chloride *in vacuo* followed by recrystallization of the residue from benzene gave 1.56 g. (74%) of the carbomethoxy derivative (XLVI), m.p. 153–157°, in two crops; $\lambda_{max(\mu)}^{KBr}$ 5.76 (ester C=O), 6.11 (lactam C=O and aryl), 6.22 (C=C), 11.32 (1,2,4,5-tetrasubstituted benzene).

Anal. Calcd. for $C_{14}H_{18}NO_3$: C, 68.6; H, 6.16; N, 5.71. Found: C, 68.6; H, 6.21; N, 5.64.

Ethyl 1,2-dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XLVII) was prepared in 78% yield, m.p. 105,–109°, by the procedure described for the carbomethoxy derivative (XLVI).

Recrystallization from benzene–Skellysolve B[5] raised the melting point to 109–110°; $\lambda_{max(\mu)}^{KBr}$ 5.78 (ester C=O), 5.90, 6.07 (lactam C=O); $\lambda_{max(m\mu)}^{pH\ 1}$ 359 (ε 7400), $\lambda_{max(m\mu)}^{pH\ 7}$ 362 (ε 7400), $\lambda_{max(m\mu)}^{pH\ 13}$ 338 (ε 8200).

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.5; H, 6.61; N, 5.40. Found: C, 69.2; H, 6.70; N, 5.24.

1,2-Dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylic acid, hydrazide (XLV). A solution of 0.117 g. (4.5 mmoles) of ethyl 1,2-dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XLVII) in 1.2 ml. of methanol was treated with 0.5 ml. of hydrazine hydrate. After about 3 min., a crystalline precipitate separated. The resulting mixture was heated on a steam bath for 1 min., then diluted with 10 ml. of water. The crystalline precipitate was filtered, then dried to yield 0.105 g. (95%), m.p. 215.0–215.5°; $\lambda_{max(\mu)}^{KBr}$ 3.07 (NH), 6.02 (C=O); $\lambda_{max(m\mu)}^{pH\ 1}$ 365 (ε 7370), $\lambda_{max(m\mu)}^{pH\ 7}$ 360 (ε 8800), $\lambda_{max(m\mu)}^{pH\ 13}$ 354 (ε 7860).

Anal. Calcd. for $C_{15}H_{15}N_3O_2$: C, 63.6; H, 6.16; N, 17.1. Found: C, 63.7; H, 6.32; N, 17.0.

2,10-Dihydro-2-imino-7,8,10-trimethylpyrimido[4,5-b]-quinoline-4(3H)one (L) *acetate.* A mixture of 290 mg. (3.06 mmoles) of guanidine hydrochloride, 500 mg. (2.04 mmoles) of methyl 1,2-dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XLVI), and 6 ml. of 1*N* methanolic sodium methoxide was refluxed for 3 hr., then cooled and diluted with 25 ml. of water and 5 ml. of saturated aqueous sodium bicarbonate. The precipitate was filtered and washed with water, then dried to give 230 mg. of crude L as a yellow solid.

The acetate salt of L was prepared by heating 50 mg. of the above yellow solid in 30 ml. of 85% acetic acid on a steam bath for 30 min. After being allowed to cool, the supernatent liquid was separated by centrifugation and the solid was dried; yield 48 mg. of yellow solid, m.p. >300°, which was homogeneous on paper chromatography in solvent B[10] with R_f 0.57.

Anal. Calcd. for $C_{14}H_{14}N_4O \cdot HC_2H_3O_2$: C, 61.1; H, 5.77; N, 17.8. Found: C, 61.0; H, 5.62; N, 17.5.

Acknowledgment. The authors wish to thank Dr. Peter Lim for interpretation of the infrared absorption spectra and his staff for the paper chromatography. The authors are also indebted to Mr. O. P. Crews, Jr., and his staff for large-scale preparation of certain intermediates.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WASHINGTON UNIVERSITY]

Synthesis and Reactions of Monosubstituted Triptych-Boroxazolidines[1]

ALFRED A. SCHLEPPNIK[2] AND C. DAVID GUTSCHE

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The synthesis of a series of 3-alkyl, 3-aryl, 3-alkoxymethyl, and 3-dialkylaminomethyltriptych-boroxazolidines has been carried out. In addition, several triptychboroxazolidines carrying reactive functional groups at the 3-position have been prepared including the 3-chloromethyl, 3-hydroxymethyl, 3-aminomethyl, and 3-cyanomethyl compounds. Certain of the reactions of the 3-chloromethyl and 3-aminomethyltriptych-boroxazolidines have been investigated with particular reference to the linking of an amino acid moiety to the triptych-boroxazolidine moiety. Although the chloromethyl compound proved to be of limited use in this respect, the aminomethyl compound has provided a boron-containing amino acid, a compound of possible interest in cancer chemotherapy.

The suggestion by Kruger that the neutron-induced disintegration of boron should be applicable to cancer chemotherapy[3] and the demonstration by Christensen *et al.*[4] that some of the amino acids selectively concentrate in certain tumor cells provided the incentive to investigate the synthesis of boron-containing amino acids.[5] The present work involves certain aspects of the chemistry of the triptych-boroxazolidine type of compound[6] and had as its aim the incorporation of this moiety in an amino acid. Triethanolamine borate (I), the simplest triptych-boroxazolidine, was reported first in 1933 in a German patent[7] and investigated in much more detail by Brown and Fletcher[8] and by Hein and Burckhardt.[9] It is with monosubstituted triethanolamine borates that the present paper is concerned, although from the standpoint of a therapeutic agent the triethanolamine borate ring is not the most desirable,

(1) This work was supported, in part, by grant no. CY-3275 from the National Institutes of Health.

(2) Postdoctoral Research Associate 1958–1959.

(3) P. G. Kruger, *Proc. Natl. Acad. Sci.*, **26**, 181 (1940).

(4) H. N. Christensen and T. R. Riggs, *J. Biol. Chem.*, **194**, 57 (1952); H. N. Christensen, T. R. Riggs, H. Fischer, and I. M. Palatine, *J. Biol. Chem.*, **198**, 1, 17 (1952); T. R. Riggs, B. A. Coyne, and H. N. Christensen, *J. Biol. Chem.*, **209**, 395, 413 (1954).

(5) For another recent report of the synthesis of a boron-containing amino acid *cf.* H. R. Snyder, A. J. Reedy, and W. J. Lennarz, *J. Am. Chem. Soc.*, **80**, 835 (1958).

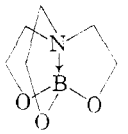
(6) This nomenclature is that suggested in the "Preliminary Report of the Advisory Committee on the Nomenclature of Organic Boron Compounds."

(7) C. A. Rojahn, DRP 582,149 (Cent., 1933, II, 2704).

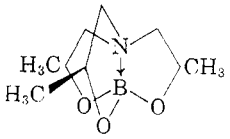
(8) H. C. Brown and E. A. Fletcher, *J. Am. Chem. Soc.*, **73**, 2808 (1951).

(9) F. Hein and R. Burckhardt, *Z. Anorg. u. Allg. Chem.*, **268**, 159 (1952).

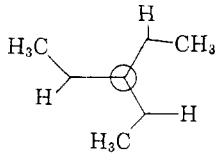
as it undergoes fairly rapid hydrolysis. Much more stable is tripropanolamine borate, which has half life in water at 25° of 618 days, over 10^5 greater than the half life of triethanolamine borate.[10] Even in the symmetrically-substituted compound, however, the possibility of diastereoisomers exists (IIa and IIb) and, in fact, Steinberg and Hunter[10] obtained evidence for two species in their tripropanolamine borate preparation, one considerably more rapidly hydrolyzed than the other. The species were not identified, but they may possibly be the two diastereoisomeric forms of II(*a* and *b*). The substitution of another group for one of the methyl groups in II obviously complicates the isomer problem further, and for this



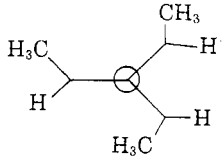
I



II

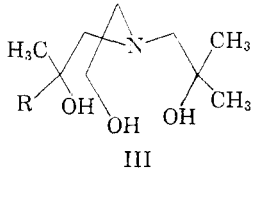


IIa

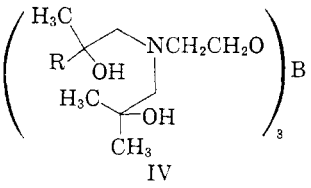


IIb

reason the initial studies avoided unsymmetrically-polysubstituted triptychboroxazolidines. It had been hoped that both the isomer problem and the hydrolysis problem could be circumvented by using *gem*-dimethyl compounds. Unfortunately, trialkanolamines containing *gem*-dimethyl groups (III) did not yield triptych compounds but gave instead what are thought to be noncyclic borate esters of structure IV. For these reasons the initial



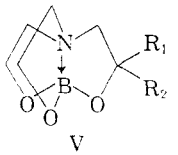
III



IV

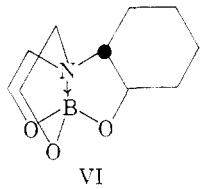
work in this laboratory has been conducted on the simplest members of the series, *viz.*, the monosubstituted triptych-boroxazolidines.

Alkyl and aryl-substituted triptych-boroxazolidines. Although it is possible to obtain the triptych compounds from boric acid and the appropriate trialkanolamine, the preparation proceeds more smoothly and with fewer complications[11] when a boric acid ester is employed. In the present instance, tri-*n*-butyl borate was generally used as the boronating agent, and the *n*-butylalcohol which was formed was removed by distillation. In this fashion compounds of structure V, VI, and VII were prepared, the products in all cases being rather high-melting, crystalline solids soluble in acetonitrile and dimethylformamide, less soluble in chloroform, and insoluble in ether, petroleum ether, dioxane

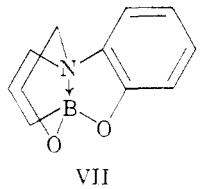


V

a. R_1 = H, R_2 = CH_3
b. R_1 = H, R_2 = C_2H_5
c. R_1 = H, R_2 = $CH{=}CH_2$
d. R_1 = H, R_2 = C_6H_5
e. R_1 = R_2 = CH_3



VI



VII

tetrahydrofuran, etc. The requisite trialkanolamines for compounds of structure V and VI were prepared from diethanolamine and the appropriate epoxide, the reaction being conducted in most cases in chloroform with a trace of water or ethanol as catalyst.[12] The starting material for VII was obtained from *o*-aminophenol and excess ethylene oxide.[13]

Alkoxy-substituted triptych-boroxazolidines. Using boron trifluoride as a catalyst[14] alcohols were condensed with epichlorohydrin to yield 1-alkoxy-2-hydroxy-3-chloropropanes which were then converted to the corresponding epoxides by the action of sodium hydroxide.[15] Using the same sequence of reactions as described above, compounds of structure VIII were prepared. These materials are lower-melting than the alkyl- and aryl-substituted analogs (V, VI, VII) and are soluble in benzene. Of particular interest in this group is 3-diethoxymethyltriptych-boroxazolidine (VIIIe), which was prepared[16] from acrolein diethyl acetal by conver-

(10) H. Steinberg and D. L. Hunter, *Ind. and Eng. Chem.*, **49**, 174 (1957).

(11) As Hein and Burckhardt observed, the use of boric acid often leads to the formation of a low-melting, extremely hygroscopic by-product which makes the purification of the triptych compound difficult. These authors suggested that this by-product was a boric acid salt of the triptych compound. On the basis of the similarity of the infrared spectrum of the by-product with that of the polymer derived from chloromethyltriptych-boroxazolidine (*cf.* later section) and with the knowledge that esters containing free B—OH groups are exceedingly susceptible to hydrolysis, it seems equally likely that the by-product is a cross-linked polymeric boric acid ester containing free B—OH groups.

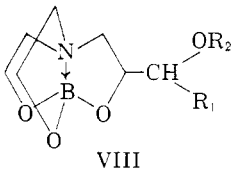
(12) J. W. Headlee, A. R. Collett, and C. L. Lazzell, *J. Am. Chem. Soc.*, **55**, 1066 (1949).

(13) I. G. Farben, DRP 296,309 (1927).

(14) *Cf.* E. Levas and H. Lefebvre, *Compt. rend.*, **222**, 555, 1439 (1946) for the use of boron trifluoride in similar condensations involving phenols.

(15) H. Flores-Gallardo and C. B. Pollard, *J. Org. Chem.*, **12**, 831 (1947).

(16) J. E. Wuller, masters thesis, Washington University, 1957.

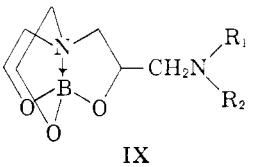


VIII

a. $R_1 = H$, $R_2 = CH_3$
b. $R_1 = H$, $R_2 = C_2H_5$
c. $R_1 = H$, $R_2 = CH_2CH{=}CH_2$
d. $R_1 = H$, $R_2 = CH_2C_6H_5$
e. $R_1 = OC_2H_5$, $R_2 = C_2H_5$

sion to the corresponding epoxide *via* the chlorohydrin, reaction of the epoxide with diethanolamine, and boronation with boric acid to VIIIe.

Dialkylamino and alkylarylamino-substituted triptych-boroxazolidines. The action of secondary amines on epichlorohydrin followed by treatment with base[17] yielded 1-dialkylamino-2,3-epoxypropanes. Treatment of these with diethanolamine followed by treatment with tri-*n*-butyl borate provided compounds of structure IX. These materials

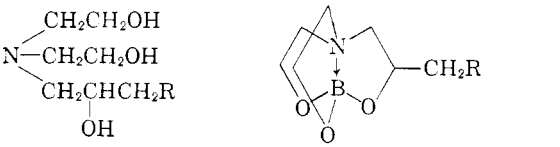


IX

a. $R_1 = R_2 = CH_3$
b. $R_1 = R_2 = C_2H_5$
c. $R_1 = R_2 = n\text{-}C_3H_7$
d. $R_1 = R_2 = n\text{-}C_4H_9$
e. $R_1 + R_2 = C_4H_8O$ (morphiline)
f. $R_1 + R_2 = C_5H_{10}$ (piperidine)
g. $R_1 = CH_3$, $R_2 = C_6H_5$

are moderately high-melting, crystalline solids, soluble in benzene and acetonitrile, distillable in high vacuum without decomposition, and possessing only very weakly basic properties as indicated by failure to form salts with hydrogen chloride and hydrogen bromide and by only a very slow reaction with ethyl iodide.

Triptych-boroxazolidines substituted with reactive functional groups. The chloromethyl compound (XIa) was obtained from β-chloromethyltriethanolamine (Xa), prepared by the action of diethanolamine on epichlorohydrin. This intermediate. which slowly polymerized as the result of intramolecular quaternization, provided the triptych compound (XIa) in 93% yield if it were subjected soon after preparation to the action of triethyl borate. The hydroxymethyl compound (XIb) was obtained from β-hydroxymethyltriethanolamine (Xb), prepared from 1-chloro-2,3-dihydroxypropane, by the action of tri-*n*-butyl borate. The aminomethyl compound (XIc) was prepared by three routes, the one of choice involving the ammonation of Xa to β-aminomethyltriethanolamine (Xc) followed by boronation with tri-*n*-butyl borate to XIc. Allylamine provided the starting material for two further syntheses of this compound. Conversion to ethyl *N*-allylcarbamate (XIIa) followed by epoxidation to XIIIa and treatment with diethanolamine yielded the trialkanolamine derivative Xd which on hydrolysis provided Xc, convertible to XIc as indicated above. Alternatively, allylamine was converted to benzyl *N*-allylcarbamate (Xd), which was then epoxidized to XIIIb and treated with diethanolamine to yield Xd. Boronation with tri-*n*-butyl borate gave 3-*N*-carbobenzoxyaminomethyltriptych - boroxazolidine (XId) from which the benzyloxy group could be removed by catalytic hydrogenolysis, providing a third synthesis of XIc. The cyanomethyl compound



X a. R = Cl
b. R = OH
c. $R = NH_2$
d. $R = NHCO_2C_2H_5$
e. R = CN

$CH_2{=}CHCH_2NHCO_2R$

XI a. R = Cl
b. R = OH
c. $R = NH_2$
d. $R = NHCO_2CH_2C_6H_5$
e. R = CN

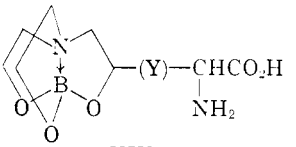
$CH_2\text{——}CHCH_2NHCO_2R$ (epoxide)

XII a. $R = C_2H_5$
b. $R = CH_2C_6H_5$

XIII a. $R = C_2H_5$
b. $R = CH_2C_6H_5$

(XIe) was prepared by treating a methanolic solution of β-chloromethyl-triethanolamine (Xa) with a concentrated aqueous solution of potassium cyanide to yield Xe, followed by boronation to XIe.

Reactions of triptych-boroxazolidines. The goal of this work, as yet incompletely realized, was to prepare compounds of the general structure XIV



XIV

where the bridge (Y) between the triptych-boroxazolidine moiety and the amino acid moiety involves a C—C link, an O—C link, or a N—C link. To this end, the compounds XIa and XIc appeared to be promising, and a number of experiments have been carried out with this pair of substances. Unfortunately, the chloromethyl compound (XIa) was ineffectual as a generally-useful alkylating agent. Thus, sodium methoxide or magnesium methoxide in boiling xylene, potassium cyanide in dimethylformamide, cuprous cyanide in pyridine, sodio diethyl malonate,[18] secondary

(17) H. Gilman, C. S. Sherman, C. C. Price, R. C. Elderfield, J. T. Maynard, R. H. Reitsema, L. Tolman, S. P. Massie, F. J. Marshall, and L. Goldman, *J. Am. Chem. Soc.*, **68**, 1291 (1946).

(18) As the possibility could not be excluded that the anion $B(OR)_3CH(CO_2C_2H_5)_2^-$ would form and interfere with the alkylation, the reaction of sodio diethylmalonate with allyl bromide in the presence of one mole-equivalent of triethyl borate was carried out. A 50% yield of diethyl allylmalonate was obtained, indicating that the failure of XIa to yield a product is probably not due to this difficulty.

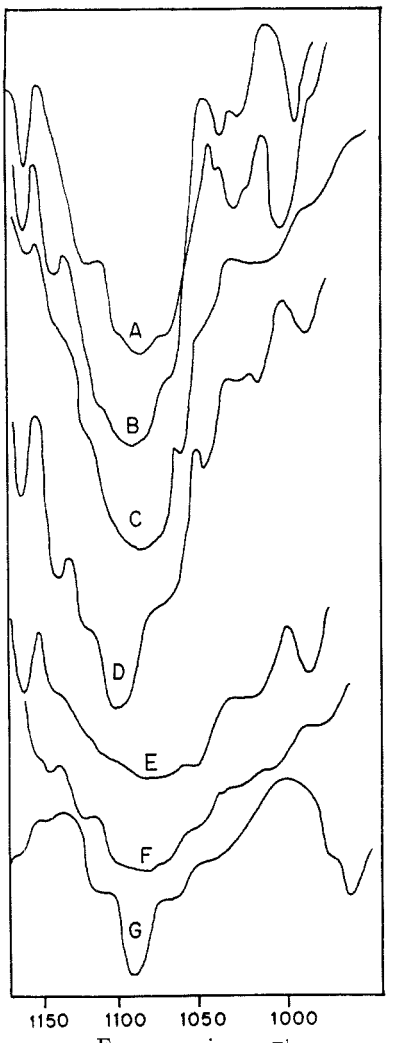
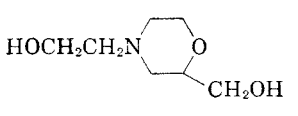


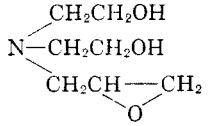
Fig. 1. Infrared spectra of triptychboroxazolidines in 1100 cm.$^{-1}$

Regions: (A) Triptychboroxazolidine (I). (B) 3-Methyltriptychboroxazolidine (Va.) (C) 3-Hydroxymethyltriptychboroxazolidine (XIb). (D) 3-Chloromethyltriptychboroxazolidine (XIa). (E) 2-Cyanomethyltriptychboroxazolidine (XIe). (F) 3-Benzoylaminomethyltriptychboroxazolidine (XVIc). (G) *N*-(3-triptychboroxazolidinylmethyl)glutamine (XVIIc)

amines in dimethylformamide, and hydrogen in the presence of palladium-charcoal all failed to react with XIa. Sodium methoxide in methanol or sodium ethoxide in ethanol, however, did react with XIa to yield the morpholine derivative XV when a 1:1 ratio of alkoxide to XIa was employed or the alkoxymethylene triptych compound when a 4:1 ratio of alkoxide to XIa was used. A

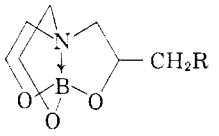


XV

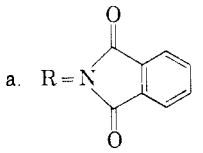


XVI

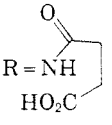
possible explanation for the formation of XV assumes a base-catalyzed alcoholysis to the trialkanolamine (Xa) which may then undergo elimination of hydrogen chloride to form the epoxide XVI. Intramolecular reaction of XVI would yield XV, while intermolecular reaction of XVI with alkoxide ion followed by reboronation could yield VIIIa. Substitution products were also obtained through the action of potassium phthalimide and sodium acetate which led to XVIa and XVIb, respectively. Sodium hydride reacted with XIa, but the product (which appears to be a polymer) was not characterized.

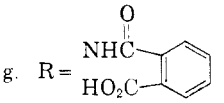


XVI

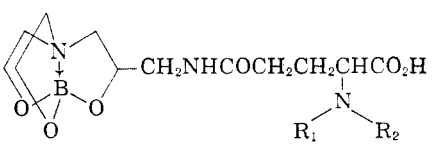


b. R = OCOCH$_3$
c. R = NHCOC$_6$H$_5$
d. R = NHCONHC$_6$H$_5$
e. R = NHCSNHC$_6$H$_5$

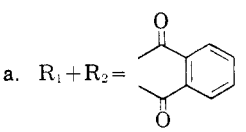




The aminomethyl-triptych compound (XIc) was more amenable to reaction than XIa and, albeit with some reluctance, formed derivatives including the *N*-benzoyl compound (XVIc), the urea derivative from phenylisocyanate (XVId), and the thiourea derivative from phenyl isothiocyanate (XVIe). Succinic anhydride reacted with XIc to yield XVIf, and phthalic anhydride gave, initially, the half amide XVIg which upon heating at 200° was converted to the imide XVIa, identical with the material obtained *via* the chloromethyl compound. An alternate synthesis of XVIa involved the conversion of 3-phthalimido-1,2-epoxypropane to the corresponding triethanolamine derivative followed by boronation. DL-Phthalimidoglutamic acid anhydride reacted with XIc to yield the amino acid derivative XVIIa and with L-*N*-carbobenzyloxyglutamic acid anhydride to yield the amino acid derivative XVIIb. Catalytic hydrogenolysis of XVIIb furnished the free amino acid XVIIc as a crystalline, low-melting solid but so hygroscopic that an analysis could not be obtained.



XVII



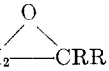
b. R_1 = H, R_2 = $CO_2CH_2C_6H_5$
c. R_1 = R_2 = H

The structural assignment is based on the fact that the compound contains boron, gives a positive ninhydrin test, possesses certain bands in the infrared characteristic of the triptych and amino acid moieties, and was prepared by a sequence of reactions which has been shown to lead to such compounds in related instances.

The present investigation has established the fact that the triptych-boroxazolidine moiety may be incorporated as a unit into more complex structures even when the triptych compound is only monosubstituted and thus hydrolytically unstable. It is anticipated that further research in this area will extend the procedures described herein to the use of more highly-substituted triptych compounds leading to the synthesis of substances of greater biological interest and utility.

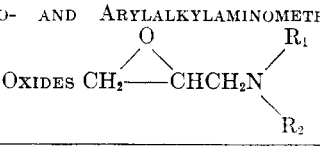
EXPERIMENTAL[19]

Analytical methods. Epoxides containing no basic nitrogen were determined by first treating the sample with a 5% solution of pyridine hydrobromide in glacial acetic acid followed then by titrating with 0.1*N* perchloric acid in glacial acetic acid using methyl violet as indicator. Epoxides containing basic nitrogen were determined by the method of Durbetaki.[20] Basic nitrogen was determined by titration with 0.1*N* perchloric acid in glacial acetic acid using methyl violet as indicator.[21] In the case of the triptych-boroxazolidines, which are such weak bases that they do not titrate smoothly with perchloric acid, the following procedure was employed. A 0.2–0.3-g. sample of the compound was dissolved in 50 ml. of 0.1*N* perchloric acid in acetic acid, and the solution was heated on the steam bath for 15 min. After cooling to room temperature, the excess perchloric acid was back titrated with 0.1*N* sodium acetate in glacial acetic acid. Boron content was determined by the method of Thomas[22] which involves treating the borate ester with methanol and sulfuric acid, distilling the methyl borate which is formed into a receiver containing water, and titrating the resulting boric acid solution with sodium hydroxide in the presence of mannitol.

Epoxides of the general structure  All of the epoxides used in the experiments described below in which R and R′ are H, alkyl, aryl, alkoxymethyl, or aryloxymethyl are readily available as items of commerce or *via* syntheses described in the literature. The aminoalkylethylene oxides, listed in Table I, were prepared by adding the appropriate secondary amine to epichlorohydrin[17] and maintaining the temperature over the 4-hr. period of addition at 20–25°. Aqueous sodium hydroxide was then added at such a rate that the temperature was maintained at 25–30°. The resulting epoxide was worked up in the usual way and purified by distillation through a short Vigreux column.

Triethanolamine derivatives of general structure $(HOCH_2CH_2)_2NCH_2C(OH)R_1R_2$. The triethanolamine derivatives listed in Table II were prepared in all cases by the addition of the appropriate epoxide to a chloroform solution of diethanolamine. After the initial exothermic reaction had subsided, the solution was refluxed for several hours and the product then worked up in the usual way and purified by distillation through a short Vigreux column. In the majority of instances a triacetyl derivative of the trialkanolamine was prepared, and in all such cases the analysis for nitrogen agreed closely with the calculated value.

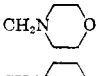
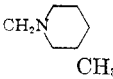
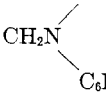
TABLE I

DIALKYLAMINO- AND ARYLALKYLAMINOMETHYLETHYLENE OXIDES 

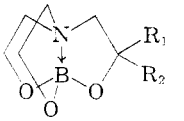
R Groups			Nitrogen, %		Epoxide Oxygen, %	
R_1	R_2	Formula	Calcd.	Found	Calcd.	Found
n-C_3H_7	*n*-C_3H_7	$C_9H_{19}NO$	8.91	9.01	10.17	10.32
n-C_4H_9	*n*-C_4H_9	$C_{11}H_{23}NO$	7.56	7.58	8.64	8.53
		$C_7H_{13}NO_2$	9.78	9.92	11.18	11.05
		$C_8H_{15}NO$	9.92	10.01	11.33	11.45
CH_3	C_6H_5	$C_{10}H_{13}NO$	8.58	8.65	9.80	9.79

TABLE II

β-SUBSTITUTED TRIETHANOLAMINES $(HOCH_2CH_2)_2NCH_2C(OH)R_1R_2$

R Groups			Nitrogen, %	
R_1	R_2	Formula	Calcd.	Found
H	CH_3	$C_7H_{17}NO_3$	8.68	8.71
H	C_2H_5	$C_8H_{19}NO_3$	7.90	7.93
H	$CH{=}CH_2$	$C_8H_{17}NO_3$	8.00	7.90
H	C_6H_5	$C_{12}H_{19}NO_3$	6.22	6.11
CH_3	CH_3	$C_8H_{19}NO_3$	7.90	7.97
H	CH_2OCH_3	$C_8H_{19}NO_4$	7.25	7.39
H	$CH_2OC_2H_5$	$C_9H_{21}NO_4$	6.76	6.90
H	$CH_2OCH_2CH{=}CH_2$	$C_{10}H_{21}NO_4$	6.39	6.25
H	$CH_2OCH_2C_6H_5$	$C_{14}H_{23}NO_4$	5.20	5.20
H	$CH_2OC_6H_5$	$C_{13}H_{21}NO_4$	5.49	5.51
H	$CH_2N(CH_3)_2$	$C_9H_{22}N_2O_3$	13.58	13.23
H	$CH_2N(C_2H_5)_2$	$C_{11}H_{26}N_2O_3$	11.96	11.67
H	$CH_2N(n\text{-}C_3H_7)_2$	$C_{13}H_{30}N_2O_3$	10.68	10.81
H	$CH_2N(n\text{-}C_4H_9)_2$	$C_{15}H_{34}N_2O_3$	9.65	9.71
H		$C_{11}H_{24}N_2O_4$	11.24	11.22
H		$C_{12}H_{26}N_2O_3$	11.37	11.39
H		$C_{14}H_{24}N_2O_3$	10.44	10.26

Triptych-boroxazolidines of general structure.



The three methods applicable to the synthesis of triptych-boroxazolidines are illustrated in the preparation of triptych-boroxazolidine (triethanolamine borate) itself.

(19) All melting points were determined on a Kofler hot stage calibrated against compounds of known melting point. All boiling points are uncorrected. Infrared spectra were determined on a Perkin Elmer Model 21 instrument. We are indebted to Mrs. Franziska Schleppnik for most of the boron and nitrogen analyses.

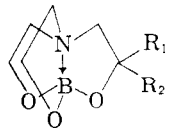
(20) A. J. Durbetaki, *Anal. Chem.*, **30**, 2024 (1958).

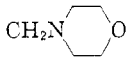
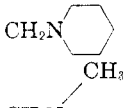
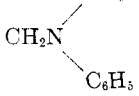
(21) E. F. Hillenbrand and C. A. Pentz, in *Organic Analysis*, Vol. III, Interscience Inc., New York, N. Y., 1956, p. 145.

(22) L. H. Thomas, *J. Chem. Soc.*, 820 (1946).

TABLE III

3-SUBSTITUTED TRIPTYCH-BOROXAZOLIDINES



R Groups		M.P.	Recrystallization Solvent[a]	Formula	Boron, %		Nitrogen, %	
R_1	R_2				Calcd.	Found	Calcd.	Found
H	CH_3	197–198°	a	$C_7H_{14}BNO_3$	6.33	6.26	8.19	8.18
H	C_2H_5	144–145°	a	$C_8H_{16}BNO_3$	5.91	5.93	7.65	7.79
H	$CH{=}CH_2$	155–156°	t	$C_8H_{14}BNO_3$	5.98	5.94	7.75	7.79
H	C_6H_5	228–229°	a	$C_{12}H_{16}BNO_3$	4.64	4.72	6.01	6.27
CH_3	CH_3	178–180°	a–e	$C_8H_{16}BNO_3$	5.91	5.97	7.65	7.65
H	CH_2OCH_3	89–90°	b–p	$C_8H_{16}BNO_4$	5.38	5.26	6.97	7.14
H	$CH_2OC_2H_5$	119–120°	b–p	$C_9H_{18}BNO_4$	5.04	4.79	6.52	6.78
H	$CH_2OCH_2CH{=}CH_2$	73–74.5°	b–p	$C_{10}H_{18}BNO_4$	4.77	4.79	6.17	6.25
H	$CH_2OCH_2C_6H_5$	108–110°	b–p	$C_{14}H_{20}BNO_4$	3.90	3.90	5.05	5.29
H	$CH_2OC_6H_5$	184–186°	b–d	$C_{13}H_{18}BNO_4$	4.11	4.35	5.33	5.23
H	$CH_2N(CH_3)_2$	152–153°	b	$C_9H_{19}BN_2O_3$	5.06	5.21	13.08	12.90
H	$CH_2N(C_2H_5)_2$	136–137°	b–p	$C_{11}H_{23}BN_2O_3$	4.47	4.27	11.57	11.31
H	$CH_2N(n\text{-}C_3H_7)_2$	126–127°	b–p	$C_{13}H_{27}BN_2O_3$	4.01	4.03	10.38	10.40
H	$CH_2N(n\text{-}C_4H_9)_2$	133–134°	b–p	$C_{15}H_{31}BN_2O_3$	3.64	3.85	9.40	9.30
H		189–190°	a–b	$C_{11}H_{21}BN_2O_4$	4.23	4.37	10.92	11.06
H		188–189°	a	$C_{12}H_{23}BN_2O_3$	4.26	4.33	11.02	11.00
H		174–175°	a–b	$C_{14}H_{21}BN_2O_3$	3.92	3.98	10.14	10.30

[a] Abbreviations for recrystallization solvents: *a*—acetonitrile, *b*—benzene, *d*—dimethylformamide, *e*—ether, *p*—petroleum ether (b.p. 63–69°), *t*—toluene.

(A) *Boric acid method.* A mixture of 31.0 g. (0.5 mole) of boric acid and 75.0 g. (0.5 mole) of triethanolamine was dissolved, with heating, in 100 ml. of dry dimethylformamide.[23] The water formed in the reaction was distilled off through a short Vigreux column, and after *ca.* 75 ml. of distillate had been collected (head temperature 148°) the solution was cooled to room temperature. The solid fraction was removed by filtration, washed with dimethylformamide, and dried to yield 75.1 g. (96%) of colorless crystals, m.p. 238–239° (reported[7] m.p. 236.5–237.5°).

(B) *Boric ester method.* A 14.9-g. (0.1 mole) sample of triethanolamine was added to 23.0 g. (0.1 mole) of tri-*n*-butyl borate. The initially turbid solution warmed and became clear and then deposited a solid. The butanol was removed by distillation, and the residue was dried to yield 15.7 g. (100%) of colorless crystals, m.p. 235–236°.

(C) *From triacetyltriethanolamine.* Triethanolamine was converted to the triacetate with acetic anhydride in acetic acid,[24] and 13.8 g. (0.05 mole) of this product was treated with 11.5 g. (0.05 mole) of tri-*n*-butyl borate containing 0.1 g. of sodium dissolved in 30 ml. of anhydrous *n*-butyl alcohol. The solution was refluxed for 1 hr., and the butanol and butyl acetate were then removed under reduced pressure. The residue was recrystallized from chloroform–petroleum ether (b.p. 63–69°) to give colorless needles, m.p. 235–236°. The triptych-boroxazolidines listed in Table III were prepared by the boric ester method, and the products were purified by recrystallization, in many cases after prior distillation in a short path apparatus at 0.01 mm. or less.

trans-3,4-Tetramethylenetriptych-boroxazolidine (VI). A 3.0-g. sample of cyclohexene oxide and 3.2 g. of diethanolamine in 30 ml. of chloroform was refluxed for 48 hr. The product consisted of 4.5 g. (74%) of a colorless, very viscous liquid which, upon boronation with tri-*n*-butyl borate gave VI in quantitative yield. Recrystallization from toluene–petroleum ether furnished colorless needles, m.p. 138–139°.

Anal. Calcd. for $C_{10}H_{18}BNO_3$: B, 5.07; N, 6.64. Found: B, 3.69; N, 6.67.

3,4-Dehydro-3,4-benzotriptych-boroxazolidine (VII). Boronation of 4.9 g. of *N,N*-bis(2′-hydroxyethyl)-*o*-aminophenol[13] with 5.8 g. of tri-*n*-butyl borate yielded a brown oil. This was extracted with boiling acetonitrile and the extract evaporated on the steam bath. The resulting semisolid residue was purified by distillation in a short path apparatus to yield colorless crystals, m.p. 155–156°.

Anal. Calcd. for $C_{10}H_{12}BNO_3$: B, 5.28; N, 6.83. Found: B, 5.21; N, 6.99.

3-Chloromethyltriptych-boroxazolidine (XIa). To a stirred and cooled solution of 21.0 g. (0.2 mole) of diethanolamine in 100 ml. of chloroform was slowly added 18.5 g. (0.2 mole) of epichlorohydrin in 50 ml. of chloroform. The mixture was stirred overnight at room temperature, and the solvent was then removed under vacuum to leave 39.6 g. (100%) of β-chloromethyltriethanolamine (Xa) as a viscous, yellow oil. A qualitative test indicated the presence of chloride ion (arising from quaternary compound), and distillation at 0.001 mm. decomposed the material. Consequently, it was used without purification and as soon as possible in the next step which consisted in treating with an

(23) Technical grade dimethylformamide was dried over calcium hydride and then distilled. The fraction with b.p. 150–151° was collected and stored over calcium hydride in brown bottles.

(24) L. W. Jones and G. R. Burnd, *J. Am. Chem. Soc.*, **47**, 2966 (1925).

equimolar amount of triethyl borate. In a reaction employing 197.5 g. (1 mole) of crude Xa and 146 g. (1 mole) of triethyl borate, the ethanol was slowly distilled through a short column; when the head temperature reached 78°, 200 ml. of dry toluene was introduced and the distillation continued until the head temperature reached 82°. The resulting pale brown solution was cooled, and the white, crystalline product was removed by filtration, washed with dry toluene and petroleum ether, and dried to yield 159 g. (81%) of material, m.p. 149–153°, pure enough for subsequent reactions. Concentration of the mother liquor under reduced pressure and extraction of the residue with hot acetonitrile left a product which was dissolved in hot benzene–petroleum ether (b.p. 33–58°). When this solution was cooled, an additional 24 g. of product was isolated, m.p. 150–153°, bringing the total yield to 171 g. (93%). An analytical sample was prepared by several recrystallizations from benzene–petroleum ether (b.p. 33–58°) and obtained as colorless needles, m.p. 153–155°.

Anal. Calcd. for $C_7H_{13}BClNO_3$: B, 5.18; N, 6.70. Found: B, 5.28 N, 7.04.

3-Hydroxymethyltriptych-boroxazolidine (XIb). A solution of 22.1 g. (0.2 mole) of glycerine-α-chlorohydrin[25] and 42.0 g. (0.2 mole) of diethanolamine in 100 ml. of ethanol was refluxed for 4 hr. The solvent was removed under reduced pressure, and the residue was dissolved in water and passed through an Amberlite IRA-400 column in the hydroxy form. The eluate was evaporated under reduced pressure and the residue was distilled in a short path apparatus to yield 22.8 g. (63%) of a viscous, colorless liquid, b.p. 185–205° (3 mm.). A center cut was taken for analysis:

Anal. Calcd. for $C_7H_{17}NO_4$: N, 7.81. Found: N, 7.88.

The tetraacetate was prepared by dissolving 2.0 g. of β-hydroxymethyltriethanolamine (Xb) in 10 ml. of acetic acid and 10 ml. of acetic anhydride and refluxing for 1 hr. The product was purified by distillation in a short path apparatus and obtained as a colorless, mobile liquid, b.p. 160–165° (0.5 mm.).

Anal. Calcd. for $C_{15}H_{25}NO_8$: N, 4.03. Found: N, 4.00. Addition of 8.7 g. of Xb to tri-*n*-butyl borate gave 9.2 g. (100%) of a glassy solid which crystallized after standing at room temperature for 3 months. Trituration with benzene–petroleum ether–acetonitrile removed a small amount of an oily impurity and left colorless crystals which did not have a sharp melting point but sintered over a rather wide range.

Anal. Calcd. for $C_7H_{14}BNO_4$: B, 5.68; N, 7.34. Found: B, 5.71; N, 7.40.

3-Aminomethyltriptych-boroxazolidine (XIc). (A) *From Ethyl N-Allylcarbamate* (XII). A solution of 25.8 g. (0.2 mole) of ethyl *N*-allylcarbamate in 200 ml. of methylene chloride was oxidized with peroxytrifluoroacetic acid obtained from 8.2 ml. of 90% hydrogen peroxide (0.3 mole) and 61 ml. of trifluoroacetic anhydride in 50 ml. of methylene chloride.[26] The crude product was distilled through a short Vigreux column to give 22.7 g. (78%) of a colorless liquid, b.p. 95.5–96° (2 mm.).

Anal. Calcd. for $C_6H_{11}NO_3$: Epoxide oxygen, 11.02. Found: Epoxide oxygen, 11.00. A 19.3-g. sample (0.133 mole) of the product described above was dissolved in 50 ml. of chloroform and treated with 13.9 g. (0.133 mole) of diethanolamine. The crude product, 33.2 g. (100%), could not be distilled without decomposition and was used without further purification. A solution of 23.0 g. (0.092 mole) of this material in 50 ml. of 20% hydrochloric acid was refluxed for 4 hr., the solvent and excess acid were removed under reduced pressure, and the residue was dissolved in 100 ml. of water and passed through an Amberlite IRA-400 column in the hydroxyl form. Evaporation of the eluate left a residue which was distilled in a short path apparatus to yield 16.1 g. (98%) of β-aminomethyltriethanolamine (Xc). Boronation of 8.9 g. of Xc with 10.7 g. of tri-*n*-butyl borate yielded 9.3 g. (100%) of a thick, yellow oil Distillation at 185–195° (0.1 mm.) gave a colorless oil which partially solidified after long standing at room temperature. Recrystallization from benzene–acetonitrile–petroleum ether (b.p. 63–69°) gave colorless crystals, m.p 60–66°, and it is this material that is compared (*cf.* below) with subsequent preparations. However, a second recrystallization from chloroform–petroleum ether (b.p. 63–69°) caused a sharp elevation in melting point to 115–116°, presumably another crystalline modification.

Anal. Calcd. for $C_7H_{15}BN_2O_3$: B, 5.70; N, 14.75. Found: B, 5.59; N, 14.87.

(*B*) *From benzyl N-allylcarbamate* (XIIb). A 16.5 g. (0.1 mole) sample of XIIb, prepared from allylamine and carbobenzyloxychloride, was epoxidized with peroxytrifluoroacetic acid[26] to yield 10.0 g. (56%) of a colorless oil, b.p. 150–151° (0.5 mm.).

Anal. Calcd. for $C_{11}H_{15}NO_3$: Epoxide oxygen, 7.72. Found: Epoxide oxygen, 7.88. Treatment of 4.1 g. (0.02 mole) of this material with 2.1 g. (0.02 mole) of diethanolamine yielded 6.2 g. (100%) of β-carbobenzyloxyamidomethyltriethanolamine, a 5.6-g. sample of which was treated with 4.2 g. of tri-*n*-butyl borate. The resulting product was recrystallized from acetonitrile to give 4.0 g. (68%) of 3-carbobenzyloxyamidomethyltriptych-boroxazolidine (XId), m.p. 143–144°.

Anal. Calcd. for $C_{15}H_{21}BN_2O_5$: B, 3.38 Found: B, 3.56. The 3-aminomethyl compound (XIc) was prepared from XId by dissolving 3.3 g. of the latter in 30 ml. of dry dimethylformamide, adding 10% palladium on charcoal catalyst, and hydrogenolyzing for 55 hr. when 90% of the calculated volume of hydrogen had been absorbed. The product was worked up to give 1.8 g. (100%) of colorless crystals, m.p. 63–65°, which did not depress the melting point when admixed with a sample prepared by method A described above.

(*C*) *From β-chloromethyltriethanolamine* (Xa). A solution of crude Xa, prepared as described above from 105 g. of diethanolamine and 94 g. of epichlorohydrin, in 200 ml. of chloroform was added with stirring over a period of 8 hr. to 1 l. of concd. ammonia heated at 60°. After stirring and heating overnight the product was worked up to give 109 g. (62%) of oil, b.p. 195–200° (0.01 mm.).

Anal. Calcd. for $C_7H_{18}N_2O_3$: N, 15.72. Found: N, 15.48. The tetraacetyl derivative of Xc was obtained as a slightly yellow oil, b.p. 175–180° (0.1 mm.).

Anal. Calcd. for $C_{15}H_{26}N_2O_7$: N_{basic}, 4.04. Found: N_{basic}, 3.91. Treatment of Xc with tri-*n*-butyl borate yielded XIc as colorless crystals, m.p. 63–65°, showing no depression in melting point when admixed with material prepared by methods A or B.

3-Cyanomethyltriptych-boroxazolidine (XIe). A solution of 0.2 mole of β-chloromethyltriethanolamine (Xa) in 80 ml. of methanol was cooled in an ice bath and treated, with stirring, with 13 g. (0.2 mole) of potassium cyanide dissolved in a small amount of water, the temperature during the addition being maintained at 10–12°. The solution was allowed to stand at room temperature for 24 hr., and the small amount of solid that had formed was removed by filtration. The filtrate was evaporated, triturated with ethanol, and filtered and evaporated again, and the residue was then treated with tri-*n*-butyl borate and *n*-butyl alcohol until a clear solution resulted. Removal of the *n*-butyl alcohol by distillation left a brown crystalline material which was dissolved in boiling acetonitrile, treated with decolorizing charcoal, and diluted with benzene to cloudiness. Upon chilling in an ice bath the impurities first separated as a black cake adhering to the walls of the flask. Decantation and further cooling then furnished the product as 14.5 g. of colorless crystals, m.p. 149–153°. Recrystallization from benzene–acetonitrile–ether gave colorless needles; m.p. 155–156° ν^{KBr} 2247 cm.$^{-1}$ (nitrile).

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(26) W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.*, **77**, 89 (1955).

Anal. Calcd. for $C_8H_{13}BN_2O_3$: B, 5.41; N_{basic}, 7.00. Found: B, 5.52; N_{basic}, 7.18.

2-Hydroxymethyl-4-(2'-hydroxyethyl)morpholine (XV). An ethanol solution of β-chloromethyltriethanolamine (Xa) prepared from 19.5 g. of epichlorohydrin and 21 g. of diethanolamine, was treated with 13.5 g. of sodium ethoxide in 150 ml. of ethanol. After stirring for 1 hr. and standing overnight at room temperature, the solvent was removed and the residue was distilled from the solid products to yield 12.3 g. of a colorless, viscous liquid, b.p. 145–147° (2 mm.).

Anal. Calcd. for $C_7H_{17}NO_3$: N, 8.60. Found: N, 8.82.

The *diacetate of 2-hydroxymethyl-4-(2' hydroxyethyl) morpholine* was obtained as a colorless oil, b.p. 120–122° (0.8 mm.).

Anal. Calcd. for $C_{11}H_{21}NO_5$: N, 5.71. Found: N, 5.55.

Reactions of triptych-boroxazolidines. Bromination of 3-vinyltriptych-boroxazolidine (Vc). An 18.1-g. (0.1 mole) sample of Vc was dissolved in 100 ml. of chloroform, cooled in an ice bath, and treated with a solution of 16.0 g. (0.1 mole) of bromine in chloroform. After 2 hr. standing at room temperature 3-(1',2'-dibromoethyl)triptych-boroxazolidine was isolated as 34.4 g. (100%) of a white powder, analytically pure but without a definite melting point.

Anal. Calcd. for $C_5H_{14}BBr_2NO_3$: B, 3.16; N, 4.08. Found: B, 3.16; N, 4.02.

Sodium methoxide and 3-chloromethyltriptych-boroxazolidine (XIa). A mixture of 1.97 g. (0.01 mole) of XIa and 0.54 g. (0.01 mole) of sodium methoxide in xylene yielded, after refluxing for 5 hr., 1.56 g. of recovered starting material. A similar experiment with magnesium methoxide yielded the same result. However, when a 1.97-g. (0.01 mole) sample of XIa was refluxed with 0.54 g. (0.01 mole) of sodium methoxide in 25 ml. of methanol, sodium chloride precipitated and the product was shown to consist of 2-hydroxymethyl-4-(2'-hydroxyethyl)morpholine (XV) and a very small amount of 2-methoxymethyltriptych-boroxazolidine (VIIIa). A similar experiment employing 4 moles of sodium ethoxide to 1 mole of XIa in ethanol yielded 65% of 2-ethoxymethyltriptych-boroxazolidine (VIIIb) as a colorless solid, m.p. 115–117°, showing no depression in melting point when admixed with VIIIb prepared as described above.

Potassium phthalimide and 3-chloromethyltriptych-boroxazolidine (XIa). A mixture of 3.9 g. of XIa, 2.7 g. of potassium phthalimide, and 50 ml. of dimethylformamide was heated to reflux. From the turbid solution a white solid slowly precipitated. After 3 hr. of refluxing, the mixture was cooled, the precipitate was removed by filtration, and the filtrate was evaporated to leave a residue which crystallized on standing, m.p. 252–260°. Recrystallization from acetonitrile-benzene gave 5.1 g. (81%) of colorless needles, m.p. 258–259°, identical with the material prepared from phthalimidomethyltriethanolamine and tri-*n*-butyl borate (XVIa) The latter material, after recrystallization and distillation in a short path apparatus, melted at 263–264°.

Anal. Calcd. for $C_{15}H_{17}BN_2O_5$: B, 3.42; N, 4.43. Found: B, 3 44; N, 4.55.

Sodium acetate and 3-chloromethyltriptych-boroxazolidine (XIa). A mixture of 7.5 g. of anhydrous sodium acetate, 9.7 g. of XIa, and 50 ml. of dry dimethylformamide was heated with stirring at 120–130° for 4 hr. The cooled mixture was separated from solid material by centrifugation, and the supernatant was evaporated to leave a brown residue. This was dissolved in benzene, filtered, and diluted with petroleum ether whereupon crystals slowly formed, m.p. 92–96°. Distillation and further recrystallization produced a colorless, rather hygroscopic waxy solid; m.p 128–130°, $\bar{\nu}^{KBr}$ 1742 cm.$^{-1}$ (ester), 1250 cm.$^{-1}$ (acetate). The hygroscopicity of the material precluded the obtention of significant analytical data.

Sodium hydride and 3-chloromethyltriptych-boroxazolidine (XIa). A slurry of 1.2 g. of 50% sodium hydride in mineral oil in dry dimethylformamide was added to a solution of 5 g of XIa in dimethylformamide. Gas was evolved, sodium hydride was consumed, and sodium chloride deposited. After heating at 90–110° for 2 hr., the mixture was worked up to give a glassy residue which after trituration with boiling benzene left a white powder, softening at 150° and decomposing above 200°; $\bar{\nu}^{KBr}$ strong flat band 1100–1000 cm.$^{-1}$

Anal. Calcd. for $C_7H_{12}BNO_3$: N, 8.69. Found: N, 8.36.

Benzoyl chloride and 3-aminomethyltriptych-boroxazolidine (XIc). A solution of 3.7 g. of XIc in chloroform was treated with 3 ml. of triethylamine followed, with cooling, by 2.8 g. of benzoyl chloride in 10 ml. of chloroform, added dropwise and with stirring. The product was a gum which, after failing to crystallize on long standing, was extracted into boiling benzene. The benzene solution was diluted with petroleum ether to cloudiness and crystals separated very slowly to give 2.0 g. (35%) of XVIc as a colorless solid; m.p. 145–146°, $\bar{\nu}^{KBr}$ 3251 cm.$^{-1}$ (amide N—H), 1642 cm.$^{-1}$ (carbonyl), 1529 cm.$^{-1}$ (secondary amide).

Anal. Calcd. for $C_{14}H_{19}BN_2O_4$: B, 3.77; N_{basic}, 4.88. Found: B, 3.89; N_{basic}, 5.01.

Phenylisocyanate and 3-aminomethyltriptych-boroxazolidine (XIc). The urea derivative XVId was obtained from XIc and phenylisocyanate as an oil which crystallized after several weeks at room temperature. Recrystallization from dioxane-dimethylformamide gave a 75% yield of colorless crystals, m.p. 205°.

Anal. Calcd. for $C_{14}H_{20}BN_3O_4$: N_{basic}, 4.59. Found: N_{basic}, 4.64.

Phenylisothiocyanate and 3-aminomethyltriptych-boroxazolidine (XIc). The thiourea derivative XVIe was obtained from XIc and phenylisothiocyanate as an immediately crystallizing compound which, after recrystallization from dioxane–petroleum ether (b.p. 63–69°), was obtained as colorless crystals, m.p. 195–196°.

Anal. Calcd. for $C_{14}H_{20}BN_3O_3S$: B, 3.37; N_{basic}, 4.48. Found: B, 3.36; N_{basic}, 4.36.

Phthalic anhydride and 3-aminomethyltriptych-boroxazolidine (XIc). To a solution of 3.7 g. of XIc in chloroform was added 3 g. of phthalic anhydride. An exothermic reaction took place, and a gummy precipitate separated. This was filtered and the filtrate was diluted with petroleum ether (b.p. 33–58°) to give 6.6 g. (100%) of a white powder, m.p. 146–148°, presumed to be the half amide XVIg.

Anal. Calcd. for $C_{15}H_{19}BN_2O_6$: B, 3.24; N, 4.19. Found: B, 2.71; N, 4.48.

When a 0.066-g. sample of XVIg was heated at 200°, it lost water and yielded 0.058 g. of colorless needles, m.p. 263–264°, identical with XVIa obtained as described above.

Succinic anhydride and 3-aminomethyltriptych-boroxazolidine (XIc). In a fashion similar to that used with phthalic anhydride, XIc was converted to XVIf, m.p. 156–158°.

Anal. Calcd. for $C_{11}H_{19}BN_2O_6$: B, 3.79; N_{basic} 4.90. Found: B, 3.39; N_{basic} 4.81.

DL-*Phthalimidoglutamic acid anhydride and 3-aminomethyltriptych-boroxazolidine* (XIc). The reaction of 5.6 g. of XIc with 7.8 g. of DL-phthalimidoglutamic acid anhydride in chloroform yielded a gum which slowly crystallized to 13.4 g. (100%) of XVIIa as a colorless solid, m.p. 48–50°. Attempted recrystallization led to decomposition.

Anal. Calcd. for $C_{20}H_{24}BN_3O_8$: B, 2.43; N_{basic} 3.15. Found: B, 2.33; N_{basic}, 4.28.

L-*Carbobenzyloxyglutamic acid anhydride and 3-aminomethyltriptych-boroxazolidine* (XIc). A solution of 5.6 g. of XIc and 7.9 g. of carbobenzyloxyglutamic acid anhydride in chloroform was allowed to stand at room temperature for several hours and was then diluted with petroleum ether (b.p. 63–69°) causing the precipitation of 13.4 g. (100%) of XVIIb as a gum which crystallized after separation from the solvent, m.p. 84–94°. Purification by recrystallization was not attempted.

Anal. Calcd. for $C_{20}H_{23}BN_3O_8$: B, 2.41; N_{basic}, 3.93. Found: B, 2.21; N_{basic}, 3.90.

A 4.5-g. sample of XVIIb was dissolved in dry dimethylformamide and hydrogenolyzed in the presence of 10% palladium on charcoal. After 4 days the uptake was 220 ml. (calculated 240 ml.), and the product was isolated by re-

moval of the catalyst and the addition of benzene to the filtrate. The material that separated consisted of colorless, fine needles that were so hygroscopic that no significant analytical data for boron and nitrogen could be obtained; m.p. 48–50°, ν^{KBr} 3125 cm.$^{-1}$ (NH_3^+), 1661 cm.$^{-1}$ (amino acid band-I), 1626 cm.$^{-1}$ (amide carbonyl), 1558 cm.$^{-1}$ (CO_2^-), 1543 cm.$^{-1}$ (amide-II band), 1493 cm.$^{-1}$ (amino acid band-II), triptych pattern 1200-950 cm.$^{-1}$ The material gave positive tests for boron and for an amino acid (ninhydrin).

ST. LOUIS, MO.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

Structures Related to Morphine. XIV.[1] 2′-Hydroxy-5-methyl-2-phenethyl-6,7-benzomorphan, the 9-Demethyl Analog of NIH 7519 (Phenazocine) from 3,4-Dihydro-7-methoxy-2(1H)naphthalenone

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3,4-Dihydro-7-methoxy-2(1H)naphthalenone has been converted to 2′-methoxy-2,5-dimethyl-9-oxo-6,7-benzomorphan methobromide (V), an interesting intermediate for the synthesis of neuropharmacologic agents. Pyrolysis of V gives a mixture of the base VII and the α,β-unsaturated ketone (VI). Compound VII, readily convertible to the 9-demethyl analog (VIII) of phenazocine (XI) is characterized by its avidity for water or alcohol with simultaneous disappearance of infrared carbonyl absorption in the presence of acids. The *N*-phenethyl compound (VIII) is an effective analgesic in mice.

As reported previously,[2] 2′-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan (XI) is a promising agent for the relief of human pain. Of interest, therefore, was the 9-demethyl analog (VIII) of XI, despite the fact that the related 2′-hydroxy-2,5-dimethyl-6,7-benzomorphan (IX)[3] is only one third as effective in mice as the 9-methyl homolog (XII),[3,4] the corresponding relative of XI.

The most feasible route to VIII appeared to be *via* the *N*-methyl compound IX which hitherto has been prepared either from γ-picoline methiodide in low yield[3] or from phenylacetonitrile in a lengthy sequence.[3,5] Still another possible approach to IX would involve the intermediate bicyclic ketone methobromide (V) which was needed for other investigations as well. The synthesis of V from 3,4-dihydro-7-methoxy-2-(1H)naphthalenone (I) as shown in Fig. 1 was achieved without particular difficulty.

Methylation of I by the method of Stork[6] gave the 1-methyl compound (II) in 80% yield. Dimethylaminoethylation (sodamide, benzene) of II and bromination of the hydrobromide salt of the resultant III yielded IV hydrobromide which, when neutralized with ammonia, cyclized rapidly

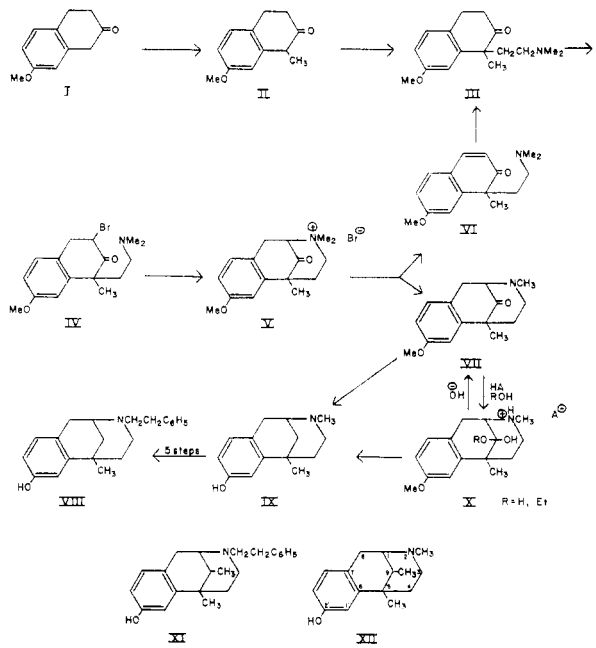

Fig. 1. Synthesis of 2′-hydroxy-5-methyl-2-phenethyl-6,7-benzomorphan, VIII

to the quaternary compound V. Pyrolysis of V by dry distillation in a high vacuum led principally to tar, the only identifiable product being the α,β-unsaturated ketone VI. However, if the pyrolysis were effected in boiling 1-octanol a 40% yield of the desired base VII could be obtained along with about 15% of VI. The use of either boiling 1-heptanol or 1-hexanol reversed this ratio, giving about 40% of VI and never more than 20% of VII. Hydrogenation of VI (palladium–barium sulfate), the ultraviolet and infrared absorption curves of which were consistent with the structure

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