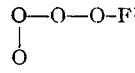
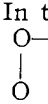
Discussion

The results from the acid hydrolysis experiments were consistent only with this structure for B_4[f]



taking into account the resistance of the α-1,6-bond and the α-1,4-bond adjacent to the flavazole unit. Only this structure could yield isomaltose and maltose flavazole as the main products.[15] It has been proposed that amyloglucosidase operates by removal of glucose units from the non-reducing end of a starch chain.[16] The stable B_4 presumably represents the reducing end of the dextrins. Dextrinase removed glucose units readily until it was partially obstructed by the α-1,6-link. Thus, except for the minor component of B_4, the salivary amylase dextrins at advanced stages of hydrolysis have a uniform arrangement at the reducing end of the chain. In the case of the panose-coupled products the reaction is analogous. In this case, however, the panose configuration, O—O—, is found at the reducing end.



It should be noted that with this enzyme preparation the α-1,6-link was by-passed, although slowly. It would be interesting to determine whether a pure amyloglucosidase preparation, if one were available, would be completely arrested at the α-1,6-link. The action patterns of the amyloglucosidase from *A. niger*,[16] *Rhizopus delemar*[17] and *Clostridium acetobutylicum*[18] have been compared with that of β-amylase. β-Amylase, however, for all practical purposes is arrested before the α-1,6-link is reached.[19] A pure amyloglucosidase preparation, therefore, could be of considerable value in structure determination.

(15) O– signifies a glucose unit with its reducing group; —O–O— signifies 2 glucose units bonded with an α-1,4-linkage;  signifies 2 glucose units bonded with an α-1,6-linkage. O–F signifies a glucose unit which has been converted into its 1-phenyl-flavazole derivative.

(16) R. W. Kerr, F. C. Cleveland and W. J. Katzbeck, THIS JOURNAL, **73**, 3916 (1951).

(17) L. L. Philips and M. L. Caldwell, *ibid.*, **73**, 3559, 3563 (1951).

(18) D. French and D. W. Knapp, *J. Biol. Chem.*, **187**, 463 (1950).

(19) R. Summer and D. French, *ibid.*, **222**, No. 1, 469 (1956).

AMES, IOWA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY]

The Deamination of 2-Amino-3-phenylbutane-1-C^{14} with Nitrous Acid[1]

BY WILLIAM A. BONNER AND DENNIS D. TANNER

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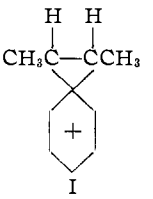
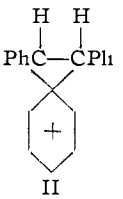
2-Amino-3-phenylbutane-1-C^{14} (IV) has been synthesized by the reaction sequence: 3-phenyl-2-butanol-1-C^{14} → 3-phenyl-2-butanone-1-C^{14} → oxime → IV. The radiochemical structure of IV was established by degradation of the 3-phenyl-2-butanol-1-C^{14} to iodoform of identical radioactivity assay, and by the known lack of rearrangements occurring during conversion of a carbinol such as 3-phenyl-2-butanol to an amine such as IV. 2-Amino-3-phenylbutane-1-C^{14} (IV) was deaminated by the action of nitrous acid at 0° in aqueous solvent. A reaction product consisting primarily of a mixture of carbinols was obtained. By the use of vapor–liquid partition chromatography, alumina column chromatography and infrared spectrophotometry, this mixture was shown to consist principally of a phenyl migration product, 3-phenyl-2-butanol (V), a hydrogen migration product, 2-phenyl-2-butanol (VI), and a methyl migration product, 1-phenyl-2-methyl-1-propanol (VII). Small amounts of olefinic and ketonic products were also noted, but were not characterized. The crude deamination reaction mixture was also degraded with sodium hypoiodite. Of the various carbinol products identified, only the phenyl migration product, 3-phenyl-2-butanol-1,4-C^{14} (V), could yield iodoform under these conditions. The iodoform obtained in this degradation showed a radioactivity assay exactly half as high as that noted for the 3-phenyl-2-aminobutane-1-C^{14} precursor (IV). This observation accords with the theoretical concept of a symmetrical phenonium ion intervening as a reaction intermediate in the formation of the phenyl migration product V.

Introduction

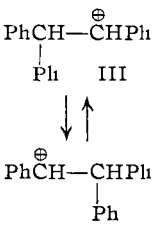
The concept of bridged, non-classical carbonium ion reaction intermediates, originally introduced[2] in 1941 by Lane and Wallis to account for the stereochemical results of the Wolff rearrangement, has been extended and amplified in recent years, particularly by the researches of Cram[3] and Roberts.[4] Perhaps the most compelling evidence for the "symmetrical phenonium ion" intermediate (I) hypothesis is to be found in the earlier investigations of Cram, wherein the stereochemical consequences of various solvolytic reactions in the 3-phenyl-2-butyl tosylate system, and closely related systems, have been described.[3] The data of these investigations were logically and economically rationalized by the postulation of bridged non-classical structures, such as I, intervening as the cation of ionic pairs[3] as intermediates in such solvolytic processes.



I



II



III

In order to test or extend these hypotheses, Collins and Bonner have more recently investigated similar solvolytic reactions in the 1,2,2-triphenylethyl system, using carbon skeletons

(1) We are indebted to the National Science Foundation for its generous support of a portion of this research.

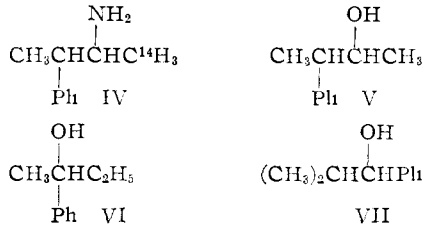
(2) J. F. Lane and E. S. Wallis, THIS JOURNAL, **63**, 1674 (1941).

(3) D. J. Cram and co-workers, *ibid.*, **71**, 3863, 3875 (1949); **74**, 2129, 2137, 2159, 5839 (1952); **75**, 339, 3189 (1953).

(4) J. D. Roberts and co-workers, *ibid.*, **74**, 5943 (1952); **75**, 2069, 5759 (1953); **77**, 5558 (1955).

labeled in alternative positions with radioactive carbon.[5] The data of these studies unambiguously indicated that analogous bridged intermediates such as II were not formed directly in solvolytic reactions in the 1,2,2-triphenylethyl system, but rather that equilibrating classical carbonium ions (III) were the sole cationic intermediates needed to explain the results.

In a more recent study Bonner and Collins similarly have shown[6] that equilibrating classical ions such as III also intervened in the deamination of 1,2,2-triphenylethylamine to 1,2,2-triphenylethanol with nitrous acid. Since such a deamination had not been investigated originally in the 3-phenyl-2-butyl system, we presently have undertaken to study the action of nitrous acid on 2-amino-3-phenylbutane-1-C^{14} (IV), to see whether or not the radiochemical results of such a deamination are in accord with the symmetrical phenonium ion (I) hypothesis.



Before our investigation was complete Cram and McCarty published[7] the results of their very extensive stereochemical researches on the deamination of the *erythro* and *threo* diastereomers of 2-amino-3-phenylbutane. In contrast to earlier solvolytic studies[3] in the 3-phenyl-2-butyl system, where the phenyl nucleus was clearly the dominant migrating group, products resulting not only from phenyl (V), but also from hydrogen (VI) and methyl (VII) migration were unambiguously noted[7] in varying amount during the deamination of both diastereomers of 2-amino-3-phenylbutane. The stereochemical results noted by Cram and McCarty during this deamination suggested that (a) the yields of the various products formed during deamination of each diastereomer were determined by the original conformational populations of each diazotized amine, solvent and neighboring groups participation playing a negligible role, (b) that symmetrical phenonium ions (I) in all probability intervened, to an extent at least, in the formation of the phenyl migration product V, and (c) that a bridged methylcarbonium ion might have intervened in the formation of the methyl migration product VII.

In our investigation of the deamination of 2-amino-3-phenylbutane-1-C^{14} (IV), conducted unknowingly under somewhat different reaction conditions from those employed[7] by Cram and McCarty, we have similarly noted the formation of the products of phenyl (V), hydrogen (VI) and methyl (VII) migration. In our study, further, we have been able to look unambiguously at the phenyl migration product V radiochemically, to ascertain whether its label distribution accorded with the postulate of a non-classical phenonium ion intermediate.

Results

A mixture of the diastereomeric 3-phenyl-2-aminobutanes-1-C^{14} (IV) was prepared by the following sequence of reactions. 3-Phenyl-2-butanol-1-C^{14} (prepared by action of radioactive methylmagnesium halide on hydratropaldehyde) was oxidized by means of the chromium trioxide–pyridine complex[10] to 3-phenyl-2-butanone-1-C^{14}. This was converted by usual techniques into the corresponding oxime. The latter was reduced in good yield by means of sodium in ethanol to a mixture of the desired diastereomeric amines IV labeled at carbon-1 with C^{14}.

A radiochemical structure proof of the amine IV was provided by an iodoform degradation of its 3-phenyl-2-butanol-1-C^{14} precursor with sodium hypoiodite. Since Roe[8] has erroneously[9] reported a "reverse isotope effect" in the iodoform degradation of acetone, we studied this degradation of our 3-phenyl-2-butanol-1-C^{14} intermediate with considerable care. Conditions were found for this reaction whereby the resulting iodoform-C^{14} product showed a radiochemical assay identical with that of its 3-phenyl-2-butanol-1-C^{14} precursor, thus establishing uniquely the location of the C^{14}-label in the carbinol. Before an iodoform yield of above 54% was achieved in this degradation, however, a similar "reverse isotope effect" was noted, *i.e.*, iodoform C^{14}-assays were unaccountably high. The reasons for those results have not been investigated. As discussed under Experimental, these results constitute a radiochemical structure proof for our 2-amino-3-phenylbutane-1-C^{14} starting material (IV).

We have subjected the mixed diastereomeric amines IV to deamination with nitrous acid in aqueous solvent at 0°. The mixture of carbinol deamination products (72% assuming isomeric carbinols only) was investigated for its components with the aid of vapor–liquid partition chromatography, product isolation therefrom, and infrared spectrophotometric product characterization. By these means the products of phenyl (V), hydrogen (VI) and methyl (VII) migration were detected in the crude deamination product. Traces of an olefinic product also were observed, in quantities too trivial for characterization efforts.

The crude deamination mixture also was subjected to the action of sodium hypoiodite. Of the various migration products (V, VI and VII) constituting this mixture, only 3-phenyl-2-butanol (V), the phenyl migration product, is capable of yielding iodoform under these conditions. The iodoform obtained from this reaction was subjected to C^{14} assay. It should be emphasized at this juncture that for the phenyl migration product (V) obtained on deamination of IV, (a) a non-rearrang-

(5) W. A. Bonner and C. J. Collins, THIS JOURNAL, **75**, 5372, 5379 (1953); **77**, 92, 99, 6725 (1955).

(6) W. A. Bonner and C. J. Collins, *ibid.*, **78**, 5587 (1956); *cf.* also B. M. Benjamin, H. J. Schaeffer and C. J. Collins, *ibid.*, **79**, 6160 (1957).

(7) D. J. Cram and J. E. McCarty, *ibid.*, **79**, 2866 (1957).

(8) A. Roe and E. L. Albenesius, *ibid.*, **74**, 2402 (1952); *Chem. Eng. News*, **31**, 3980 (1953).

(9) G. A. Ropp, W. A. Bonner, M. T. Clark and V. F. Raaen, THIS JOURNAL, **76**, 1710 (1954).

ing classical ion intermediate would produce carbinol V yielding iodoform of identical assay with IV, (b) totally *concerted* phenyl migration would yield product V whose iodoform degradation produce would be void of radioactivity, (c) a symmetrical phenonium ion intermediate I would lead to a carbinol V whose iodoform degradation product would have exactly 50% of the C^{14} originally contained in the amine IV, and (d) any "mixed mechanism" would be expected to provide iodoform assaying somewhere within the limits 0–50–100% of the original radioactivity noted in amine IV.

By comparing the C^{14} assay of the iodoform degradation product from the crude deamination mixture (0.513 mc./mole) with the average (1.025 mc./mole) of all precursors having "base-level" radioactivity assay, one notes that this iodoform degradation product has almost exactly 50% of the C^{14} content originally in the 2-amino-3-phenylbutane-1-C^{14} (IV). These results, within experimental error, are identical with those predicted in the instance that a symmetrical phenonium ion I was the reaction intermediate involved in the formation of the 3-phenyl-2-butanol (V) phenyl migration product obtained during the deamination of diastereomeric 2-amino-3-phenylbutane (IV).

These observations and conclusions stand somewhat in contrast to those of Cram and McCarty.[7] Their stereochemical data suggested that a symmetrical phenonium ion could not be the only intermediate yielding 3-phenyl-2-butanol, and that a classical, open ion must have intervened to a varying extent, both in the *erythro* and *threo* series. Our present results do not require this conclusion. One explanation for the discrepancy is the differing reaction conditions (with respect to temperature and solvent) in the two studies. Another explanation is the unknown diastereomeric composition of our starting amine. If, for example, our starting amine were predominantly of the *erythro* configuration (previously found[7] to yield predominantly optically active 3-phenyl-2-butanol of starting configuration), which deaminates with stereochemical results largely in accord with a symmetrical phenonium intermediate, then the detection of a small amount of open ion contribution might be beyond the range of our experimental detection. We have no idea at present as to the diastereomeric composition of our original 2-amino-3-phenylbutane-1-C^{14} (IV). In the above connection it would be of considerable interest to separate our starting labeled amine into its *erythro* and *threo* isomers, and to observe the radiochemical consequences on similar deamination of each. This problem is currently under investigation.

The interesting question of whether the bridged phenonium ion shown to be phenyl migration intermediate in the present deamination is formed directly or results only after initial formation of an open ion precursor, cannot be answered directly with the radiochemical data at hand. Cram's observation,[7] however, that conformation controls the products of this deamination (*i.e.*, H and CH_3 also undergo varying amounts of migration), in fact seems to suggest that phenyl participates at best only trivially in the removal of $-N_2^{\oplus}$ from the original diazonium ion precursor, and that an open ion is the immediate result of the loss of nitrogen from this diazonium ion. If this be the case, our present observations would indicate that, in proper conformation for phenyl migration, such an open ion is extremely short-lived with respect to its bridged successor.

Experimental

Radioactivity Assays.—Radioactivity levels of the various products in the present investigation were determined by wet combustion of the products to carbon dioxide[10] and assay of the latter using a Cary model 31 vibrating reed electrometer.[11] All determinations were run in duplicate, and a reproducibility of ±0.3% was generally achieved.

3-Phenyl-2-butanone-1-C^{14}.—Non-radioactive 3-phenyl-2-butanol (prepared by action of methylmagnesium iodide on 2-phenylpropionaldehyde) was added to 3-phenyl-2-butanol-1-C^{14} (approximately 32 mc./mole; prepared as above using methyl-C^{14}-magnesium iodide; generously furnished by Dr. C. J. Collins, Oak Ridge National Laboratory) in sufficient quantity to yield a carbinol sample having tracer-level activity of 1.015 ± 0.011 mc./mole.

A pyridine–chromium trioxide complex solution was made from C.P. pyridine (220 g.) and chromium trioxide (21 g.) according to the procedure of Sarett and co-workers.[12] To this was added a solution of the above tracer-level 3-phenyl-2-butanol-1-C^{14} (5 g.) in C.P. pyridine (50 ml.). The mixture was shaken well, allowed to stand at room temperature during 24 hours, then poured into water (250 ml.). The solution was extracted three times with 150-ml. portions of a 1:1 mixture of benzene and ether. The extract was washed twice with 150-ml. portions of 6 *N* hydrochloric acid, followed by two washings with 150-ml. portions of water. The extract was dried (anhydrous sodium sulfate), filtered, and the solvent was evaporated (aspirator pressure) through a small fractionating column. The above procedure was repeated. The combined residues were distilled in a Claisen-head still, and the fraction, b.p. 110–115° (24 mm.), was collected. The total yield of 3-phenyl-2-butanone-1-C^{14} was 8.9 g. (88%).

3-Phenyl-2-butanone-1-C^{14} Oxime.—The above ketone (8.9 g.) was dissolved in a mixture of pyridine (120 ml.) and absolute ethanol (120 ml.). Hydroxylamine hydrochloride (27.8 g.) was added, and the resulting solution was heated under reflux during 24 hours. The solvents were thereupon removed by distillation *in vacuo*, and the crystalline residue was leached thoroughly with ether (50 ml.). The extract was washed once with water, then with 20% hydrochloric acid, and again with water. After drying (anhydrous sodium sulfate), the extract was filtered and freed of solvent, leaving 9.2 g. (95%) of crude oxime. A 0.3-g. portion of this product was recrystallized thrice from dilute (1:1) aqueous ethanol for analytical purposes, m.p. 59.5–60°. The remaining crude oxime was reduced as described below.

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.50; H, 8.03. Found: C, 73.53; H, 8.03; radioactivity assay, 1.041 ± 0.007 mc./mole.

2-Amino-3-phenylbutane-1-C^{14} (IV).—The crude oxime above (8.9 g.) was dissolved in absolute ethanol (300 ml.), and the solution was placed in a 500-ml. flask equipped with a reflux condenser. Through the condenser sodium (30 g.) was added in small pieces, at a sufficient rate to maintain continuous reflux. After completion of the addition the semi-solid mass was poured into water (350 ml.), and the solution was acidified carefully with concd. sulfuric acid. The acidic solution was concentrated at 100° *in vacuo* to a volume of *ca.* 150 ml., then cooled and extracted with ether to remove unreacted oxime. Solvent evaporation yielded 0.2 g. of neutral material which was discarded. The acidic layer was made alkaline by addition of solid sodium hydroxide, whereupon the amine separated as an oil. This was extracted from the cooled solution with two 50-ml. portions of ether. The extract was dried (anhydrous sodium sulfate), filtered, and freed of solvent, yielding a 6.06-g. (75%)

(10) O. K. Neville, THIS JOURNAL, **70**, 3501 (1948).

(11) V. A. Raaen and G. A. Ropp, *Anal. Chem.*, **25**, 174 (1953).

(12) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 427 (1953).

residue of crude 2-amino-3-phenylbutane-1-C^{14}. A portion of this residue was subjected to vapor–liquid partition chromatographic purification as described below (packing A). The amine (98.5% of the total) was collected. Only 1.5% impurity appeared to be present in the crude amine.

Anal. Calcd. for $C_{10}H_{15}N$: C, 80.48; H, 10.13. Found: C, 80.07; H, 10.16; $n^{26.5}D$ 1.5159, in agreement with the lit. value[13] of 1.5137–1.5161.

Radiochemical Structure Proof of 2-Amino-3-phenylbutane-1-C^{14} (IV).—This was accomplished by the iodoform degradation of the 3-phenyl-2-butanol-1-C^{14} precursor. In a 500-ml. flask the above 3-phenyl-2-butanol-1-C^{14} (0.50 g.) was dissolved in a mixture of dioxane (15 ml.), methanol (15 ml.) and water (10 ml.) containing sodium hydroxide (1.0 g.). A potassium iodide–iodine solution, prepared according to Shriner and Fuson[14] was added to the above solution with stirring until a slight excess was indicated by a persistent iodine color. The mixture was heated at 60° for two minutes, then allowed to stand for 30 minutes, whereupon the excess iodine was destroyed by the addition of sufficient 10% sodium hydroxide solution. The crude iodoform, 0.70 g. (54%), was filtered, washed with water and air-dried. It was recrystallized three times from dilute ethanol containing a trace of sodium bisulfite. The purified product so obtained had m.p. 120–121° and a radioactivity assay of 1.020 ± 0.010 mc./mole.

The chromium trioxide–pyridine oxidation of a secondary alcohol to a ketone in the sterol series has been found to proceed without rearrangement.[12] Similarly, the formation of an oxime from a ketone, followed by reduction of the oxime to an amine has also been shown to occur without rearrangement.[6] By analogy, the above degradation of 3-phenyl-2-butanol-1-C^{14} (sp. act. 1.015 mc./mole) to iodoform-C^{14} (sp. act. 1.020 mc./mole) constitutes a radiochemical structure proof of the 2-amino-1-phenylbutane-1-C^{14} in question.

Deamination of 2-Amino-3-phenylbutane-1-C^{14} (IV).—In a 250-ml. flask fitted with a magnetic stirrer and a low temperature thermometer was placed a mixture of the above 2-amino-3-phenylbutane-1-C^{14} (6.06 g.), water (100 ml.), concd. hydrochloric acid (8.5 ml.) and glacial acetic acid (7 ml.). The slightly turbid solution was cooled to −3 to 0°, which temperature was maintained during the gradual addition of a solution of sodium nitrite (14 g.) in water (50 ml.). The mixture was allowed to come to room temperature, then extracted twice with 50-ml. portions of ether. The extract was washed twice with sodium bicarbonate solution, then with water, then dried (anhydrous sodium sulfate), filtered, and freed of solvent through a fractionating column. The crude residue of deamination product weighed 4.32 g. (72%), and was separated into its components as described below.

Vapor–Liquid Partition Chromatographic Columns.—The VLPC column employed in the present study consisted of several 10-mm. interchangeable inner tubes packed as described below. Each of these packed tubes could be inserted within a double glass jacket, the inner one of which was lagged with nichrome ribbon to provide for electrical heating of the packing. The column jackets were four feet in length. The sample under investigation (*ca.* 0.10 ml.) was injected with a hypodermic syringe through a three-way stopcock at the top of the column, then helium under the specified pressure for each packing was admitted as carrier gas to the top of the column. The thermal conductivity detector at the exit of the column consisted of a 6-volt flashlight bulb filament arranged as one arm of a Wheatstone bridge.[15] The unbalance signal of this bridge during exit of a fraction was recorded on a Leeds and Northrup or Varian G-10 Recorder. Small U-tubes, attached to the exit end of the thermal conductivity cell and chilled in an ice-bath, provided for collection of fractions carried through the column by the helium stream. The several column packings used in the present investigation, and the operating conditions for each packing are described below.

Packing A consisted of a four-foot tube packed with a mixture of coarse graded Celite impregnated with silicone oil (2:1). The jacket temperature was 198°, and the helium pressure was 5 p.s.i.

Packing B consisted of a four-foot tube filled with a mixture of Fluorolube 2000 (4 parts) and crushed firebrick (6 parts). The operating temperature was 187° and pressure 2.2 p.s.i.

Hypoiodite Degradation of the Amino Deamination Mixture.—An iodoform reaction similar to the one described above was conducted on the crude carbinol mixture (0.50 g.) obtained on deamination of the above 3-phenyl-2-butylamine-1-C^{14} (IV). The yield of iodoform, m.p. 121–122° after recrystallization, was 0.50 g. Its radioactivity assay was 0.513 ± 0.001 mc./mole. Of the various carbinol deamination products, only 3-phenyl-2-butanol (V) could yield iodoform on treatment with KOI solution. The present assay thus indicates that essentially 50% net phenyl migration occurred during the production of the 3-phenyl-2-butanol (V) component of the deamination mixture.

Vapor–Liquid Partition Chromatographic Separations on Known Mixtures and on the Deamination Mixture. 1. Deamination Mixture. Packing A.—A 0.1-ml. sample of the above deamination mixture was placed on the VLPC column fitted with packing A, operating under the specified conditions. Two peaks were noted; at 6.8 minutes and 11.1 minutes, respectively. The area under the 6.8-minute peak was only 3% of the total area under both peaks. The products corresponding to each peak were isolated by chilling the exit gas stream. The 6.8-minute product had $n^{22}D$ 1.5268 and gave an infrared pattern showing bands in the double bond region. In view of its minor presence in the deamination mixture it was assumed to be an olefinic product, and was not investigated further. Infrared investigation of the product corresponding to the 11.1-minute peak suggested that it was a complex mixture. Further attempts at its separation were accordingly undertaken, as described below.

2. Synthetic Mixture. Packing B.—A known mixture containing equal volumes of 3-phenyl-2-butanol (V), 2-phenyl-2-butanol (VI) and 1-phenyl-2-methyl-1-propanol (VII) was prepared. About 0.1 ml. of this mixture was placed on the VLPC column fitted with packing B and operating as specified. Two peaks were observed at 14 and 22 minutes, respectively. When 3-phenyl-2-butanol (V) was placed on the column under identical conditions its peak appeared at 22 minutes. When a mixture of 2-phenyl-2-butanol (VI) and 1-phenyl-2-methyl-1-propanol (VII) was placed on the VLPC column similarly, it came through unresolved in 14 minutes.

3. Deamination Mixture. Packing B.—When a 0.1-ml. sample of the above deamination mixture was placed on the VLPC column fitted with packing B and operating under identical conditions, two peaks at 14 and 22 minutes, respectively, were again observed. The areas under each peak, as determined with a planimeter, were equal, indicating that the 3-phenyl-2-butanol (V) component of the deamination mixture comprised approximately 50% thereof. The question as to whether the 14-minute peak observed for the deamination mixture contained one or two components was investigated below with the aid of alumina column chromatography.

The Partial Dehydration and Chromatographic Resolution of a Known Mixture and of the Deamination Mixture.—Cram has shown[7] that the action of warm glacial acetic acid on the acetate of 2-phenyl-2-butanol (VI) results in its conversion to an olefin. We have employed his method for the dehydration of the alcohol VI itself, followed by separation of the resulting olefin from other alcohol components by alumina column chromatography.

A mixture containing 2-phenyl-2-butanol (VI) (0.78 g.), 3-phenyl-2-butanol (V) (0.84 g.) and 1-phenyl-2-methyl-1-propanol (VII) (0.90 g.), total weight 2.52 g., was placed in 97 g. of glacial acetic acid (refluxed with a small amount of acetic anhydride, then fractionated). The mixture was maintained at 75° for 26 hours, then diluted with water (100 ml.) and extracted three times with pentane (100 ml. each). The extract was washed with sodium carbonate solution, then with water, then dried over anhydrous sodium sulfate. The solvent was removed through a short column, and the residue was dissolved in a small volume of pentane. The solution was placed on an alumina column containing 104 g. of activated alumina, which was then eluted with 1000 ml. of pentane. The pentane eluate containing the olefin frac-

(13) D. J. Cram and J. E. McCarty, THIS JOURNAL, **76**, 5740 (1954).

(14) R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Edition, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 156.

(15) R. H. Eastman and H. S. Mosher, private communication.

tion was freed of solvent by distillation through a short column, yielding an olefin residue weighing 0.73 g. (106 %), having $n^{23}D$ 1.5277, showing infrared olefinic bands at 11.23, 12.45 and 12.90 μ, and showing no infrared hydroxyl absorption. The alumina column was then eluted with one liter of absolute ethanol. The eluate was freed of solvent through a column, and the residue was subjected to rotary evaporation at aspirator pressure, yielding 1.79 g. of residual oil, $n^{22}D$ 1.4890. The infrared spectrum of this oil showed no absorption at 11.23 or 12.90 μ, but a strong OH band at 2.95 μ. A sample of this oil was subjected to VLPC on packing B (pressure of helium, approx. 2 p.s.i.). Two peaks at 14.5 and 40.2 minutes were observed. Since the 2-phenyl-2-butanol (VI) component in the original reaction mixture had been shown previously to dehydrate quantitatively to an olefin, the two presently observed peaks in the VLP chromatogram corresponded, respectively, to 1-phenyl-2-methyl-1-propanol (14.5 min.) and 3-phenyl-2-butanol (40.2 min.). The efflux time differences between this and the previous VLP chromatogram were due to differences in the helium carrier gas pressure.

The above deamination mixture (1.57 g.) was dissolved in anhydrous acetic acid (100 ml.), and the solution was maintained at 75° for 26 hours. Similar alumina column chromatography led to an olefin fraction weighing 0.23 g., and showing an identical infrared pattern as the olefin from the above synthetic mixture. Further elution of the alumina column with ethanol, as above, led to a carbinol residue of 1.27 g., having an infrared spectrum identical with that of the previous synthetic mixture at the same stage. A VLP chromatogram was run (packing B, *ca.* 2 p.s.i. helium pressure) on this carbinol residue, resulting in peaks at 14.5 and 40.2 minutes, corresponding to 1-phenyl-2-methyl-1-propanol and 3-phenyl-2-butanol, respectively. The planimeter determined area under the 14.5 min. peak was 1.04 in.^{2}, and that under the 40.2 min. peak was 4.23 in.^{2}. These data, involving the weight of the olefin fraction and the areas under the peaks of the other two carbinol fractions, permit the calculation that the composition of the crude deamination mixture was approximately 67% 3-phenyl-2-butanol (V), 16.5% 2-phenyl-2-butanol (VI) and 16.5% 1-phenyl-2-methyl-1-propanol (VII). The discrepancy (50% *vs.* 67%) in the quantity of 3-phenyl-2-butanol between this and the above estimation, is presumably within the experimental error of the rather coarse analytical methods employed.

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[CONTRIBUTION FROM THE MILES-AMES RESEARCH LABORATORY]

Some New Amebicidal Diamines[1]

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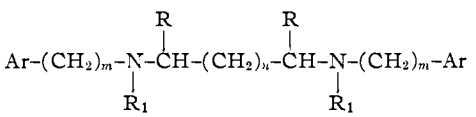
A number of bis-aminoalkanes and the related bis-tetrahydro-1-isoquinolylalkanes have been prepared for testing as amebicidal and trypanocidal agents. Some of these compounds showed sufficient activity *in vitro* to warrant *in vivo* and clinical study.

Emetine has been much used as a prototype for the synthesis of new compounds in the search for a more effective amebicide. Both open-chain bis-amines[2] and bis-tetrahydroisoquinolines[3] have been studied for this purpose and several have been reported to be effective both *in vitro* and *in vivo*. Of the open chain bis-amines, those of Hall, *et al.*,[2b] were of particular interest. They reported 7,13-diamino-5,15-diethylnonadecane dihydrochloride to be active *in vitro* against *E. histolytica* at a dilution of 1:500,000.

Thinking that reductive alkylation of amines of this type with alkoxy aromatic aldehydes would give compounds having a closer formal relationship to emetine, we have prepared a series represented by the general formula



R = H, C_2H_5, *n*-C_4H_9, *i*-C_5H_{11} and C_6H_{11}
R_1 = H or CH_3
m = 1 or 3; *n* = 0, 2, 4, 5, 6 and 10

Ar = C_6H_5, 4-(HO)C_6H_4, 4-(MeO)C_6H_4, 3,4-(CH_2O_2)C_6H_3, 3,4-(MeO)$_2C_6H_3$, 3,4-(MeO)$_2C_6H_3$ and 3,4,5-(MeO)$_3C_6H_2$

The primary amines required for this study were prepared by the method of Hall,[2b] which involves a Schmidt reaction on a dicarboxylic acid prepared by a malonic ester synthesis. When R is not hydrogen the dicarboxylic acids, the diamines, the Schiff bases and the final products are capable of existing as racemic and *meso* forms. In the only member of the series which was studied extensively, (R = *n*-C_4H_9, *n* = 5, *m* = 1 and Ar = 3,4-(CH_2O_2)C_6H_3), the intermediate dicarboxylic acid was obtained as a heavy oil from which a crystalline product could be isolated by crystallization from ligroin (b.p. 60–90°). The non-crystalline residue from evaporation of the solvent could be partially isomerized by distillation followed by crystallization of the distillate from ligroin (b.p. 60–90°), and this process could be repeated several times to give additional quantities of the crystalline acid. The presumed unstable isomer was not isolated and the stereochemical structure of the crystalline acid was not determined.

That the crystalline acid was not stereochemically pure was suggested by the isolation of two Schiff bases on reaction of the derived diamine with piperonal. The major portion of the Schiff base melted at 105–107° and on reduction gave a final product melting at 180–182°. When working with large quantities of material a small amount of Schiff base melting at 74–74.5° was isolated by fractional crystallization from absolute alcohol.

(1) Presented at the 132nd National Meeting of the American Chemical Society, September 10, 1957, New York, N. Y. (Abstracts p. 21-O).

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