78 (1 H, s), 4.43 (1 H, m; disappeared on treatment with D$_2$O), 6.5 − 7.8 (8 H, m). MS [IP 70 eV; *m/e* (%)]: 315 M$^+$ (30), 208 (7), 180 (100), 152 (34), 135 (17), 107 (4), 93 (11), 91 (7), 81 (16), 79 (17).

*Reduction of 1,10-phenanthroline, 11* (*n* = 3,9). The crude product (1.9 g) was separated by preparative GLC on silica with cyclohexane − ethyl acetate, 10:1, as eluent. The following products were isolated:

2,7-Di-(1-adamantyl)-1,10-phenanthroline (*25*), m.p. 275 °C. Yield: 15 %). $R_F$ = 0.25 (silica, cyclohexane − ethyl acetate, 10:1). $^1$H NMR (CDCl$_3$): $\delta$ 1.55 − 2.25 (30 H, m), 7.40 (1 H, d, *J* 8 Hz), 7.43 (1 H, d, *J* 4.5 Hz), 7.60 (1 H, d, *J* 9 Hz), 8.05 (1 H, d, *J* 8 Hz), 8.53 (1 H, d, *J* 9), 9.07 (1 H, d, *J* 4.5 Hz). MS [IP 70 eV; *m/e* (%)]: 448 M$^+$ (100), 405 (5), 391 (16), 379 (11), 151 (9), 95 (49), 93 (12), 91 (7), 81 (16), 79 (16), 77 (11), 67 (15), 56 (11).

2,8-Di-(1-adamantyl)-1,10-phenanthroline (*26*), m.p. 152 °C. Yield: 10 %. $R_F$ = 0.37 (silica, cyclohexane − ethyl acetate, 10:1. $^1$H NMR (CDCl$_3$): $\delta$ 1.4 − 2.2 (30 H, m), 7.61 (1H, d, *J* 8.5 Hz), 7.68 (2 H, s), 7.98 (1 H, d, *J* 2.5 Hz), 8.09 (1 H, d, *J* 8.5 Hz), 9.25 (1H, d, *J* 2.5 Hz). MS [IP 70 eV; *m/e* (%)]: 448 M$^+$ (100), 391 (9), 135 (5), 79 (6), 67 (5).

## REFERENCES

1. Jonak, J., Zakrewski, S., Mead, L. and Allshouse, L. *J. Med. Chem. 15* (1972) 1331.
2. Fiorentino, M., Testaferri, L., Tiecco, M. and Troisi, L. *J. Chem. Soc., Chem. Commun.* (1976) 329.
3. Fiorentino, M., Testaferri, L., Tiecco, M. and Troisi, L. *J. Chem. Soc. Perkin Trans. 2* (1977) 87.
4. Fiorentino, M., Testaferri, L., Tiecco, M. and Troisi, L. *J. Chem. Soc. Chem. Commun.* (1977) 316.
5. Simonet, J., Michel, M.-A. and Lund, H. *Acta Chem. Scand. B 29* (1975) 489.
6. Hansen, P. E., Berg, A. and Lund, H. *Acta Chem. Scand. B 31* (1977) 267.
7. Degrand, C. and Lund, H. *Acta Chem. Scand. B 31* (1977) 593.
8. Smith, W. H. and Bard, A. J. *J. Am. Chem. Soc. 97* (1975) 6491.
9. Degrand, C. and Lund, H. *Nouv. J. Chim. 1* (1977) 35.
10. Doering, W. von E., Levitz, M., Sayigh, A., Sprecher, M. and Whelan, W. P. *J. Am. Chem. Soc. 75* (1953) 1008.
11. Brown, R. D. and Harcourt, R. D. *J. Chem. Soc.* (1959) 3451.
12. Chaudhuri, J., Kume, S., Jagur-Grodzinski, J. and Szwarc, M. *J. Am. Chem. Soc. 90* (1968) 6421.
13. Iversen, P. E. *J. Chem. Educ. 48* (1971) 136.