Substituted 1,4-Diazepino[5,6,7-*kl*]acridines as Unexpected Side Products in Reaction of 2-(Dialkylamino)ethylamine with 1-Chloro-7-methyoxy-4-nitro-9-phenoxyacridine

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Substituted 1,4-diazepino[5,6,7-*kl*]acridines were obtained in reaction of 2-(dialkylamino)ethylamine with 1-chloro-7-methoxy-4-nitro-9-phenoxyacridine. The mechanism of their formation was studied. The correct structure of these compounds was established on the basis of their ^{1}H nmr studies.

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Introduction.

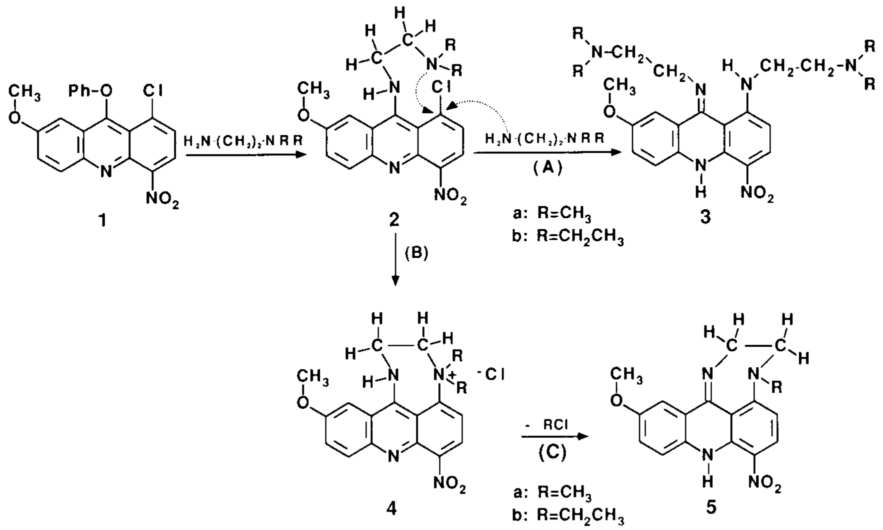
We have recently reported a convenient method for the synthesis of disubstituted 1-amino-9-imino-7-methoxy-4-nitro-9,10-dihydroacridines (**3**) [1]. In the last step of the synthesis, 1-chloro-7-methoxy-4-nitro-9-phenoxyacridine (**1**) was reacted with an excess of the corresponding (dialkylamino)alkylamine. We found that **1**, being more resistant to hydrolysis, was more convenient as a substrate for this synthesis than the corresponding 1,9-dichloroacridine. Having two very reactive positions, **1** easily formed "two-armed" compounds **3** in reaction with different amines. However, in the case of 2-dimethylaminoethylamine, formation of some side products was observed. A more detailed study of these products revealed an unexpected side reaction in which the 1,4-diazepino[5,6,7-*kl*]acridine ring system was generated. Such ring system was previously reported to be formed by intramolecular reaction of 9-[[2-(methylamino)ethyl]amino]-1-nitroacridine [2,3]. Additionally, a similar diazepinothioxanthene compound was claimed to be obtained as the major product in the reaction of 1-chloro-7-methoxy-4-methylthioxanthenone with *N*-methylethylenediamine [4].

In this paper we report a detailed study of the title reaction and structure determination, on the basis of ^{1}H nmr data, for some representative 2,3-dihydro-1,4-diazepino[5,6,7-*kl*]acridines. Compounds possessing such structure are of great interest as model compounds for structure-activity relationship studies on the biologically active acridines described earlier [5,6,1] as well as potentially antitumor agents.

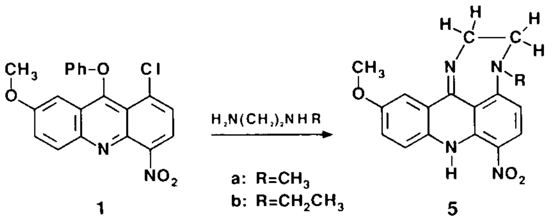
Results and Discussion.

The formation of 1,9-disubstituted compounds **3** from 1-chloro-7-methoxy-4-nitro-9-phenoxyacridine occurs in

Scheme 1



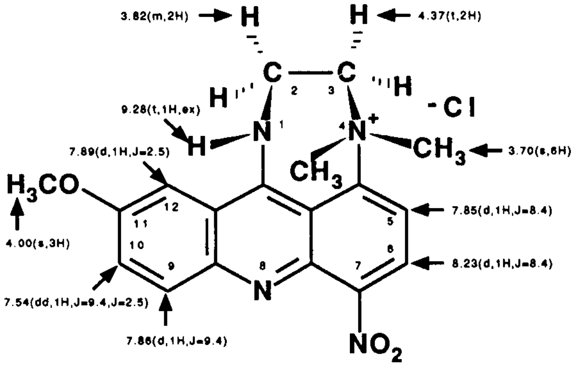
Scheme 2



two steps. In the first step, the 9-phenoxy group is substituted to give the highly reactive intermediate **2** (Scheme 1). The formation of the 9-substituted derivative in the first step could be accounted for either by a higher reactivity of position 9 in comparison with position 1, or by the better leaving ability of the phenoxy group. The corresponding 1,9-dichloro derivative reacted with 2-diethylaminoethylamine to give, under analogous conditions, the same intermediate **2b**, thus demonstrating that a stronger activation toward nucleophilic substitution must be effective on position 9.

We found that, in the case of 2-dialkylaminoethylamine, the intermediate **2**, besides the "normal" reaction (A) leading to the formation of the two-armed compounds **3**, can easily undergo an unexpected reaction (B) of an intramolecular quaternization of the dialkylamino group (Scheme 1). The preferred way of further transformation of the intermediate **2** strongly depends on kind of substituents at the distal amino group in the side chain. In the case of diethylamino group (**2b**), it very easily gave, at room temperature and in the presence of excess of amine, the disubstituted compound **3b**. Even when one equivalent of the amine was used in reaction with **1**, it was impossible to avoid formation of **3b**. This probably was mainly due to the fact that, as the substrate **1** is poorly soluble in the commonly used solvents, the reaction was

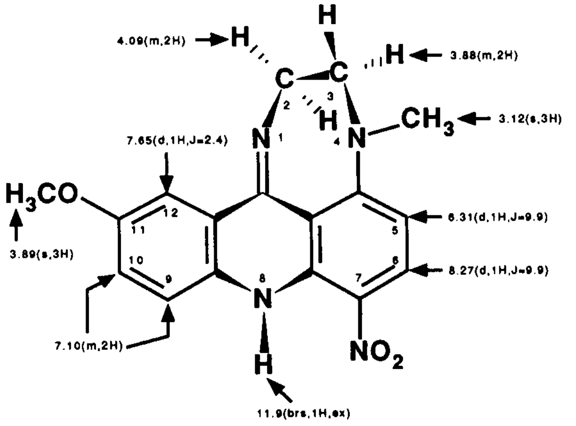
Scheme 3



4a (in $Me_2SO\text{-}d_6$)

ROESY crosspeaks

N(1)-H	x	C(12)-H	(strong)
N(4)-Me	x	C(5)-H	(strong)
N(4)-Me	x	C(3)-H	(weak)
C(5)-H	x	C(6)-H	(strong)
C(9)-H	x	C(10)-H	(strong)
11-OMe	x	C(10)-H	(weak)
11-OMe	x	C(12)-H	(strong)



5a (in $CDCl_3$)

ROESY crosspeaks

N(4)-Me	x	C(3)-H	(strong)
N(4)-Me	x	C(5)-H	(strong)
C(5)-H	x	C(6)-H	(strong)
N(8)-H	x	C(9)-H	(weak)
11-OMe	x	C(10)-H	(strong)
11-OMe	x	C(12)-H	(weak)

carried out in a DMF suspension. Under such conditions the effective ratio of both substrates in solution was always higher than 1 in favour of the amine and the reaction resulted in a mixture of unchanged **1**, **2b** and **3b**. The highest yield of **2b** was obtained when **1** was dissolved by heating in large amount of DMF and reacted with about two equivalents of amine. The intermediate **2b** was stable enough to be separated by column chromatography and characterized.

Drastically different behaviour was found for the compound with dimethylamino group. Compound **2a** was so reactive at room temperature that it was undetectable by tlc throughout the reaction. However, in contrast to **2b**, path (B) was preferred in the case of the dimethylamine side chain even when a large excess of the amine was used, and at a temperature of 35-40° the quaternary salt **4a** was formed as the main product. The preference of path (A) in the case of **2b** is probably due to steric hindrance of the ethylene groups which made the intramolecular nucleophilic attack difficult. However, pure **2b** gave the corresponding quaternary salt **4b** when heated at 50° in DMF.

When heated in DMF at a temperature of 90-100°, the quaternary salts **4a** and **4b** undergo further stabilization (reaction (C)) to give 4-methyl(ethyl)diazepinoacridine derivative **5**, respectively. To confirm their structures they were prepared by the different route given in Scheme 2 which seems to be a very convenient method for preparation of compounds with structure **5**.

The reaction (C) probably consists of a simple elimination of chloroalkane by S_N2 pathway. Similar N-C bond-cleavage was previously described for hydrazino-substituted-anthracene-9,10-diones [7].

Structures of the compounds synthesized were determined on the basis of their ^{1}H spectra (300 MHz). As previously described for 1-amino-9-imino-4-nitro-9,10-dihydroacridines [1], also for compounds with structures **2**, **4** and **5** there is possibility for the imino-amino tautomerism. The ^{1}H nmr spectrum of **2b** pointed out that this compound exists in hexadeuteriodimethyl sulfoxide as the 9-amino tautomer (evident from the signal of C9-N-H as an exchangeable triplet at 7.94 ppm coupled with a quartet (in fact, a doublet of triplets) at 3.75 ppm from the methylene protons on the α-carbon which collapses to a triplet by addition of deuterium oxide).

Analogous coupling between N1-H and the methylene protons on C2 was observed in the case of **4a** and **4b**. A little surprising is the fact that the two methyl groups at N4 in compound **4a** are equivalent, as well as the two ethyl groups in compound **4b**.

The ^{1}H nmr spectra for **5a** and **5b**, both in DMSO and chloroform, suggested that these compounds exist as "imino" tautomers (signals of N8-H as exchangeable singlets at about 12 ppm). Additionally, it is worthy of note that they show a significant difference in chemical shifts of the proton at positions 9 depending on the type of solvent (see Experimental).

To confirm the proposed structure and to get information about the stereochemical details, an analysis of the nuclear Overhauser effects in the rotating frame (ROESY) [8] was undertaken on compounds **4a** and **5a**. The results, presented in Scheme 3, clearly show that **4a** exists as an "amino" tautomer and **5b** as an "imino" tautomer. Additionally, trials with Dreiding's models suggested that in structures **5** the acridine ring system is not planar but should have a butterfly conformation.

Conclusions.

The above studies reveal in 9-substituted-1-chloro-4-nitroacridines an exceptional susceptibility of the position 1 to nucleophilic substitution and stimulated our interest in derivative **2b** as a likely biologically active arylating agent. On the other hand, the ^{1}H nmr results pointed out that, in contrast to the compounds with structures **2** and **4** which exist as "amino" tautomers, structures **5** exist in solution in the iminoacridan tautomeric form and probably, in a butterfly conformation similar to that reported for 9-(aminoalkylamino)-1-nitroacridines in the crystalline state [9,10]. Because of this structural feature, compounds with structure **5** could be of interest in further developing of the "iminoacridan hypothesis" formulated recently by Denny *et al.* [11].

EXPERIMENTAL

Melting points were taken on a Buchi 510 capillary apparatus and are uncorrected. Microanalytical results were obtained from the Laboratory of Elemental Analyses, Department of Chemical Sciences, University of Camerino. The ^{1}H nmr spectra were recorded on a Varian VXR-300 spectrometer. Chemical shifts are reported as δ values (ppm) downfield from internal tetramethylsilane. The nmr abbreviations used are as follows: br (broad), s (singlet), d (doublet), t (triplet), qu (quartet), m (multiplet), ex (exchangeable with deuterium oxide). Quartets which by addition of deuterium oxide are transformed into triplets are labeled with*. Coupling constants are given in Hz. Single frequency decoupling and two dimensional nuclear Overhauser effect in the rotating frame (ROESY) was utilized to assign specific protons. ROESY spectra were run on 0.02 *M* DMSO-d_6 (**4a**) or 0.04 *M* deuteriochloroform (**5a**) solutions using the time-shared spin-lock pulse sequence according to Kessler *et al.* [8]. A spectral window of 2400 Hz was chosen for both dimensions; 1024 data points were used along F_2, while 256 traces were collected of 48 transients each; 1024 data points were used for the second Fourier transformation. A mixing time of 0.8 sec was selected for all experiments.

1-Chloro-9-[[2-(diethylamino)ethyl]amino]-7-methoxy-4-nitroacridine (**2b**).

A suspension of 381 mg (1 mmole) of **1** in 20 ml of *N,N*-dimethylformamide was stirred at 80° until complete dissolution. Then, heating was stopped and 232 mg (2 mmoles) of 2-diethylaminoethylamine was added with stirring. The reaction mixture was left for 2 hours at room temperature. Then, 100 ml of water and 50 ml of benzene were added and shaken. The benzene layer was separated, dried, condensed and chromatographed on flash silica gel 60 column with chloroform-methanol (20:1) mixture as eluent. The collected main fraction, after evaporation of the solvent and crystallization at room temperature from acetone-water gave 254 mg (63%) of orange **2b**, mp 118-120°; ^{1}H nmr (DMSO-d$_6$): δ 7.98 (d, 1H, J = 7.9, C3-*H*), 7.94 (t, 1H, ex, C9-N-*H*), 7.75 (d, 1H, J = 8.3, C5-*H*), 7.59 (d, 1H, J = 2.7, C8-*H*), 7.46 (dd, 1H, J$_o$ = 8.3, J$_m$ = 2.7, C6-*H*), 7.43 (d, 1H, J = 7.9, C2-*H*), 3.94 (s, 3H, -OC*H*$_3$), 3.75 (qu*, 2H, -NH-C*H*$_2$-CH$_2$-), 2.50 (t, 2H, -CH$_2$-C*H*$_2$-NEt$_2$), 2.40 (qu, 4H, -N(C*H*$_2$- CH$_3$)$_2$), 0.80 (t, 6H, -N(CH$_2$-C*H*$_3$)$_2$).

Anal. Calcd. for $C_{20}H_{23}ClN_4O_3$: C, 59.63; H, 5.75; N, 13.91. Found C, 60.00; H, 6.01; N, 13.82.

The same product **2b** was obtained in a yield of 32% in an analogous manner starting from 1,9-dichloro-7-methoxy-4-nitroacridine [1].

4,4-Dimethyl-11-methoxy-7-nitro-1,2,3,4-tetrahydro-1,4-diazepino[5,6,7-*kl*]acridinium Chloride (**4a**).

A mixture of 381 mg (1 mmole) of **1**, 4 ml of *N,N*-dimethylformamide and 166 mg (2 mmoles) of 2-dimethylaminoethylamine was stirred at 40° for 1 hour. To the reaction mixture 25 ml of chloroform was added and stirred for 5 minutes. The product was collected by filtration and washed with chloroform, then with acetone, to give 340 mg (91%) of yellow **4a**, mp 215-217° (dec); ^{1}H nmr (DMSO-d$_6$): δ 9.28 (t, 1H, ex, N1-*H*), 8.23 (d, 1H, J = 8.4, C6-*H*), 7.89 (d, 1H, J = 2.5, C12-*H*), 7.86 (d, 1H, J = 9.4, C9-*H*), 7.85 (d, 1H, J = 8.4, C5-*H*), 7.54 (dd, 1H, J = 9.4, J = 2.5, C10-*H*), 4.37 (t, 2H, C3-*H*), 4.00 (s, 3H, C11-OC*H*$_3$), 3.82 (qu*, 2H, C2-*H*), 3.70 (s, 6H, N4-C*H*$_3$).

Anal. Calcd. for $C_{18}H_{19}ClN_4O_3$: C, 57.68; H, 5.11; N, 14.95. Found: C, 57.48; H, 5.37; N, 14.82.

4,4-Diethyl-11-methoxy-7-nitro-1,2,3,4-tetrahydro-1,4-diazepino[5,6,7-*kl*]acridinium Chloride (**4b**).

A solution of 201 mg (0.5 mmole) of **2b** in 2 ml of *N,N*-dimethylformamide was stirred at 50° for 2 hours. Then, to the reaction mixture 20 ml of ethyl ether was added and stirred for 5 minutes. The precipitated product was collected by filtration and washed with ether to give 180 mg (89%) of brown **4b**, mp 102-105° dec; ^{1}H nmr (DMSO-d$_6$): δ 9.12 (t, 1H, ex, N1-*H*), 8.21 (d, 1H, J = 8.3, C6-*H*), 7.85 (d, 1H, J = 8.3, C5-*H*), 7.84 (d, 1H, J = 9.3, C9-*H*), 7.74 (d, 1H, J = 2.5, C12-*H*), 7.53 (dd, 1H, J$_o$ = 9.3, J$_m$ = 2.5, C10-*H*), 4.32 (t, 2H, C3-*H*), 4.10 (qu, 4H, N4-(C*H*$_2$-CH$_3$)$_2$), 3.97 (s, 3H, C11-OC*H*$_3$), 3.85 (qu*, 2H, C2-*H*), 0.98 (t, 6H, N4-(CH$_2$-C*H*$_3$)$_2$).

Anal. Calcd. for $C_{20}H_{23}ClN_4O_3$: C, 59.63; H, 5.75; N, 13.91. Found: C, 59.84; H, 5.80; N, 13.88.

11-Methoxy-4-methyl-7-nitro-4*H*,8*H*-2,3-dihydro-1,4-diazepino[5,6,7-*kl*]acridine (**5a**).

Method A.

To a mixture of 381 mg (1 mmole) of **1** and 4 ml of *N,N*-dimethylformamide stirred at 80°, 166 mg (2 mmoles) of 2-dimethylaminoethylamine was added. The temperature was risen to 100° and stirring was continued at this temperature for 2 hours. To the reaction mixture 50 ml of water was added and made basic with aqueous potassium hydroxide. The precipitate was collected, washed with water and crystallized from acetone-water to give 280 mg (86%) of **5a** as red needles, mp 228-229°; ^{1}H nmr (DMSO-d$_6$): δ 11.76 (s, 1H, ex N8-*H*), 8.16 (d, 1H, J = 10.3, C6-*H*), 7.58 (d, 1H, J = 2.5, C12-*H*), 7.48 (d, 1H, J = 8.0, C9-*H*), 7.09 (dd, 1H, J$_o$ = 8.0 J$_m$ = 2.5, C10-*H*), 6.50 (d, 1H, J = 10.3, C5-*H*), 3.98 (m, 2H, C2-*H*), 3.79 (s, 3H, C11-OC*H*$_3$), 3.70 (m, 2H, C3-*H*), 3.12 (s, 3H, N4-C*H*$_3$); ^{1}H nmr (deuteriochloroform): δ 11.90 (br s, 1H, ex, N8-*H*), 8.27 (d, 1H, J = 9.9, C6-*H*), 7.65 (d, 1H, J = 2.4, C12-*H*), 7.10 (m, 2H, C9-*H* and C10-*H*), 6.31 (d, 1H, J = 9.9, C5-*H*), 4.09 (m, 2H, C2-*H*), 3.89 (s, 3H, C11-OC*H*$_3$), 3.88 (m, 2H, C3-*H*), 3.12 (s, 3H, N4-C*H*$_3$).

Anal. Calcd. for $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.27. Found: C, 62.99; H, 4.89; N, 17.32.

Method B.

A suspension of 381 mg (1 mmole) of **1** in 10 ml of freshly distilled *N,N*-dimethylformamide was heated with stirring to 80°. Then, 176 mg (2 mmoles) of *N*-methylethylenediamine was added and stirring was continued at this temperature for 2 hours. To the reaction mixture 100 ml of 5% aqueous potassium hydroxide solution was added and stirred for 30 minutes. Product was filtered off, washed with water and crystallized from acetone-water to give 305 mg (94%) of **5a** with identical mp and ^{1}H nmr spectrum as above.

4-Ethyl-11-methoxy-7-nitro-4*H*,8*H*-2,3-dihydro-1,4-diazepino[5,6,7-*kl*]acridine (**5b**).

Method A.

A mixture of 101 mg (0.25 mmole) of **4b** and 2 ml of *N,N*-dimethylformamide was stirred at 90° for 1 hour. Then, 50 ml of water was added and stirred for 10 minutes. The precipitated product was collected by filtration, washed with water and crystallized from ethanol-water to give 70 mg (83%) of red **5b**, mp 170-172°; ^{1}H nmr (DMSO-d$_6$): δ 12.00 (s, 1H, ex, N8-*H*), 8.12 (d, 1H, J = 9.7, C6-*H*), 7.62 (d, 1H, J = 3.0, C12-*H*), 7.46 (d, 1H, J = 9.2, C9-*H*), 7.10 (dd, 1H, J$_o$ = 9.2, J$_m$ = 3.0, C10-*H*), 6.54 (d, 1H, J = 9.2, C5-*H*), 4.04 (m, 2H, C2-*H*), 3.80 (s, 3H, C11-OC*H*$_3$), 3.70 (m, 2H, C3-*H*), 3.56 (qu, 2H, N4-C*H*$_2$-CH$_3$), 1.22 (t, 3H, N4-CH$_2$-C*H*$_3$); ^{1}H nmr (deuteriochloroform): δ 12.16 (br s, 1H, ex, N8-*H*), 8.24 (d, 1H, C6-*H*), 7.68 (d, 1H, C12-*H*), 7.08 (m, 2H, C9-*H* and C10-*H*), 6.34 (d, 1H, C5-*H*), 4.14 (m, 2H, C2-*H*), 3.90 (s, 3H, C11-OC*H*$_3$), 3.78 (m, 2H, C3-*H*), 3.52 (qu, 2H, N4-C*H*$_2$-CH$_3$), 1.34 (t, 3H, N4-CH$_2$-C*H*$_3$).

Anal. Calcd. for $C_{18}H_{18}N_4O_3$: C, 63.89; H, 5.36; N, 16.56. Found: C, 64.14; H, 5.50; N, 16.52.

Method B.

The same compound **5b** was obtained with the yield of 95%, in reaction of **1** and *N*-ethylethylenediamine, under analogous conditions as described above for **5a** (Method B).

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REFERENCES AND NOTES

[1] W. M. Cholody, J. Konopa, I. Antonini and S. Martelli, *J. Heterocyclic Chem.*, **28**, 209 (1991).

[2] S. Skonieczny, A. Organiak, A. Snarska, A. Kunikowski, S. Nowak and A. Ledochowski, *Pol. J. Chem.*, **52**, 2125 (1978).

[3] S. Skonieczny and A. Ledochowski, *Rocz. Chem.*, **51**, 2279 (1977).

[4] S. Archer, K. J. Miller, R. Rej, C. Periana and L. Fricker, *J. Med. Chem.*, **25**, 220 (1982).

[5] W. M. Cholody, S. Martelli, J. Paradziej-Lukowicz and J. Konopa, *J. Med. Chem.*, **33**, 49 (1990).

[6] W. M. Cholody, S. Martelli and J. Konopa, *J. Med. Chem.*, **33**, 2852 (1990).

[7] A. P. Krapcho and K. L. Avery, Jr., *J. Org. Chem.*, **53**, 5927 (1988).

[8] H. Kessler, C. Griesinger, R. Kerssebaum, K. Wagner and R. R. Ernst, *J. Am. Chem. Soc.*, **109**, 607 (1987).

[9] Z. Dauter, M. Bogucka-Ledochowska, A. Hempel, A. Ledochowski and Z. Kosturkiewicz, *Rocz. Chem.*, **49**, 859 (1975).

[10] J. J. Stezowski, P. Kollat, M. Bogucka-Ledochowska and J. P. Glusker, *J. Am. Chem. Soc.*, **107**, 2067 (1985).

[11] W. A. Denny, G. J. Atwell, R. F. Anderson and W. R. Wilson, *J. Med. Chem.*, **33**, 1288 (1990).