Anal. Calcd. for $C_{19}H_{14}N_4S$: N, 17.0. Found: N, 16.7.

4'-Methylthio-4-phenylaminoazobenzene. This was prepared by the standard procedure. Crystallization from aqueous alcohol and heptane gave glistening orange crystals, m.p. 126–127°.

Anal. Calcd. for $C_{19}H_{17}N_3S$: N, 13.2. Found: N, 13.0.

Absorption spectral data. The intense long wavelength band of all compounds was measured with a Beckman Model DU Spectrophotometer in commercial 95% ethanol. The spectra of some of the compounds was determined in 50% and 25% aqueous alcohol. By 50% aqueous alcohol is meant a solution containing 50 ml. of water diluted to 100 ml. with 95% ethanol; by 25% aqueous alcohol is meant a solution containing 75 ml. of water diluted to 100 ml. with 95% ethanol.

GAINESVILLE, FLA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, KANSAS STATE COLLEGE]

Reaction of Sodium Methoxide with 2-Alkyl-2,3-dichloroaldehydes[1]

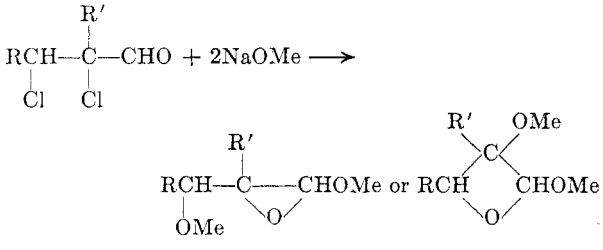
SCOTT SEARLES, JR., EDWIN K. IVES, AND HARRISON M. KASH

Received February 7, 1957

The reactions of sodium methoxide with 2-methyl-2,3-dichlorovaleraldehyde and 2-ethyl-2,3-dichlorohexanal in dry methanol and in dry ether have been investigated. The previous report that 4-membered cyclic acetals were formed in methanol solution was found to be incorrect, the products actually being α,β-epoxy dimethyl acetals. In ether, the products are 2-methoxy-3-chloroaldehydes. The effect of solvent differs from that observed for the reactions of various α-chlorocarbonyl compounds with sodium methoxide, apparently due to the large electrical effect of chlorine in the β-position.

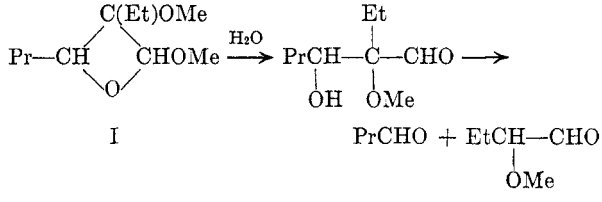
2-Alkyl-2,3-dichloroaldehydes undergo smooth substitution of both chlorine atoms when treated with alcoholic sodium methoxide (2 moles), whereas 2,3-dichloroaldehydes possessing α-hydrogen undergo dehydrohalogenation to unsaturated aldehydes.[2] The products from the former, however, are not the corresponding dimethoxyaldehydes, as they possess neither the chemical properties of aldehydes[2] nor the bond characteristic of the carbonyl group in the Raman spectrum.[3]

Since these compounds give the usual aldehyde reactions after they have been treated with aqueous acids, Lichtenberger and his coworkers considered them to be cyclic acetals possessing either the oxirane or the oxetane ring. More recently these products have been reinvestigated by Krausz,[4] who believed that he had definitely established the oxetane structure.



Negatively substituted oxetanes of this type appeared to be completely unknown[5–7] and would be of great interest in connection with current studies on substituted oxetanes.[8]

Krausz's argument for the presence of the oxetane ring in these compounds is based on his study of their hydrolysis products. After dilute sulfuric acid hydrolysis of the dimethoxy compound (I) obtained from 2-ethyl-2,3-dichlorohexanal (II), butyraldehyde was identified. This might have formed by a retrograde-aldol cleavage of a β-hydroxyaldehyde, formed as follows:



This would not be possible if (I) were a cyclic acetal with the oxirane structure and cleaved to a hydroxymethoxyaldehyde.

For additional evidence on the structure of these compounds, Krausz subjected the dimethoxy compound (III) from 2-methyl-2,3-dichloropentanal (IV) to mild acid hydrolysis, obtained the prod-

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(1) Abstracted in part from the Ph.D. thesis of Edwin K. Ives, Kansas State College, 1957.

(2) J. Lichtenberger and M. Naftali, *Bull. soc. chim. France*, [5], **4**, 325 (1937).

(3) R. Kirmann and J. Lichtenberger, *Compt. rend.*, **206**, 1259 (1939).

(4) F. Krausz, *Ann. chim.*, [12], **4**, 811 (1949).

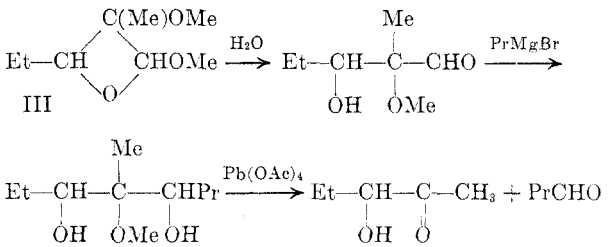
(5) The report of 2-acetoxyoxetane from the reaction of 3-hydroxypropionaldehyde with acetic anhydride (M. Bergmann, A. Mickley, and E. O. Lippmann, *Ber.*, **62**, 1467 (1929)) has been shown to be incorrect by E. Spath and L. Pallam-Raschik (*Monatsh.*, **79**, 447 (1948)).

(6) "3-Chlorooxetane," reported by H. Bigot [*Ann. Chim. phys.*, [6], **22**, 433 (1891)], has been shown by W. E. Noland and B. N. Bastian [*J. Am. Chem. Soc.*, **77**, 3395 (1955)] to be actually 2-chloroallyl alcohol.

(7) Recently 2-phenyloxetane [S. Searles, K. A. Pollart, and E. F. Lutz, *J. Am. Chem. Soc.*, **79**, 948 (1957)] and a steroid derivative having a 3,3-ethylenedioxyoxetane structure [W. S. Allen, S. Bernstein, M. Heller, and R. Littell, *J. Am. Chem. Soc.*, **77**, 4784 (1955)] have been reported.

(8) S. Searles, K. A. Pollart, and F. Block, *J. Am. Chem. Soc.*, **79**, 952 (1957) and preceding papers.

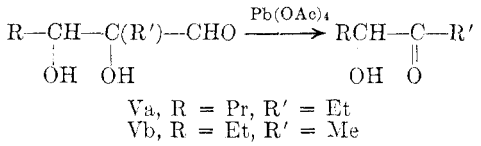
uct as a crude sirup, which he added to excess propylmagnesium bromide. The Grignard product also was obtained as a sirup which was not purified, but after it was treated with lead tetraacetate in benzene, butyraldehyde and 3-hydroxy-2-pentanone were isolated and characterized. This sequence was interpreted as supporting the oxetane structure by the following reasoning. The hydrolysis product of the cyclic acetal with an oxirane ring would be expected to be a 2-hydroxy-3-methoxyaldehyde, and the Grignard product from such would be a *vic*-diol, which on oxidative cleavage would have given 3-methoxy-2-pentanone rather than 3-hydroxy-2-pentanone. Krausz considered that this sequence of reactions confirmed the oxetane structure for III, even though the lead tetraacetate cleavage involved seemed most unusual:



Two intrinsic weaknesses of this proof of the oxetane structure are the assumption that the dimethoxy compounds hydrolyze only to hydroxymethoxyaldehydes, and the failure to consider the isomeric 2,3-epoxy dimethyl acetals as possible structures. These would be expected to hydrolyze easily to 2,3-dihydroxyaldehydes, which would lead to all the reactions reported. Furthermore, since the yields of identified degradation products were quite low, the reactions reported might have been caused by formation of a small amount of 2,3-dihydroxyaldehydes during the hydrolysis of either type of cyclic acetal structure.

Recent data on the infrared spectra of cyclic ethers suggested that the oxetane structures favored by Krausz might be readily confirmed or possibly rejected on a spectral basis. Oxetanes have characteristic strong absorption bands at 970–980 and 1200–1240 cm.$^{-1}$,[9] while oxiranes are characterized by a medium to strong band at 1240–1260 cm.$^{-1}$ as well as a band near 900 cm.$^{-1}$ (sometimes found around 830 cm.$^{-1}$).[10,11] The spectra of I and III, however, possessed bands characteristic of both structures. Although they confirmed the absence of carbonyl and hydroxyl and indicated the presence of an ordinary ether linkage, no conclusion could be drawn regarding the size of the epoxide ring.

Chemical evidence on the structures of these compounds was then sought by studying the structures of their hydrolysis products. Dilute acid hydrolysis of I and III, as carried out by Krausz, was found to give only dihydroxyaldehydes. Assignment of structures Va and Vb to these aldehydes is supported by the isolation of 4-hydroxy-3-heptanone and 3-hydroxy-2-pentanone after lead tetraacetate oxidation.



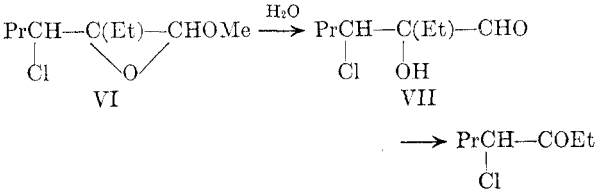
Va, R = Pr, R′ = Et
Vb, R = Et, R′ = Me

No success was realized in finding conditions suitable for hydrolysis of I and III to monomethoxy compounds. This may be significant, as such would be the expected behavior of 2,3-epoxy dimethyl acetals.

Of considerable help in the problem at this point was the isolation in moderate yield of a methoxychloro compound (VI) from the reaction of 2-ethyl-2,3-dichlorohexanal (II) and one equivalent of sodium methoxide. This was apparently an intermediate in the formation of the dimethoxy compound (I), since it reacted with an additional mole of methoxide to form I. It was a neutral compound, analyzing as $C_8H_{14}OCl(OCH_3)$, which was not an aldehyde, since it gave Tollen's and Schiff's tests only after long standing and the infrared spectrum did not contain a carbonyl group.

Hydrolysis of VI with dilute sulfuric acid gave a chlorohydroxy aldehyde, analyzing as $C_8H_{14}O_2Cl$. This was cleaved readily by lead tetraacetate, forming 4-chloro-3-heptanone, indicating it to be the α-hydroxy aldehyde, VII.

It follows that VI has the oxirane structure, shown below. Thus, the reaction of the α,β-dichloroaldehyde with the first mole of methoxide follows the same course as the reaction of various α-chlorocarbonyl compounds with sodium methoxide.[12] In the latter cases, however, the α-methoxyoxiranes react with methanol solvent to give α-hydroxy acetals and α-hydroxy ketals.[12]



Apparently compound VI is less reactive than simple α-methoxyoxiranes towards methanol though it is reactive towards sodium methoxide,

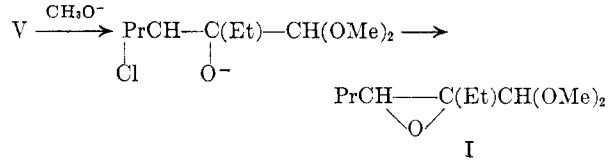
(9) G. M. Barrow and S. Searles, *J. Am. Chem. Soc.*, **75**, 1175 (1953).

(10) J. E. Fields, J. O. Cole, and D. E. Woodford, *J. Phys. Chem.*, **18**, 1298 (1950); O. D. Shreve, *et al.*, *Anal. Chem.*, **53**, 282 (1951).

(11) The infrared spectrum of a cyclic acetal with an oxirane ring, 1-methoxy-1,2-epoxybutane, has been published by C. L. Stevens, E. Farkas, and Bernard Gillis, Ref. 12. Strong bands were observed at 1270 and 890 cm.$^{-1}$ and a medium band at 950 cm.$^{-1}$; there were no bands between 950 and 1020 cm.$^{-1}$

(12) C. L. Stevens, E. Farkas, and B. Gillis, *J. Am. Chem. Soc.*, **76**, 2695 (1954) and previous papers.

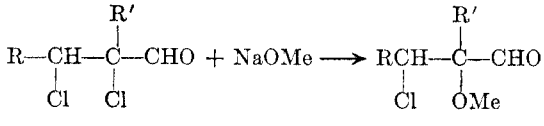
as seen above. Attack of the second mole of sodium methoxide might reasonably be expected to cleave the oxirane ring, resulting in an acetal intermediate, in which another oxirane ring can form.[13] This would give 2-ethyl-2,3-epoxyhexanal dimethyl acetal as the structure of the dimethoxy product (I), which is in complete agreement with all the hydrolysis studies. By analogy, the dimethoxy compound (III) must be 2-methyl-2,3-epoxypentanal dimethyl acetal because of the close similarity of mode of formation, spectra, and chemical properties.



I

Stevens has found the solvent to be a very important factor in the reaction of sodium methoxide with α-chlorocarbonyl compounds. In dry ether α-methoxyoxiranes (epoxy ethers) were formed, while in methanol α-hydroxy acetals (or ketals) were the products, due to the reaction of the oxiranes with the solvent. Therefore, it seemed likely that excellent yields of chloromethoxy compounds, such as VI, would be obtained from the dichloro aldehydes in dry ether.

To our surprise, however, the reaction took a different course in ether, forming 3-chloro-2-methoxyaldehydes, rather than epoxides. The same results



were obtained when up to 2.3 molecular equivalents of sodium methoxide was used in ether and also when toluene was used as the solvent.[14] The evidence for the free aldehyde group in each of these compounds is the strong infrared absorption band at 1740 cm.$^{-1}$ and the immediate rendering of positive Tollens' and Schiff's tests. The presence of one chlorine atom and one methoxyl group was indicated by the elemental and Zeisel analyses, and their positions were shown by hydrolysis of the compounds to chlorohydroxyaldehydes which were cleaved by means of lead tetraacetate to the corresponding α-chloroketones.

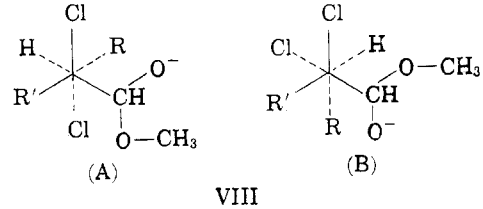
The reason for the solvent being able to alter the course of the reaction of sodium methoxide with α,β-dichloroaldehydes may be ascribed to one or both of the following two factors: (1) ability of methanol to aid the attack of methoxide ion at the carbonyl carbon and (2) solvation of a possible subsequent dipolar reaction intermediate.

(13) Originally suggested by Dr. B. Gillis and Dr. C. L. Stevens.

(14) It was claimed by Krausz (Ref. 4) that II gave the same dimethoxy product with toluene as with methanol as solvent.

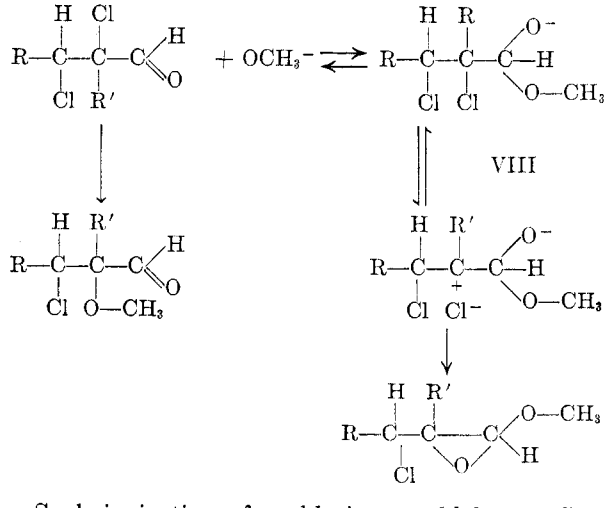
Inspection of molecular models of these aldehydes indicates that when the chlorine atoms are *anti* to each other, the β-chlorine atom shields the carbonyl carbon (as do also the α-chlorine and the α-alkyl group). Since this would be expected to be the most stable conformation, it seems likely that attack of methoxide at the carbonyl carbon is sterically hindered in α,β-dichloroaldehydes. As a result, polarization of the carbonyl group by hydrogen bonding may be a deciding factor as to the principal sites of attack by methoxide.

Attack by the methoxide ion on the carbon atom of the carbonyl group would produce a methoxydichloroalkoxide ion (VIII), which would be highly strained. Examination of molecular models of this intermediate show that when the chlorine atoms are in the *anti* conformation (VIIIA), one or the other of them has to lie extremely close to one of the oxygen atoms. The only way the chlorine-oxygen distances can be reduced is to have the chlorines *syn* to each other (VIIIB).



VIII

In either case there will be considerable direct repulsive force on the α-chlorine, while displacement of it by the negatively charged oxygen is greatly inhibited, since the back face of the α-carbon is largely covered by the β-chlorine or the alkyl groups. The strain in this intermediate, however, could be relieved by ionization of the α-chlorine, to give a transitory dipolar intermediate, which would cyclize by a front-side attack.



Such ionization of α-chlorine would be an S_N1 process, requiring a polar solvent. In a non-polar solvent VIII might merely revert to dichloro aldehyde and methoxide. A molecular model shows that the back-side displacement of the α-chlorine is much

less hindered in the dichloro aldehyde than in VIII. In ether or toluene apparently attack of methoxide at that sight predominates over attack at the carbonyl.

EXPERIMENTAL

2,3-Dichloro-2-methylvaleraldehyde (IV) was prepared in 60% yield by bubbling chlorine into a dry chloroform solution of 2-methyl-2-pentenal at 5–15°, b.p. 78° (20 mm.) n_D^{20} 1.4540 [literature[2,4] b.p. 68° (14 mm.), n_D^{23} 1.4563].

2,3-Dichloro-2-ethylhexanal (II) was prepared in like manner, 80% yield, b.p. 110–112° (20 mm.), n_D^{20} 1.4523 [lit.[2,4] b.p. 95° (14 mm.), n_D^{22} 1.4518].

2,3-Epoxy-2-methylvaleraldehyde dimethyl acetal (III) was obtained from the reaction of IV and 2.3 molecular equivalents of sodium methoxide in dry methanol by the literature procedure.[2,5] After a reaction time of 12 hr. at 25°, the yield was 73%. The properties of the product were: b.p. 84–85° (20 mm.), n_D^{20} 1.4192 (lit.[2,4] 70° (15 mm.), $n_D^{18.5}$ 1.4196). Strong infrared bands were observed at 950, 980, 1220, and 1270 cm.$^{-1}$ and a medium band at 890 cm.$^{-1}$

2-Ethyl-3-chloro-1-methoxy-1,2-epoxyhexane (VI). A mixture of 50 g. of II and 15 g. of sodium methoxide in 400 ml. of anhydrous methanol was heated at 40° for 30 hr. and then processed in the usual manner,[2,4] giving 29 g. (60%) of a colorless liquid, b.p. 123–125° (30 mm.), n_D^{20} 1.4470. This product gave a positive test for chlorine after sodium fusion and gave Schiff's and Tollens' tests only after heating and standing for 30 min. The infrared spectrum possessed strong bands at 900, 950, 980, 1270, and 1310 cm.$^{-1}$, medium bands at 1120 and 1300 cm.$^{-1}$, and a weak band at 1210 cm.$^{-1}$

Anal. Calcd. for $C_9H_{17}O_2Cl$: C, 56.1; H, 8.8; Cl, 17.8; OCH_3, 17.1. Found[15]: C, 56.7; H, 8.8; Cl, 17.8; OCH_3, 16.1.

2,3-Epoxy-2-ethylhexanal dimethyl acetal (I). (*A*) From a mixture of 50 g. of II and 31.5 g. of sodium methoxide in 600 ml. of dry methanol, heated under reflux for 3 days and then processed as usual, was obtained 30 g. (63%) of a colorless liquid, b.p. 107–108° (25 mm.), n_D^{20} 1.4285 (lit.,[2,4] b.p. 95° (17 mm.), n_D^{16} 1.4304).

(*B*) A mixture of 20 g. of VI and 6 g. of sodium methoxide in 200 ml. of anhydrous methanol was heated at 40° for 3 days. After the usual isolation procedure, 11.5 g. (59%) of a product identical to that in A was obtained, b.p. 104° (24 mm.), n_D^{20} 1.4280. The compound gave a negative test for halogen and positive Schiff's and Tollens' tests after heating and standing 30 min. Strong infrared bands were observed at 900, 890, 1000, 1170, 1270, and 1310 cm.$^{-1}$

Anal. Calcd. for $C_{10}H_{20}O_3$: OCH_3, 32.9. Found: OCH_3, 32.1.

3-Chloro-2-methoxy-2-methylvaleraldehyde. A solution of 169 g. of IV in 400 ml. of dry ether was added dropwise to a stirred suspension of 124 g. of sodium methoxide in 1.5 l. of dry ether at 0–5°. The reaction mixture was allowed to warm to room temperature and to stand overnight and was then filtered. Distillation of the filtrate gave 111 g. (68%) of a colorless oil, b.p. 85–90° (23 mm.), n_D^{20} 1.4400. It gave the usual aldehyde tests and had infrared bands at 1070 (m) and 1740 (s) cm.$^{-1}$

Anal. Calcd. for $C_7H_{13}O_2Cl$: C, 51.1; H, 7.9; Cl, 21.6; OCH_3, 18.8. Found: C, 50.9; H, 7.5; Cl, 21.5; OCH_3, 18.8.

3-Chloro-2-methoxy-2-ethylhexanal (VI). The reaction of 198 g. (1 mole) of II and 124 g. (2.3 moles) of sodium methoxide in ether was carried out in the same manner as described above to give 118 g. (60%) of a colorless oil, b.p. 95–100° (20 mm.), n_D^{20} 1.4250. Titration of the inorganic precipitate dissolved in water indicated that only 1.1 moles of sodium methoxide had been consumed in the reaction. The organic product gave a positive chlorine test and positive Tollens' and Schiff's tests; it had infrared bands at 1170 (m) and 1740 (s) cm.$^{-1}$

Anal. Calcd. for $C_9H_{17}O_2Cl$: C, 56.1; H, 8.8; Cl, 17.8; OCH_3, 16.1. Found: C, 56.3; H, 8.8; Cl, 17.7; OCH_3, 16.2.

By the same procedure except for using dry toluene as solvent, this compound was obtained in 63% yie d.

Hydrolysis of cyclic acetals and methoxy aldehyd s. Twenty g. of the compound to be hydrolyzed was heated on the steam bath for 30 min. with 100 ml. of 1*N* sulfuric acid with frequent shaking. The mixture was then cooled, neutralized with saturated sodium bicarbonate and extracted with ether. The product was isolated by distillation of the dried extracts. The infrared spectrum of each indicated hydroxyl and aldehyde carbonyl groups but no ether function. Each gave positive Tollens' and Schiff's tests and Zeisel analysis showed a methoxyl content of 0.7% or less in each case.

The lead tetraacetate oxidations of these products were carried out by dissolving in dry benzene (75 ml. for 10 g. of hydroxyaldehyde) and adding a 10% excess of lead tetraacetate in several portions. After heating on the steam bath 2 hr., the reaction mixture was filtered. The filtrate was shaken with dilute sulfuric acid, dried and distilled. The infrared spectra of the products were in agreement with the structures assigned.

From compound VI was obtained *3-chloro-2-hydroxy-2-ethylhexanal* (VII) in 55% yield, b.p. 105–110° (16 mm.), n_D^{20} 1.4370, m.p. of 2,4-DNP 203–204°.

Anal. Calcd. for $C_{18}H_{15}O_2Cl$: C, 53.8; H, 8.4; Cl, 19.9. Found: C, 53.7; H, 8.5; Cl, 19.9.

Lead tetraacetate cleavage of VII gave a 56% yield of *4-chloro-3-heptanone*, b.p. 85–87° (16 mm.), n_D^{20} 1.4408.

Anal. Calcd. for $C_7H_{13}OCl$: C, 56.6; H, 8.7; Cl, 23.2. Found: C, 56.8; H, 8.7; Cl, 23.0.

The 2,4-DNP melted at 204°.

Anal. Calcd. for $C_{13}H_{17}O_4N_4Cl$: C, 46.86; H, 5.3; Cl, 9.9; N, 15.6. Found: C, 46.53; H, 5.2; Cl, 9.5; N, 15.9.

Hydrolysis of compound I produced 2,3-dihydroxy-2-ethylhexanal (Va) (46% yield), b.p. 130–135° (15 mm.), n_D^{20} 1.5206.

Anal. Calcd. for $C_8H_{16}O_3$: C, 60.0; H, 10.1. Found: C, 60.0; H, 10.7. Lead tetraacetate oxidation of Va gave *4-hydroxy-3-heptanone*, (37%), b.p. 71–73° (16 mm.), n_D^{20} 1.4620 [lit.[16] b.p. 74–75° (18 mm.)], m.p. of semicarbazone 120–122° (lit.[16] 121–122°).

Hydrolysis of compound III lead to *2-methyl-2,3-dihydroxyvaleraldehyde* (Vb) in 53% yield, b.p. 130–135° (30 mm.), n_D^{20} 1.4447, m.p. of 2,4-DNP 222–223°.

Anal. Calcd. for $C_6H_{12}O_3$: C, 54.5; H, 9.1. Found: C, 54.8; H, 9.3. Lead tetraacetate oxidation of Vb gave *3-hydroxy-2-pentanone*, b.p. 105–107° (50 mm.), [lit.[17] b.p. 77° (35 mm.)], n_D^{20} 1.4350, which forms a *bis*-2,4-DNP melting at 226–228° (mixed m.p. with 2,4-DNP of the aldehyde 215–219°).

Anal. Calcd. for $C_{17}H_{16}O_8N_8$: C, 43.9; H, 3.4; N, 24.2. Found: C, 44.4; H, 3.5; N, 24.4.

Hydrolysis of VI gave 66% yield of 2-ethyl-2-hydroxy-3-chlorohexanal, identical to the compound obtained by hydrolysis of compound III.

From 3-chloro-2-methoxy-2-methylvaleraldehyde was obtained 2-methyl-2-hydroxy-3-chlorovaleraldehyde (55%), b.p. 95–97° (27 mm.), n_D^{20} 1.4581.

Anal. Calcd. for $C_6H_{11}O_2Cl$: C, 47.4; H, 7.3. Found: C, 47.4; H, 7.2.

(15) Carbon-hydrogen microanalyses reported in this paper were done by Geller Laboratories, Hackensack, N. J. The chlorine and methoxyl analyses were done by the Carius and Zeisel methods, respectively.

(16) E. D. Venus-Danilova, *Bull. soc. chim. France* [4], **43**, 479 (1928).

(17) H. von Peckmann and F. Dahl, *Ber.*, **23**, 2425 (1890).

Lead tetraacetate oxidation of the above gave 3-chloro-2-pentanone (38%), b.p. 123–125° (730 mm.) (lit. b.p. 130°[18]), n_D^{20} 1.4280, which formed a 2,4-DNP melting at 106–107°.

Anal. Calcd. for $C_{11}H_{13}O_4N_4Cl$: C, 43.8; H, 4.3; Cl, 11.8; N, 18.7. Found: C, 43.9; H, 4.3; Cl, 11.5; N, 18.6.

(18) M. Conrad, *Ann.*, **186**, 241 (1877).

Acknowledgments. This work was supported in part by a research grant from the National Science Foundation. We are greatly indebted to Dr. Calvin L. Stevens for his kind encouragement and helpful discussions.

MANHATTAN, KAN.

[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

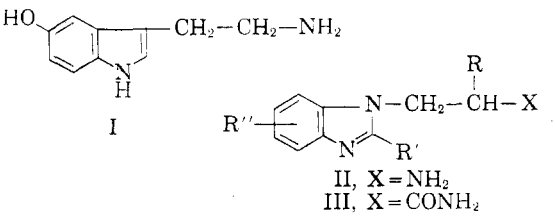
1-(β-Aminoalkyl)benzimidazoles[1a]

WILLIAM B. WHEATLEY AND GERALD F. STINER[1b]

Received February 6, 1957

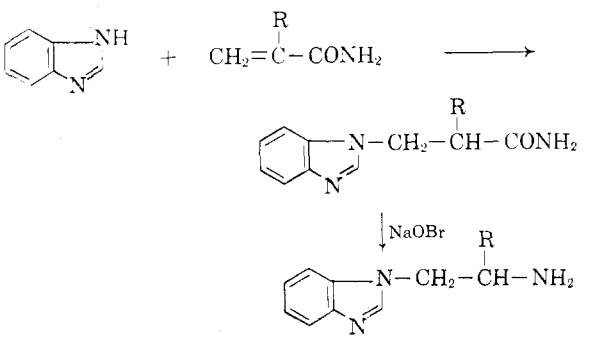
A series of 1-(β-aminoalkyl)benzimidazoles has been synthesized by a reaction sequence involving the base-catalyzed addition of acrylamide or methacrylamide to benzimidazoles and subsequent Hofmann rearrangement of the amides thus obtained.

During the past few years, the role of serotonin (I), 5-hydroxytryptamine, in certain physiological functions has been the subject of much investigation. Of particular interest have been its effect on the cardiovascular system and its place in mental processes, neither of which is completely understood as yet. It does indeed have a powerful vasoconstrictor action, and the hypothesis that an excess of serotonin is a significant factor in essential



hypertension has been proposed.[2] This hypothesis has prompted the synthesis of a number of indoles related to serotonin which might be antagonists.[3] The authors became interested in this problem and decided to attack it by replacing the indole nucleus of serotonin with the isosteric benzimidazole nucleus. At this time the authors wish to report the synthesis of a series of compounds, the simplest of which is 1-(β-aminoethyl)benzimidazole (II, R, R′, R″ = H).

Since benzimidazoles are readily obtained from *o*-phenylenediamine and organic acids,[4] it was felt that introduction of the β-aminoethyl group into a preformed benzimidazole would be the best synthetic approach. A sequence involving cyanomethylation of benzimidazole, followed by reduction to the primary amine, was attempted first, with quite unpromising results. Recalling that acrylonitrile adds to benzimidazole,[5] we tried the addition of acrylamide, to be followed if successful by a Hofmann rearrangement.



This synthesis proved to be acceptable, and could be adapted to the preparation of β-aminopropyl (R = CH_3) benzimidazoles by the use of methacrylamide. The synthesis of β-aminopropyl compounds had been contemplated, since it is known that the methyl group adjacent to the amine function is effective in inhibiting *in vitro* enzymatic degradation of many primary amines.[6]

Acrylamide and methacrylamide add to benzimidazoles, on boiling several hours in pyridine solution with Triton B as catalyst, to yield β-(1-benzimidazole)propionamides and β-(1-benzimidazole)-isobutyramides in reasonably good yields. In Table I are summarized a number of such amides; benzimidazoles substituted in the 2 and 5 positions were used. In the case of those benzimidazoles having a substituent in the benzene ring, the expected

(1) (a) Presented before the Division of Medicinal Chemistry, AMERICAN CHEMICAL SOCIETY, Atlantic City, September, 1956. (b) Present address: State University of New York, College of Medicine, Syracuse, N. Y.

(2) D. W. Woolley and E. N. Shaw, *J. Am. Chem. Soc.*, **74**, 2948 (1952).

(3) D. W. Woolley and E. N. Shaw, *Science*, **124**, 34 (1956).

(4) J. B. Wright, *Chem. Revs.*, **48**, 397 (1951).

(5) (a) British patent **457,621** [*Chem. Abstr.*, **31**, 3068 (1937)]; (b) L. S. Efros and B. A. Poral-Koshits, *Zhur. Obshchei Khim.*, **23**, 697 (1953)[*Chem. Abstr.*, **48**, 7603 (1954)].

(6) W. H. Hartung, *Ann. Rev. Biochem.*, **15**, 593 (1946).