Anal. Calcd. for $C_{16}H_{27}ClN_2O_3$: N, 8.47; Cl, 10.72. Found: N, 8.40; Cl, 10.48.

Summary

A series of dialkylaminoalkyl 4-butylaminobenzoates, 4-(5-hydroxyamylamino)-benzoates, and intermediates in their preparation have been described. The 4-alkylamino compounds showed marked local anesthetic activity in most cases.

RENSSELAER, N. Y. RECEIVED JULY 20, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

Synthesis of the Branched Chain 5-Isopropylaminoamyl and 4-Isopropylaminobutyl Ethers and of the Bromides Derived from Them[1,2]

BY ROBERT C. ELDERFIELD, BURNETT M. PITT AND IRIS WEMPEN

The series of drugs comprising derivatives of 8-aminoquinoline carrying an alkylaminoalkylamino or aminoalkylamino side chain in the 8-position is unique in that the members of the group are the only drugs presently known which possess the property of effecting a high percentage of permanent cures of relapsing vivax malaria when administered in conjunction with quinine. Despite the impressive amount of work which has been done along synthetic lines in the exploitation of this group of substances, several gaps remain to be filled in before a complete understanding of the relationship between structure and antimalarial action can be achieved.[3] While the most effective 8-aminoquinoline drugs presently known carry a methoxyl group in the 6-position of the quinoline ring, the effect of other substituents in the aromatic portion of the drug molecules is incompletely understood and forms the basis for separate investigations both in these laboratories and elsewhere.

In the 6-methoxy-8-aminoquinoline series, available data on the effect of branching the carbon side chain between the two nitrogen atoms is scanty if one excludes the familiar 1-methyl-4-alkylaminobutylamino configuration present in such drugs as pamaquin and isopentaquin. Indeed only two drugs embracing such variations have been reported in the literature, namely, SN-13,355 and SN-13,371.[3] Available pharmacological data on these two drugs are summarized in Table I together with similar data for pamaquin as a point of reference.[3] In addition to the data of Table I, SN-13,355 showed about one-half the toxicity of pamaquin in the monkey.

An analysis of the meager data available (Table I) indicates that in SN-13,355 in which the alkyl side chain is branched at the 4- rather than at the 1-carbon atom, both specificity to the host and to the test species of malaria have disappeared as compared to pamaquin. In SN-13,371 in which branching of the alkyl side chain occurs both at the 1- and 4-carbon atoms, such species and/or host specificity is partially restored. Further, the reported toxicity of SN-13,355 compares at worst not unfavorably with that of pamaquin.

In the light of the above data, it appeared to be worth while to undertake a systematic study of the effect of branching of the alkyl side chain of such drugs other than at the 1-carbon atom. In order to limit the scope of the investigation certain limitations have been imposed. The terminal amino group of the side chain has been restricted to the isopropylamino group because of the apparently unique effectiveness of this group on general curative antimalarial action and toxicity.[3,4] Further, the number of carbon atoms in the straight chain connecting the two nitrogen atoms of the side chain of the drugs has been limited to 4 and 5 and the total number of carbon atoms between the two nitrogens of the side chain has been limited to 5 and 6. The basis for this rather arbitrary choice is found in the pharmacology of a number of 8-aminoquinoline derivatives in which such variations are taken into account.[3] The arrangements selected appear to be the optimum ones.

As defined by the above restrictions, the 6-methoxy-8-aminoquinoline drugs selected for synthesis as candidate antimalarials are shown in Table II.

The most convenient procedure for the preparation of 8-aminoquinoline drugs consists in the alkylation of an 8-aminoquinoline with an appropriate amino halide.[5] In the present work the synthesis of the isopropylamino ethers XI–XIX and of the amino halides derived from them by cleavage of the ethers is described. The yields, properties and analytical data for the isopropylamino ethers are tabulated in Table III and the salts prepared for characterization of several of them are also listed in this table.

(1) This work was done with the aid of a grant from the National Institutes of Health to Columbia University.

(2) A portion of the work here described forms part of a dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy by Burnett M. Pitt at Columbia University.

(3) For a survey of existing data on such substances see Wiselogle, "Survey of Antimalarial Drugs," Edwards Bros., Ann Arbor, Mich., 1946.

(4) Private communications from Dr. Leon Schmidt, Christ Hospital Institute for Medical Research, Cincinnati, Ohio, and Dr. Alf Alving, University of Chicago.

(5) See THIS JOURNAL, August, 1946, for a number of papers dealing with this.

TABLE I

Drug	Structure[a]	Quinine equivalent	Malaria	Test animal
SN-13,355	R—NH(CH$_2$)$_3$CHN(C$_2$H$_5$)$_2$ C$_2$H$_5$	40	*P. Cathemerium*	Duck
		40	*P. Lophurae*	Duck
		40	*P. Gallinaceum*	Chick
SN-13,371	R—NHCH(CH$_2$)$_2$CHN(C$_2$H$_5$)$_2$ CH$_3$ CH$_3$	30	*P. Gallinaceum*	Chick
		40	*P. Lophurae*	Duck
Pamaquin Sn-971	R—NHCH(CH$_2$)$_3$N(C$_2$H$_5$)$_2$ CH$_3$	60	*P. Lophurae*	Duck
		40	*P. Lophurea*	Chick
		15	*P. Gallinaceum*	Chick
		150	*P. Cathemerium*	Duck

[a] R = 6-Methoxy-8-quinolyl-.

TABLE II

In I–X, R = 6-methoxy-8-quinolylamino; R_1 = isopropyl. In XI and XVIII, R = OC$_2$H$_5$; R_1 = isopropyl. In XII–XVII and in XIX, R = OCH$_3$; R_1 = isopropyl. In VIIIa R = Br; NR_1 = phthalimido

I R—CH$_2$—CH$_2$—CH$_2$—CH(CH$_3$)—NHR$_1$

XI R—CH$_2$—CH$_2$—CH$_2$—CH$_2$—CH(CH$_3$)—NHR$_1$

II R—CH$_2$—CH$_2$—CH$_2$—CH(C$_2$H$_5$)—NHR$_1$

XII R—CH$_2$—CH$_2$—CH$_2$—CH$_2$—CH(C$_2$H$_5$)—NHR$_1$

III R—CH$_2$—CH$_2$—CH(CH$_3$)—CH$_2$NHR$_1$

XIII R—CH$_2$—CH$_2$—CH$_2$—CH(CH$_3$)—CH$_2$NHR$_1$

IV R—CH$_2$—CH(C$_2$H$_5$)—CH$_2$—CH$_2$—NHR$_1$

XIV R—CH$_2$—CH$_2$—CH$_2$—CH$_2$—CH(C$_2$H$_5$)—NHR$_1$

V R—CH$_2$—CH(CH$_3$)—CH$_2$—CH$_2$—CH$_2$—NHR$_1$

XV R—CH$_2$—CH$_2$—CH$_2$—CH$_2$—CH$_2$—CH(CH$_3$)—NHR$_1$

VI R—CH$_2$—CH(CH$_3$)—CH$_2$—CH$_2$NHR$_1$

XVI R—CH$_2$—CH$_2$—CH(CH$_3$)—CH$_2$—CH$_2$—NHR$_1$

VII R—CH$_2$CH$_2$—CH(CH$_3$)—CH$_2$—CH$_2$—NHR$_1$

XVII R—CH$_2$—CH$_2$—CH$_2$—CH(CH$_3$)—CH$_2$—CH$_2$—NHR$_1$

VIII R—CH$_2$—CH$_2$—CH(C$_2$H$_5$)—CH$_2$—NR$_1$

VIIIa R—CH$_2$—CH$_2$—CH(C$_2$H$_5$)—CH$_2$—NR$_1$

IX R—CH$_2$—CH$_2$—CH$_2$—CH(CH$_3$)—CH$_2$—NHR$_1$

XVIII R—CH$_2$—CH$_2$—CH$_2$—CH$_2$—CH(CH$_3$)—CH$_2$—NHR$_1$

X R—CH$_2$—CH$_2$—CH$_2$—CH$_2$—CH$_2$—CH$_2$—CH(CH$_3$)—NHR$_1$

XIX R—CH$_2$—CH$_2$—CH$_2$—CH$_2$—CH$_2$—CH$_2$—CH$_2$—CH(CH$_3$)—NHR$_1$

TABLE III

THE ISOPROPYLAMINO ETHERS

Compound	Method of synthesis	Yield, %	B. p. °C.	B. p. Mm.	n^{25}D	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
XI	A	60	84–85	18	1.4205	69.3	69.1	13.4	13.1	8.1	8.0
XII	A	48	89–91	18	1.4250	69.3	68.7	13.4	13.1	8.1	8.2
XIII	A	46	81–84	17	1.4257	69.3	69.3	13.4	13.5	8.1	8.1
XIV	A	31	74–75	18	1.4222	67.9	67.2	13.3	13.3	8.8	8.7
XV	B	84	93–94	23	1.4265	69.3	69.3	13.4	13.2	8.1	8.2
XVI	C	88	75–76	18	1.4210	67.9	67.8	13.3	13.1	8.8	8.8
XVII	C	89	96–98	19	1.4259	69.3	69.2	13.4	13.3	8.1	8.2
XVIII	C	80	102–103	19		70.5	69.8	13.4	12.7	7.5	8.3
XIX	C	85	87–89	13		69.3	68.9	13.4	12.8	8.1	7.9

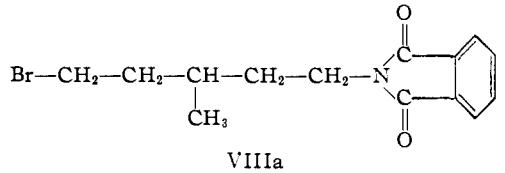
TABLE IV

SALTS OF THE ISOPROPYLAMINO ETHERS

Amino ether	Salt	Solvent for crystallization	M. p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
XI	Picryl sulf.	EtOAc	153–155 d.	41.2	41.3	5.6	5.8	12.1	12.2
XII	Picryl sulf.	EtOAc	144–145 d.	41.2	41.6	5.6	5.8	12.1	11.9
XIV	Oxalate	Acetone	134–135	53.0	53.2	9.3	9.3	5.6	5.8
XVI	Oxalate	Acet.–EtOH	156–157	53.0	53.2	9.3	9.2	5.6	5.6
XVII	Oxalate	Acetone	145–146	54.7	54.8	9.6	9.3	5.3	5.4
XVIII	Oxalate	EtOAc	153–154	56.3	56.4	9.8	9.9	5.1	5.0

The amino bromide hydrobromides are summarized in Table IV.

Due to difficulties to be discussed, the aminohalide required for the drug VIII has been prepared in the form of the bromophthalimide VIIIa from which the drug can be prepared by reductive

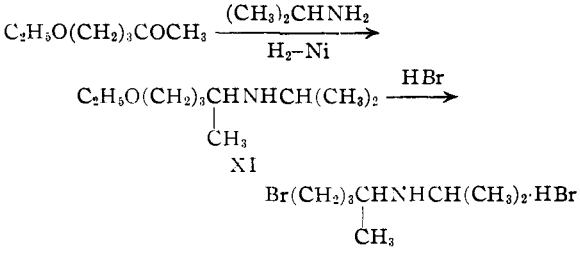


VIIIa

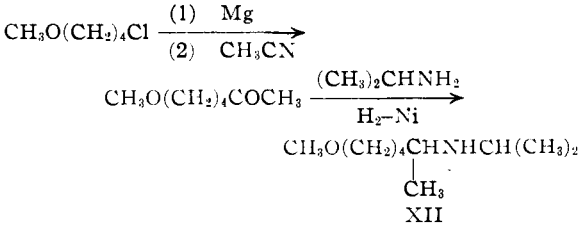
amination of acetone by the quinoline base derived from VIII.[6] The synthesis of the drugs I–X will be described in a later paper.

The isopropylamino group was introduced into the ethers by three general procedures: (A) reductive alkylation of isopropylamine with the appropriate alkoxy ketone, used to prepare XI–XIV; (B) reductive alkylation of the appropriate amino ether with acetone, used to prepare XV; (C) alkylation of isopropylamine with an appropriate alkoxylalkyl chloride, used to prepare XVI–XIX. The problem thus resolved itself into developing suitable syntheses for the intermediates required for the various alkylation reactions.

The amino ether XI was readily prepared by the first of the above methods from easily available 1-ethoxypentanone-4.[7] The amino bromide hydrobromide was readily obtained on cleavage of the ether. The reactions are



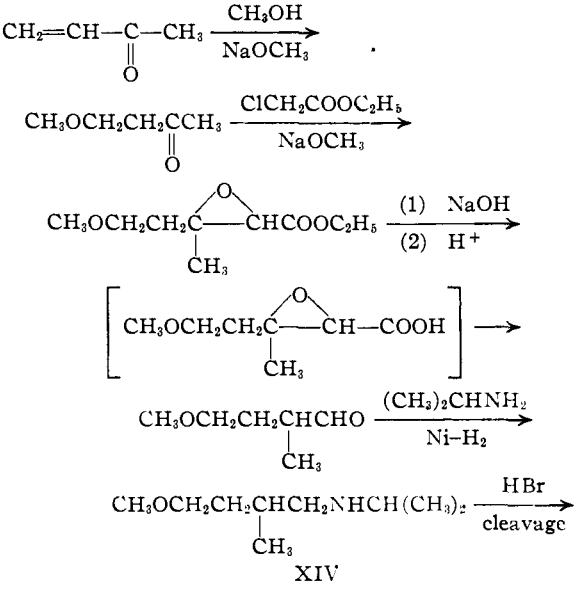
Synthesis of the amino ether XII was carried out by the following sequence of reactions from the recently commercially available 1,4-dichlorobutane[8] which offers a convenient source of 4-methoxybutyl chloride.



The yield of 1-methoxyhexanone-5 from the Grignard reagent prepared from XIX and acetonitrile was low (22.5%) which is in accord with the observation of Baerts[9] that poor yields are obtained with lower aliphatic Grignard reagents and acetonitrile. The yield of 1-methoxyhexanone-4 was considerably higher (54%).

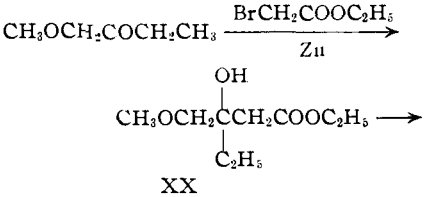
For the synthesis of XIII a scheme similar to the preceding one was employed except that propionitrile was substituted for acetonitrile. The final amino bromide hydrobromide, 1-bromo-4-ethyl-6-isopropylaminohexane hydrobromide, was obtained as a very viscous oil which has resisted all attempts at crystallization.

The preparation of the amino ether XIV was readily achieved *via* a Darzens glycidic ester synthesis as shown



The synthesis of 1-methoxybutanone-3 was first attempted from methylmagnesium iodide and β-methoxypropionitrile but only resinous, horny products were formed. The ketone was then prepared by base-catalyzed addition of methanol to methyl vinyl ketone at 10–15° at which temperature the yield was higher than when the reaction is run at −40° as given in the patent literature.[10] No difficulty was encountered in application of the Darzens reaction to the labile methoxybutanone, but the yield in the reductive alkylation step was low (31%) in common with experience elsewhere in such reactions with aldehydes.[11]

Synthesis of the amino ether (XV) caused considerable difficulty. The original scheme contemplated is shown in the equations



(6) Mosher, THIS JOURNAL, **68**, 1565 (1946); Elderfield, *et al.*, *ibid.*, **68**, 1568 (1946).

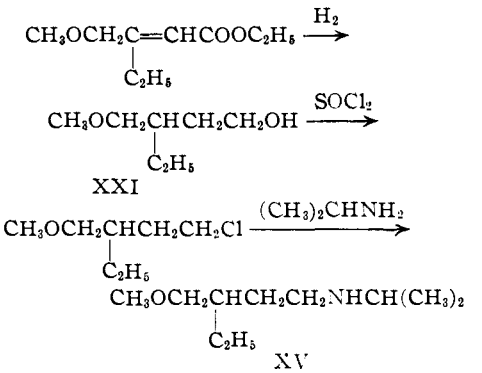
(7) Tracy and Elderfield, *J. Org. Chem.*, **6**, 63 (1941).

(8) Courtesy of the Electrochemicals Division, E. I. du Pont de Nemours & Co., Inc.

(9) Baerts, *Bull. soc. chim. Belg.*, **31**, 184 (1922).

(10) French Patent 842,724.

(11) Henze and Humphreys, THIS JOURNAL, **64**, 2878 (1942).

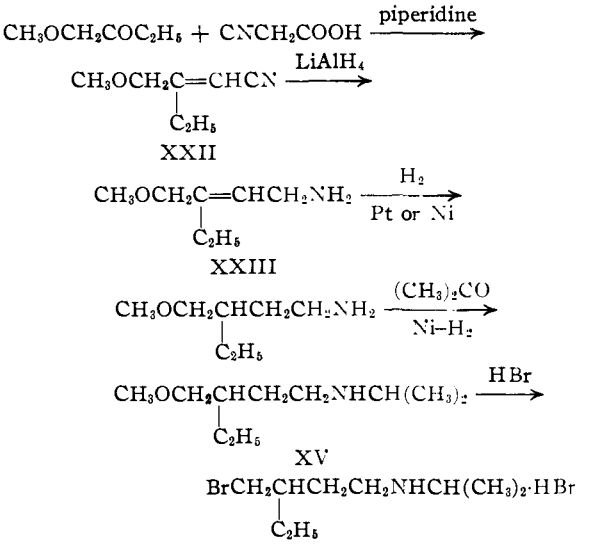


The possibility of direct conversion of XX to XXI was suggested by the work of Adkins and co-workers[12,13] who have noted that hydrogenolysis of β-keto- or β-hydroxy- esters as well as of certain glycols over copper chromite and over nickel results in hydrogenolysis of one or the other of the hydroxyl groups. Recent work by Mozingo and Folkers[14] has shown that reduction of β-hydroxy- and alkoxy-esters and malonic esters to the corresponding glycols or glycol ethers can be carried out over copper chromite at lower temperatures, higher pressure and with a larger amount of catalyst than that usual in ester reductions.

As an orienting experiment, ethyl β-ethoxypropionate was reduced over copper chromite at 250°. Only cleavage products were obtained. When XX was heated at 250° and 230 atm. of hydrogen over copper chromite, the major portion of the hydroxy ester was recovered unchanged. Similar hydrogenolysis of the β-hydroxyl group in XX over Raney nickel at 180° was unsuccessful.

In view of the failure of the direct conversion of XX to XXI the intermediate dehydration of XX to the acrylic ester was attempted. Although it was realized that the configuration of XX presented opportunity for the operation of the Stoermer aldehyde synthesis with formation of either a β-formylpropionic ester or an unsaturated butenolide,[15] it was hoped that conditions might be found whereby the tertiary hydroxyl group in XX might be eliminated in such a fashion that the double bond introduced would conjugate with the ester group. Such a dehydration of ethyl γ-ethoxy-β-hydroxybutyrate over phosphorus pentoxide has been reported by Lespieau,[16] but the yield is not given. When a solution of XX in benzene was refluxed with phosphorus pentoxide or oxychloride, partial dehydration apparently occurred since the product took up about 25% of the amount of hydrogen calculated for the unsaturated ester on hydrogenation. The product also gave a positive Tollens test indicating the occurrence of the Stoermer reaction at least to some extent. Similar results were noted when the free acid derived from XX was distilled, although the acid was recovered for the major part unchanged.

The desired amino ether (XV) was prepared by a different route as shown in the equations



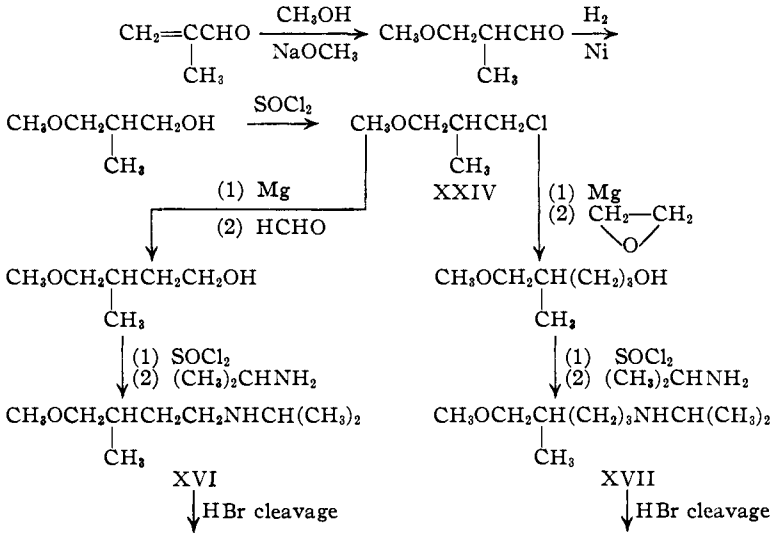
1-Methoxybutanone-2 condensed with cyanoacetic acid in the presence of a large amount of piperidine according to Shemyakin and Trakhtenberg[17] to give the unsaturated nitrile, XXII, in good yield. XXII on reduction with lithium aluminum hydride gave the unsaturated amine, XXIII. This reaction deserves comment. No example of the reduction of an unsaturated nitrile by this reagent appears in the literature. Several examples of the reduction of compounds containing non-conjugated nitriles or double bonds conjugated with a functional group are reported. Nystrom and Brown reduced crotonaldehyde to crotyl alcohol,[18] cinnamic acid to hydrocinnamyl alcohol,[19] and sorbyl chloride[18] and sorbic acid[19] to sorbyl alcohol with lithium aluminum hydride. Uffer and Schlittler,[20] using a much longer reaction time than that used by Nystrom and Brown, or in the present work, found that α-ethylcrotonamide was reduced to β-ethylbutylamine. In XXII both a conjugated double bond and a potentially labile allyl ether linkage are present. Neither was affected in the reduction with lithium aluminum hydride.

Reduction of the unsaturated amine (XXIII) to the saturated amine was slow over Adams catalyst at room temperature and rapid over Raney nickel at 75–100°. In neither case was appreciable cleavage of the allyl ether noted. Reductive

(12) Adkins and Connor, THIS JOURNAL, **54**, 4678 (1932).
(13) Adkins and Covert, *J. Phys. Chem.*, **35**, 1684 (1931).
(14) Mozingo and Folkers, THIS JOURNAL, **70**, 227 (1948).
(15) Rubin, Paist and Elderfield, *J. Org. Chem.*, **6**, 260 (1941).
(16) Lespieau, *Bull. soc. chim. France*, [3] **33**, 460 (1905).
(17) Shemyakin and Trakhtenberg, *Compt. rend. acad. sci. U. R. S. S.*, **24**, 763 (1938); Trakhtenberg and Shemyakin, *J. Gen. Chem. (U. S. S. R.)*, **13**, 477 (1943); *C. A.*, **38**, 3248 (1944).
(18) Nystrom and Brown, THIS JOURNAL, **69**, 1197 (1947); **70**, 3738 (1948).
(19) Nystrom and Brown, *ibid.*, **69**, 2548 (1947).
(20) Uffer and Schlittler, *Helv. Chim. Acta*, **31**, 1397 (1948).

alkylation to the amino ether, XV, proceeded in better yield than did any similar alkylation in the present work, possibly because the amino group alkylated is on a primary carbon atom.

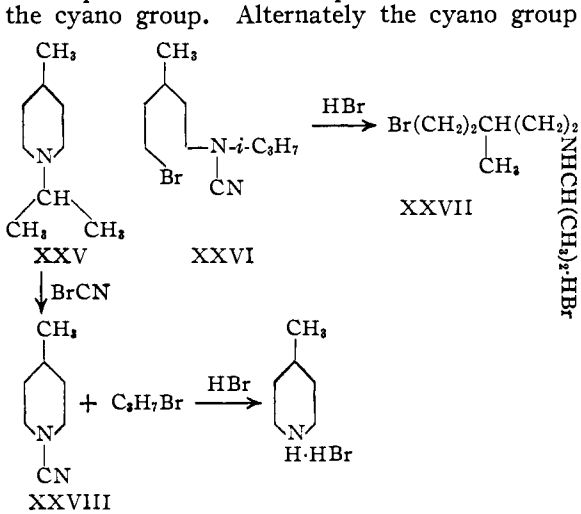
For the synthesis of the amino ethers XVI and XVII, the recently available α-methylacrolein was used as the key starting material. By base catalyzed addition of methanol in the presence of a trace of water at 10°, this offered a convenient source of β-methoxyisobutyraldehyde from which the amino ethers and bromide hydrobromides were prepared without difficulty by the schemes shown.

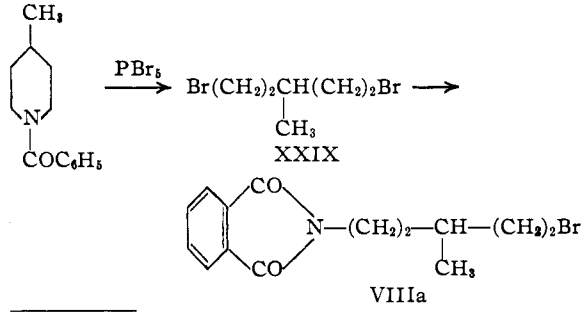


A possible approach to amino halides of the type here under consideration is found in von Braun's cyanogen bromide ring opening of appropriately substituted heterocycles. For example cleavage of 1-isopropyl-4-pipecoline (XXV) could lead to the bromocyanamide XXVI which can be used as such for the alkylation of 6-methoxy-8-aminoquinoline with subsequent elimination of the cyano group. Alternately the cyano group may be eliminated from the bromocyanamide to yield the bromo amine hydrobromide (XXVII). With the exception of the opening of the symmetrical pipecoline, XXV, this scheme at present does not appear to be applicable to other amino halides, since all of the others are derived from unsymmetrically substituted pipecolines or pyrrolidines in which ring opening in two directions is possible. No information is available in the literature as to the mode of ring opening to be expected and this approach was deferred pending the outcome of such a study currently underway in these laboratories.[21]

However, the cyanogen bromide reaction was investigated with the symmetrical pipecoline, XXV, as a route to the bromo amine hydrobromide, XXVII. After hydrolysis of the cyanamide resulting from ring opening with hydrobromic acid, only 4-pipecoline hydrobromide was isolated. Apparently the dealkylation reaction XXV–XXVIII predominated. The literature on this point is confused so that one would not have been able to predict the result of the cyanogen bromide reaction. von Braun[22] reports that with N-ethylpiperidine the ratio of dealkylation to ring opening is 2:1, and with N-*n*-propylpiperidine 2:3. He also found that the isopropyl group is more difficult to remove from a tertiary amine than a normal propyl group,[23] and that dealkylation is considerably more appreciable in the piperidine than in the pyrrolidine series.[24]

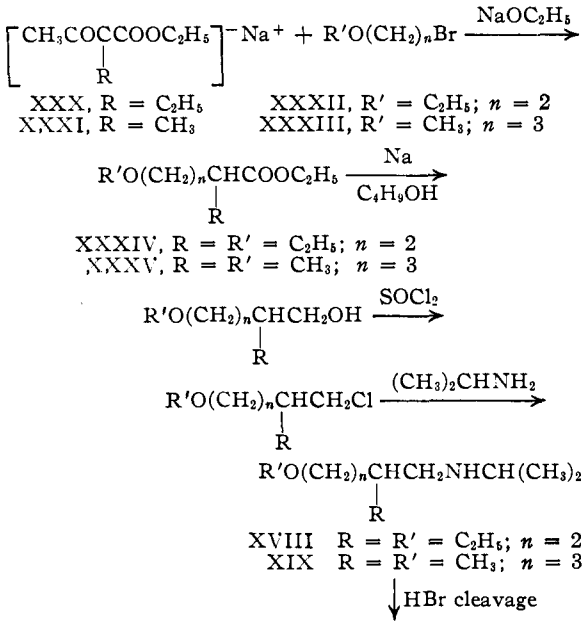
The alternate von Braun ring cleavage of 1-benzoyl-4-pipecoline with phosphorus pentabromide[25] according to Leonard and Wicks[26] readily yielded the dibromide XXIX which on reaction with potassium phthalimide gave the bromophthalimide, VIIIa. This is an acceptable intermediate for the synthesis of the drug, VIII.





(21) Elderfield and Hageman, *J. Org. Chem.*
(22) von Braun, *Ber.*, **42**, 2035 (1909).
(23) von Braun, *ibid.*, **33**, 2728 (1900).
(24) von Braun, *ibid.*, **44**, 1252 (1911).
(25) von Braun, *ibid.*, **37**, 3210 (1904).
(26) Leonard and Wicks, THIS JOURNAL, **68**, 2402 (1946).

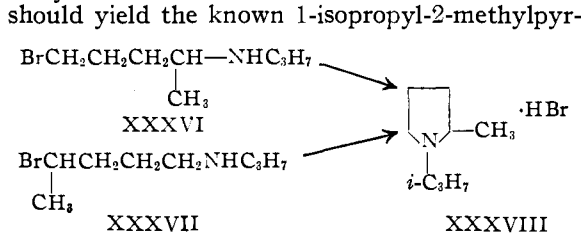
The amino ethers XVIII and XIX were prepared by similar series of reactions as indicated by the equations



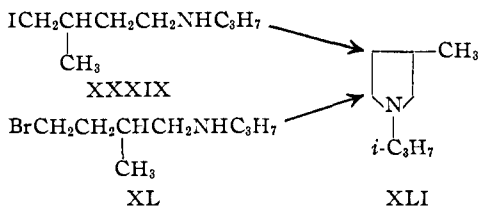
The sodioacetoacetic esters (XXX and XXXI) were condensed with the bromo ethers XXXII and XXXIII, respectively, in absolute alcohol solution. The esters XXXIV and XXXV were obtained directly as a result of alcoholysis.[27] In this way the usual acid decomposition of the disubstituted acetoacetic esters and subsequent reesterification was avoided. Preparation of the ester XXXIV was first attempted from the commercially available diethyl ethylmalonate and XXXII. However, the yields of the acid corresponding to XXXIV were so poor and variable that this approach was dropped. γ-Methoxypropanol required for XXXIII was prepared more easily by reduction of γ-methoxypropionaldehyde than from trimethylene glycol and methyl iodide in the presence of sodium.[28]

In the last steps of all of the above syntheses, with the exception of VIIIa, the possibility of rearrangements during cleavage of the ethers in the amino ethers to the amino halides must be considered. Available evidence indicates that such rearrangements did not occur.

Cyclization of the amino bromide XXXVI should yield the known 1-isopropyl-2-methylpyrrolidine (XXXVIII) resulting from cyclization of the aminobromide (XXXVII).[21] XXXVIII has also been prepared from 1,4-dichloropentane and isopropylamine.[21] The hydrobromides of the pyrrolidines prepared either from XXXVI or XXXVII were identical as judged by melting points and mixed melting points.

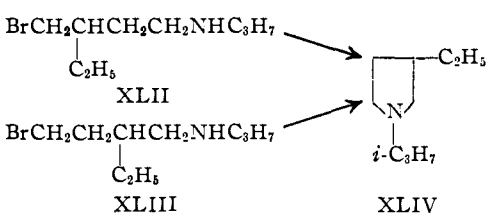


Reference pyrrolidines were not available for comparison with the ring closure products of the other amino halides, but significant information was obtained by comparison of the pyrrolidines arising from various pairs of the amino halides. Thus the halides XXXIX and XL gave the same



pyrrolidine (XLI) as judged by mixed melting points of the picrates of XLI prepared from the two.

Similarly the amino bromides XLII and XLIII should lead to the same 3-ethylpyrrolidine (XLIV).



The cyclized bases derived from XLII and XLIII were shown to be identical as judged by the melting points of the hydrobromides; on mixing no depression was observed.

Attempted alkylations of 6-methoxy-8-aminoquinoline with the bromide hydrobromide derived from XI were carried out by the procedure of Rohrmann and Shonle[29] and by "Procedure B" of Elderfield, *et al.*[30] With the bromide hydrobromide corresponding to XXXIX, an alkylation in a citrate buffered medium at *p*H 4.0 was attempted. These experiments resulted only in the recovery of unreacted 6-methoxy-8-aminoquinoline and cyclization of the bromobutylamine hydrobromide. Low yields are reported in alkylation of 6-methoxy-8-aminoquinoline with a number of 1-bromo-4-aminobutane derivatives.[30] The alkylation of 6-methoxy-8-aminoquinoline has consequently been postponed pending a study now under way in this Laboratory of the kinetics of ring closure of the side chain intermediate, and of the alkylation of the aminoquinoline under conditions where ring closure is not appreciable.

(27) Finkelstein and Elderfield, *J. Org. Chem.*, **4**, 365 (1939).
(28) Noyes, *Am. Chem. J.*, **19**, 766 (1897).
(29) Rohrmann and Shonle, THIS JOURNAL, **66**, 1640 (1944).
(30) Elderfield, *et al.*, *ibid.*, **68**, 1524 (1946).

TABLE V

THE BROMOAMINE HYDROBROMIDES

Amino ether from which derived	Yield, %	M. p., °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XI	76	117–118	33.2	6.6	4.9	32.8, 33.2	6.5, 6.6	4.9
XII	56	96–97	35.7	7.0	4.6	35.6	7.0	4.8
XIII	Unable to bring product to analytical purity							
XIV	55	112–113	33.2	6.6	4.9	33.4	6.6	5.3
XV	Instability of product prevented satisfactory analyses							
XVI	64	136–137	33.2	6.6		33.6	6.9	
XVII	Product too hygroscopic to be brought to analytical purity							
XVIII	60	148–149.5	35.7	7.0	4.6	36.0	6.8	5.0[a]
XIX	90	91–92.5	35.7	7.0		36.0, 36.1	6.8, 6.9	

[a] *Anal.* Calcd.: Br, 52.7. Found: Br, 52.4.

Experimental[31,32]

1-Ethoxy-4-isopropylaminopentane (XI). (Procedure A).—The following procedure is representative of Procedure A except as noted in one case for the preparation of the isopropylamino ethers by reductive amination of ketones or aldehydes. The properties, yields and analytical data for the amino ethers are summarized in Table III. Ethyl α-(β-ethoxyethyl)-acetoacetate, b. p. 135–140° (30 mm.) was prepared according to the procedure of Clarke and Gurin[33] and was converted to 1-ethoxypentanone-4, XVII, b. p. 169–172° as described by Tracy and Elderfield.[7] A mixture of 65 g. (0.5 mole) of 1-ethoxypentanone-4, 29.5 g. (0.5 mole) of isopropylamine and 75 ml. of ethanol was placed in a bomb with 10 g. of Raney nickel under 1400 lb. of hydrogen. The mixture was shaken for four hours at 150°. The product was distilled through an 8-in. Vigreux column to yield 70 g. of a mixture, b. p. 94° (20 mm.), of the desired amine and a neutral product (presumably 1-ethoxypentanol-4), which was used directly for the subsequent step. The amine was separated by acidifying a portion of the distillate with hydrochloric acid, followed by extraction of the neutral portion with ether. The base was regenerated by the addition of excess 20% sodium hydroxide, extracted into ether, dried over anhydrous potassium carbonate and distilled through a 10-in. helix-packed column.

The amine failed to yield a crystalline derivative with picric, styphnic, oxalic, picrolonic, chloroplatinic, chloroauric, hydrochloric and hydrobromic acids. (Aside from oxalic acid salts, this was general throughout the present series of amino ethers.) The addition of a saturated solution of picryl sulfonic acid in acetone to the amine in ethyl acetate yielded an oil, which crystallized on standing overnight. The properties and analytical data of salts prepared for characterization of certain of the other amino ethers are summarized in Table IV. When no salt is reported, it is to be understood that no suitable salt could be found.

1-Bromo-4-isopropylaminopentane Hydrobromide (XXXVI).—This represents the general procedure used for cleavage of the ethers in the isopropylamino ethers. The properties and analytical data for the bromoamine hydrobromides are summarized in Table V. A mixture of 75 g. of crude 1-ethoxy-4-isopropylaminopentane was refluxed for five hours with 750 g. of 48% hydrobromic acid according to the general procedure described by Elderfield, *et al.*[34] An oily halide layer resulting from reaction of the hydrobromic acid with the neutral product present in the crude amine, separated shortly after the start of the reaction. The major portion of the hydrobromic acid together with the halide layer was distilled at atmospheric pressure. The residue was then distilled on a water-pump to near dryness; the resultant viscous oil was taken up in absolute ethanol and concentrated on the water-pump until a solid cake of crude bromide hydrobromide was obtained. The crude product crystallized from 90% ethyl acetate–10% ethanol.

4-Methoxybutyl Chloride (XIX).—In a 3-liter 3-necked flask equipped with stirrer, reflux condenseer, thermometer and addition funnel, was placed 827 g. (6.5 moles) of tetramethylene chloride[8] in 250 ml. of methanol. The mixture was heated to reflux and a solution of 5 moles of sodium methoxide in 1200 ml. of methanol, was added over a five-hour period. The mixture was refluxed until neutral as measured by Universal indicator paper (thirty hours). The sodium chloride formed was filtered off and the filtrate was then rapidly distilled to separate the product from the residual sodium chloride. The distillate was fractionated to yield 228 g. (36%) of 4-methoxybutyl chloride, b. p. 142–143°, $n^{20}D$ 1.4244.

Palomaa and Jansson[35] prepared 4-methoxybutyl chloride from 4-methoxybutanol and phosphorus trichloride and found b. p. 142.5–142.8°, $n^{20}D$ 1.42444. On the basis of recovered starting material, a 40% yield was obtained. Little diether was formed, and, during the reaction, moderate gas evolution was observed, presumably from the formation of butadiene.

1-Methoxyhexanone-5.—A Grignard reagent was prepared from 159 g. (1.3 moles) of 4-methoxybutyl chloride and 36.6 g. (1.5 moles) of magnesium in 500 ml. of ether. During this preparation a fine white precipitate of the sparingly soluble Grignard reagent formed. The mixture was refluxed for an additional one-half hour after the completion of the addition of the chloride. Then a solution of 49 g. (1.2 moles) of acetonitrile in 150 ml. of ethyl ether was added, which resulted in the formation of a gummy precipitate making stirring difficult. The mixture was refluxed an additional hour and finally decomposed with ice and acidified with hydrochloric acid. The ether layer was removed and the aqueous layer washed with two 200-ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate and fractionated through a 10-in. helix-packed column to give 35 g. (22.5%) of 1-methoxyhexanone-5, b. p. 65–67° (8 mm.), $n^{25}D$ 1.4180.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.6; H, 10.8. Found: C, 64.2; H, 10.8.

The 2,4-dinitrophenylhydrazone of 1-methoxyhexanone-5 crystallized in red-orange plates from ethanol, m. p. 69–70°.

Anal. Calcd. for $C_{13}H_{18}N_4O_5$: C, 50.3; H, 5.9. Found: C, 50.3; H, 6.1.

1-Methoxyhexanone-4.—γ-Methoxypropyl chloride was prepared according to the method of Haworth and Perkin[36]

(31) All melting points are corrected for stem exposure. All boiling points are uncorrected and unless otherwise indicated are at atmospheric pressure.

(32) Microanalyses by Miss Lois May of these laboratories; the Clark Microanalytical Laboratories, Urbana, Illinois; and Miss Renate Rother, Department of Biochemistry, College of Physicians and Surgeons, Columbia University.

(33) Clarke and Gurin, THIS JOURNAL, **57**, 1876 (1935).

(34) Elderfield, *et al.*, *ibid.*, **68**, 1579 (1946).

(35) Palomaa and Jansson, *Ber.*, **64B**, 1606 (1931).

(36) Haworth and Perkin, *J. Chem. Soc.*, **65**, 591 (1894).

from the trimethylene chlorobromide and sodium methoxide. The product boiling at 108–110° was used for the following synthesis. A solution of 147 g. (1.36 moles) of γ-methoxypropyl chloride in 400 ml. of ether was added to 34 g. of magnesium (1.40 moles) to give a sparingly soluble Grignard reagent. The Grignard reagent was refluxed for one-half hour and 61 g. (1.1 moles) of propionitrile in 100 ml. of ether was then added over one hour. The gummy product, diluted with 100 ml. of ether to ease stirring, was heated under reflux for an additional hour. The mixture was hydrolyzed with ice, acidified with sulfuric acid, extracted with ether and dried over anhydrous magnesium sulfate. Distillation through a 10-in. helix-packed column yielded 76 g. (54%) of 1-methoxyhexanone-4, b. p. 82–83° (30 mm.), d^{20}_4 0.9103, $n^{20}D$ 1.4179; M_D calcd. 36.18, found 35.98.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.6; H, 10.8. Found: C, 64.4; H, 10.6.

The 2,4-dinitrophenylhydrazone of 1-methoxyhexanone-4 was recrystallized from ethanol in red-orange plates, m. p. 49–50°.

Anal. Calcd. for $C_{13}H_{18}N_4O_5$: C, 50.3; H, 5.9. Found: C, 50.8; H, 5.9.

1-Methoxybutanone-3.—Methyl vinyl ketone azeotrope (du Pont) was dried over anhydrous magnesium sulfate. The crude material was filtered from the drying agent, 1% by weight of hydroquinone was added and the mixture was distilled rapidly under a stream of nitrogen to give 30–40% of methyl vinyl ketone, b. p. 70–95°. To 368 g. (11.5 moles) of anhydrous methanol containing 4.5 g. of sodium methoxide was added with stirring 231 g. (3.3 moles) of methyl vinyl ketone at 10–15° during two hours. The reaction mixture, cooled in an ice-bath, was further stirred for three hours and then neutralized with hydrogen chloride in methanol to *p*H 7 to Universal indicator paper and allowed to stand overnight at 5°. (This did not influence the yield.) The mixture was then distilled through a 10-in. helix-packed column at 50 mm. with a Dry Ice-cooled flask in the line to trap the unreacted methyl vinyl ketone for use in subsequent runs. There was obtained 246 g. (73%) of 1-methoxybutanone-3, b. p. 137–140°, b. p. 64–66° (50 mm), $n^{20}D$ 1.4050. Killian, Hennion and Nieuwland[37] give b. p. 139–140°, $n^{12}D$ 1.4091; b. p. 137–138°, $n^{23}D$ 1.4041.

α-Methyl-γ-methoxybutyraldehyde.—A mixture of 104 g. (1.02 moles) of 1-methoxybutanone-3 and 160 g. (1.3 moles) of ethyl chloroacetate was placed in a 1-liter 3-necked flask equipped with stirrer and thermometer and protected from air with a potassium hydroxide filled tube. The flask was connected by means of a rubber sleeve to a 200-ml. flask containing 65 g. (1.2 moles) of commercial sodium methoxide. The reaction mixture was cooled in a Dry Ice-bath to −10°. The sodium methoxide was added over a one-hour period at such a rate that the temperature of the reactants was maintained at −15 to −5°. The mixture was further stirred for four hours at −5°, and was then neutralized with glacial acetic acid. The precipitated sodium chloride was dissolved by the addition of 300 ml. of water and the product was extracted with 200 ml. of ether and dried over anhydrous magnesium sulfate. On fractionation through a 10-in. helix-packed column, 118 g. (61.5%) of ethyl β-methyl-β-(β'-methoxyethyl)-glycidate was obtained, b. p. 114–118° (15 mm.), b. p. 125–129° (25 mm.).

A mixture of 118 g. of the glycidic ester and 300 ml. of an ice-cold 10% solution of sodium hydroxide was placed in a 1-liter flask immersed in an ice-bath and stirred for three hours. The mixture was then acidified by the cautious addition of a cold solution of 50 g. (0.5 mole) of sulfuric acid in 100 ml. of water. The free glycidic acid was extracted into ether and dried over anhydrous sodium sulfate. The ether was distilled and the residual acid decarboxylated spontaneously. The decarboxylation was completed by heating under slightly reduced pressure and the α-methyl-γ-methoxybutyraldehyde was distilled as formed. On redistillation, 43 g. (59%) of α-methyl-γ-methoxybutyraldehyde was obtained, b. p. 65–66° (55 mm.), b. p. 140–142° (760 mm.), $n^{25}D$ 1.4280.

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.0; H, 10.4. Found: C, 61.6; H, 10.1.

The 2,4-dinitrophenylhydrazone of α-methyl-γ-methoxybutyraldehyde crystallized in yellow-orange plates from ethanol, m. p. 87–88°.

Anal. Calcd. for $C_{12}H_{16}N_4O_5$: C, 48.7; H, 5.4. Found: C, 48.9; H, 5.5.

4-Methoxy-2-methylbutylisopropylamine (XIV).—A mixture of 70 g. of α-methyl-γ-methoxybutyraldehyde (0.6 mole), 59 g. (1.0 mole) of isopropylamine and 100 ml. of cyclohexane was placed in a bomb with 10 g. of Raney nickel under 1700 lb. of hydrogen. The mixture was shaken at 150° for two hours and worked up as in the preceding cases.

1-Methoxybutanone-2.—1-Methoxybutanone-2 was prepared by the addition at 0° of 142 g. (2 moles) of methoxyacetonitrile[38] in 100 ml. of ether to the Grignard reagent prepared from 327 g. (3 moles) of ethyl bromide and 78 g. (3.25 moles) of magnesium in 1500 ml. of ether. The mixture was allowed to stand overnight and was then hydrolyzed with ice, acidified with hydrochloric acid and extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and distilled to give a 59% yield (120 g.) of 1-methoxybutanone-2, boiling at 129–132°. Barnes and Budd[39] prepared 1-methoxybutanone-3 by the same method at −50°, with larger excess of Grignard reagent and obtained the ketone in 59% yield, b. p. 129–132°.

Ethyl β-Hydroxy-β-methoxymethylvalerate (XX).—Granulated zinc was activated by washing first with 2% hydrochloric acid, then water, alcohol, acetone and lastly with ether and was finally dried *in vacuo* at 100°. To 115 g. of zinc in a 2-liter 3-necked flask equipped with stirrer, addition funnel and reflux condenser was added 150 ml. of a solution of 181 g. (1.77 moles) of 1-methoxybutanone-2 and 296 g. (1.77 moles) of ethyl bromoacetate in 700 ml. of anhydrous benzene. Within five minutes the reaction started spontaneously and proceeded vigorously. When the initial reaction had subsided, the remainder of the reactants was added during one and one-half hours at such a rate as to maintain moderate reflux. The reaction mixture was refluxed for one and one-half hours after the addition was completed. On cooling, the product was hydrolyzed by addition of an ice-cold solution of 60 ml. of sulfuric acid in 300 ml. of water. The benzene layer was then separated and the aqueous layer was extracted with two 200-ml. and one 100-ml. portions of benzene. The combined benzene extracts were washed with saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. On fractionation through a 10-in. helix-packed column there was obtained 230 g. (68%) of ethyl β-hydroxy-β-methoxymethylvalerate, b. p. 113–116° (20 mm.), $n^{20}D$ 1.4324, d^{20}_4 1.0189; M_D calcd. 48.58; found 48.47.

Anal. Calcd. for $C_9H_{18}O_4$: C, 56.8; H, 9.5. Found: C, 56.4; H, 9.5.

β-Ethyl-γ-methoxycrotononitrile (XXII).—The condensation of 1-methoxybutanone-2 with cyanoacetic acid was carried out according to the general procedure of Shemyakin and Trakhtenberg[17] for condensation of aliphatic ketones with cyanoacetic acid. A mixture of 147 g. (1.44 moles) of 1-methoxybutanone-2 and 255 g. (2.88 moles) of cyanoacetic acid was placed in a 1-liter 3-necked flask equipped with stirrer, reflux condenser and addition funnel. One hundred and fifty ml. of piperidine was added rapidly to the mixture during which considerable heat was evolved. Then 110 ml. of piperidine was added over a ten-minute period so that the vigorous decarboxylation which occurred at this point remained under control.

(37) Killian, Hennion and Nieuwland, THIS JOURNAL, **56**, 1786 (1934); *ibid.*, **58**, 892 (1936).

(38) Scarrow and Allen, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 387.

(39) Barnes and Budd, THIS JOURNAL, **68**, 2339 (1946).

After completion of the addition, the mixture was stirred under rapid reflux for three and one-half hours. Distillation at 40 mm. removed the major portion of the piperidine. After cooling, a slight excess of hydrochloric acid was added and the unsaturated nitrile was extracted into ether. The ether layer was dried over anhydrous magnesium sulfate and distilled to give 124 g. (69%) of β-ethyl-γ-methoxycrotononitrile, b. p. 95–97° (23 mm.), $n^{25}D$ 1.4501.

Anal. Calcd. for $C_7H_{11}NO$: C, 67.2; H, 8.9. Found: C, 67.3; H, 8.8.

3-Methoxymethyl-1-aminopentene-2 (XXIII).—To a solution of 35 g. (0.92 mole) of lithium aluminum hydride in 700 ml. of ether, was added over a thirty-minute period 88 g. (0.71 mole) of β-ethyl-γ-methoxycrotononitrile in 100 ml. of ether, resulting in the formation of a canary yellow precipitate. The mixture was stirred for one-half hour after the completion of the addition, and was then hydrolyzed by the cautious addition of 25 ml. of water. Then 500 ml. of 10% sodium hydroxide was added. The ether layer was removed with some difficulty because of the gelatinous nature of the aluminum hydroxide precipitate. The aqueous layer was then extracted again with 500 ml. of ether in four portions. The combined ether layers were dried over anhydrous potassium carbonate and distilled to give 61 g. (67%) of 3-methoxymethyl-1-aminopentene-2, b. p. 75–76° (23 mm.), $n^{25}D$ 1.4499. Two other preparations using a ratio of one mole of nitrile to 1.0 and 0.75 mole of lithium aluminum hydride, respectively, both resulted in 50% yields of the desired amine.

Anal. Calcd. for $C_7H_{15}NO$: C, 65.1; H, 11.7. Found: C, 64.8; H, 11.4.

The oxalate, prepared by the addition of oxalic acid in acetone to the amine, was recrystallized from ethanol as shimmering white needles, and decomposed at 139.5–141°.

Anal. Calcd. for $C_9H_{17}NO_5$: C, 49.3; H, 7.8. Found: C, 49.5; H, 8.0.

3-Methoxymethylamylamine Oxalate.—A solution of 21 g. of 3-methoxymethyl-1-aminopentene-2 in 150 ml. of methanol was placed in the shaker together with 0.25 g. of Adams platinum oxide under 2 atm. of hydrogen. The mixture was shaken for eighteen hours and on distillation through a 6-in. Vigreux column gave 18 g. of amine boiling at 73–74° (23 mm.).

A similar reduction of the unsaturated amine was carried out in the bomb with 95 g. of 3-methoxymethyl-1-aminopentene-2 in 150 ml. of cyclohexane with 10 g. of Raney nickel. The reduction took place in thirty minutes at 75–100° under 1500 lb. of hydrogen. The solvent was first distilled off and the product was then distilled through a 10-in. helix-packed column, b. p. 73–74° (20 mm.). A solution of 0.75 g. of the amine in 2 ml. of acetone was converted to 3-methoxymethylamylamine oxalate with 0.75 g. of oxalic acid in 5 ml. of acetone yielding 1.0 g. of 3-methoxymethylamylamine oxalate, m. p. 145.5–146.5°.

Anal. Calcd. for $C_9H_{19}NO_5$: C, 48.9; H, 8.7. Found: C, 48.8; H, 9.0.

3-Methoxymethylamylisopropylamine (XV). (Procedure B).—A mixture of 105 g. (0.80 mole) of 3-methoxymethylamylamine in 100 ml. of isopropyl alcohol and 66 g. of acetone was placed in the bomb with 10 g. of Raney nickel under 1500 lb. of hydrogen. The mixture was heated to 125° for two hours. The catalyst was removed and the product was fractionated through a 10-in. helix-packed column.

β-Methoxyisobutyraldehyde.—An attempt to prepare β-methoxyisobutyraldehyde by the acid-catalyzed formation of β-methoxyisobutyraldehyde acetal from methacrolein, methanol and hydrochloric acid, as claimed by Schulz,[40] and hydrolysis of the acetal was unsuccessful.

The optimum procedure found for the preparation of β-methoxyisobutyraldehyde was as follows: Eastman Kodak Co. α-methylacrolein (93%) was dried over anhydrous magnesium sulfate and distilled under a stream of nitrogen immediately prior to use with 1% added hydroquinone. α-Methylacrolein, b. p. 65–85°, was obtained in 30–75% yield depending upon the age of the lot. In a 1-liter 3-necked flask equipped with stirrer, thermometer and addition funnel was placed a cold solution of 2 g. of sodium methoxide in 288 g. (9.0 moles) of methanol and 2 ml. of water. To the solution was added 140 g. (2 moles) of α-methylacrolein over a two-hour period during which the temperature was maintained at 5–15°. The reaction mixture was stirred an additional two hours at 5°, and neutralized to *p*H 7 as measured by Universal indicator paper with acetic acid in methanol. The mixture was distilled directly at 40–60 mm. with a Dry Ice-trap inserted in the line to collect starting material for recycle runs, and the product was collected at 40–65°. On redistillation of the distillate through a 10-in. helix-packed column, 103 g. (51%) of β-methoxyisobutyraldehyde was obtained, b. p. 127–129°, $n^{27}D$ 1.4030.

Anal. Calcd. for $C_5H_{10}O_2$: C, 58.8; H, 9.9. Found: C, 58.9; H, 9.9.

The 2,4-dinitrophenylhydrazone recrystallized from ethanol in yellow-orange plates, m. p. 101–102°.

Anal. Calcd. for $C_{11}H_{14}N_4O_5$: C, 46.8; H, 5.0. Found: C, 46.4; H, 5.3.

3-Methoxy-2-methylpropanol-1.—Four hundred and eight grams (4 moles) of β-methoxyisobutyraldehyde was placed in the bomb with 20 g. of Raney nickel under 1500 lb. of hydrogen. The aldehyde was reduced at 80–100° in one-half hour. The product was distilled to yield 389 g. (93.5%) of 3-methoxy-2-methylpropanol-1, b. p. 154–155°, $n^{27}D$ 1.4140, d^{27}_4 0.9168; M_D calcd. 28.46, found 28.43.

Anal. Calcd. for $C_5H_{12}O_2$: C, 57.7; H, 11.6. Found: C, 57.7; H, 11.5.

3-Methoxy-2-methylpropanol-1 and 3,5-dinitrobenzoyl chloride yielded the 3,5-dinitrobenzoate as fine white needles from aqueous ethanol, m. p. 63–64°.

Anal. Calcd. for $C_{12}H_{14}N_2O_7$: C, 48.3; H, 4.7. Found: C, 48.2; H, 4.8.

3-Methoxy-2-methyl-1-chloropropane (XXIV).—In a 1-liter, 3-necked flask equipped with stirrer, thermometer, addition funnel and condenser, were placed 208 g. (2.0 moles) of 3-methoxy-2-methylpropanol-1 and 158 g. (2.0 moles) of anhydrous pyridine. The mixture was cooled to 5° with an ice-brine bath, and 357 g. (3.0 moles) of thionyl chloride was added over a four-hour period, maintaining the temperature below 20°. When half the thionyl chloride had been added, the mixture was virtually a solid mass. After all the thionyl chloride had been added, the reaction was completed by allowing the mixture to heat spontaneously to 60°, and stirring for two and one-half hours at 60–65°. It was necessary to cool the mixture initially in order not to exceed the desired temperature. On cooling, the mixture was hydrolyzed in 400 g. of ice containing 100 ml. of concentrated hydrochloric acid. The chloride was then taken up in an equal volume of ether, and the ether layer was washed with water followed by 10% sodium hydroxide. After drying over anhydrous magnesium sulfate, the product was distilled through a 10-in. helix-packed column to give 225 g. (92%) 3-methoxy-2-methyl-1-chloropropane, b. p. 124–124.5°, $n^{27}D$ 1.4143, d^{27}_4 0.9661; M_D calcd. 31.80, found 31.73.

Anal. Calcd. for $C_5H_{11}ClO$: C, 49.0; H, 9.0. Found: C, 49.1; H, 9.1.

4-Methoxy-3-methylbutanol-1.—The Grignard reagent of 3-methoxy-2-methyl-1-chloropropane was prepared by the reaction of 122.5 g. of the chloride (1.0 mole) with 27 g. of magnesium in 500 ml. of ether. The Grignard reagent was sparingly soluble and appeared as a fine white precipitate after one-quarter of the halide had been added. The mixture was refluxed for one-half hour after the completion of the addition of the chloride. Gaseous formaldehyde was then added by heating 50 g. of paraformaldehyde to 170–200° in a 2-necked flask connected to the reaction flask by a 12-mm. gas inlet tube terminating 2 cm.

(40) Schulz, U. S. Patent 2,288,211.

above the surface of the Grignard solution. The formaldehyde generated was swept into the reaction mixture behind a stream of nitrogen. When the Michler ketone test for Grignard reagent was negative, the formaldehyde addition was terminated (the procedure employed is essentially that of Gilman and Catlin[41] for the preparation of cyclohexyl carbinol). The product was hydrolyzed with ice, acidified with one mole of dilute sulfuric acid and extracted into ether. The ether layer was dried over anhydrous magnesium sulfate and distilled to give 79 g. (67%) of 4-methoxy-3-methylbutanol-1, b. p. 88–90° (25 mm.), $n^{27}D$ 1.4213, d^{27}_4 0.9087; M_D calcd. 33.08, found 33.00.

Anal. Calcd. for $C_6H_{14}O_2$: C, 60.9; H, 11.9. Found: C, 61.1; H, 11.9.

The 3,5-dinitrobenzoate of 4-methoxy-3-methylbutanol-1, recrystallized from ethanol, melted at 56–57°.

Anal. Calcd. for $C_{13}H_{16}N_2O_7$: C, 50.0; H, 5.2. Found: C, 50.1; H, 5.0.

1-Methoxy-2-methyl-4-chlorobutane.—1-Methoxy-2-methyl-4-chlorobutane was prepared as described above for 3-methoxy-2-methyl-1-chloropropane from 201 g. (1.7 moles) of 4-methoxy-3-methylbutanol-1, 134 g. (1.7 moles) of anhydrous pyridine and 303 g. (2.55 moles) of thionyl chloride. Distillation through a 10-in. helix-packed column gave 207 g. (90%) of 1-methoxy-2-methyl-4-chlorobutane, b. p. 152–153°, $n^{27}D$ 1.4233, d^{27}_4 0.9573; M_D calcd. 36.42, found 36.36.

Anal. Calcd. for $C_6H_{13}ClO$: C, 52.7; H, 9.6. Found: C, 52.6; H, 9.4.

4-Methoxy-3-methylbutylisopropylamine (XVI). (Procedure C).—This procedure is representative of the amination of the ether halides with isopropylamine. A mixture of 186 g. (1.37 moles) of 1-methoxy-2-methyl-4-chlorobutane and 642 g. (10.9 moles) of isopropylamine was placed in the bomb and heated for forty-eight hours at 120°. The liquid was decanted from the bomb and the crystalline residue of isopropylamine hydrochloride together with some gummy product was removed with 300 ml. of water. The decantate was fractionated to remove the excess isopropylamine. The aqueous washings from the bomb were made strongly basic with 20% sodium hydroxide and the bulk of the isopropylamine was removed by distillation. The residue was then acidified with excess hydrochloric acid and combined with the residue from the decantate. The resulting combined acid solution was then extracted twice with 200-ml. portions of ether to remove unreacted halide. Excess 20% alkali was added and the amine was extracted into ether. The ether layer was dried over anhydrous potassium carbonate and distilled.

4-Bromo-3-methylbutylisopropylamine Hydrobromide.—A mixture of 30 g. of 4-methoxy-3-methylbutylisopropylamine and 300 g. of 48% hydrobromic acid was refluxed for six hours. The bromide hydrobromide was isolated as described previously. On standing, this compound changed to a glassy material.

When the ether cleavage of 4-methoxy-3-methylbutylisopropylamine was carried out over a longer period, elimination of hydrogen bromide occurred, presumably with the formation of an unsaturated amine. A mixture of 8.0 g. of 4-methoxy-3-methylbutylisopropylamine and 120 g. of 48% hydrobromic acid was refluxed for eight hours. The hydrobromic acid was then distilled off at atmospheric pressure and finally on the water-pump. The residue was part crystalline and part a viscous oil and was taken up in absolute ethanol and concentrated to dryness *in vacuo*. This procedure was repeated three times and the final residue was then dissolved in ethyl acetate–ethanol. The first crop of crystals was filtered off and recrystallized from the same solvent to give 0.70 g. of hydrobromide, prisms, m. p. 121–122°.

Anal. Calcd. for $C_8H_{18}BrN$: C, 46.2; H, 8.7; N, 6.7. Found: C, 46.5; H, 8.5; N, 6.7.

(41) Gilman and Catlin, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., p. 188.

The analysis corresponds to an elimination of hydrogen bromide either through cyclization or elimination to yield an olefin. The free base generated from this hydrobromide failed to yield a crystalline picrate. The hydrobromide gave a positive test for unsaturation with bromine water and has not been investigated further.

5-Methoxy-4-methylpentanol-1.—A Grignard reagent was prepared from 1 mole of 3-methoxy-2-methyl-1-chloropropane as previously described. After cooling the Grignard reagent to 0° with a solid carbon dioxide-bath, 200 g. of a 25% by weight solution of ethylene oxide in ether was added over a one-hour period. On completion of the addition of the ethylene oxide, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature and then heated to reflux for one hour. The condenser was then arranged for distillation and 275 ml. of ether was distilled. With the addition of 275 ml. of benzene, the distillation was continued until the vapor temperature rose to 65°, after which the reaction mixture, which was a viscous gum at this stage, was refluxed with continued stirring for one and three-quarter hours. After cooling, the product was hydrolyzed with ice, and 50 ml. of sulfuric acid in 225 g. of ice was added. The organic layer was then separated and the aqueous layer was extracted with two 200-ml. portions of ether. On distillation through a 10-in. helix-packed column, 98 g. (74%) of 5-methoxy-4-methylpentanol-1 was obtained, b. p. 96–98° (15 mm.), $n^{27}D$ 1.4272, d^{27}_4 0.9033; M_D calcd. 37.69, found 37.59.

Anal. Calcd. for $C_7H_{16}O_2$: C, 63.6; H, 12.2. Found: C, 63.3; H, 12.3.

1-Methoxy-2-methyl-5-chloropentane.—A solution of 257 g. (1.95 moles) of 5-methoxy-4-methylpentanol-1 in 154 g. (1.95 moles) of pyridine was placed in a 2-liter 3-necked flask and treated with 357 g. (3.0 moles) of thionyl chloride. The reaction procedure and the isolation of the product were identical with that described above for 3-methoxy-2-methyl-1-chloropropane. The product was obtained in 85% yield (249 g.), b. p. 177–178°, b. p. 72–73° (20 mm.), $n^{27}D$ 1.4272, d^{27}_4 0.9468; M_D calcd. 41.04, found 40.94.

Anal. Calcd. for $C_7H_{15}ClO$: C, 55.8; H, 10.0. Found: C, 55.8; H, 9.9.

Attempted Preparation of 5-Bromo-3-methylamylisopropylamine Hydrobromide via Cyanogen Bromide Degradation

4-Pipecoline.—4-Pipecoline has been previously prepared by Ladenburg[42] by sodium and alcohol reduction of 4-picoline and by Adams and Leonard[43] by catalytic reduction of 4-picoline. The present preparation was carried out with a slight modification of the latter procedure. Hydrogenation of 511 g. (5.5 moles) of 4-picoline was carried out in the bomb with 30 g. of Raney nickel under 1400 lb. of hydrogen. The compound was reduced by shaking at 260° for twenty hours; frequent recharge of hydrogen at 1400 lb. was necessary. There was obtained on distillation 332 g. (60%) of 4-pipecoline, b. p. 126–129°.

N-Isopropyl-4-pipecoline (XXV).—A mixture of 100 g. of 4-pipecoline and 78 g. of acetone was placed in the bomb with 10 g. of Raney nickel and 1500 lb. of hydrogen. The mixture was heated to 150° and shaken for a total of five hours. The product was fractionated through a 10-in. helix-packed column to yield 110 g. (77%) of N-isopropyl-4-pipecoline, b. p. 165–166°, $n^{25}D$ 1.4411.

Anal. Calcd. for $C_9H_{19}N$: C, 76.5; H, 13.6; N, 9.9. Found: C, 76.3; H, 13.8; N, 9.9.

The picrate of N-isopropyl-4-pipecoline was prepared from the amine and saturated picric acid in ethanol and was recrystallized from ethanol, m. p. 139–140°.

Anal. Calcd. for $C_{15}H_{22}N_4O_7$: C, 48.6; H, 6.00. Found: C, 48.7; H, 5.9.

(42) Ladenburg, *Ann.*, **247**, 1 (1888).

(43) Adams and Leonard, THIS JOURNAL, **66**, 257 (1944).

Reaction of 1-Isopropyl-4-pipecoline with Cyanogen Bromide.—To a solution of 48 g. (0.45 mole) of cyanogen bromide in 100 ml. of benzene, was added 58 g. (0.41 mole) of 1-isopropyl-4-pipecoline diluted to 275 ml. in benzene. The amine was added slowly over one hour and the temperature rose to a maximum of 46° during the addition. After the addition was completed, the mixture was heated to 55–60° for three-quarters of an hour and then allowed to stand at room temperature for thirty-six hours. The basic material was removed by extraction into 150 ml. of 5% hydrochloric acid. The benzene layer was then dried and the solvent removed by distillation leaving a residue of 44 g. Sixteen grams of basic material was recovered from the hydrochloric acid extract.

A mixture of 39 g. of the neutral product and 300 ml. of 48% hydrobromic acid was refluxed for ten hours. The hydrobromic acid was removed by distillation on the water-pump. The residue was leached with 80% ethyl acetate–20% ethanol, and the solution was then decolorized with Norite and concentrated. Ammonium bromide was separated by filtering the hot concentrate, which on cooling deposited handsome needles (27 g.), m. p. 171–173°. Twice recrystallized from ethyl acetate and ethanol, the product melted at 174–175°. A sample of authentic 4-pipecoline hydrobromide prepared from 4-pipecoline in ether and gaseous hydrogen bromide melted at 174–175°. Mixed melting point of the product from the cyanogen bromide reaction and 4-pipecoline hydrobromide showed no depression.

Anal. Calcd. for $C_6H_{14}BrN$: C, 40.0; H, 7.8. Found: C, 40.1; H, 7.8.

No other product was isolable from the reaction. When 5 g. of the neutral portion was refluxed for two hours with 5 g. of diethylamine in 10 ml. of ethanol and the solvent and amine distilled, there was no product obtained soluble in 3% hydrochloric acid.

N-5-Bromo-3-methylamylphthalimide (VIIIa).—In a 1-liter 3-necked flask equipped with stirrer, thermometer and condenser, were placed 56 g. (0.30 mole) of potassium phthalimide and 220 g. (0.90 mole) of 1,5-dibromo-3-methylpentane.[26] The mixture was heated with stirring at 145–150°[44] for five hours until neutral to litmus. The mixture was then taken up in a small volume of ethanol and the potassium bromide was filtered off. The solvent and unreacted halide were stripped off on the water-pump and the residue was distilled, yielding 71 g. (79%) of N-5-bromo-3-methylamylphthalimide, b. p. 179–183° (0.8 mm.). The product was crystallized by the addition of a seed prepared by dissolving a small amount of the oil in ether and cooling the solution in Dry Ice. The crude product melted at 52–54°. On recrystallization from heptane–ether, the phthalimide crystallized in stout prisms and melted at 54.5–55°.

Anal. Calcd. for $C_{14}H_{16}BrNO_2$: C, 54.2; H, 5.2; N, 4.5. Found: C, 53.9; H, 5.4; N, 4.2.

Ethyl β-Bromoethyl Ether.—In the preparation of this substance substantially according to Palomaa and Kenetti,[45] it was found to be vital that the crude bromo ether be washed until all free mineral acid is removed since the ether is very unstable in the presence of traces of acid. It is advisable to store the substance over a small amount of potassium carbonate in a brown bottle.

Ethyl α-Ethyl-γ-ethoxybutyrate (XXXIV).—To a hot solution of sodium ethoxide prepared from 57.5 g. of sodium and 2 l. of absolute ethanol was added gradually 395 g. of α-ethylacetoacetic ester[46] after which the mixture was refluxed for an hour. To this mixture 364 g. of ethyl β-bromoethyl ether was added dropwise and 5 g. of sodium iodide. The mixture was refluxed until neutral. After distilling off the alcohol, the residue was taken up in water and extracted with ether. The ether solution was washed with dilute sodium hydroxide solution for removal of unreacted acetoacetic ester. Distillation gave 30% of product, b. p. 93–95° (15 mm.).[47]

2-Ethyl-4-ethoxybutanol-1.—To a boiling solution of 282 g. of ethyl α-ethyl-γ-ethoxybutyrate in 3 l. of anhydrous *n*-butanol in a 5-l. flask equipped with two very efficient reflux condensers was added as rapidly as possible 180 g. of sodium in large chunks. The mixture was boiled after addition of the sodium until all of the sodium had dissolved. After cooling slightly, 160 ml. of water was added carefully with gentle shaking and the mixture was refluxed for an hour in order to saponify any unreduced ester. After cooling, 1200 ml. of water was added, the butanol layer was separated, and almost neutralized with hydrochloric acid. The butanol was fractionated off through a one-meter Vigreux column until the volume of the residue was somewhat less than a liter. The residue was then fractionated at reduced pressure yielding 60% of 2-ethyl-4-ethoxybutanol-1, b. p. 91–93° (10 mm.).

Anal. Calcd. for $C_8H_{18}O_2$: C, 65.7; H, 12.4. Found: C, 65.9; H, 12.5.

2-Ethyl-4-ethoxy-1-chlorobutane.—This was prepared by substantially the same procedure used in the preceding cases. From 300 g. of 2-ethyl-4-ethoxybutanol-1 and 378 g. of thionyl chloride in 160 g. of dry pyridine an 84% yield of material, b. p. 78–80° (18 mm.) was obtained.

Anal. Calcd. for $C_8H_{17}ClO$: C, 58.4; H, 10.4. Found: C, 58.8; H, 10.5.

γ-Methoxypropanol.—A considerable quantity of γ-methoxypropanol was required. The compound was prepared by a modification of the method described by Heyse.[48] The reaction was carried out with 280 g. (5 moles) of acrolein and 560 g. (17.5 moles) of methanol containing 1 g. of sodium as sodium methoxide. The acrolein was added slowly over a two-hour period to the methanol. The mixture was stirred an additional hour, then neutralized by the addition of Dry Ice. The solution of γ-methoxypropionaldehyde so obtained was reduced directly over Raney nickel at 100°. The effect of the temperature of the reaction on the yield of product is shown in Table V.

TABLE VI

EFFECT OF TEMPERATURE ON YIELD OF γ-METHOXYPROPANOL

Temperature range, °C.	Yield of γ-methoxypropanol, %
− 5 to +5	33
−10 to 0	46
−15 to −5	53
−20 to −10	63

The γ-methoxypropanol was distilled at 30 mm., b. p. 69–70°. Heyse[48] reports b. p. 66° (27 mm.).

Ethyl α-methyl-δ-methoxyvalerate (XXXV), b. p. 81–91° (13 mm.), was prepared in 60% yield by the same procedure as that used for XXXIV.

Anal. Calcd. for $C_9H_{18}O_3$: C, 62.0; H, 10.4. Found: C, 61.9; H, 10.2.

2-Methyl-5-methoxypentanol-1.—Reduction of 261 g. of XXXV in 3 l. of anhydrous butanol with 180 g. of sodium as in the preparation of 2-ethyl-4-ethoxybutanol-1 gave 85% of material, b. p. 93–95° (10 mm.).

Anal. Calcd. for $C_7H_{16}O_2$: C, 63.6; H, 12.2. Found: C, 63.8; H, 11.9.

2-Methyl-5-methoxy-1-chloropentane, b. p. 62–63° (9 mm.), was prepared in 77% yield as in the preceding cases.

Anal. Calcd. for $C_7H_{15}ClO$: C, 55.8; H, 10.0. Found: C, 55.9; H, 10.3.

Cyclization of Some Aminobromide Hydrobromides

Cyclic Amine Derived from XXXVI.—To a solution of 1 g. of 1-bromo-4-isopropylaminopentane hydrobromide

(44) *Cf.* Müller and Kraus, *Monatsh.*, **61**, 219 (1932).

(45) Palomaa and Kenetti, *Ber.*, **64**, 797 (1931).

(46) Michael, *ibid.*, **38**, 2091 (1905).

(47) Cope and McElvain, THIS JOURNAL, **54**, 4319 (1932).

(48) Heyse, German Patent 554,949 [*Friedländer*, **19**, 955 (1932)],

(XXXVI) in 10 ml. of water was added 10 ml. of 5% sodium hydroxide. The mixture was shaken vigorously for five minutes and allowed to stand one-half hour. The base was extracted into ether, the ether layer was dried over anhydrous potassium carbonate and then concentrated to 15 ml. When hydrogen bromide was added to the ether solution the hydrobromide was obtained as an oil, which crystallized on standing overnight at 5°. On filtration, 0.60 g. of crude product (83%) was obtained. Recrystallized from ethyl acetate–ethanol, the compound melted at 192.5–193.5°; mixed melting point with an authentic sample of the hydrobromide of 1-isopropyl-2-methylpyrrolidine (XXXVIII)[21] showed no depression.

Cyclic Amines Derived from XXXIX and XL.—The cyclization of 4-bromo-2-methylbutylisopropylamine hydrobromide (XL) was carried out as described above. The amine was extracted into ether and dried; the ether was removed and saturated picric acid in ethanol was added. The picrate was obtained as yellow needles, melting after recrystallization from ethanol at 140–141° (yield 0.64 g., 51%); this was presumably the picrate of 1-isopropyl-3-methylpyrrolidine (XLI).

Cleavage of 5 g. of 4-methoxy-3-methylbutylisopropylamine was carried out by refluxing with 30 ml. of hydriodic acid for three hours. The product separated as a viscous tar. The hydriodic acid was distilled under reduced pressure, and the residue was made basic with 10% sodium hydroxide and shaken for five minutes, extracted into ether and dried over anhydrous potassium carbonate. The amine was distilled, giving 3.0 g. of product, b. p. 150–165°. The picrate prepared from 0.50 g. of this amine (yield 0.60 g., 56%) after recrystallization from ethanol, melted at 140–141°. Mixed melting points with the picrate derived from (XL) showed no depression.

Anal. Calcd. for $C_{14}H_{20}N_4O_7$: C, 47.2; H, 5.7; N, 15.7. Found: C, 47.4, 47.6, 47.2; H, 5.5, 5.4, 5.5; N, 15.8, 15.6.

Cyclic Amines Derived from XLII and XLIII.—To a solution of 1.00 g. of crude 4-bromo-3-ethylbutylisopropylamine hydrobromide (XLII) dissolved in 10 ml. of water was added 10 ml. of a 5% sodium hydroxide solution. The mixture was allowed to stand one-half hour with frequent shaking and the product was extracted into ether and dried over anhydrous potassium carbonate. The same procedure was employed with XLIII. The ether layers were concentrated to 15 ml. and hydrogen bromide was added. Oils separated in both cases which crystallized in fine needles on standing for thirty-six hours. Yields of 0.50 g. and 0.45 g. of crude hydrobromide were obtained from XLIII and XLII, respectively (68% and 62%). Recrystallized from ethyl acetate–ethanol, the hydrobromides, presumably of 1-isopropyl-3-ethyl pyrrolidine (XLIV), melted at 163–165° and showed no depression on mixing.

Anal. Calcd. for $C_9H_{20}BrN$: C, 48.7; H, 9.1; N, 6.3. Found: C, 48.7; H, 9.0; N, 6.3.

Summary

The synthesis of nine isopropylaminoamyl and isopropylaminobutyl ethers, and one bromoamylphthalimide of interest as intermediates for the synthesis of 6-methoxy-8-aminoquinoline antimalarials is described. The reaction of the ethers with hydrobromic acid is discussed, and the relationships of the cyclic derivatives derived from certain of the bromobutylisopropylamines is shown.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

D-Manno-L-*fructo*-octose[1]

BY M. L. WOLFROM AND PASCAL W. COOPER

In continuation of our work on the preparation of the higher ketoses, we report herein the synthesis of a ketoöctose, designated D-manno-L-*fructo*-octose, from D-manno-D-*gala*-heptonic acid through the reaction series $R\text{–}CO_2H \xrightarrow{PCl_5} R\text{–}COCl \xrightarrow{CH_2N_2} RCOCHN_2 \xrightarrow[Cu^{++}]{HOAc} RCOCH_2OAc \xrightarrow{Ba(OH)_2} CH_2OH\text{–}(CHOH)_5\text{–}CO\text{–}CH_2OH$, wherein $R = CH_2OAc\text{–}(CHOAc)_5\text{–}$. All of the intermediates were obtained in crystalline condition. Although the final octose was not crystallized, it was characterized by its keto acetate and phenylosazone, the latter being first described by Fischer and Passmore.[2] The initial heptonic acid is the one obtainable in preponderant amount on subjecting D-mannose to the cyanohydrin reaction.[2,3] This acid was designated D-α-mannoheptonic acid by Peirce[4] and its complete stereochemical structure was elucidated by him. In the present work, the preparative directions of Hudson and co-workers[5] were followed in obtaining a suitable salt of the heptonic acid.

Hudson[6,7] has noted that "the physical and chemical properties (though not the biological) of an aldose and most of its derivatives are conditioned in first measure by the space configurations of carbons one to five inclusive." Dr. Hudson[8] has called our attention to the fact than an extension of this rule to ketoses would involve carbons two to six inclusive and that therefore the two substances, D-gluco-L-*tagato*-octose and D-gala-L-*tagato*-octose, compared in our preceding communication,[1] while having the upper configuration of L-tagatose, differ in the configuration of carbon six. The wide divergence in optical rotation, therein noted, between these two ketoöctoses, is then predictable and is not in disagreement with the general rule. Table I lists the rotations of three ketoöctoses in comparison with the configurationally related ketoheptose and the data indi-

(1) Paper No. 12 in the series entitled "The Action of Diazomethane upon Acyclic Sugar Derivatives"; previous communication, M. L. Wolfrom and P. W. Cooper, THIS JOURNAL, **71**, 2668 (1949).

(2) E. Fischer and F. Passmore, *Ber.*, **23**, 2226 (1890).

(3) E. Fischer and J. Hirschberger, *ibid.*, **22**, 365 (1889).

(4) G. Peirce, *J. Biol. Chem.*, **23**, 327 (1915).

(5) C. S. Hudson, Olive Hartley and C. B. Purves, THIS JOURNAL, **56**, 1248 (1934).

(6) R. M. Hann, Alice T. Merrill and C. S. Hudson, *ibid.*, **57**, 2100 (1935).

(7) C. S. Hudson, *Advances in Carbohydrate Chem.*, **1**, 26 (1945).

(8) Private communication.