Metallations of 5*H*-Dibenz[*b*,*f*]azepine and 10,11-Dihydro-5*H*-dibenz[*b*,*f*]azepine. Synthesis of 4-Substituted Derivatives

T. Dahlgren, A. Hallberg, R. Helitzer and A. R. Martin*

Department of Pharmaceutical Sciences, College of Pharmacy, University of Arizona, Tucson, Arizona 85721

Received June 28, 1982

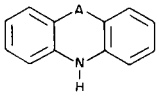
The synthesis of 4-substituted 5*H*-dibenz[*b*,*f*]azepines and 10,11-dihydro-5*H*-dibenz[*b*,*f*]azepines resulting from the reaction of the corresponding 4,5-dilithio derivatives and different *N*,*N*-dimethylamides is reported. The total assignment of the pmr spectra of the prepared formyl derivatives based on decoupling experiments is also described.

J. Heterocyclic Chem., **20**, 341 (1983).

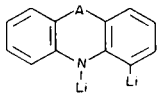
Recently we have studied the dilithiation of phenothiazine (1) and the subsequent reaction with some *N*,*N*-dimethylamides, yielding 1-acylphenothiazines, which are important precursors for the synthesis of derivatives related to phenothiazine tranquilizers with restricted rotation in the side chain. We have now extended the investigation to the metallation and subsequent acylation of 5*H*-dibenz[*b*,*f*]azepine (**1a**) and 10,11-dihydro-5*H*dibenz[*b*,*f*]azepine (**2a**).

An extensive survey of the literature reveals that metallation of **1a** and **2a** with butyllithium has only been utilized in *N*-alkylation reactions (2) of **1a** and **2a** and, in a single instance, the reaction of **2a** with butyllithium followed by carbonation to give 10,11-dihydro-5*H*dibenz-[*b*,*f*]azepine-4-carboxylic acid (3). Formylation under Vilsmeier conditions occurs at the nitrogen, or when this site is occupied, in the 2-position (2).

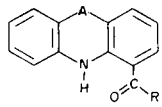
We found that both **1a** and **2a**, upon treatment with 2-3 equivalents of *n*-butyllithium gave highly colored intermediates which in subsequent reactions with slightly more than an equivalent amount of *N*,*N*-dimethylformamide, *N*,*N*-dimethylbenzamide, *N*,*N*-dimethyl-4-methoxybenzamide and *N*,*N*-diethylnicotinamide respectively gave **1b-1e** and **2b-2e** in yields from 40-60%. Only one identifiable product, which turned out to be the 4-isomer, was formed from each of the reactions along with unreacted starting materials. Addition of two or more equivalents of the alkylamides did not improve yields.



1 (a) A = CH=CH
2 (a) A = CH_2CH_2



1 (b)
2 (b)



1 (c) - **2**(f)
2 (c) - **2**(f)

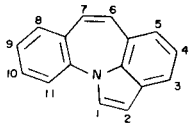
1c, **2c**: R = H; **1d**, **2d**: R = C_6H_5; **1e**, **2e**: R = p-$CH_3OC_6H_4$; **1f**, **2f**: R = 3-pyrido

We would like to interpret this result in analogy with the mechanism previously proposed by us for phenothiazine under the same reaction conditions. In short, the amide initially bonds to the nitrogen atom, and in an irreversible step, is rearranged to the 4-position before the leaving group (dimethylamine) is removed, or that the former complex is in an equilibrium with the dilithio compound (**1b** or **2b**) and the latter is successively trapped by the acylation reagent.

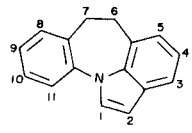
In the pmr spectra of compounds **1c** and **1f** the NH resonance occurs at 8.8-9.6 ppm and in **2c-2f** at 10.6-11.4 ppm, where in both series the high field values are due to the compounds with the *p*-methoxy-substituent. Furthermore, in spectra of both **1c** and **2c** a set of lowfield doublets of a doublet assigned to the proton next to the carbonyl group are observed with coupling constants in the range of 7.5 Hz and 1.5 Hz. Lack of another lowfield doublet rules out 2- or 3-substitution. Also 1-substitution can be excluded because of substituent in this position cannot possibly affect the NH-resonance in the observed way.

Decoupling experiments permitted the complete assignment of signals in spectrum of **1c** and **2c**. The chemical shift values and the coupling constants along with the values for **1a** (5) are also given in Table 1. The aromatic region in spectrum of **1c** shows four well separated groups of signals; a doublet split into doublets at 7.13 ppm, a triplet split into doublets at 6.90 ppm, a multiplet centered at 6.65 ppm (where at both lowest, 6.72 ppm, and at highest field, 6.59, ppm doublets of doublets are observed), finally a broad doublet at 6.38 ppm. Irradiation of the lowfield doublet at 7.13 ppm sharpens the signal at 6.72 into a doublet, J = 7.5 Hz, and also a triplet centered at 6.67 ppm is distinguished. These signals are consequently assigned to the protons in the ring bearing the 4-substituent and are the 1- and 2-protons. Decoupling of the signal at 6.90 ppm causes the doublet of doublet at 6.59 ppm to collapse into a sharp doublet, J = 7.5 Hz, and the broad doublet at 6.38 ppm changes to a doublet, J = 1.2 Hz, also a triplet at 6.65 ppm is observed. The resonance at 6.90 belongs either to the 7- or 8-proton. The resolved spectra of **1a** (5) and of 5*H*-indolo[1,7-*ab*][1]benzazepine (**3**) (6) show that the resonance for the 7-proton and correspondent proton in **3** occurs at approximately

0.2 ppm downfield from the 8-proton. In comparison with this result the signals at 6.90, 6.65, 6.59 and 6.38 ppm are thus assigned in given order to the 7-, 8-, 9-and 6-protons. The signals for the 10- and 11-protons appear as an AB-quartet at 5.79 and 5.86 ppm respectively, $J_{10,11}$ = 12.0 Hz. Irradiation of the signal at 6.38 ppm was performed giving the remaining coupling constants.



3



4

In the spectrum of **2c** the following groups of signals are observed: at 7.37 ppm a set of doublets of a doublet, at 7.17 ppm a broad doublet, at 7.13 a triplet split into doublets, at 7.03 ppm and 6.99 ppm two doublets of doublets, at 6.84 ppm triplet split into doublets, and finally at 6.74 ppm a triplet. Irradiation of the signal at 7.37 ppm caused the signal at 7.17 ppm to become a sharp doublet, J = 7.6 Hz, and the triplet at 6.74 changed to a doublet, J = 7.7 Hz. These are all protons in the substituted ring and in the given order are the 3-, 1- and 2-protons. Upon decoupling of the signal at 6.84 ppm the signal at 7.13 ppm went into a set of doublets, J = 8.0 Hz and 1.5 Hz. The signal at 7.13 ppm went into a set of doublets, J = 8.0 Hz and 1.5 Hz. The signal at 7.03 ppm became a doublet, J = 1.5 Hz, and at 6.99 ppm sharp doublet, J = 8.0 Hz was found. In comparison with spectra of **1a**, **1c**, **3** and that of 6,7-dihydro-5*H*-indolo[1,7-*ab*][1]benzazepine (**4**) (5) the assignment was made as follows in the given order: 7.17, 7.03, 6.99 and 6.84 ppm for the 7-, 9-, 6- and 8-protons respectively. Further decouplings were made to estimate remaining coupling constants and these experiments also confirmed the evaluation given above. The resonance for the 10- and 11-protons occurs as a singlet at 3.05 ppm.

EXPERIMENTAL

Infrared spectra were obtained on a Beckman IR-33 spectrophotometer. The nmr spectra were recorded on a Varian EM 360 L spectrometer (60 mHz) and on a Bruker WM-250 spectrometer (250 mHz) using tetramethylsilane as an internal standard. The high resolution mass spectra were recorded on a Varian MAT 311A double focusing mass spectrometer.

General Procedure for the Metallation Reactions.

To a solution of purified 5*H*-dibenz[*b*,*f*]azepine (**1a**) or 10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine (**2a** (10 mmoles) in 80 ml dry ether, *n*-butyllithium (30 mmoles) in hexane was added with stirring at room temperature under an argon atmosphere. After 24 hours the reaction mixture was cooled to -70° and the amide (13 mmoles) dissolved in 10 ml dry ether was added dropwise. The reaction mixture was then allowed to warm to room temperature and stirred for an additional 24 hours before it was hydrolyzed with ice aqueous 0.5 *N* hydrochloric acid. The organic layer was separated and the aqueous phase was extracted with ether. The combined organic phases were washed with water and dried (magnesium sulfate). The residue left after evaporation of the solvent was chromatographed (silica) to remove unreacted starting materials giving pure product in yields from 40-60%. The compounds thus prepared along with their purification and physical data are described below.

4-Formyl-5*H*-dibenz[*b*,*f*]azepine (**1c**).

Compound **1c** was obtained as a dark red oil (1.35 g, 61%) from **1a** and *N*,*N*-dimethylformamide using hexane/ethylacetate (9:1) as eluent in the chromatography; ir (potassium bromide): ν 1625 cm^{-1} (C=O); nmr (deuteriochloroform): see Table 1.

Anal. molecular weight calcd. for $C_{15}H_{11}NO$: 221.0841. Found (high resolution mass spectrum): 221.0832.

Anal. Calcd. for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.51; H, 5.41; N, 5.94.

4-Benzoyl-5*H*-dibenz[*b*,*f*]azepine (**1d**).

Compound **1d** was obtained as a red oil (1.40 g, 47%) from **1a** and

Table 1

Proton NMR Data for 1-Substituted 5*H*-Dibenz[*b*,*f*]azepines and 10,11-Dihydro-5*H*-dibenz[*b*,*f*]azepines

A. ^1H NMR Chemical Shifts (δ Values) in Deuteriochloroform at 27°C

Compound	1H	2H	3H	4H	5H	6H	7H	8H	9H	10H	11H	CHO
1c	6.72	6.67	7.13	—	9.57	6.38	6.90	6.65	6.59	5.79	5.86	9.65
2c	7.17	6.74	7.37	—	11.24	6.99	7.13	6.84	7.03	3.05	3.05	9.82
1a (1)	6.62	6.64	6.84	6.23	4.61						6.01	

B. ^1H NMR Coupling Constants (Hz) in Deuteriochloroform at 27°C

Compound	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{6,7}$	$J_{6,8}$	$J_{7,8}$	$J_{7,9}$	$J_{8,9}$	$J_{10,11}$
1c	7.5	1.8	7.6	—	—	7.9	1.2	7.3	1.8	7.5	12.0
2c	7.6	1.6	7.7	—	—	8.0	1.3	7.3	1.5	7.5	—
1a (1)	7.6	1.6	7.4	1.2	7.8						

(1) In carbon disulfide. (4)

N,N-dimethylbenzamide, hexane/ethyl acetate (9:1); ir (potassium bromide): ν 1625 cm^{-1} (C=O); nmr (deuteriochloroform): 9.40 (s, 1H, NH), 7.75-6.25 (m, 12H, aryl), 6.10 (s, 2H, CH=CH).

Anal. molecular weight calcd. for $C_{21}H_{15}NO$: 297.1154. Found (high resolution mass spectum): 297.1144.

Anal. Calcd. for $C_{21}H_{15}NO$: C, 84.82; H, 5.08; N, 4.71. Found: C, 84.99; H, 5.46; N, 4.90.

4-Anisoyl-5*H*-dibenz[*b,f*]azepine (**1e**).

Compound **1e** was obtained as a light red oil (1.73 g, 53%) from **1a** and *N,N*-dimethyl-4-methoxybenzamide, toluene; ir (potassium bromide): ν 1625 cm^{-1} (C=O); nmr (deuteriochloroform): 8.83 (s, 1H, NH), 7.75-6.25 (m, 11H, aryl), 6.17 (s, 2H, CH=CH), 3.88 (s, 3H, OCH_3).

Anal. molecular weight calcd. for $C_{22}H_{17}NO_2$: 327.1259. Found (high resolution mass spectrum): 327.1246.

Anal. Calcd. for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.28. Found: C, 81.14; H, 5.33; N, 4.46.

4-Nicotinoyl-5*H*-dibenz[*b,f*]azepine (**1f**).

Compound **1f** was obtained as a orange oil (1.10 g, 40%) from **1a** and *N,N*-diethylnicotinamide, toluene/ethyl acetate (4:1). Ir (potassium bromide): ν 1630 cm^{-1} (C=O); nmr (deuteriochloroform): 9.40 (s, 1H, NH), 8.90-6.35 (m, 11H, aryl), 6.10 (s, 2H, CH=CH).

Anal. molecular weight calcd. for $C_{20}H_{14}N_2O$: C, 298.1106. Found (high resolution mass spectrum): 298.1086.

Anal. Calcd. for $C_{20}H_{14}N_2O$: C, 80.52; H, 4.73; N, 9.39. Found: C, 80.63; H, 4.93; N, 9.12.

4-Formyl-10,11-dihydro-5*H*-dibenz[*b,f*]azepine (**2c**).

Compound **2c** was obtained as a yellow solid, (1.25 g, 56%) from **2** and *N,N*-dimethylformamide, toluene/hexane (1:1); ir (potassium bromide): ν 1645 cm^{-1} (C=O); nmr (deuteriochloroform): see Table 1.

Anal. molecular weight calcd. for $C_{15}H_{13}NO$: 223.0997. Found (high resolution mass spectrum): 223,0989.

Anal. Calcd. for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.73; H, 6.14; N, 6.33.

4-Benzoyl-10,11-dihydro-5*H*-dibenz[*b,f*]azepine (**2d**).

Compound **2d** was obtained as an orange oil (1.49 g, 50%) from **2** and *N,N*-dimethylbenzamide, hexane/ethyl acetate (9:1); ir (potassium bromide): ν 1635 cm^{-1} (C=O); nmr (deuteriochloroform): 11.29 (s, 1H, NH), 7.65-6.45 (m, 12H, aryl), 3.08 (s, 4H, CH_2CH_2).

Anal. molecular weight calcd. for $C_{21}H_{17}NO$: 299.1310. Found (high resolution mass spectrum): 299.1296.

Anal. Calcd. for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.68. Found: C, 84.02; H, 6.15; N, 3.76 (6).

4-Anisoyl-10,11-dihydro-5*H*-dibenz[*b,f*]azepine (**2e**).

Compound **2e** was obtained as a yellow oil (1.48 g, 45%) from **2** and *N,N*-dimethyl-4-methoxybenzamide, toluene/hexane (1:1); ir (potassium bromide): ν 1640 cm^{-1} (C=O); nmr (deuteriochloroform): 10.65 (s, 1H, NH), 7.70-6.50 (m, 11H, aryl), 3.78 (s, 3H, OCH_3), 3.07 (s, 4H, CH_2CH_2).

Anal. molecular weight calcd. for $C_{22}H_{19}NO_2$: C, 329.1416. Found (high resolution mass spectrum): 329.1405

Anal. Calcd. for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 79.98; H, 6.01; N, 3.95.

4-Nicotinoyl-10,11-dihydro-5*H*-dibenz[*b,f*]azepine (**2f**).

Compound **2f** was obtained as a red oil (1.26 g, 42%) from **2** and *N,N*-diethylnicotinamide, toluene/ethyl acetate (10:1); ir (potassium bromide): ν 1635 cm^{-1} (C=O); nmr (deuteriochloroform): 11.40 (s, 1H, NH), 8.80-6.45 (m, 11H, aryl), 3.10 (s, 4H, CH_2CH_2).

Anal. molecular weight calcd. for $C_{20}H_{16}N_2O$: 300.1263. Found (high resolution mass spectrum): 300.1257.

Anal. Calcd. for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33. Found: C, 79.74; H, 5.28; N, 8.95.

Acknowledgement.

This investigation was supported by Grant NS14997 from the National Institute of Neurological and Communicative Disorders and Stroke. The authors thank Ms. S. R. Harvey and Dr. K. Christiansen for the 250 mHz data.

REFERENCES AND NOTES

(1) A. Hallberg and A. R. Martin, *J. Heterocyclic Chem.*, **19**, 433 (1982).

(2) L. J. Kricka and A. Ledwith, *Chem. Rev.*, **74**, 101, 1974 and references therein.

(3) N. Gruenfeld, U. S. Patent 3,624,074 (1971); *Chem. Abstr.*, **76**, P59479k (1972).

(4) J. A. G. Drake and D. W. Jones, "Nuclear Magnetic Resonance Spectroscopy in Molecular Biology" in "Jerusalem Symposium on Quantum Chemistry and Biochemistry," Vol 11, B. Pullman, ed, D. Reidel Pub. Co., Dordrecht, Holland, 1978, p 493.

(5) A. Hallberg and A. R. Martin, *J. Heterocyclic Chem.*, in press.

(6) Three attempts to repurify this compound failed to improve the nitrogen analysis.