TETRACYCLIC PHENOTHIAZINES. X. LITHIATION OF PYRROLO[3,2,1-kl] PHENOTHIAZINE

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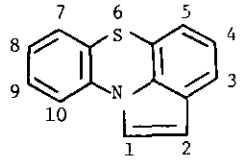
Abstract - The lithiation of pyrrolo [3,2,1-kl] phenothiazine and subsequent reactions of the lithio intermediates giving 1- and 10-mono- and 1,10-disubstituted derivatives are reported. The reaction sites were determined from decoupled ^{1}H and ^{13}C NMR spectra.

In our efforts towards the synthesis of certain phenothiazines with restricted conformational rotation in the N,N-dialkylaminopropyl side chain, one approach is to utilize appropriately substituted pyrrolophenothiazines as important precursers. Recently, we have developed a more convenient route[1] to the parent pyrrolo [3,2,1-kl] phenothiazine (1) utilizing a modified Bishler indole synthesis. The present work describes the lithiation of 1 and also represents an extension of the investigation of the lithiation of phenothiazine[2] and 5H-dibenz [b, f]-azepines[3] that we have undertaken.

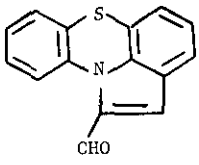


1

Pyrrolo [3,2,1-kl] phenothiazine was first synthesized in 1978 by Hollins and Pinto[4]. These authors also investigated some electrophilic substitution reactions of 1, such as the Mannich condensation and the Vilsmeier formylation, from which 2-substituted derivatives of 1 could be isolated in good yields. No further reactions have so far been reported. Since 1-substituted indoles selectively metallate at the 2-position[5,6], we hoped that 1 would likewise form the 1-lithio derivative and thereby provide convenient access for 1-substituted derivatives. In the presence of excess n-butyl lithium, however, 1-phenyl indole also lithiates at the 2'-position of the phenyl group[5]. Lithiation of N-substituted phenothiazines with N-butyllithium occurs mainly in the 1- and 4-positions[7]. Thus, the 5, 7 and/or 10-positions of 1 might also be metallated.

When 1 was treated with an equivalent amount of n-butyl lithium or s-butyl lithium in hexane at room temperature, followed by the addition of either deuterated water or N,N-dimethylformamide, the product composition was found (from nmr-analysis in combination with TLC) to consist of more than 75% unreacted 1. Some deuterium incorporation was observed and, in the cases where N,N-dimethylformamide was used, a small

amount of aldehyde (10-20%) was detected. Adding tetramethylethylenediamine or prolonging the reaction time from 5 to 24 hours did not affect the lithiation in any positive direction. Increasing the amount of n-butyl lithium, which we found superior to s-butyl lithium in the reaction with 1, decreased the amount of unreacted starting material. However, when two equivalents of n-butyl lithium was used, the product composition then consisted of approximately 10% disubstituted 1, along with approximately 50% mono-substituted 1 and unreacted 1. From the reaction of 1 with three equivalents of n-butyl lithium and N,N-dimethylformamide, the following products identified as: 1-formylpyrrolo[3,2,1-kl] phenothiazine (2) (5%), 10-formylpyrrolo[3,2,1-kl] phenothiazine (3) (10%) and 1,10-diformylpyrrolo [3,2,1-kl]phenothiazine (4) (51%), were isolated pure along with recovered 1 (16%). From the reaction of 1 and four equivalents of n-butyl lithium, followed by trapping the lithio intermediate with deuterated water, almost exclusively a dideutero derivative, identified by ^{1}H NMR analysis as 1,10-dideuteropyrrolo [3,2,1-kl] phenothiazine (5), was obtained.



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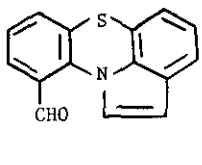

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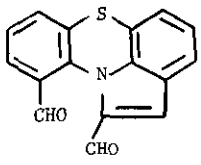

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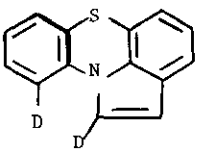


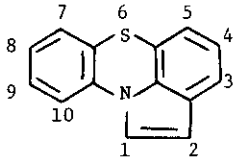
5

From these results, it seems evident that selective lithiation of the 1-position of 1 is not possible by direct metallation because of the equal, or perhaps greater, reactivity at the 10-position. Both sites appear to metallate independently and, in fact, once one site has been metallated, reactivity at the second site may actually increase. The chemistry of 1 so far investigated thus very much resembles that of simple N-substituted indoles and phenothiazines with respect to electrophilic substitution and metallation reactions. The total assignment of the ^{1}H NMR spectra of 1 has previously been performed by us[8]. The signals for the 1-, 2-, 3- and 5-protons are well separated from the other signals and are readily recognized as lowfield and highfield doublets at 7.31 and 6.49 ppm (J = 3.5 Hz) for the 1- and 2-protons, respectively; and two sets of doublets of a doublet at 7.04 ppm (J = 8.0 and 0.9 Hz) and at 6.56 ppm (J = 7.4 and 0.9 Hz) for the 3- and 5-protons respectively. In comparison with spectrum of 1, the spectrum of 4 is shifted 0.3-0.4 ppm downfield and the pyrrolo doublets are gone, while the signals for the 3- and 5-protons, now at 7.34 and 6.97 ppm, remain unchanged. Instead a lowfield set of doublets of a doublet at 7.56 ppm (J = 7.7 and 1.8 Hz) and a very sharp singlet at 7.43 ppm are observed, both assigned to the protons next to the carbonyls. The singlet is thus assigned to the 2-proton and accordingly, one of the carbonyl groups is to be found in the 1-position. 2-substitution is ruled out by comparison of the chemical shifts for the protons affected. Concerning the position of the second carbonyl group, 8- or 9-substitution is not in accordance with the observed spectrum of 4 because of lack of another lowfield doublet. The distinction between 7- and 10-substitution can not simply be made just by the comparison of the chemical shifts for the observed signals. The signals for either the 7- or

or the 10-proton in 4 have disappeared compared to the spectrum of 1. Decoupling experiments where the lowfield and the highfield doublets at 7.56 and 6.97 ppm were irradiated confirmed the above assignments and also made it possible to determine accurate chemical shifts, coupling constants and tentative assignments (see Tables 1 and 2). However, since analogous 3 spin systems are anticipated with either 7- or 10-substitution, ^{1}H NMR alone could not distinguish between them. In the spectrum of 3, the two pyrrolo doublets are still present now at 7.18 and 6.55 ppm respectively (J = 3.5 Hz), also two sets of doublets of a doublet are well separated and found at 6.66 ppm (J = 7.4 and 0.9 Hz) assigned to the 5-proton, and at 7.42 ppm (J = 7.7 and 1.7 Hz) assigned to a proton next to the carbonyl group. Again, it is obvious that the observed pattern can only be in accordance with 7- or 10-substitution. However, inspection of the chemical shifts as well as decoupling experiments again failed to distinguish between 7- and 10-substitution. The spectrum of 2 reveals that both

TABLE 1

PMR Chemical Shifts (δ Values) in $CDCl_3$ at 27°C



Compound	1H	2H	3H	4H	5H	7H	8H	9H	10H	CHO
1	7.31	6.39	7.04	6.83	6.56	6.92	6.78	6.88	6.97	
2		7.45	7.32	7.08	6.97	7.06	- 7.17 -*		7.42	9.98
3	7.18	6.55	7.13	6.95	6.66	7.14	6.97	7.42		10.20
4		7.43	7.34	7.11	6.97	7.30	7.17	7.56		9.68, 9.75
5		6.39	7.04	6.81	6.54	6.94	6.77	6.89		

* Protons 8 and 9 are nearly coincident and could not be resolved on the basis of decoupling experiments.

TABLE 2

^{1}H NMR Coupling Constants (Hz) in $CDCl_3$ at 27°C

Compound	J12	J34	J35	J45	J78	J79	J89	J810	J910
1	3.4	8.0	0.9	7.4	6.6	1.7	7.9	1.7	8.1
2		7.9	0.9	7.4	6.6	1.3	7.9	1.3	8.6
3	3.5	8.0	0.9	7.4	7.7	1.7	7.7		
4		7.9	0.7	7.4	7.7	1.8	7.7		
5		7.9	0.8	7.3	6.9	1.7	8.0		

the pyrrolo doublets are missing and are replaced by a lowfield singlet at 7.45 ppm, which is in agreement with 1-substitution. Assignment of the second metallation (and therefore, formylation) site in 1 as the 10-position was unequivocally made on the basis of comparison of the ^{1}H and ^{13}C NMR spectra of 1 and its dideuteroderivative (5) (the latter was prepared by treatment of 1 with excess n-butyl lithium followed by quenching with deuterium oxide). In the ^{1}H nmr spectrum of 5 (Tables 1 and 2) the doublet at 7.31 ppm corresponding to the 1-proton, and the multiplet at 6.97 ppm corresponding to the 10-proton, of 1 are absent. The 9-proton simplifies to a quartet with ortho ($J_{8,9}$= 8.0 Hz) and meta ($J_{7,9}$= 1.7 Hz) couplings; the 8-proton simplifies to a quartet with 2 ortho couplings ($J_{7,8}$= 6.9 Hz and $J_{8,9}$= 8.0 Hz); and the 7-proton remains essentially unchanged.

The chemical shift assignments of the 4 proton spin system of 1 (protons 7, 8, 9 and 10) are based[8], in large part, on the chemical shift assignments of the corresponding protons in N-substituted phenothiazines[9-14]. It is conceivable, however, that the assignments for the 7- and 10-protons (which are within 0.05 ppm) and the 8- and 9-protons (which are within 0.05 ppm) could be reversed, since the 4 protons could be uniformly affected by the fused-pyrrole ring system. This question was unequivocally resolved, and the second site of metallation confirmed as the 10-position, by examination of the ^{13}C NMR spectra of 1 and 5.

^{13}C chemical shift data for 1 and 5 are compared in Table 3. The chemical shift values and assignments for 1 are in essential agreement with those reported by Gampe, et al[16], with the exception that the assignments for C-5 and C-10 are reversed. The use of specific proton-carbon decoupling confirmed the assignments of all proton bearing carbons, including C-5 and C-10. Thus, selective irradiation of H-5 (6.56 ppm) caused the carbon doublet at 116.0 ppm to collapse to a singlet and similarly, selective irradiation of H-10 (6.97 ppm) and simultaneously H-7 (6.92 ppm) caused the carbon doublets at 114.2 and 127.1 ppm to collapse to singlets. The assignments of the ^{13}C signals of 114.2 ppm as C-7 and 127.1 as C-10, based (in part) on comparison with the ^{13}C spectral assignments in phenothiazine[13,16], appear to be unequivocal. The C_1 and C_{10} protons of 5, therefore, are observed as weak triplets in the proton coupled spectrum with $J_{^{13}C^{2}H}$ coupling constants of 28.2 and 24.1 Hz, respectively. The expected isotopic shieldings are observed for the adjacent carbon atoms[17], i.e., 0.12 ppm for C-9 and 0.17 for C-2, adding further confirmation to the structural assignment.

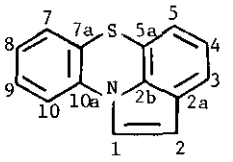
EXPERIMENTAL

Infrared spectra were obtained on a Beckman IR-33 spectrophotometer. NMR spectra were recorded on a Brucker WM (250 mHz) spectrometer using tetramethylsilane as an internal standard. The high resolution mass spectra were recorded on a Varian MAT 311A double focusing mass spectrometer.

Formylpyrrolo [3,2,1-kl] phenothiazines. To a solution of 1.12 g (5 m mol) pyrrolo[3,2,1-kl]phenothiazine (1) in 100 ml dry ether, 15 m mol n-butyl lithium was added at room termperature and under an argon atmosphere. After 5 hours, the reaction mixture was cooled to -70°C and 1.1g (15 m mol) of freshly distilled N,N-dimethylformamide was added dropwise. The mixture was stirred for an additional 4 hours at room temperature before

Table 3

Carbon-13 Chemical Shift Data



Position	Type	Chemical Shift (ppm)[a] Compound 1	Compound 5
10_a	q	134.22	134.20
2_b	q	131.83	131.85
2_a	q	127.83	127.85
9	CH	127.14	127.02
7	CH	127.10	127.02
8	CH	124.61	124.58
4	CH	123.14	123.13
7_a	q	121.37	121.37
1	CH	120.68	(120.92)[b]
3	CH	117.58	117.57
5_a	q	116.97	116.99
5	CH	116.00	115.98
10	CH	114.22	(113.90)[c]
2	CH	105.16	104.99

a Broad band proton decoupled spectrum in deuterochloroform with TMS as the internal standard.
b Triplet with $J_{^{13}C^2H}$ = 28.2 Hz
c Triplet with $J_{^{13}C^2H}$ = 24.1 Hz

it was hydrolyzed with cold water and dilute hydrochloric acid was carefully added until neutral reaction. The organic phase was separated, washed with water and dried (magnesium sulfate). Evaporation of the solvent left a crystalline residue which was chromatographed (silica/toluene). The products which were eluted and isolated in the order 1, 3, 2 and 4, are given below along with their physical data.

Pyrrolo [3,2,1-kl] phenothiazine (1), unreacted, 180 mg (16%) was recovered.

7-Formylpyrrolo [3,2,1-kl] phenothiazine (3), 130 mg (10%) with mp 110-112°C; IR (KBr): 1635 cm^{-1} (C = O, s); ^1H NMR ($CDCl_3$); see tables 1 and 2. Anal. molecular weight calcd for $C_{15}H_9NOS$: 251.0406. Found (high resolution mass spectrum): 251.0396.

1-Formylpyrrolo [3,2,1-kl] phenothiazine (2), 63 mg (5%) with mp 107-109°C. ^{1}H NMR ($CDCl_3$), see tables. Anal molecular weight calcd for $C_{15}H_9NOS$: 251.0406. Found (high resolution mass spectrum): 251.0409. 1,10-Diformylpyrrolo [3,2,1-kl] phenothiazine (4), 712 mg (51%), with mp 203-205°C; IR (KBr): 1625 cm^{-1} (C = O, m); ^{1}H NMR ($CDCl_3$): see tables 1 and 2. Anal molecular weight calcd for $C_{16}H_9NO_2S$: 279.0355. Found (high resolution mass spectrum): 279.0345.

1,10-Dideuteropyrrolo [3,2,1-kl] phenothiazine (5). According to the procedure described above, 1.12 g (5 m mol) pyrrolo [3,2,1-kl] phenothiazine was reacted with 20 m mol n-butyl lithium. Excess deuterated water was added and the mixture was worked up as above giving 1,10-dideuteropyrrolo[3,2,1-kl]phenothiazine, m.p. 116-117°C (Lit. 116-117°C for the nondeuterated derivative 1). ^{1}H NMR ($CDCl_3$): see Tables 1 and 2. ^{13}C NMR: see Table 3. Anal. molecular weight calcd. for $C_{14}{}^1H_7{}^2H_2NS$: 225.0581. Found (high resolution mass spectrum): 225.0575.

REFERENCES

1. A. Hallberg, D. Deardorff and A. Martin, Heterocycles, 1982, 19, 75.
2. A. Hallberg and A.R. Martin, J. Heterocyclic Chem., 1982, 19, 433.
3. T. Dahlgren, A. Hallberg, R. Helitzer and A.R. Martin, J. Heterocyclic Chem., submitted for publication.
4. R. A. Hollins and A.C. Pinto, J. Heterocyclic Chem., 1978, 15, 711.
5. D.A. Shirley and P.A. Roussel, J. Amer. Chem. Soc., 1955, 75, 375.
6. R.J. Lundberg and H.F. Roussel, J. Org. Chem., 1973, 38, 3324.
7. G. Cauquil, A. Casadevall and E. Casadevall, Bull. Soc. Chem. France 1960, 1049.
8. A. Hallberg, T. Dahlgren, A.R. Martin and K. Christiansen, J. Heterocyclic Chem., in press.
9. J. Cymerman-Craig, D.E. Green, S.K. Roy, L.H. Piette and K.O. Loeffler, J. Med. Chem., 1965, 8, 392.
10. N.E. Sharpless, R.B. Bradley and J.A. Ferretti, Org. Magn. Reson., 1974, 6, 115.
11. M. Rouillard, N. Giulieri and M. Azzaro, Bull. Soc. Chim. France, 1974, 9-10, 2141.
12. R.I. Mital and R.C. Chaudhary, J. Chem. Eng. Data, 1975, 20, 204.
13. G. Fronza, R. Mondelli, G. Scarpini, G. Ronsisvalle and F. Vittoro, J. Magn. Reson., 1976, 23, 437.
14. I.C. Caler, R.B. Johns and J.M. Demarchelier, Aust. J. Chem., 1971, 24, 325.
15. L.R. Isenbrandt, R.K. Jensen and L. Petrakis, J. Magn. Reson., 1973, 12, 143.
16. R.T. Gampe, G.E. Martin, A.C. Pinto and R.A. Hollins, J. Heterocyclic Chem., 1981, 18, 155.
17. G.C. Levy, R.L. Lichter and G.L. Nelson, "Carbon-13 Nuclear Magnetic Resonance Spectrometry, 2nd Ed., John Wiley & Sons, New York, P. 95.

ACKNOWLEDGEMENTS. This research was supported by Grant MH31184 from the National Institutes of Health. The authors thank Ms. R.S. Harvey and Dr. K. Christiansen for providing the 250 mHz NMR data.

Received, 25th May, 1982