uct was obtained; b. p. 158–165° (0.5 mm.). An analytical sample was collected at 160–161° (0.5 mm.).

Anal. Calcd. for $C_{15}H_{18}ON_2$: C, 74.35; H, 7.49. Found: C, 74.61; H, 7.33.

1-Methyl-3-ethyl-3-(2'-dihydroimidazolylmethyl)-oxindole.—By application of the fusion procedure of Oxley and Short[11] to 1-methyl-3-ethyl-3-cyanomethyloxindole the corresponding imidazoline was obtained (42%) by evaporation distillation at 95–130° (0.3 mm.) as a viscous oil which solidified on long standing, m. p. 93–97°.

Anal. Calcd. for $C_{15}H_{19}ON_3$: C, 70.01; H, 7.44. Found: C, 70.10; H, 7.41.

The picrate was recrystallized from ethanol; m. p. 181–182.5°.

Anal. Calcd. for $C_{15}H_{19}ON_3 \cdot C_6H_3O_7N_3$: C, 51.85; H, 4.56. Found: C, 52.15; H, 4.90.

1-Methyl-3-ethyl-3-[β-(2'-dihydroimidazolyl)-ethyl]-oxindole was prepared in the same way from the corresponding nitrile in 50% yield. The solid product, m. p. 178–180.5°, could not be obtained in analytical purity, but a **picrate**, m. p. 142.5–143.5°, served for identification.

Anal. Calcd. for $C_{16}H_{21}ON_3 \cdot C_6H_3O_7N_3$: C, 52.80; H, 4.83. Found: C, 52.83; H, 5.00.

1-Methyl-3-ethyl-3-[γ-(2'-dihydroimidazolyl)-propyl]-oxindole was prepared in the same way (76% yield): m. p. 101–103.5°, identified as the **picrate**, m. p. 177–178°.

Anal. Calcd. for $C_{17}H_{23}ON_3 \cdot C_6H_3O_7N$: C, 53.59; H, 5.28. Found: C, 53.57; H, 5.10.

Cyclization Experiments.—Attempts were made to carry out a cyclization of an acid chloride derived from 1-methyl-3-ethyl-3-(β-carboxyethyl)-oxindole with stannic chloride, aluminum chloride and aluminum bromide in various solvents. These were unsuccessful, although normal reactivity of the acid chloride was indicated by the fact that use of aluminum bromide and benzene gave a ketonic product, m. p. 87.5–89°, resulting from reaction with the solvent.

Anal. Calcd. for $C_{17}H_{23}O_3N$: C, 78.15; H, 6.89. Found: C, 78.01; H, 7.01.

The orange **2,4-dinitrophenylhydrazone** melted at 157–158°.

Anal. Calcd. for $C_{26}H_{25}O_6N_5$: C, 64.05; H, 5.17. Found: C, 63.92; H, 4.99.

A different cyclization procedure, applied to the formyl derivative obtained from the Claisen condensation of ethyl formate with the methyl ester of 1-methyl-3-ethyl-3-(β-carboxyethyl)-oxindole, was also unsuccessful.

These experiments were extended to the homologous acid, **1-methyl-3-ethyl-3-(γ-carboxypropyl)-oxindole**, m. p. 115–116.5° (*Anal.* Calcd. for $C_{15}H_{19}O_3N$: C, 68.94; H, 7.33. Found: C, 68.96; H, 7.21), without success.

Summary

The synthesis of 1-methyl-3-ethyl-3-(β-dimethylaminoethyl)-oxindole and related amines and imidazolines is described.

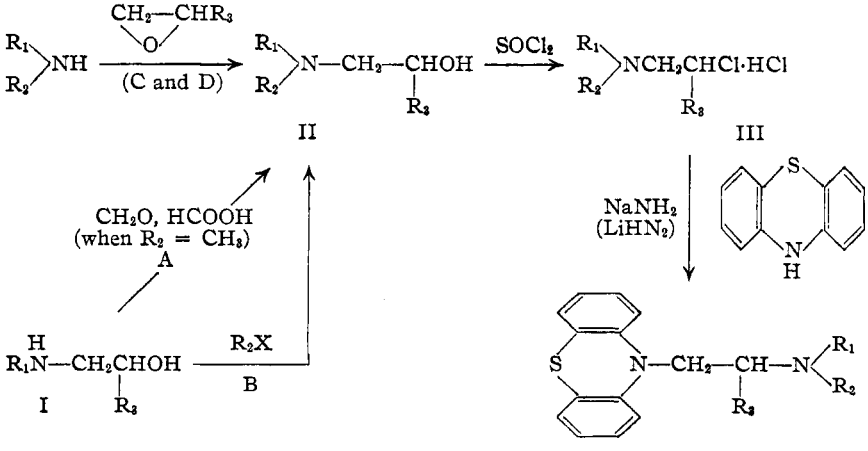
PHILADELPHIA, PENNA. RECEIVED JANUARY 29, 1950

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Histamine Antagonists. VII. Phenothiazine Derivatives[1]

BY JOHN B. WRIGHT, EDWARD H. LINCOLN, RICHARD V. HEINZELMANN AND JAMES H. HUNTER

A review[2–4] of the literature of antihistamine drugs reveals that the most active compounds possess the N-(β-dimethylaminoethyl) grouping.



Although such variations as N-(β-diethylaminoethyl), N-(β-piperidinoethyl), N-(β-morpholinoethyl), N-(β-pyrrolidinoethyl) and N-[(2-imidazolyl)-methyl] have been reported, it seemed to us that a systematic study was necessary to reveal the relationship between antihistaminic activity and this type of chemical structure. Therefore, a series of N-disubstituted aminoalkylphenothiazine derivatives has been prepared. These compounds, together with the results[5] of the screening for antihistaminic activity, are listed in Table III.

The amino alcohols (II) used in this work were prepared either by treatment of secondary amines with epoxides[6] (Procedures C and D) or from secondary aminoalcohols (I) by (a) reductive alkylation[7] (Procedure A); (b) alkyla-

(1) For previous papers in this series see Lincoln, Heinzelmann and Hunter, THIS JOURNAL, **71**, 2902 (1949).

(2) Huttrer, *Enzymologia*, **12**, 277 (1948).

(3) Viaud, *Technologie Produits Pharmaceutiques*, **2**, 53 (1947).

(4) Bovet and Bovet-Nitti, "Medicaments du Systeme Nerveau Vegetative," S. Karger, New York, N. Y., 1948, p. 741.

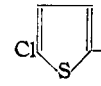
(5) For conducting these tests, grateful acknowledgment is made to Dr. Milton J. Vander Brook of our Department of Pharmacology and Endocrinology.

(6) Horne and Shriner, THIS JOURNAL, **54**, 2928 (1932).

(7) Clarke, Gillespie and Weisshaus, *ibid.*, **55**, 4571 (1933).

TABLE I

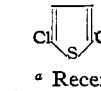
N-DISUBSTITUTED AMINOALKANOLS $HOCHCH_2N\langle^{R_1}_{R_2}$ (R₃ on CH)

R_1	R_2	R_3	B. p. °C.	Mm.	$n^{25}D$	Procedure	Yield, %	Formula	Nitrogen analyses, % Calcd.	Found
CH_3	$(CH_3)_2CH$	H	84	46	1.4379	A[a,b]	73	$C_6H_{15}NO$	11.95	11.89
CH_3	n-C_4H_9	H	97	39	1.4381	B	55	$C_7H_{17}NO$	10.68	10.77
CH_3	iso-C_4H_9	H	88	45	1.4302	B[c]	42	$C_7H_{17}NO$	10.68	10.69
CH_3	CH_2=$CHCH_2$	H	93	54	1.4523	B[d]	44	$C_6H_{13}NO$	12.16	12.29
C_2H_5	CH_2=$CHCH_2$—	H	74–74.5	15	1.4528	B[e]	60	$C_7H_{15}NO$	10.84	11.15
CH_2=$CHCH_2$—	CH_2=$CHCH_2$—	H	114–115	49	1.4671	C[f]	78	$C_8H_{15}NO$	9.92	9.64
CH_3	$(CH_3)_2CH$	CH_3	77	42	1.4242	A[b]	66	$C_7H_{17}NO$	10.68	10.69
n-C_3H_7	iso-C_3H_7	H	80.5–81	17	1.4390[g]	D[h]	59	$C_8H_{19}NO$	9.65	9.68
n-C_3H_7	CH_2=$CHCH_2$—	H	82–83.5	14	1.4550[g]	B[i]	40	$C_8H_{17}NO$	9.78	9.65
iso-C_3H_7	CH_2=CH—CH_2—	H	77.5–80	16	1.4551[g]	B[j]	53	$C_8H_{17}NO$	9.78	9.78
	n-C_3H_7	H	169–172	14	.....	B[k]	71	$C_{10}H_{16}ClNOS$	5.99	6.02

[a] This compound has been reported recently by Biel.[14] [b] Prepared by Robert D. Birkenmeyer. [c] Methylethanolamine and isobutyl iodide were used. [d] Methylethanolamine and allyl bromide were used. [e] Ethylethanolamine and allyl bromide were used. [f] This compound has been reported previously by Ladenburg, *Ber.*, **14**, 1879 (1881). [g] $n^{20}D$. [h] 2-Isopropylaminoethanol and propyl iodide were used. [i] 2-*n*-Propylaminoethanol and allyl bromide were used. [j] 2-Isopropylaminoethanol and allyl bromide were used. [k] 2-*n*-Propylaminoethanol and 5-chlorothenyl chloride were used.

TABLE II

N-DISUBSTITUTED AMINOALKYL CHLORIDES $ClCHCH_2N\langle^{R_1}_{R_2}$ (R₃ on CH) (or $ClCH_2CHN\langle^{R_1}_{R_2}$ (R₃ on CH))[a]

R_1	R_2	R_3	B. p. °C.	Mm.	Yield, %	Salt	M. p., °C.	Formula	Nitrogen analyses, % Calcd.	Found
CH_3	$(CH_3)_2CH$	H	61	30	50.7[b]	HCl[c]	122–124	$C_6H_{14}NCl$·HCl	8.14	8.27
C_2H_5[c]	$(CH_3)_2CH$[c]	H[c]	87–89	72	69[b]	Picrate[f]	116–118	$C_7H_{16}NCl$·$C_6H_3N_3O_7$	14.79	14.70
CH_3	$C_6H_5CH_2$	H	.....	..	94[d]	HCl[g]	140–141	$C_{10}H_{14}NCl$·HCl	6.36	6.70
CH_3	n-C_4H_9	H	.....	..	83[d]	HCl[h]	119–120	$C_7H_{16}HCl$·HCl	7.53	7.37
CH_3	iso-C_4H_9	H	.....	..	94[d]	Picrate[f]	113–114.5	$C_7H_{16}NCl$·$C_6H_3N_3O_7$	14.79	15.08
CH_3	CH_2=$CHCH_2$—	H	65	33	96[d]	HCl[i]	115–116	$C_6H_{12}NCl$·HCl	8.24	8.39
C_2H_5	CH_2=$CHCH_2$—	H	65	16	73[d]	HCl[j]	126–127.5	$C_7H_{14}NCl$·HCl	7.61	7.79
CH_2=$CHCH_2$—	CH_2=$CHCH_2$—	H	97	42	68.6[b]	HCl[k]	97.5–98.5	$C_8H_{14}NCl$·HCl	7.14	7.09
CH_3	$(CH_3)_2CH$	CH_3	88	77	80[b]	.....	.....	$C_7H_{16}NCl$	9.36	9.64
n-C_3H_7	n-C_3H_7	H	71.5–73.5	18	77[b]	HCl[i]	123–124	$C_8H_{18}NCl$·HCl	6.99	6.87
n-C_3H_7	iso-C_3H_7	H	72–73	20	66[b]	HCl[i]	172–173	$C_8H_{18}NCl$·HCl	6.99	7.03
n-C_3H_7	CH_2=$CHCH_2$—	H	69.5–71	15	93[b]	HCl[i]	115.5–116	$C_8H_{16}NCl$·HCl	7.07	7.07
iso-C_3H_7	iso-C_3H_7	H	66–67	13	45[b]	HCl[i]	132	$C_8H_{18}NCl$·HCl	6.99	6.83
iso-C_3H_7	CH_2=$CHCH_2$—	H	70	18	48[b]	HCl[i]	137–138	$C_8H_{16}NCl$·HCl	7.07	7.27
	n-C_3H_7	H	164–167	14	75[b]	HCl[i]	118–118.5	$C_{10}H_{15}NCl_2$·HCl	4.85	5.06

[a] Recent work [*cf.* Fuson and Zirkle, THIS JOURNAL, **70**, 2760 (1948); ref. (2)] indicates that either structure is possible. [b] Yield based upon the weight of distilled free base. [c] The requisite 2-isopropylethylaminoethanol was prepared by procedure B in 71% yield from 2-isopropylaminoethanol and ethyl iodide (b. p. 74° at 20 mm.). This alcohol has been reported previously by Brill [THIS JOURNAL, **54**, 2486 (1932)]. [d] Based on the weight of crude hydrochloride salt. [e] Recrystallized from methyl ethyl ketone–ethyl acetate (2:3). [f] Recrystallized from absolute ethanol. [g] Recrystallized from acetone–absolute ethanol (10:1). [h] Recrystallized from ethyl acetate–absolute ethanol (50:1). [i] Recrystallized from absolute ethanol–anhydrous ether. [j] Recrystallized from methyl ethyl ketone–ethyl acetate (4:1). [k] Recrystallized from ethyl acetate.

tion with the requisite halide (Procedure B). Procedures A and B were particularly convenient since the secondary amino alcohols were either commercially available[8] or readily prepared by the excellent method of Cope and Hancock.[9,10] Any unreacted secondary aminoalcohol present in Procedure B was separated from the desired product by acetylation and extraction of the acidified solution. The resulting tertiary aminoalcohols (II) are listed in Table I.

The conversion of the aminoalcohols to the corresponding chlorides (III) was effected with thionyl chloride. The aminoalkyl chlorides thus prepared are listed in Table II. They reacted

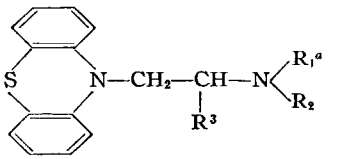
(8) The N-methylethanolamine and N-ethylethanolamine used in this work were obtained from Carbide and Carbon Chemicals Corp. and Sharples Chemicals, Inc., respectively.

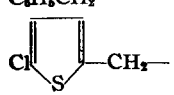
(9) Cope and Hancock, THIS JOURNAL, **64**, 1503 (1942).

(10) "Organic Syntheses," Vol. **26**, p. 38.

TABLE III

N-(DIALKYLAMINOALKYL)-PHENOTHIAZINES



R_1	R_2	R_3	B. p. °C.[b]	Mm.	Yield, %	M. p., °C. hydrochloride[b]	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	Activity[c]
CH_3	*iso*-C_3H_7	H	.....	...	86[d]	178–179[e]	$C_{18}H_{22}N_2S$·HCl	64.55	6.92	8.37	64.56	6.59	8.31	3
C_2H_5	*iso*-C_3H_7	H	168–172	0.1	41[f,g]	172.5–173.5[h]	$C_{19}H_{24}N_2S$·HCl	65.40	7.22	8.03	65.26	7.23	9.92	1/2
CH_3	$C_6H_5CH_2$	H	.....	...	49[d,g]	91.5– 92.5[i,j]	$C_{22}H_{22}N_2S$	76.26	6.40	8.09	76.53	6.48	8.13	<1/100
CH_3	*n*-C_4H_9	H	185–195	0.7	25[f,g]	142.5–144[k]	$C_{19}H_{24}N_2S$·HCl	65.40	7.22	8.03	65.50	7.03	7.79	1/3–1/2
CH_3	*iso*-C_4H_9	H	162–164	0.3	38[f]	153–154[k]	$C_{19}H_{24}N_2S$·HCl	65.40	7.22	8.03	65.24	7.07	7.96	1/5
CH_3	CH_2=$CHCH_2$—	H	187–190	1.0	68[f]	178–179[l]	$C_{18}H_{20}N_2S$·HCl	64.94	6.36	8.42	65.01	6.11	8.58	1 1/2–2
C_2H_5	CH_2=$CHCH_2$—	H	165–185	0.1	68[f]	126.5–127.5[m]	$C_{19}H_{22}N_2S$·HCl	65.78	6.68	8.08	66.02	6.60	7.91	1/4
CH_2=$CHCH_2$—	CH_2=$CHCH_2$—	H	220–223	2.6	42[f]	125–126[k]	$C_{20}H_{22}N_2S$·HCl	66.92	6.46	7.81	66.89	6.43	7.76	<1/200
CH_3	*iso*-C_3H_7	CH_3	.....	...	51	69.5– 70[i,n]	$C_{19}H_{24}N_2S$	73.03	7.74	8.97	72.90	7.51	9.90[p]	1
n-C_3H_7	*n*-C_3H_7	H	204–207	0.5	59[f]	171–172[q]	$C_{20}H_{26}N_2S$·HCl	66.20	7.50	7.72	66.19	7.72	7.98	<1/2, >1/20
n-C_3H_7	*iso*-C_3H_7	H	203–209	0.7	73[f]	202.5[q]	$C_{20}H_{26}N_2S$·HCl	66.20	7.50	7.72	66.30	7.46	8.14	<1/10
n-C_3H_7	CH_2=$CHCH_2$—	H	212.5–216.5	0.5	68[f]	146–148[q]	$C_{20}H_{24}N_2S$·HCl	66.55	6.98	7.76	66.44	6.87	7.80	<1/20
iso-C_3H_7	*iso*-C_3H_7	H	180–181	0.5	45[f]	197.5–199[q]	$C_{20}H_{26}N_2S$·HCl	66.20	7.50	7.72	65.97	7.33	8.04	1/10
iso-C_3H_7	CH_2=$CHCH_2$—	H	212–213	0.9	55[f]	170–171[q]	$C_{20}H_{24}N_2S$·HCl	66.55	6.98	7.76	66.54	6.81	7.80	<1/2, >1/20
$C_6H_5CH_2$—	$C_6H_5CH_2$—	H	.....	...	..	200[q]	$C_{28}H_{26}N_2S$·HCl	73.26	5.93	6.10	73.55	5.91	6.14	..[t]
	*n*-C_3H_7	H	.....	...	51[r]	147.5–148.5[s]	$C_{22}H_{23}N_2ClS_2$·HCl	58.53	5.36	6.21	58.55	5.12	6.14	..[t]

Standards for Comparison

β-Dimethylaminoethyl benzhydryl ether hydrochloride	1
N-(2-Dimethylaminoethyl)-phenothiazine hydrochloride (3015 RP)[u]	3–5
N-(2-Pyrrolidinoethyl)-phenothiazine hydrochloride (Pyrrolazote)	4–5

[a] The 2-dialkylamino-1-propyl structure (when R^3=CH_3) is assigned rather than the 1-dialkylamino-2-propyl- structure because of the analogy to the structure of N-(2-dimethylamino-1-propyl)-phenothiazine (3277 RP), prepared by the same general method *cf.* Charpentier, *Compt rend.*, 225, 306 (1947). [b] Uncorrected. [c] These tests were carried out on isolated guinea pig intestinal strip. [d] Based on the amount of crude hydrochloride salt. [e] Recrystallized from ethyl acetate–absolute ethanol (2:1). [f] Based on the yield of distilled product. [g] Lithium amide was used instead of sodium amide. [h] Recrystallized from isopropyl alcohol-isopropyl ether. [i] Melting point of the free base. [j] Recrystallized from methanol. [k] Recrystallized from acetone. [l] Recrystallized from ethyl acetate–isopropyl alcohol (2:1). [m] Recrystallized from ethyl acetate–acetone (10:1). [n] Recrystallized from ethanol. [p] Calcd. for S, 10.26. Found: S, 10.17. [q] Recrystallized from ethanol–ether. [r] Yield based on the weight of undistilled free base. [s] Recrystallized from methanol–acetone–ether mixture (1:1:5). [t] Not tested because of the extreme insolubility of the compound in water. [u] N-(2-Dimethylaminopropyl)-phenothiazine hydrochloride (3277 R. P.) has been reported to have an activity of 2.7 (Marsh, paper presented at the meeting of the American Society for Pharmacology and Experimental Therapeutics, Indianapolis, Ind., Nov. 17–19, 1949.

with phenothiazine in the presence of sodamide (or lithium amide), according to known procedures.[11]

The introduction of groups larger than methyl on the terminal amino nitrogen does not increase the effectiveness of these phenothiazine derivatives as antihistamines; more often the activity is lowered as is shown in Table III.

Experimental[12,13]

Procedure A. N-Isopropyl-N-methylethanolamine was prepared by treatment of 2-isopropylaminoethanol[10] with formic acid and formaldehyde according to the method of Biel.[14]

Procedure B. N-(*n*-Butyl)-N-methylethanolamine.—A mixture of 49.8 g. (0.664 mole) of methylethanolamine,[8] 61.1 g. (0.332 mole) of *n*-butyl iodide and 200 ml. of dry benzene was refluxed for three hours. When cool, the mixture was transferred to a separatory funnel, the upper benzene layer separated and the lower layer extracted with benzene. The benzene extracts were combined and the solvent removed through a short Vigreux column. To the residue was added 75 ml. of acetic anhydride, the solution heated on the steam-bath for two hours and, when cool, poured into 500 ml. of a 5% hydrochloric acid solution. The resulting solution was extracted with ether and these ethereal extracts discarded. The acid extract was basified with solid potassium carbonate, a large excess being added to saturate the solution, and the resulting mixture extracted with ether. The ether was removed and the residue refluxed for five hours with 25% sodium hydroxide solution. The resulting mixture was extracted with ether, the extracts dried over anhydrous magnesium sulfate, the solvent removed and the residue distilled *in vacuo;* yield 23.9 g. (55%), b. p. 97° (39 mm.).

Procedure C. β-Diallylaminoethanol.—The general method of Horne and Shriner[6] was employed using 48.6 g. (0.5 mole) of diallylamine[15] and 29.3 g. (0.67 mole) of ethylene oxide; yield, 54.8 g. (78%), b. p. 114–115° (49 mm.).

Procedure D. N-Isopropyl-N-(*n*-propyl)-ethanolamine.—Procedure B was modified in that 30.9 g. (0.30 mole) of 2-isopropylaminoethanol, 63.6 g. (0.60 mole) of anhydrous sodium carbonate, 53.6 g. (0.315 mole) *n*-propyl iodide and 40 ml. of xylene were refluxed together for five hours. When cool, the reaction mixture was filtered. To the filtrate was added 50 ml. of acetic anhydride, the solution heated on the steam-bath for one hour and then worked up as described in Procedure B; yield, 25.5 g. (59%), b. p. 80.5–81° (17 mm.).

β-(Ethylisopropylamino)-ethyl Chloride.—To a stirred solution of 29.8 g. (0.25 mole) of thionyl chloride in 60 ml. of dry benzene cooled in an ice-bath was added, dropwise, 26.2 g. (0.2 mole) of N-ethyl-N-isopropylethanolamine. The mixture was heated under reflux for two hours and the benzene and excess thionyl chloride removed by distillation, the last traces being removed *in vacuo.* The residue was dissolved in a small amount of water, the solution filtered, the filtrate extracted once with ether and the ethereal extract discarded. The aqueous extract was basified with potassium carbonate, a large excess being added to saturate the solution. The mixture was extracted with ether, the ethereal extracts dried over anhydrous magnesium sulfate, the ether removed and the residue distilled *in vacuo* through a Vigreux column; yield, 20.6 g. (69%); b. p. 87–89° (72 mm.). The freshly distilled product very slowly precipitates long thin needles of the cyclic dimer. By the same general procedure all of the compounds reported in Table II were prepared.

N-[β-Isopropylmethylamino)-ethyl]-phenothiazine Hydrochloride.—The general method for the preparation of N-(alkylaminoalkyl)-phenothiazines previously reported[11a] was employed using equivalent amounts of β-(isopropylmethylamino)-ethyl chloride and sodamide.[16]

All of the compounds reported in Table III were prepared by this general procedure. In several instances toluene was used in place of xylene as a solvent with corresponding longer reflux times (eight to twenty-four hours).

Summary

1. Nine new 2-disubstituted aminoalcohols and fifteen new 2-disubstituted aminoalkyl chlorides have been prepared.

2. Sixteen new N-disubstituted aminoalkylphenothiazines have been prepared.

3. The results of preliminary pharmacological tests on these phenothiazine derivatives for antihistaminic activity is reported.

(11) (a) British Patent 608,208; (b) Reid, Wright, Kolloff and Hunter, THIS JOURNAL, **70**, 3100 (1948); (c) Dahlbom, *Acta Chem. Scand.*, **3**, 247 (1949); (d) French Patent 917,595.

(12) All melting points and boiling points are uncorrected.

(13) Appreciation is expressed to Mr. Harold C. Emerson and his staff for analyses reported.

(14) Biel, THIS JOURNAL, **71**, 1308 (1949).

(15) "Organic Syntheses," Coll. Vol. I, 1944, p. 201.

(16) Vaughn, Vogt and Nieuwland, THIS JOURNAL, **56**, 2120 (1934).

KALAMAZOO, MICHIGAN RECEIVED JANUARY 23, 1950

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Synthesis of Some β-Aminoethyldiazines as Histamine Analogs

BY REUBEN G. JONES, EDMUND C. KORNFELD AND KEITH C. MCLAUGHLIN

The histamine-like activities of a number of β-aminoethyl heterocyclic nitrogen compounds were reported[1] recently. Among this group were 2-β-aminoethylquinoxaline, 2-β-aminoethylpyrazine, 3-β-aminoethylpyridazine and the 2- and 4-β-aminoethylpyrimidines. These compounds, presented in Table I, were synthesized by the same general procedure, and it is the purpose of this paper to describe their preparation.

After considering a number of possible synthetic routes, a method similar to that used by Walter, Hunt and Fosbinder for the preparation of 2-β-aminoethylpyridine[2] appeared to be the most promising. The method is outlined in the accompanying sequence of reactions.

$$RCH_3 + CCl_3CHO \xrightarrow[\Delta]{\text{Pyridine}}$$

$$\underset{\text{I}}{RCH_2CHOHCCl_3} \xrightarrow{NaOH} \underset{\text{II}}{RCH{=}CHCO_2H} \xrightarrow[Ni]{(H)}$$

(1) Lee and Jones, *J. Pharmacol.*, **95**, 71 (1949).

(2) Walter, Hunt and Fosbinder, THIS JOURNAL, **63**, 2771 (1941).