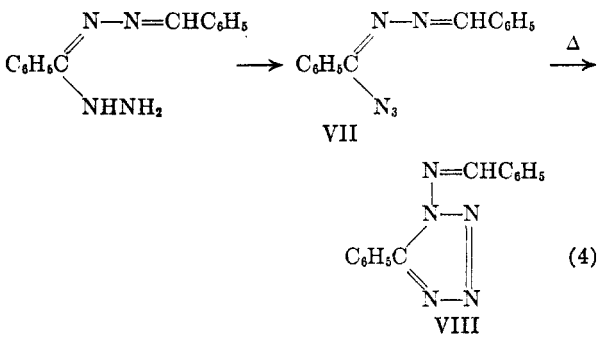
The following table summarizes the conclusions from this study.

TABLE I

R	Ref.	Structure of the Stable Product
H	[a]	T
C_6H_5	[b]	T
CH_3	[c]	T
OH[d]	[e,f]	A
OCH_3	[g]	A
$OCOC_6H_5$	[e]	A
$-N{=}CHC_6H_5$	[h,i]	A → T

[a] A. Pinner, *Ber*, **27**, 984 (1894).
[b] G. Schroeter, *Ber.*, **42**, 3356 (1909).
[c] J. v. Braun and W. Rudolph, *Ber.*, **74**, 264 (1941).
[d] The azide structure could also be confirmed in oxazidoxime (III).
[e] See ref. 7. [f] See ref. 8.
[g] Prepared from phenylazidoxime with diazomethane.
[h] R. Stollé and E. Helwerth, *Ber.*, **47**, 1132 (1914).
[i] R. Stollé and A. Netz, *Ber.*, **55**, 1297 (1922).

In all cases, except the last one, only the indicated structure is stable; Stollé[15,16] had already shown that when R = $-N=CHC_6H_5$, a stable azide (VII) could be formed which on heating in a neutral solvent isomerizes to the tetrazole (VIII):



(4)

No such isomerization occurs with azidoximes or their *O*-substituted derivatives.

Azidoximes are in fact surprisingly stable. Although they may be detonated, they can be recrystallized from boiling alcohol and several can be heated to 200° before exploding. This stability is doubtless linked to the electron donating power of the R group.

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(15) See footnote *h*, Table I.
(16) See footnote *i*, Table I.

Quinoxalines. II. Basic Ethers from 2-Chloroquinoxaline[1,2]

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The pharmacological activity of many aromatic and heteroaromatic compounds which have a tertiary amine function in a side chain linked through an ether, ester, or amide linkage prompted the synthesis of this series of quinoxaline ethers and their salts.

2-Chloroquinoxaline was allowed to react with the sodio derivative of the tertiary amino alcohol in anhydrous benzene solution. The yields of the ethers after purification by distillation under reduced pressure are high. These yields are somewhat higher than the corresponding 4-cinnoline ethers.[4] It seems likely that this is due to the greater stability of 2-chloroquinoxaline under the conditions of the reaction.

The ethers and their salts which were prepared are listed in Table I.

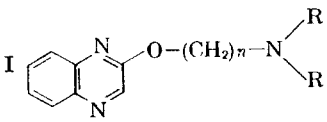
The pharmacological testing was performed in the Smith Kline and French Laboratories. Compounds II, III, IV, V and IX were found to be inactive in the Plasma Cholesterol Lowering Test. Compounds III, V, and IX were found to be inactive as diuretics. Compounds IV and IX were found to possess slight central nervous system depression in rats. Compounds II, III, V, VI, and IX all produced more than 93% inhibition of cholesterol biosynthesis at a concentration of $10^{-3}M$. Compound IV produced a 37% inhibition at a concentration of $10^{-3}M$. All inhibitions dropped to less than 11% at a concentration of $10^{-5}M$ except Compound VI which exhibited a 49% inhibition at this concentration. Screening data on the other compounds are not yet available.

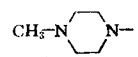
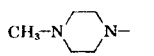
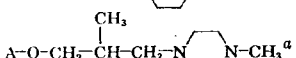
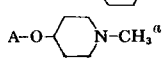
EXPERIMENTAL[5]

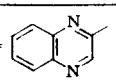
2-Chloroquinoxaline. The procedure of Gowenlock, Newbold, and Spring[6] was improved by using a mixture of phosphorus oxychloride and phosphorus pentachloride. A mixture of 17 g. of 2-hydroxyquinoxaline, 23 g. of phosphorus pentachloride, and 34 ml. of phosphorus oxychloride was

(1) For Paper I in this series see R. N. Castle, A. Aldous, and C. Moore, *J. Org. Chem.*, **21**, 139 (1956).
(2) The authors are grateful to Dr. S. Yamada and to Dr. K. Abe of the Tanabe Seiyaku Co., Ltd., Tokyo, Japan for the carbon, hydrogen, and nitrogen analyses.
(3) Smith Kline and French Laboratories Post-doctoral Research Fellow, 1958–60. Present address: Tokyo Research Laboratory, Tanabe Seiyaku Co., Ltd., Toda-Cho, Saitama-Ken, Japan.
(4) R. N. Castle and M. Onda, unpublished data.
(5) All melting points are uncorrected. The infrared spectra of all of the free bases were determined on a Perkin-Elmer Infracord.
(6) A. H. Gowenlock, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, 622 (1945).

TABLE I



No.	n	R N— R	B.P.	mm.	M.P.	Yield, %	Salt	Formula	M.P.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Description of Salt and Solvent Used for Crystallization
I	2	CH_3 N— CH_3	112–114	0.005		91	Acidic *d*-tartrate	$C_{16}H_{21}N_3O_7$	123–125	52.31	5.76	11.44	52.44	5.71	11.47	Colorless granules, ethanol
II	2	C_2H_5 N— C_2H_5	120–123	0.015		96	Acidic citrate	$C_{20}H_{27}N_3O_8$	140–141	54.90	6.22	9.60	54.86	6.13	9.34	Colorless needles, ethanol
III	2		149–152	0.025	63–64	87	Acidic citrate	$C_{21}H_{27}N_3O_8$	108–110	56.11	6.05	9.35	56.26	5.95	8.97	Colorless needles, ethanol
IV	2		150–153	0.025	76–78	90	Acidic succinate	$C_{18}H_{32}N_3O_6$	99–100	57.28	6.14	11.13	57.66	5.99	10.97	Colorless granules, ethanol
V	2		146–148	0.01	61–62	87	Diacidic *dl*-malate	$C_{23}H_{32}N_4O_{11}$	142–144	51.10	5.95	10.36	51.25	5.53	10.36	Colorless needles, ethanol
VI	3	CH_3 N— CH_3	143–146	0.02		96	Acidic *d*-tartrate	$C_{10}H_{23}N_3O_7$	133–135	53.53	6.07	11.02	53.26	6.10	10.99	Colorless granules, ethanol
VII	3	C_2H_5 N— C_2H_5	134–137	0.02		89	Acidic citrate	$C_{21}H_{29}N_3O_8$	159–161	55.87	6.47	9.31	55.31	6.37	9.42	Colorless needles, ethanol
VIII	3		164–168	0.02	90–92	94	Diacidic *d*-tartrate	$C_{24}H_{34}N_4O_{15}\cdot 2H_2O$	168–170	47.68	5.95	9.27	47.94	5.59	9.68	Colorless granules, ethanol
IX			147–149	0.005		95	Diacidic *dl*-malate	$C_{25}H_{36}N_4O_{11}$	116–118	52.81	6.38	9.85	53.45	6.25	9.97	Colorless needles, ethanol
X			145–148	0.005	86–87	91	Acidic *d*-tartrate	$C_{18}H_{23}N_3O_7$	148–150	54.97	5.90	10.68	55.03	5.80	10.53	Colorless granules, ethanol

[a] A = 

allowed to reflux for 20 min. at 120–130° (oil bath). The mixture was allowed to cool, poured into 400 g. of crushed ice containing 160 ml. of water, and extracted with ether. The ether solution was washed with dilute sodium carbonate solution and then with water, dried, and the ether removed by evaporation. The residue was distilled at 104–107° at 0.25 mm. There was obtained 18.1 g. (94%) of colorless needles, m.p. 47–48°.

Preparation of the 2-quinoxalyl tertiary aminoalkyl ethers. The procedure is illustrated with the synthesis of 2-β-dimethylaminoethoxyquinoxaline. To a solution of 6.5 g. of β-dimethylaminoethanol in 50 ml. of anhydrous benzene was added 0.83 g. of sodium metal and the mixture was allowed to reflux on a steam bath for 1 hr. until all the sodium was dissolved. After cooling in an ice bath, 5.0 g. of 2-chloroquinoxaline was added and the mixture was allowed to reflux for 4 hr. The mixture was diluted with ether and washed with water. After drying and removal of solvents by evaporation, the residue was distilled. There was obtained 6.0 g. (91%) of a light yellow oil, boiling at 112–114° at 0.005 mm.

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3-Methyl-8-nitroisoquinoline[1]

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The nitration of isoquinoline has been shown[2] to give 5-nitroisoquinoline as a major product and 8-nitroisoquinoline as a minor product. A methyl group in the 3-position of isoquinoline would not be expected to alter the orientation appreciably and in fact two products, m.p. 109–110° (major product) and m.p. 85–90° (minor product), have been reported from the nitration of 3-methylisoquinoline.[3,4]

Elderfield and co-workers[4] demonstrated that the major product (m.p. 109–110°) of this nitration was indeed 3-methyl-5-nitroisoquinoline by oxidation to the carboxylic acid followed by decarboxylation to 5-nitroisoquinoline. At that time no attempt was made to prove the structure of the minor product from the nitration reaction although it was presumed to be 3-methyl-8-nitroisoquinoline. The earlier workers[3] had considered that the two products might be isomers or that they might be different crystalline modifications of the same substance since amines of identical melting points and mixed melting point were formed on reduction.

Since we required various nitroisoquinolines for several projects in progress in this laboratory, it was decided to investigate the structure of the minor nitration product of 3-methylisoquinoline. In order to determine if the nitration products were isomers or crystalline modifications they were converted to the picrates. 3-Methyl-5-nitroisoquinoline picrate melted sharply at 190–191° without recrystallization while the picrate of the minor product had m.p. 177–186°. Several recrystallizations gave a m.p. 185–187° and a mixed melting point with 3-methyl-5-nitroisoquinoline picrate of 178–188°. These results indicate that while the minor product might contain some 3-methyl-5-nitroisoquinoline it did contain a second substance.

Oxidation of the 3-methylnitroisoquinoline, m.p. 89–91°, with selenium dioxide gave a crude aldehyde which was not purified but rather oxidized in the crude state to a nitroisoquinoline-3-carboxylic acid. The use of hydrogen peroxide, as described for the oxidation of isoquinoline-3-carboxaldehyde,[5] gave somewhat better results than the use of sodium dichromate.[4] When the crude carboxylic acid was heated above its melting point *in vacuo* fine light yellow needles of 8-nitroisoquinoline sublimed indicating that the minor nitration product was, at least in part, 3-methyl-8-nitroisoquinoline.

EXPERIMENTAL[6]

Selenium dioxide oxidation. A solution of 8.66 g. of the minor product from the nitration of 3-methylisoquinoline,[3,4] m.p. 89–91°, in 130 ml. of nitrobenzene was added slowly with agitation to a suspension of 6.5 g. of selenium dioxide in 60 ml. of nitrobenzene. During the addition the mixture was brought to reflux and refluxing was continued for 1.5 hr. After cooling, the solution was washed with 100 ml. of 5% sodium hydroxide solution and 100 ml. of water and then extracted with five 50-ml. portions of 10% hydrochloric acid. The acid extracts were neutralized with 20% sodium hydroxide solution, chilled, and filtered. The filtrate was extracted with chloroform and the filter cake was leached with chloroform. Concentration of the combined chloroform solutions gave 2.6 g. of solid, m.p. 140–160° which gave positive tests with 2,4-dinitrophenylhydrazine and had an infrared spectrum indicating a mixture of aldehyde and unoxidized methyl compound.

Hydrogen peroxide oxidation. An acetone solution of 1 g. of the crude aldehyde prepared above and 3 ml. of hydrogen peroxide (30%) was allowed to stand several hours at room temperature. An additional 5 ml. of hydrogen peroxide was added and the solution allowed to stand overnight. Partial evaporation and filtration gave a solid. A solution of this solid percarboxylic acid was boiled in water for an hour. Upon partial evaporation and cooling about 0.8 g. of crude carboxylic acid, m.p. 230–240° was obtained.

(1) This investigation was supported in part by funds from an Institutional Grant of the American Cancer Society to the University of Miami, in part by Research Grant CY 4814 from the National Cancer Institute, U.S. Public Health Service, and in part by a grant from the Research Corporation.

(2) M. J. S. Dewar and P. M. Maitlis, *J. Chem. Soc.*, 2521 (1957).

(3) F. W. Bergstrom and R. E. Patterson, *J. Org. Chem.*, 10, 479 (1945).

(4) R. C. Elderfield, J. M. Lagowski, O. L. McCurdy, and S. L. Wythe, *J. Org. Chem.*, 23, 435 (1958).

(5) C. E. Teague, Jr., and A. Roe, *J. Am. Chem. Soc.*, 73, 688 (1951).

(6) All melting points are uncorrected.