SYNTHESIS OF 11-PHENYL-5,6-DIHYDRO-11H-DIBENZ(b,e)AZEPINE DERIVATIVES

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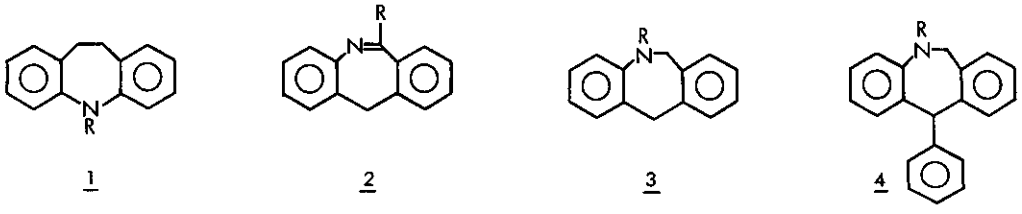
Abstract —— A simple synthesis of a new type of dibenz(b,e)azepine having basic side chain 4 is described.

A series of dibenzazepines having basic side chains 1, 2 and 3 have been known as useful psychotropic drugs.[1] However, 11-phenyl-5,6-dihydro-11H-dibenz(b,e)azepines 4 has not been reported in literature. Hoping to find unique CNS activity for 4, we readily synthesized 4 as follows.

Chart 1



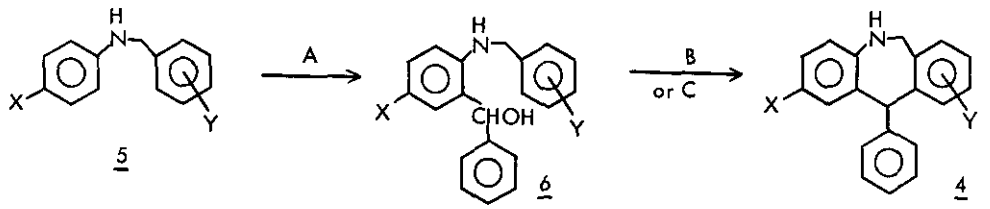
1 2 3 4

R: aminoalkyls

The method for obtaining 4 (R = H) consists of two steps from N-benzylanilines 5: i) exclusive ortho hydroxybenzylation of 5 into 2-aminobenzylbenzhydrols 6 using boron trichloride and benzaldehyde in the presence of triethylamine[2] and ii) subsequent cyclization of 6 to 4 (R = H) by treatment with conc. sulfuric acid. Namely, crude 6a (17.2 g, oil) obtained easily from 5a by our reported procedure[2] was treated in dichloromethane (25 ml) with conc. sulfuric acid (17.2 ml) at room temperature for 0.5 h. Basic (potasium carbonate-ice) work-up, extraction with dichloromethane and concentration gave 4a (mp 195-198° C, CH_2Cl_2-CH_3OH, 83% based on 5a). 4b could be obtained in a similar way (mp 195-196° C, CH_2Cl_2-CH_3OH, 86% based on 5b). 4c was prepared by treatment of crude 6c (1.23 g, oil) with conc. sulfuric acid (0.4 ml) in acetic acid (2 ml) for 4 h at room temperature (mp 215-218° C, CH_2Cl_2-CH_3OH, 48% based on 5c[3]). The most clear spectral proof for the

structure 4 was the appearance of an AB quartet of $-NCH_2-$ (δ, 3.5 ± 0.05 and 4.3 ± 0.05, J = 15 Hz) and a singlet of $\rightarrow CH$ (5.0 ± 0.05 and 5.71 for 4c), while the corresponding peaks of 6 were two singlets (δ, 4.25 ± 0.05 and 5.87 ± 0.07).

Chart 2



5 6 4

a: X = Y = H b: X = Cl, Y = H c: X = H, Y = 3,4,5-OCH_3

A i) BCl_3, Δ, 2 h in benzene; ii) PhCHO, Et_3N, rt, 1 h

B conc. H_2SO_4 in CH_2Cl_2, rt, 0.5 h

C conc. H_2SO_4 in AcOH, rt, 4 h

As shown in Chart 3, 4a was converted into iodacetamide 8 (Methods A and B) and subsequent aminolysis (Methods C, D and E) or amidolysis (Methods F and G) followed by hydrazinolysis (Method H) gave the corresponding aminoacetoamido derivatives 9, 10, 11, 13, 14. Reduction of 9, 10 and 11 with lithium aluminum hydride containing aluminum chloride (Method I) afforded the aminoethyl azepines 15, 16 and 17. Reduction with lithium aluminum hydride alone (Method J) led to cleavage of the amido bond giving 4a in about 50% yield, besides the desired product. Treatment of 4a with 2-phthalimidopropionylchloride (Method K) and subsequent hydrazinolysis gave compound 19, which was dimethylated (Method L) or cathylated (Method M) to compounds 20 and 21. Reduction of 20 (Method I) and 21 (Methods I and J) gave N-methylamino propylazepines 22 and 23. 4b was treated in a similar way to 4a to obtain the corresponding 3-aminobutyrylamidoazepine 24 (Methods N and H) and 3-aminopropylaminoazepines 29 and 30 (Methods K, H, L, M, I and J). Next, we tried to prepare lactam 33 directly from 4b, but treatment with chromic anhydride in pyridine (Method O) gave only imine 32 (97%, mp 165-167° C, $CH_3OH-CH_2Cl_2$, $\nu_{max}^{CHCl_3}$ 1600 cm^{-1}) and that with Mancera's manganese dioxide afforded aminoaldehyde 31 (95%, mp 163-166° C, $CH_3OH-CH_2Cl_2$, $\nu_{max}^{CHCl_3}$ 3528, 3405, 1700, and 1675 cm^{-1}), which was converted again into 32 by subsequent treatment with silica gel in benzene (Method P). Compound 33 (36%, mp 266-167° C, $CH_3OH-CH_2Cl_2$, $\nu_{max}^{CHCl_3}$ 1660 cm^{-1}) could be obtained by treatment of 32 with m-chloroperbenzoic acid (Method Q) and successive treatment of 33 with phosphorus pentachloride in benzene and N-methylpiperazine (Method R) afforded the 11-piperazinyl derivative 34 (67%, mp 176-177° C, $CH_3OH-CH_2Cl_2$).

Chart 3 (1)

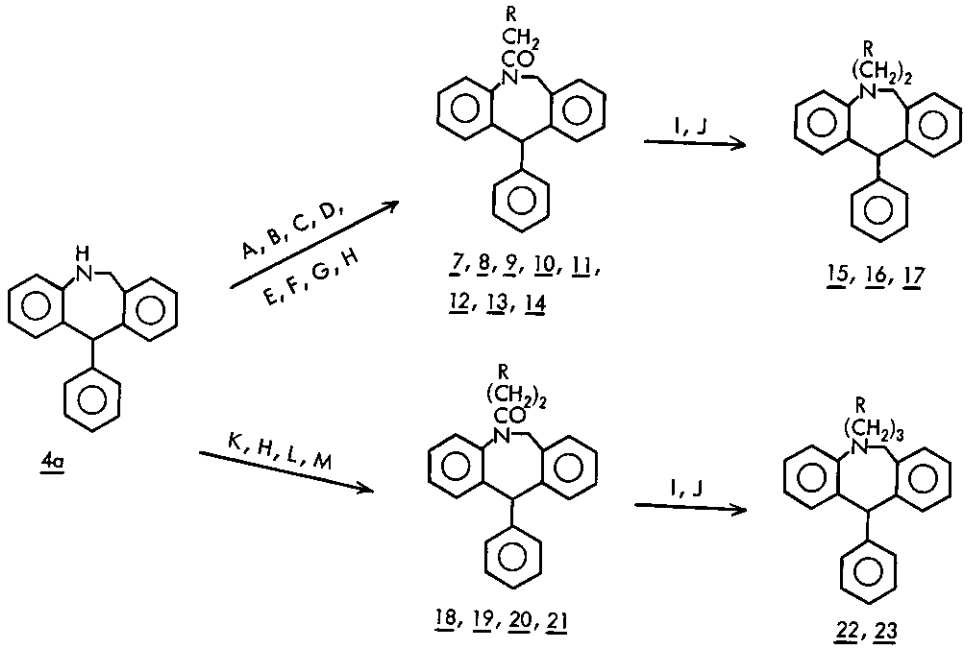
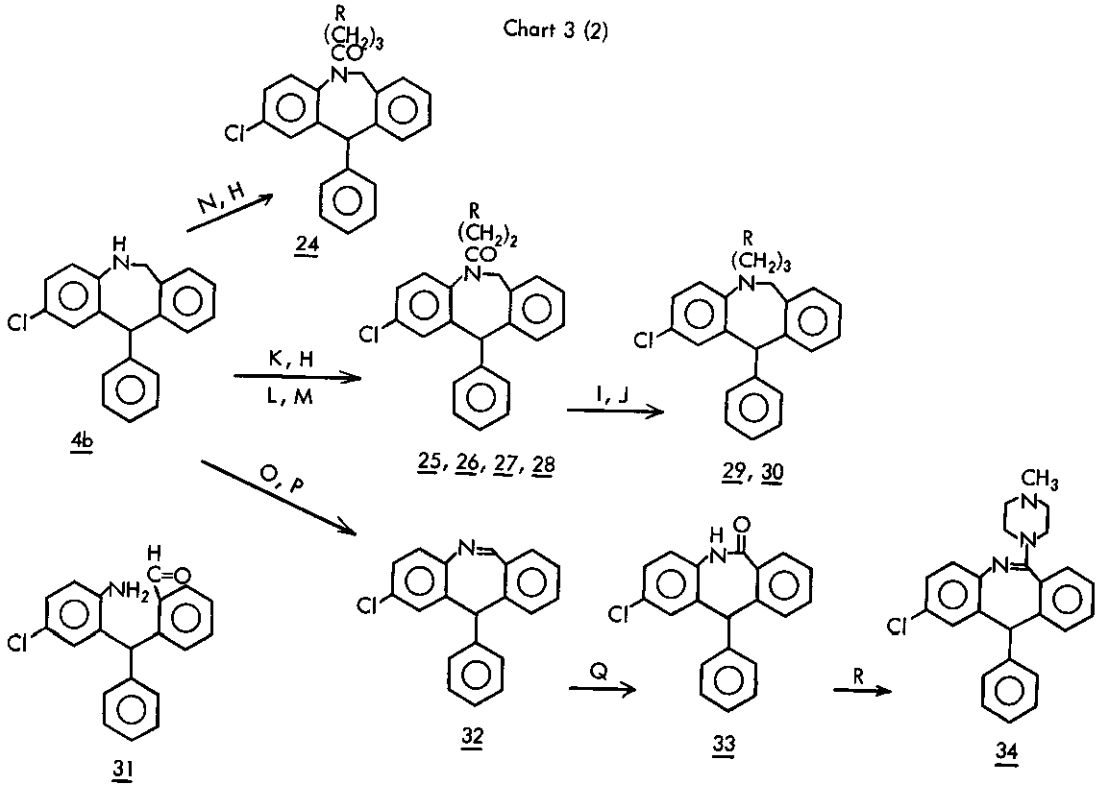
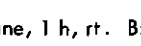
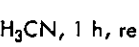
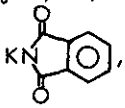
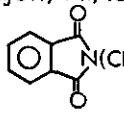
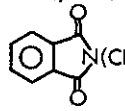
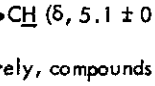


Chart 3 (2)



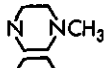
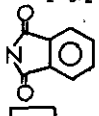
Method

A: $ClCOCH_2Cl$ (3 eq), K_2CO_3, dioxane, 1 h, rt. B: NaJ, acetone, 5 h, reflux. C:  (2 eq), CH_3CN, 1 h, reflux. D:  (2 eq), CH_3CN, 1 h, reflux. E: $HN(C_2H_5)_2$ (excess), 3 h, reflux. F:  , DMF, 4 h, 90° C. G: NaH,  (excess), 2 h, 100° C. H: $NH_2NH_2 \cdot H_2O$ (5 eq), C_2H_5OH, 1 h, reflux. I: $LiAlH_4$, $AlCl_3$ (2:1), ether, 1 h, ice-cooling. J: $LiAlH_4$, ether or THF, 1 h, reflux. K:  , K_2CO_3, dioxane, 0.5 h, reflux. L: HCOOH, CH_2O, 1 h, reflux. M: $ClCOOC_2H_5$ (2.5 eq), K_2CO_3, dioxane, 3 h, reflux. N:  , K_2CO_3, dioxane, 0.5 h, reflux. O: CrO_3, pyridine, 20 h, rt. P: MnO_2 (Mancera), CH_3CN, 2 h, rt, silica gel, benzene. Q: m-Cl-PhCOOOH, $CHCl_3$, 2 h, rt. R: PCl_5, benzene, 1 h, reflux,  (excess), 4 h, 100° C.

The ^{1}H-NMR spectra of the alkylamidoazepines 7, 8, 9, 10, 12, 13, 14, 18, 19, 20, 21, 25, 26 and 28 showed an AB quartet for $-NCH_2-$ (δ, 4.2 ± 0.1 and 6 ± 0.1, J = 17 Hz) and a singlet for $\rangle CH$ (δ, 5.2 ± 0.1), while that of the alkylaminoazepines 15, 16, 29 and 30 showed an AB quartet for $-NCH_2-$ (δ, 3.6 ± 0.2 and 4.4 ± 0.1, J = 15 Hz) and a singlet for $\rangle CH$ (δ, 5.1 ± 0.1). All compounds gave satisfactory elemental analyses (C ± 0.5, H ± 0.3, N ± 0.3). Unfortunately, compounds 4a, 4c, 9, 10, 13, 14, 15, 16, 17, 22, 23, 24, 29, 30 and 34 showed no significant pharmacological activity.

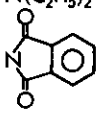
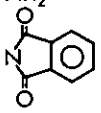
Table

Synthesis of N-substituted 11-phenyl-5,6-dihydro-11H-dibenz(b,e)azepines

Compound	R	mp, ° C (from)	Yield, %
7	Cl	149–151 (CH_2Cl_2-ether)	92
8	J	154–160	96
9		150–152 (ether)	93
10		182–184 (CH_2Cl_2-ether)	95
11	$N(C_2H_5)_2$	oil	90
12		112–115 (CH_2Cl_2-ether)	98
13		156–159 (CH_2Cl_2-ether)	57
14	NH_2	189–192 (CH_2Cl_2-CH_3OH)	99

(Continued)

Table (Continued)

Compound	R	mp, °C (from)	Yield, %
15		118-120 (ether-petroleum ether)	56 based on 8
16		140-142 (CH_2Cl_2-ether)	91
17	$N(C_2H_5)_2$	172-174 (CH_3OH-ether)[a]	52
18		213-215 (CH_2Cl_2-CH_3OH)	98
19	NH_2	163-166 (CH_2Cl_2-CH_3OH)[b]	71
20	$N(CH_3)_2$	230-232 (CH_3OH)[a]	78
21	$NHCOOC_2H_5$	156-158 (CH_2Cl_2-CH_3OH)	97
22	$N(CH_3)_2$	185-187 (CH_3OH-ether)[a]	67 based on 19
23	$NHCH_3$	203-207 (dp) (CH_2Cl_2-CH_3OH)[a]	64 based on 19
24	NH_2	235-239 (dp) (CH_3OH)[b]	93 based on 4b
25		213-215 (CH_2Cl_2-CH_3OH)	78
26	NH_2	183-185 (CH_2Cl_2-CH_3OH)	82
27	$N(CH_3)_2$	resin	
28	$NHCOOC_2H_5$	resin	
29	$N(CH_3)_2$	160-163 (dp) (CH_3OH)[a]	44 based on 27
30	$NHCH_3$	202-205 (dp) (CH_2Cl_2-CH_3OH)[a]	67 based on 27

a: oxalate b: hydrochloride

References

* Dedicated to Prof. T. Kametani on the occasion of the retirement from the Chair of Organic Chemistry at the Pharmaceutical Institute of Tohoku University.

1. (a) J. Schmutz, Arzneim-Forsch., 1975, 25, 712; (b) D. Bar, IL FARMACO, 1972, 27, 414.
2. T. Sugasawa, T. Toyoda, M. Adachi and K. Sasakura, J. Am. Chem. Soc., 1978, 100, 4842.
3. 5c (mp 76-78° C, CH_3OH) was prepared from aniline and 3,4,5-trimethoxybenzaldehyde in 92% yield [i) 130° C, 4 h; ii) $NaBH_4$ in CH_3OH, rt, 0.5 h].

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