Active Structures in the 2-Aminoethylbenzimidazoles Series

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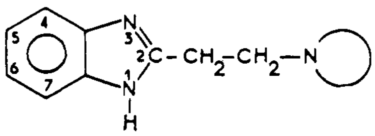
In a previous paper[1] we have shown that a 5- (6-) NO_2 radical has an influence on the biological activity of compounds I, the N-heterocycle being piperidine, pyrrolidine, or morpholine. The unsubstituted deriv-



I

atives I are only very slightly active and possess only a rather low papaverine-like spasmolytic activity. On the other hand, their nitro derivatives have a slightly or mildly marked analgetic activity and also a higher papaverine-like spasmolytic ability and exhibit convulsant reactions at average or sublethal doses.

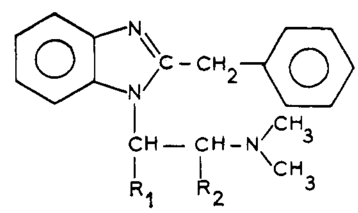
Hunger, *et al.*,[2-5] who have studied a series of 2-benzylbenzimidazoles found that 5 nitration (in the 6 position, effects are weaker) increased very strongly the morphine-like analgetic activity; in this respect 5-nitro-2-(*p*-ethoxybenzyl)-1-diethylaminoethylbenzimidazole (etonitazene) is particularly interesting; we have not noticed similar morphine-like features in our series.

The work presented in this paper concerns the preparation and the pharmacodynamic study of compounds of type I, N-substituted by classical dialkylaminoalkyl chains which seem to play a great part in benzimidazole series, as well as their 5-nitro derivatives. Some 2-benzylbenzimidazoles previously described (**1**, **8**) were prepared for comparison.

Owing to a possible additivity of the effects of the amino chain and the NO_2 group, a higher analgetic activity could have been expected. Decreased convulsant effects were unlikely because substitution by a sufficiently large group in the 1 or 2 positions seems to render benzimidazoles more or less convulsant,[6] whereas benzimidazole itself is an anticonvulsant agent.

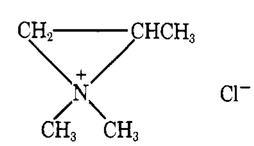
Synthesis.—The benzimidazole ring cyclization here employed is performed through the imino ether hydrochloride and a suitable aromatic diamine condensation.[7] Aminocyanides of the type $(>NCH_2CH_2CN$ are obtained by reaction of acrylonitrile with cyclic amine. The three synthetic methods are shown in Schemes I–III. The nitro compounds are prepared according to Scheme III which gives only the 5-nitro isomer.[3] The reaction is performed in glacial acetic acid at 45°; we always noticed a very small quantity of 2-methyl derivatives which results from the condensation of acetic acid and aromatic *o*-diamine. The condensation of 2-chloro-1-dimethylaminopropane *via* Scheme II gives two isomers differing in the α- or β-methyl position. We have attempted a separation of the two isomers of 2-benzylbenzimidazole derivative. Distillation of the crude reaction mixture leads to the B_1 base which is converted to the hydrochloride. The hydrochloride is recrystallized several times from ethanol; the base is liberated and chromatographed. The product B_2 is eluted. The nmr study on B_1 and B_2 gives the results (solvent, $CDCl_3$, TMS internal reference, 60 MHz, shifts in hertz) shown in Table I. Thus, while it was not possible to

Table I



Compd	R_1	R_2	*sec*-Me doublet (*J*, cps)	Integration ratio
B_1	H	CH_3	46.5 (7)	6
	CH_3	H	78 (7)	1
B_2	H	CH_3	48.5 (7)	9
	CH_3	H	79.5 (7)	1

isolate one isomer in a pure state, we have at least obtained an enrichment of one isomer (R_2 = CH_3, R_1 = H). Methyl R_1 assignment is unambiguous by comparison with spectra of products synthetized by Scheme I using 2-amino-1-dimethylaminopropane; we obtained only one isomer in this way. These results are in good agreement with those of Casy and Wright:[8] the opening of the probable cyclic intermediate ion



which operates preferably by rupture of the $N-CH_2$ bond for a hindered molecule as is known in the preparation of promethazine.[9] This scheme which uses a sodium salt was inconvenient in the case of our aminoethyl derivatives.

For studying the possibility of lengthening the alkyl chain in the 2 position, we tried the preparation of **18** and its 5- (6-) nitro homolog **19**. Scheme IV gave a mixture of two products in a ratio of 1:1. One was identified, by reference to the literature[10,11] and by nmr spectra, as 2,3-dihydro-1H-pyrrolo[1,2-*a*]benzimidazole, and the other as the desired chloro product which never gave the desired benzimidazole. Finally **18** was prepared by Scheme V. Because of the low pharmaco-

(1) M. Mousseron, J. M. Kamenka, and A. Stenger, *Chim. Therap.*, 95 (1967).

(2) A. Hunger, J. Kebrle, A. Rossi, and K. Hoffmann, *Helv. Chim. Acta*, **43**, 800 (1960).

(3) A. Hunger, J. Kebrle, A. Rossi, and K. Hoffmann, *ibid.*, **43**, 1032 (1960).

(4) A. Hunger, J. Kebrle, A. Rossi, and K. Hoffmann, *Experientia*, **13**, 400 (1957).

(5) F. Gross and H. Turrian, *ibid.*, **13**, 401 (1957).

(6) W. G. Bywater, W. R. Coleman, O. Kamm, and H. Houston Merritt, *J. Am. Chem. Soc.*, **67**, 905 (1945).

(7) F. E. King and R. M. Acheson, *J. Chem. Soc.*, 1396 (1949).

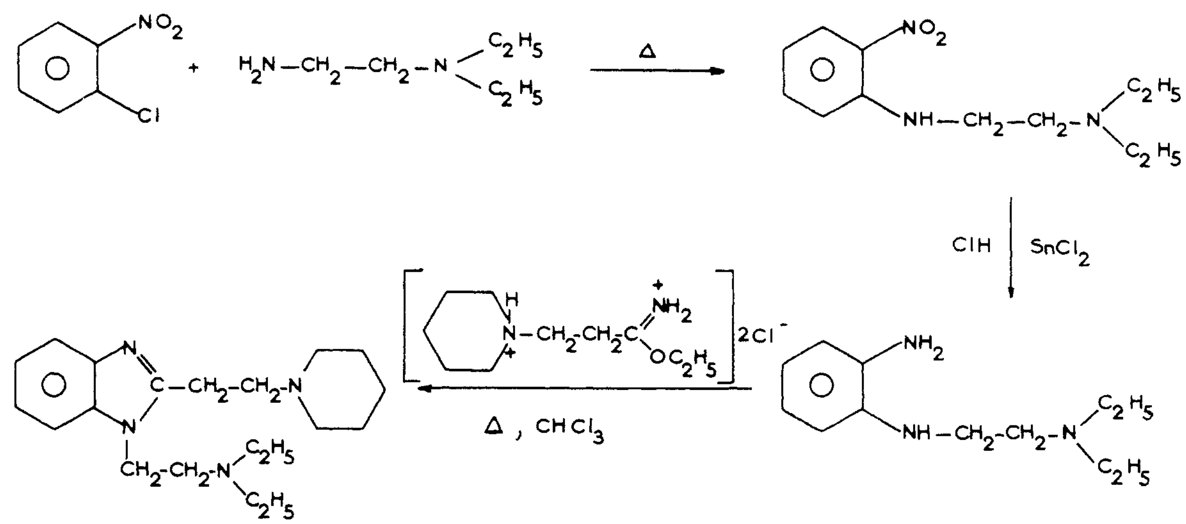
(8) A. F. Casy and J. Wright, *J. Chem. Soc., C*, 1167 (1966).

(9) F. Charpentier, *Compt. Rend.*, **225**, 306 (1947).

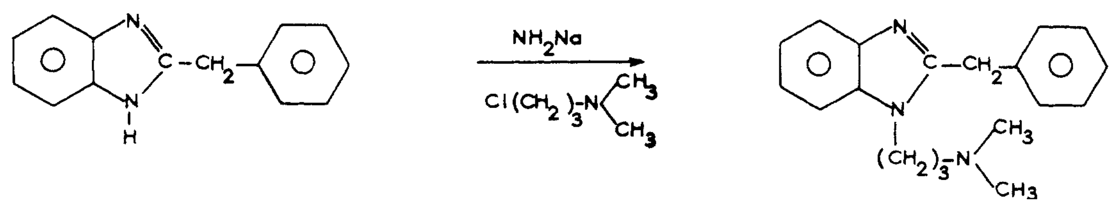
(10) A. R. Freedman, D. S. Payne, and A. R. Day, *J. Heterocycl. Chem.*, 257 (1966).

(11) W. Reppe, *Ann.*, **596**, 176 (1955).

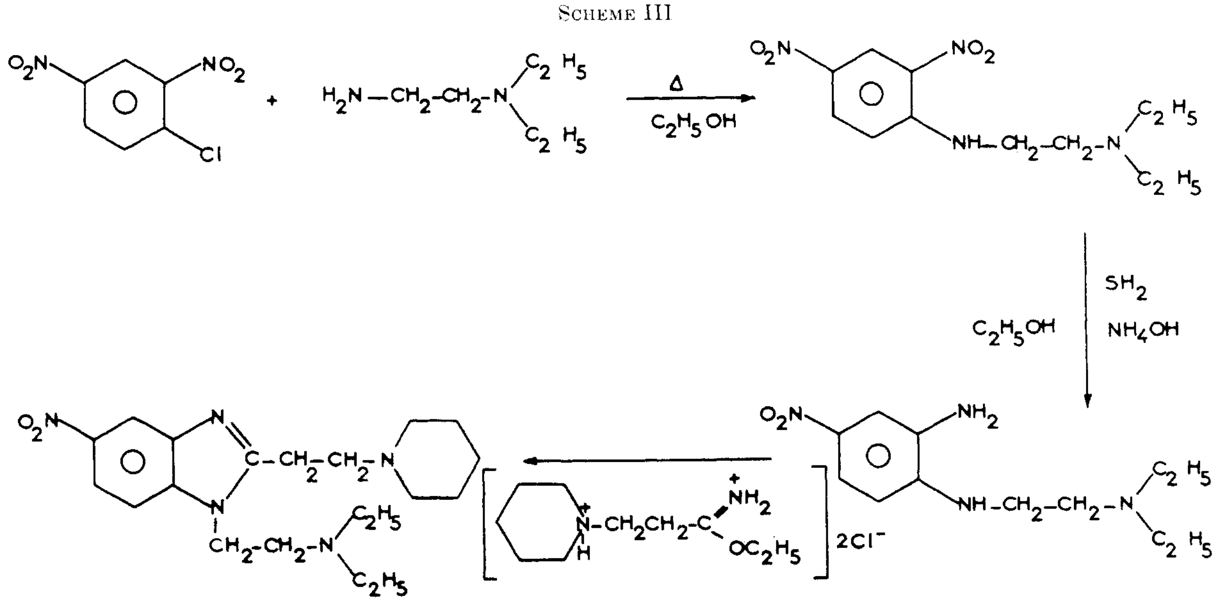
SCHEME I



SCHEME II



SCHEME III



logical interest of this product and its nitro derivative, work in this series was not pursued further.

All compounds prepared are presented in Tables II–IV. The bases are generally oxydizable, hygroscopic, and noncrystallizable oils. Some hydrochlorides are delinquescent.

Experimental Section

Spectroscopic Results.—Ir spectra were recorded on a Beckman I.R. 8 apparatus (solvent, $CHCl_3$ or CCl_4): $\nu_{C=N}$ and $\nu_{C_6H_5}$ at 1620–1590 cm^{-1} sharpened in the nitro compounds, ν_{NO_2} at 1530 and 1330 cm^{-1}. The spectra were in agreement with the literature.[12] Uv spectra were recorded on a Unicam S.P. 800 apparatus (solvent, alcohol, 95°) and were as expected. Nmr spectra were recorded on a Varian A60 apparatus (solvent, $CDCl_3$, TMS as internal reference). Melting points were measured on the Kofler hot plate microscope and are uncorrected.

The condensation of piperidine and acrylonitrile is described in the literature[13] as is the preparation of the imino ether hydrochlorides.[1,2] The reduction of substituted *o*-nitroanilines was performed with $SnCl_2 \cdot 2H_2O$ in HCl[14] and the selective reduction of 2,4-dinitroanilines with H_2S and alcoholic NH_3.[3] The synthesis of 2-benzyl derivatives has been reported in the literature[2,3] using benzyl cyanide as a starting material.

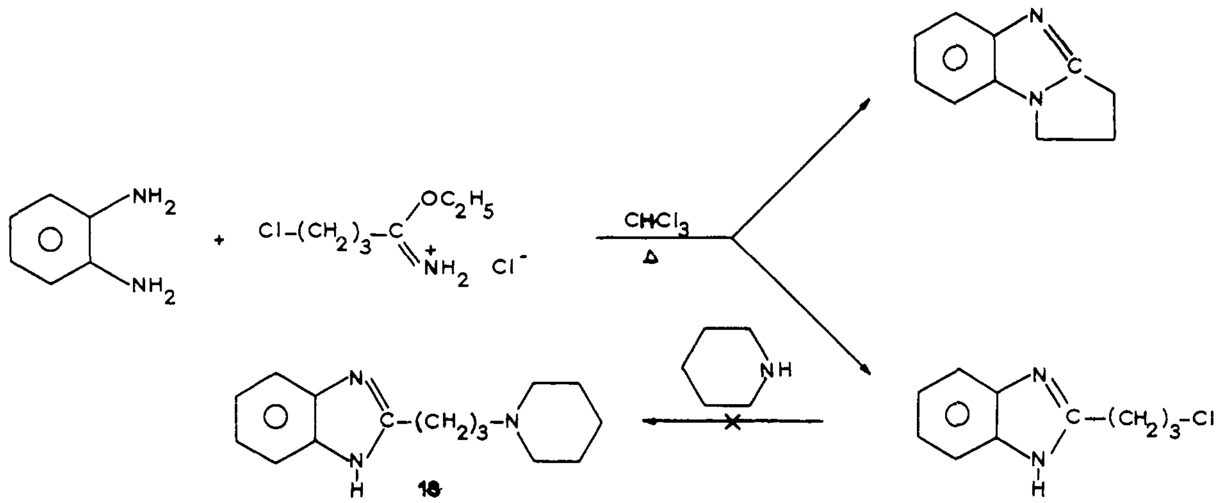
Scheme I. 2-(N-Piperidinoethyl)-1-diethylaminoethylbenzimidazole (2).—To the imino ether hydrochloride prepared with 6.9 g (0.05 mole) of β-piperidinopropionitrile was added 10.3 g (0.05 mole) of 2-β-diethylaminoethylaminoaniline in 100 ml of

(12) K. J. Morgan, *J. Chem. Soc.*, 2343 (1961).

(13) F. C. Whitmore, H. S. Mosher, R. R. Adams, R. B. Taylor, E. C. Chapin, C. Weissel, and W. Yanko, *J. Am. Chem. Soc.*, **66**, 725 (1944).

(14) J. B. Wright, *ibid.*, **71**, 2034 (1949).

Scheme IV



Scheme V

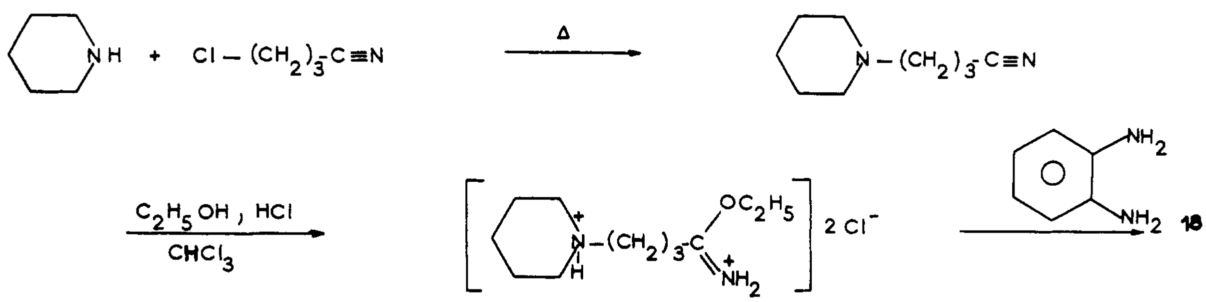
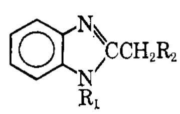
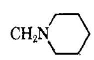
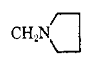
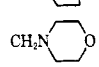
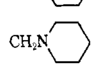
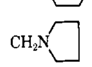
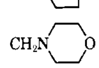
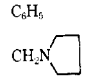


Table II



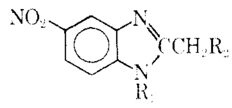
No.	R_1	R_2	Scheme	Yield, %	Mp, °C[c] HCl salt	Formula[d]
1	$CH_2CH_2N(C_2H_5)_2$	C_6H_5	I	75	183–185[b]	$C_{20}H_{25}N_3$
2	$CH_2CH_2N(C_2H_5)_2$		I	55	182–184	$C_{20}H_{32}N_4$
3	$CH_2CH_2N(C_2H_5)_2$		I	45	165 dec	$C_{19}H_{30}N_4$
4	$CH_2CH_2N(C_2H_5)_2$		I	50	184–186	$C_{19}H_{30}N_4O$
5	$CH(CH_3)CH_2N(CH_3)_2$		I	65	182–184	$C_{19}H_{30}N_4$
6	$CH(CH_3)CH_2N(CH_3)_2$		I	60	...	$C_{18}H_{28}N_4$
7	$CH(CH_3)CH_2N(CH_3)_2$		I	50	155–158	$C_{18}H_{28}N_4O$
8	$CH_2CH(CH_3)N(CH_3)_2$[a]	C_6H_5	II	50	203–208	$C_{19}H_{23}N_3$
9	$(CH_2)_3N(CH_3)_2$	C_6H_5	II	50	192–195	$C_{19}H_{23}N_3$
10	$(CH_2)_3N(CH_3)_2$		II	40	...	$C_{18}H_{28}N_4$

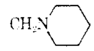
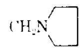
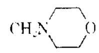
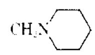
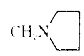
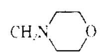
[a] Major product mixed with about 1/9 of isomeric form. [b] Lit.[2] 181–183°. [c] Uncorrected. [d] All compounds were analyzed for C, H, N. Analytical results were within ±0.4% of theoretical values.

$CHCl_3$. After stirring and refluxing for 16 hr, the cooled solution was extracted with H_2O (200 ml), and the aqueous extract was made alkaline with NH_4OH with cooling and extracted with 150 ml of $CHCl_3$. The organic solution was washed (50 ml of 10% NaOH, 200 ml of H_2O), dried (Na_2SO_4), and evaporated *in vacuo* on a steam bath. The residue, a yellow oil (13.3 g), was dissolved in petroleum ether (bp 60–70°) and Et_2O (9:1) and filtered quickly over 40 g of Al_2O_3 (Merck). After evaporation *in vacuo* the residue weighed 9 g. To this oil dissolved in 100 ml of Et_2O was added 100 ml of saturated ethereal HCl and the mixture was allowed to stand overnight in cold. The solvent was evaporated *in vacuo* on a steam bath, and the residue (trihydrochloride) crystallized from a little EtOH; mp 182–184°.

Scheme II. 2-Benzyl-1-(2-dimethylaminopropyl)benzimidazole (8).[2]—The starting material for this synthesis was 2-benzylbenzimidazole. The base B_1 obtained from the reaction boiled at 179–182° (0.05 mm); it was converted to the hydrochloride in ether. Several crystallizations from EtOH gave a salt, mp 203–

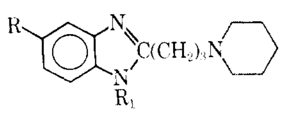
TABLE III



No.	R_1	R_2	Yield, %	Mp, °C[b] HCl salt	Formula[c]
11	$(CH_2)_3N(CH_3)_2$	C_6H_5	60	98–99[a]	$C_{19}H_{22}N_4O_2$
12	$(CH_2)_3N(CH_3)_2$		45	124–126	$C_{19}H_{29}N_5O_2$
13	$(CH_2)_3N(CH_3)_2$		50	207–210	$C_{18}H_{27}N_5O_2$
14	$(CH_2)_3N(CH_3)_2$		45	141–144	$C_{18}H_{27}N_5O_3$
15	$(CH_2)_2N(C_2H_5)_2$		45	138–141	$C_{20}H_{31}N_5O_2$
16	$(CH_2)_2N(C_2H_5)_2$		40	132–133	$C_{19}H_{29}N_5O_2$
17	$(CH_2)_2N(C_2H_5)_2$		30	143–145	$C_{19}H_{29}N_5O_3$

[a] Melting point of pure base. [b] Uncorrected. [c] See footnote *d*, Table II.

TABLE IV



No.	R	Yield, %	Mp, °C[b]	Formula[c]
18	H	60	116–118[a]	$C_{15}H_{23}N_3O$
19	NO_2	60	67–69	$C_{15}H_{22}N_4O_3$

[a] Dihydrate, mp 65–68°. [b] Uncorrected. [c] See footnote *d*, Table II.

208°. The liberated base was chromatographed on silica gel (Merck) and eluted with MeOH–Et_2O (3:7) giving B_2. Nmr analysis indicated a ratio of major to minor isomer of 6/1 for B_1, and 9/1 for B_2.

Scheme III. 5-Nitro-2-(N-piperidinoethyl)-1-diethylaminoethylbenzimidazole (15).—To the imino ether hydrochloride from 6.9 g (0.05 mole) of β-piperidinopropionitrile was added 13.7 g (0.05 mole) of 5-nitro-2-(diethylaminoethylamino)aniline monohydrochloride[3] in 200 ml of AcOH. The solution was stirred for 24 hr at 45° and cooled, and 50 ml of 5 *N* HCl was added. The mixture was evaporated *in vacuo*. The residue was dissolved in 2 *N* HCl, extracted with $CHCl_3$, cooled, made alkaline with NH_4OH, and extracted with $CHCl_3$ (200 ml). The organic layer was washed (50 ml of 10% NaOH, 200 ml of H_2O), dried (Na_2SO_4), and evaporated *in vacuo* on a steam bath. The red residue (10.3 g) was dissolved in petroleum ether–Et_2O (1:1) and filtered quickly through Al_2O_3 (40 g). The head fractions contained 8.4 g of the expected base. The trihydrochloride was boiled with acetone and filtered, mp 138–141°.

Scheme IV. 2-(γ-Chloropropyl)benzimidazole and 2,3-Dihydro-1H-pyrrolo[1,2-*a*]benzimidazole.—To the imino ether hydrochloride from 10.3 g (0.1 mole) of γ-chlorobutyronitrile was added 10.4 g (0.1 mole) of *o*-phenylenediamine in 200 ml of $CHCl_3$ as described for **2**. The product weighed 14 g, mp 72–75°; 2 g of it was chromatographed on silica gel giving fraction A (930 mg, mp 130–131°, eluted with Et_2O) and B [945 mg, mp 110–111°, eluted with $CHCl_3$–Et_2O (7:3)]. A was identified as 2-(γ-chloropropyl)benzimidazole and B as 2,3-dihydro-1H-pyrrolo[1,2-*a*]benzimidazole (lit.[10,11] mp 115°).

Scheme V. 2-(N-Piperidinopropyl)benzimidazole (18).—To 21 g (0.25 mole) of piperidine heated to 70° was added dropwise with stirring 26 g (0.25 mole) of γ-chlorobutyronitrile, the temperature being kept below 100°. Slowly, the mixture became solid; after standing 2 hr at 100°, the reaction products were dissolved after cooling, in 10% HCl, then made ammoniacal and extracted (Et_2O). The ether fractions were dried and evaporated, and the residue was distilled, bp 125° (25 mm), giving 28 g of γ-piperidinobutyronitrile; as indicated in Scheme IV, its imino ether hydrochloride was condensed on *o*-phenylenediamine (0.02 mole). The oily product obtained was filtered over Al_2O_3 in Et_2O; after evaporation at room temperature, the oil crystallized on contact with air. The crystals of dihydrate, mp 65–68°, were dried *in vacuo* at 100° for 4 hr giving a monohydrate, mp 116–118°.

5-Nitro-2-(N-piperidinopropyl)benzimidazole (19).—Using Scheme III with 4-nitro-2-aminoaniline and the imino ether hydrochloride from γ-piperidinobutyronitrile we obtained an oil; it was filtered over Al_2O_3 in $CHCl_3$, the solvent was evaporated, and the compound crystallized on contact with air, mp 66–70°. This solid, when warmed *in vacuo* at 100° and kept anhydrous, remained oily; in the atmosphere it slowly gave a monohydrate (**19**), mp 67–68°.

Pharmacology.—All compounds were administered as their hydrochlorides in physiological saline solution and tested in Swiss mice. Doses were generally administered in 0.5-log intervals.

Qualitative Study.—By increasing parenteral doses we noticed the following changes in the animals: decreased locomotor activity, distinctive paralysis at the posterior limb level, dyspnea and a decrease of respiratory rate, subconvulsive movements (tremors, tail catatonus), tonic–clonic convulsions. There was an irregular appearance of ptosis in **8–10** and mydriasis in **1, 2, 5, 8, 11, 17.** A weak analgetic effect (tail pinching) was observed chiefly in the nitro series.

Quantitative Study.—MED_{50}, LD_{50}, and ED_{50} (rotarod) values, defined as the lowest dose giving, in 50% of the animals, respectively, reactive signs, death, loss of equilibrium, were determined. These values were calculated according to the method of Thomson and Weil.[15] The results with 95% confidence limits are listed in Table V.

Analgesia.—Analgesia was measured by the writhing test with AcOH.[16] In our previous work we used also the hot-plate test (at 65°) according to Jacob[17] but in the present case, this test showed no analgesia. A comparison was made with pethidine and etonitazene. The therapeutic index is calculated (Table V).

Spasmolytic activity *in vitro* was determined on an isolated rat duodenum according to the classical method, counteracting the contractions caused by acetylcholine hydrochloride and $BaCl_2$. The ED_{50} was the dose which suppressed 50% of the control contraction. Results expressed in μg/10 ml of solution are reported in Table VI. Results with 2-benzylbenzimidazole hydrochloride synthesized and tested previously[1] (Tromasedan[®]) are also reported.

Conclusions

The compounds showed distinctive convulsant properties; central properties were ill-defined, and analgesia was weak and not accompanied by morphine-like

(15) W. R. Thomson and C. S. Weil, *Biometrics*, **8**, 249 (1952).

(16) R. Koster, N. Anderson, and E. J. de Beer, *Fed. Proc.*, **22**, 248 (1963).

(17) J. Jacob and M. Blozovski, *Arch. Intern. Pharmacodyn.*, **132**, 196 (1961).

TABLE V
ANALGETIC TESTS[a]

Compd	MED_{50}	ED_{50}	LD_{50}	R[e]	Analgesia[b]	Writhing test[c] ED_{50}	TI[d]
1[f]	17.8 (10.7–29.6)	56.2 (33.7–93.8)	100 (51.4–194)	5.6	(+)	40	2.5
2	17.8 (5.6–56.2)	56.2 (33.7–93.8)	178 (56.2–562)	10	0		
3	56.2 (17.8–178)	LD_{50}	178 (107–296)	3.1	0		
4	56.2 (17.8–178)	316 (251–398)	398 (251–631)	7.1	0		
5	56.2 (33.7–93.8)	LD_{50}	133 (75–237)	2.4	0		
6	56.2 (33.7–93.8)	LD_{50}	178 (107–296)	3.1	0		
7	56.2 (33.7–93.8)	LD_{50}	178 (107–296)	3.1	0		
8[g]	17.8 (10.7–29.6)	56.2 (33.7–93.8)	178 (107–296)	10	0		
9	17.8 (5.6–56.2)	LD_{50}	50.1 (39.8–63.1)	2.8	0		
10	31.6 (10–100)	LD_{50}	158 (126–200)	5	0		
11	5.6 (3.3–9.3)	100 (51.4–194)	178 (107–296)	31.6	+(+)	35	5
12	56.2 (17.8–178)	178 (107–296)	398 (316–501)	7	(+)	150	2.6
13	31.6 (10–100)	562 (337–938)	750 (422–1330)	23.7	(+)	100	7.5
14	56.2 (17.8–178)	LD_{50}	750 (422–1330)	13.3	(+)	110	6.8
15	17.8 (5.6–56.2)	LD_{50}	178 (56.2–562)	10	(+)	>100	
16	17.8 (5.6–56.2)	178 (56.2–562)	224 (178–282)	12.6	0		
17	17.8 (5.6–56.2)	178 (56.2–562)	562 (337–938)	31.6	+	90	6.2
18	31.6 (10–100)	53	70.8 (50.1–100)	2.2	0		
19	17.8 (5.6–56.2)	LD_{50}	79.4 (63.1–100)	4.4	0		
Etonitazene	1.7×10^{-5} (0.5–5)	56.2×10^{-3} (33.7–93.8)	126 (100–158)	7×10^{6}	+++	1.2×10^{-5}	10^{7}
Pethidine			178 (107–296)		+++	4	44.5

[a] All doses are in mg/kg with dose range in parentheses. [b] Qualitative test: 0 < (+) < + < +(+) < ++ < +++. [c] Subcutaneous injection. [d] Therapeutic index = LD_{50}/ED_{50}. [e] R = LD_{50}/MED_{50}. [f] Given in the literature as one-tenth the analgetic activity of morphine.[2] [g] Not analgetic in literature.[2]

TABLE VI
SPASMOLYTIC ACTIVITY

Compd	ED_{50}, μg/10 ml BaCl$_2$	ED_{50}, μg/10 ml Acetylcholine (HCl)	Compd	ED_{50}, μg/10 ml BaCl$_2$	ED_{50}, μg/10 ml Acetylcholine (HCl)
1	30	56.2	12	178	178
2	100	100	13	178	178
3	178	178	14	>1000	>1000
4	300	300	15	178	100
5	568	316	16	178	300
6	31.6	31.6	17	178	178
7	316	178	18	300	300
8	56.2	56.2	19	100	100
9	56.2	56.2	Tromasedan®	200	200
10	178	178	Papaverine	30	
11	56.2	56.2	Atropine		0.03

effects. The papaverine-like spasmolytic activity lies generally between papaverine and Tromasedan®. Atropine-like activity was in all cases weak or absent.

Substitution at the 1 position of 2-aminoethylbenzimidazoles did not give rise to important modifications; a more pronounced papaverine-like activity, however, was noticed as was also an increase of the ratio LD_{50}/MED_{50} in compounds without nitro substituents. In contrast to the 2-benzyl series it appears that no additivity exists for the chain at the 1 position and the 5-NO_2 groups as far as analgesia is concerned since 1-substituted 5-nitro derivatives were less analgetic than their N-unsubstituted homologs.[1] Convulsant effects were constant in the series. 2-Aminopropylbenzimidazoles did not appear to give interesting biological results.

Acknowledgments.—The authors wish to thank the "Direction des Recherches et Moyens d'Essais" who have permitted this work to be done; we also thank Ciba Laboratories (Bâle) who kindly furnished a sample of etonitazene and J. Wylde for the English translation.

5-(Dimethylaminopropyl)-10,11-dihydro-5H-benzo[2,3]pyrido[6,7-*b*]azepine[1]

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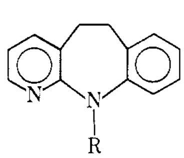
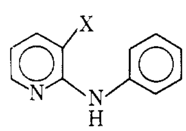
The title compound, Ib, was prepared to study the biological effects of isosteric substitution of a 2-pyridyl ring for a phenyl ring in the 10,11-dihydro-5H-dibenz[*b,f*]azepine series of antidepressant agents. Our initial attempts at the synthesis of this heterocyclic



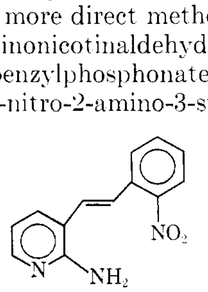
Ia, R = H
b, R = $(CH_2)_3N(CH_3)_2$



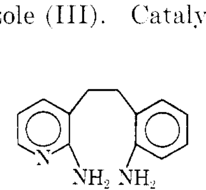
IIa, X = COOH
b, X = CH_2OH
c, X = CH_2Cl
d, X = CH_2CN
e, X = CH_2OCH_3

amine by homologation (IIb → IId) of the readily available 2-anilinonicotinic acid (IIa) followed by intramolecular cyclization were abandoned in favor of the present more direct method.

2-Aminonicotinaldehyde was condensed with ethyl *o*-nitrobenzylphosphonate[2] to give a 41% yield of *trans*-2'-nitro-2-amino-3-stibazole (III). Catalytic hy-



III



IV

drogenation of III in the presence of 5% Pd–C gave the diaminodihydrostilbazole IV which was converted to Ib by procedures previously described.[1] Compound Ib was isolated and characterized as the monohydrochloride and monomaleate salts.

In the attempted homologation sequence mentioned above, 2-anilinonicotinic acid (IIa) was converted by $LiAlH_4$ reduction into 3-(hydroxymethyl)-2-anilinopyridine (IIb). This compound on reaction with $SOCl_2$ gave the chloromethyl compound IIc. Attempts to convert IIc·HCl to the corresponding nitrile gave the alkoxy ethers as the major product.

Compound Ib[3] at oral doses of 1 and 3 mg/kg did not antagonize tetrabenazine-induced sedation in mice. The approximate ED_{50} for this compound is between 5 and 10 mg/kg orally in mice, whereas the dibenzo compound has an oral ED_{50} in the range of 1–3 mg/kg. At 30 mg/kg orally in the mouse, there was marked decrease in motor activity accompanied by tremors, twitches, and convulsions. The compound is lethal at 100 mg/kg.

These and our previously reported data demonstrate that substitution of one or both aromatic groups by pyridyl rings in the dibenzo(*b,f*)azepine series results in compounds having greater toxicity and lower antidepressant properties. However, these results are in contrast to similar substitutions in the dibenzo[*a,d*]cycloheptene series, which will be discussed in future communications from this laboratory.

Experimental Section[4]

***trans*-2'-Nitro-2-amino-3-stilbazole (III).**—To a solution of ethyl *o*-nitrobenzylphosphonate[2] prepared from 27.1 g (0.125 mole) of *o*-nitrobenzyl bromide and 20.8 g (0.125 mole) of redistilled triethylphosphite was added, slowly, a suspension of 8.1 g of NaOMe in 40 ml of dry DMF at 0–5°. 2-Amino-3-pyridinealdehyde[5] (15.4 g, 0.125 mole) in 40 ml of DMF was added dropwise with stirring a 0 to −10°. After 15 min, the mixture was permitted to warm to room temperature and stirred for an additional 90 min. The dark brown reaction mixture was poured into 2 l. of ice water and allowed to crystallize overnight. The product was filtered, air dried, and recrystallized from *i*-Pr_2O to give 12.5 g (41%) of product, mp 126–127°. *Anal.* ($C_{13}H_{11}N_3O_2$) C, H, N.

2,2'-Diamino-3-phenethylpyridine (IV).—A solution of 11.8 g of III in 250 ml of EtOH was reduced in a Parr hydrogenator at 50° in presence of 1 g of 5% Pd–C. After cooling, the catalyst was removed and the solution was concentrated *in vacuo* on the steam bath. The residue was recrystallized from a mixture of $CHCl_3$–hexane to give 8.2 g (78.5%) of product, mp 114–115°. *Anal.* ($C_{13}H_{15}N_3$) C, H, N.

10,11-Dihydro-5H-benzo[2,3]pyrido[6,7-*b*]azepine (Ia).—To a solution of 7.8 g (0.036 mole) of IV in 400 ml of EtOH, 85% H_3PO_4 was added dropwise until precipitation of the salt was complete. The phosphate salt was filtered, washed with anhydrous ether, air dried, transferred to a round-bottom flask, and heated at 250° (inner temperature) for 2 hr. After cooling the residue was suspended in H_2O, made basic with 50% NaOH, and extracted with $CHCl_3$. The solvent was removed and the residue was extracted several times with refluxing hexane (total 600 ml). Concentration of the combined hexane solutions gave the product (2.5 g, 37%) which was recrystallized several times from hexane; mp 96–97°. *Anal.* ($C_{13}H_{12}N_2$) C, H, N.

5-(Dimethylaminopropyl)-10,11-dihydro-5H-benzo[2,3]pyrido-[6,7-*b*]azepine Hydrochloride (Ib).—A solution of 5.9 g (0.03 mole) of Ia in 70 ml of anhydrous xylene was treated with 1.5 g of NaH (52.7% in mineral oil) and heated under reflux for 30 min. Dimethylaminopropyl chloride (4.0 g in 30 ml of xylene) was added dropwise and the mixture was heated with stirring for 14 hr. H_2O was added, the product was extracted (Et_2O)

(1) For the first paper in this series see F. J. Villani, *J. Med. Chem.*, **10**, 497 (1967).

(2) R. J. Sundberg and T. Yamazaki, *J. Org. Chem.*, **32**, 290 (1967).

(3) We are indebted to Dr. Robert Taber of the Biological Division of the Schering Corp. for the biological data herein reported.

(4) Where analyses are indicated only by the symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Melting points were taken in a Thomas–Hoover melting point apparatus and are uncorrected. Spectral data, uv, ir, and nmr, and combustion elemental analyses were obtained by the Physical Analytical Department of the Schering Corp. and are in accord with the proposed structures.

(5) A. Albert and F. Reich, *J. Chem. Soc.*, 1370 (1960).