resulting simultaneous differential equations. The actual value of these steady-state concentrations probably depends, however, on the concentrations of each of the enzymes present, which in turn would depend on the previous history of the organism (*cf.* Table I).

Conclusion

In conclusion one might say that perhaps the most important result of this work is the general insight it gives into the complicated interrelated system of chemical reactions which occur in living systems. The living cell is seen as a finely balanced dynamic network of chemical reactions which by its very nature operates as a negative feedback system: the cycle adapting itself to a change impressed on any part of it in such a manner that the new steady state is but little removed from the original one. A change of concentration in any intermediate is transmitted around the cycle and results in a compensating change in the corresponding precursor(s). We can thus understand why an organism can survive relatively rapid changes in its environmental conditions, and how it can adapt itself to new conditions. One can also see how rapidly changing external variables can upset the delicate balance and how these disturbances are damped out. These disturbances can be used as a new tool for the investigation of the complicated network of interrelated chemical reactions which may very well constitute the essential features of the dynamics of living organisms.

BERKELEY, CALIFORNIA

[CONTRIBUTION FROM THE WESTERN UTILIZATION RESEARCH BRANCH[1]]

The Reaction of Fructose with Aliphatic Amines

BY JOHN F. CARSON

RECEIVED MAY 27, 1955

Reaction of fructose with excess anhydrous *n*-propylamine and *n*-butylamine at low temperatures yields the crystalline rearranged products 2-*n*-propylamino- and 2-*n*-butylamino-2-deoxyhexoses (II) in low yields. From the reaction of fructose with anhydrous ethylamine, the intermediate fructosylethylamine I was crystallized in good yield. This compound in methanol at 25° rearranges, in part, to the 2-ethylamino-2-deoxyhexose. Evidence for the glucose configuration for the 2-alkylamino-2-deoxyhexoses is obtained from consideration of optical rotations and by application of the Levene salt–acid rule. The α-configuration for the free bases and the corresponding hydrochlorides is advanced on the basis of rotational behavior. This is supported by infrared data. The ring structures of the rearranged products are probably pyranose.

This paper reports additional results of our investigations[2] of the reactions of D-fructose with aliphatic amines. These reactions are being studied as model systems for investigating possible pathways for the non-enzymatic browning of foodstuffs resulting from a preliminary reaction of amino compounds with reducing sugars.

In a previous communication,[2] the reaction of fructose with cyclohexylamine and with isopropylamine has been shown to produce, in small yields, the crystalline 2-isopropyl- and 2-cyclohexylamino-2-deoxyaldohexoses (II) (R = isopropyl or cyclohexyl) presumably by rearrangement of the intermediate fructosylalkylamine I. The preparation of additional compounds of this type II might help in determining the configuration of the number 2 carbon atom, which was assumed to be of the glucose configuration. Also, the isolation of the intermediate fructosylalkylamines, in crystalline form, might facilitate further study of this rearrangement and may aid in the discovery of other rearranged products from the fructose–amine reactions.

It has been found that fructose and anhydrous ethylamine, under proper conditions, will yield the crystalline fructosylethylamine I (R = ethyl), the desired intermediate, in 70–80% yields. With *n*-propylamine or *n*-butylamine, however, the corresponding fructosyl derivatives could not be isolated. Instead, the rearranged 2-*n*-propyl- and 2-*n*-butylamino-2-deoxyaldohexoses (II), homologs of the previously isolated isopropyl- and cyclohexylamino derivatives, were crystallized in low yields. Evidence is here presented supporting the glucose configuration for the 2-carbon atom and the α-configuration for the anomeric carbon of the 2-alkylamino-2-deoxyaldohexoses. Rotational behavior suggests a pyranose ring structure for these rearranged amino sugars and for their hydrochloride salts.

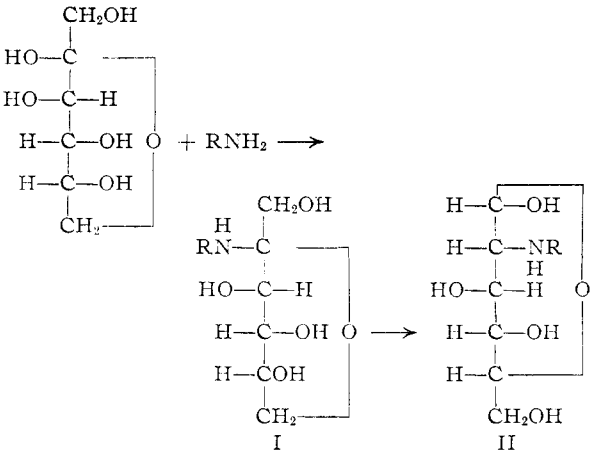
Fructosylethylamine in dilute aqueous hydrochloric acid rapidly hydrolyzes at room temperature to the amine and fructose. The compound is unusually reactive either in the solid state or in solution. When exposed to air at 25°, the crystalline material becomes yellow and resinous in 3 or 4 days. Under a vacuum, the change requires several weeks. Solutions in water, pyridine or methanol at 25° become yellow in 1 to 2 days. The compound mutarotates in methanol and in pyridine but because of decomposition, no conclusions as to configuration can be reached. In methanol at room temperature, fructosylethylamine rearranges to the stable 2-ethylamino-2-deoxy-α-D-glucose in low yields accompanied by formation of resinous material. This rearrangement and the concurrent production of dark resinous material is catalyzed by traces of acetic acid in the solvent. The great instability of fructosylethylamine is interesting since Helferich and Portz[3] and Barry and Honeyman[4] have reported that fructosylarylamines are more stable than the corresponding glucosyl derivatives. Fructosylethylamine is less stable than the typical glucosyl aliphatic amines.

(1) Agricultural Research Service, U. S. Department of Agriculture. Article not copyrighted.

(2) J. F. Carson, THIS JOURNAL, **77**, 1881 (1955).

(3) B. Helferich and W. Portz, *Ber.*, **86**, 604 (1953).

(4) C. P. Barry and John Honeyman, *J. Chem. Soc.*, 4147 (1952).



The new 2-alkylamino-aldohexoses, like the previously reported products,[2] give the Elson–Morgan test[5] for 2-amino sugars, reduce Fehling solution only on heating and are stable in dilute aqueous hydrochloric acid from which the crystalline hydrochlorides can be isolated. The free bases are dextrorotatory in pyridine and mutarotate in a negative direction suggesting an α-configuration. The hydrochlorides in water are likewise dextrorotatory and mutarotate to lower values with rates that are first order and independent of pH between 2 and 5.[2] The new 2-alkylamino-2-deoxyhexoses exhibit the same unusually slow mutarotation in water at pH 9.2–9.4 requiring from 5 to 8 days for constant rotation.

The absence of any appreciable thermal mutarotation of the equilibrium solutions of the free bases in hydrochloric acid or of the hydrochlorides in water is consistent with a pyranose structure. For example a temperature variation of 2° from 25–27° yields a difference of less than 0.2° in specific rotation. Pyranose–furanose mutarotations generally have a higher temperature coefficient for the equilibrium rotation.[6] For example, the equilibrium specific rotation of a 1% solution of D-fructose changes approximately 0.6° per degree centigrade at 25°.

Table I lists the molecular rotations of the 2-alkylamino-2-deoxyhexose hydrochlorides (extrapolated to zero time) in water compared with the molecular rotations of α-D-glucosamine hydrochloride and of the corresponding N-methyl derivative. The high positive molecular rotations of these derivatives together with the fact that mannose derivatives usually have smaller rotations than the corresponding glucose derivatives supports the α-D-glucose configuration for the new compounds.

The salt–acid rule of Levene[7] as generalized and extended by Woods and Neish[8] has been applied to one of the derivatives. According to this generalization, if the sodium salt of an aldonic acid is more dextrorotatory than the free acid, the free hydroxyl group on the number 2 carbon atom is to the right when written in a Fischer projectional formula. If the reverse holds, the hydroxyl group is on the left. Levene[7] showed that glucosaminic acid conformed to this rule with respect to the position of the amino group. Oxidation of 2-*n*-butylamino-2-deoxyaldohexose with mercuric oxide has yielded the corresponding 2-*n*-butylamino-2-deoxyhexonic acid. In sodium hydroxide solution, the compound has the rotation $[\alpha]^{25.5}D$ +24.5°. Acidification with hydrochloric acid gives a rotation after four minutes of $[\alpha]^{26}D$ +6.5° which slowly increases to +19.8° as a result of lactone formation. Assuming that the rule can be extended to the alkylamino derivatives, then these compounds must have the D-glucose configuration.

TABLE I

OPTICAL ROTATIONS OF 2-AMINO-SUGAR HYDROCHLORIDES

Amino sugar	$[\alpha]^{25}D$ initial[a]	$[M]$
2-Amino-2-deoxy-α-D-glucose	+100°[b]	+21,600
2-Methylamino-2-deoxy-α-D-glucose	+104[c]	23,900
2-Ethylamino-2-deoxyaldohexose	+93.6	22,800
2-*n*-Propyldeoxyaldohexose	99.5	25,600
2-Isopropyldeoxyaldohexose	100[d]	25,800
2-*n*-Butyldeoxyaldohexose	94.5	25,700
2-Cyclohexyldeoxyaldohexose	87.8[d]	26,100

[a] Except for the first two values, which are from the literature, rotations are values obtained by extrapolation to zero time. [b] A. Neuberger and R. Pitt-Rivers, *J. Chem. Soc.*, 122 (1939). [c] From data of F. A. Kuehl, Jr., E. H. Flynn, F. W. Holly, R. Mozingo and K. Folkers, THIS JOURNAL, 69, 3032 (1947). [d] J. F. Carson, *ibid.*, **77**, 1881 (1955).

Infrared spectra give additional evidence for an α-configuration for both the free bases and their hydrochlorides but fail to establish the glucose configuration. Table II lists absorption maxima for mull samples in mineral oil of the 2-alkylamino-2-deoxyaldoses and their hydrochlorides in the range of 740–935 cm.$^{-1}$. According to the generalizations of Barker, *et al.*,[9] based on infrared spectra of a variety of crystalline pyranose derivatives of glucose, galactose and mannose, the presence or absence of absorption at 835–855 cm.$^{-1}$ determines whether the configuration is α or β. All of the derivatives have absorption in this range with the exception of the 2-ethylamino derivative and the hydrochloride of the 2-isopropylamino derivative with maxima slightly outside the range at 856 and 858 cm.$^{-1}$, respectively. α-D-Glucosamine hydrochloride, of known configuration, is on the high side of the range at 855 cm.$^{-1}$.

An attempt was made to correlate the maxima with those reported for glucose derivatives. According to Barker, *et al.*,[9] galactose derivatives show an absorption maximum at 871 ± 7 cm.$^{-1}$ and mannose derivatives at 876 ± 9 cm.$^{-1}$ independent of anomeric configuration while glucopyranose derivatives do not absorb in this region. Of the eleven derivatives listed, three have an absorption maximum within this range (864–885 cm.$^{-1}$) and two more have a band within 2 cm.$^{-1}$ of this range. The other six derivatives are in agreement with the generalization. Apparently this rule, which appears to be useful for many glucose derivatives, is not applicable for distinguishing glucose from mannose configurations of the 2-amino sugars.

(5) L. A. Elson and W. T. J. Morgan, *Biochem. J.*, **27**, 1824 (1953).

(6) "Polarimetry, Saccharimetry, and the Sugars," National Bureau of Standards Circular C440, Frederick J. Bates and Associates, 1942, p. 449.

(7) P. A. Levene, *J. Biol. Chem.*, **63**, 95 (1925).

(8) R. J. Woods and A. C. Neish, *Can. J. Chem.*, **32**, 404 (1954).

(9) S. A. Barker, E. J. Bourne, R. Stephens and D. H. Whiffen, *J. Chem. Soc.*, **171**, 3468 (1954).

TABLE II

INFRARED ABSORPTION MAXIMA OF 2-ALKYLAMINO-2-DEOXYALDOHEXOSES AND THEIR HYDROCHLORIDES

2-Alkylamino-2-deoxyhexose and hydrochloride	Absorption, cm.$^{-1}$ [a]						
2-Ethylamino-2-deoxyhexose		881M	856M	818M	764M		
2-Ethylamino-2-deoxyhexose hydrochloride		874W	843W	798M	761M		
n-Propylamino-2-deoxyhexose	901M	881M	853M		763M		
n-Propylamino-2-deoxyhexose hydrochloride	907W	890W	850S	824W	776M	756M	
Isopropylamino-2-deoxyhexose	915S		853M	818M	762M		
Isopropylamino-2-deoxyhexose hydrochloride	915M	890M	858W	814W	781M		
n-Butylamino-2-deoxyhexose	923M	899W	849M[b]	830W	809W	766M	
n-Butylamino-2-deoxyhexose hydrochloride	916M	893W	860M	835W	792M	773W	754W
Cyclohexylamino-2-deoxyhexose	929S	896M	(853S, 840S)		784W	761M	
Cyclohexylamino-2-deoxyhexose hydrochloride	916W	899M	(862M, 854M)	839W	771M		
2-Amino-2-deoxy-α-D-glucose hydrochloride	912M	887M	855M		775M		

[a] Samples examined as mineral oil mulls: M = medium, S = strong, W = Weak. [b] Broad band, probably two bands superposed.

Acknowledgment.—The author expresses his appreciation to Mr. L. M. White and Miss Geraldine Secor for elemental analyses and to Mr. Glen Bailey for infrared determinations.

Experimental

2-*n*-Butylamino-2-deoxy-α-D-glucose.—To 40 g. (0.22 mole) of D-fructose there was added 130 g. (1.8 moles) of anhydrous *n*-butylamine (previously cooled to −20°). The mixture was shaken for several minutes to dissolve the fructose, and the colorless solution was held at −20° for two days and then at 0° for four days. The pale yellow solution was concentrated *in vacuo* at 0° or less to a stiff sirup which was covered with 100 ml. of acetone, seeded and allowed to crystallize at 0° for a week. A yield of 4.1 g. of white crystalline material, dec. 146–147.5°, was obtained. Several additional fractions totalling 5.2 g. were obtained from the mother liquor. The third crystalline fraction was heavily contaminated with unreacted fructose and was discarded. The combined fractions, 9.3 g., were recrystallized by dissolving in 100 ml. of boiling methanol, adding 200 ml. of acetone to the cooled solution and storing at 0° for several days. Analytically pure 2-*n*-butylamino-2-deoxy-α-D-glucose was obtained in a yield of 7.6 g. (14.5%) as clusters of jagged needles, dec. (gas), 147–148° (preheat 135°). *Specific Rotations:* In pyridine, $[\alpha]^{26}D$ +135°(0) → +97.6° (24 hr.) (*l* 2, *c* 1.1). In 0.1 *N* hydrochloric acid, $[\alpha]^{26}D$ +106°(0) → +91.4° (2 hr.) (*l* 2, *c* 1.1) (equil. $[\alpha]D$ calcd. as hydrochloride +79.1°). In carbon dioxide-free water, *p*H 9.4, $[\alpha]^{26}D$ +55.3° (6 min.) → +41.9° (6 days) (*l* 2, *c* 1.02).

Anal. Calcd. for $C_{10}H_{21}NO_5$: C, 51.05; H, 9.00; N, 5.95. Found: C, 51.1; H, 8.95; N, 5.93.

Hydrochloride of 2-*n*-Butylamino-2-deoxy-α-D-glucose.—The butylamino derivative, 1.14 g., was dissolved in 60 ml. of abs. ethanol to which 10 ml. of normal hydrochloric acid was added. The solution was concentrated *in vacuo* to 10 ml. An additional 100 ml. of ethanol was added and the solution concentrated *in vacuo* to a dry white solid. This was dissolved in 25 ml. of boiling absolute ethanol, 50 ml. of acetone was added and the solution allowed to crystallize for several days at −20°. A yield of 1.15 g. of white crystalline product was obtained and a second crop of 0.12 g. was isolated (yield 96%). The salt can also be isolated from the aqueous hydrochloric acid solution used for specific rotations by concentrating to dryness *in vacuo* and recrystallizing as above. The hydrochloride decomposes with the evolution of gas at 186–187° when preheated to 165°.

Anal. Calcd. for $C_{10}H_{21}NO_5$·HCl: N, 5.15; Cl, 13.05. Found: N, 5.10; Cl, 13.0. $[\alpha]^{26}D$ (H_2O, *p*H 5.4) + 94.5° (0) → +79.1° (constant 2 hr.) (*l* 2, *c* 1.0).

2-*n*-Propylamino-2-deoxy-α-D-glucose.—D-Fructose, 40 g. (0.222 mole) and *n*-propylamine, 110 g. (1.86 moles) reacted together under the same conditions as for the *n*-butylmine product. The yield of crude crystalline material, dec. 125–126°, was 15 g. A fraction, 10 g., consisting largely of fructose, was discarded. Recrystallization of the crude fractions from methanol–acetone yielded 7.0 g. (14%) as small stubby prisms dec. (gas) 153–154° (preheat 140°).

Anal. Calcd. for $C_9H_{19}NO_5$: C, 48.85; H, 8.66; N, 6.33. Found: C, 49.1; H, 8.75; N, 6.33.

Specific Rotations.—In pyridine, $[\alpha]^{25}D$ +128° (30 min.) → +103.4° (const. 8 hr.) (*l* 2, *c* 1.0). In 0.1 *N* hydrochloric acid, $[\alpha]^{24.5}D$ +117° (0) → +97.3° (3 hours) (*l* 2, *c* 1.0) (calcd. as the hydrochloride $[\alpha]^{24.5}D$ +100° (0) → +83.5°). In carbon dioxide-free water $[\alpha]^{25}D$ +57.8° (0) → +46.4° (190 hours) (*l* 2, *c* 1.5).

2-*n*-Propylamino-2-deoxy-α-D-glucose Hydrochloride.—The crystalline salt was prepared in the same way as the hydrochloride of the butylamino sugar, tiny prisms, dec. 182.5–183.5 when preheated to 170°.

Anal. Calcd. for $C_9H_{19}NO_5HCl$: N, 5.44; Cl, 13.76. Found: N, 5.44; Cl, 13.8; $[\alpha]^{24.5}D$ (water, *p*H 5.2) +99.5° (0) → +84.2° (3 hours).

D-Fructosylethylamine.—A mixture of D-fructose, 52 g. (0.289 mole), and anhydrous ethylamine, 130 g. (2.9 moles) (previously cooled to −20°), was shaken for five minutes when most of the fructose dissolved. The mixture was kept at −20° for two days when complete solution was attained and then at 0° for five days. The pale yellow solution was concentrated *in vacuo* at 0° or less to a pale yellow sirup. Absolute methanol, 200 ml., was added and the solution concentrated *in vacuo* at low temperature to a sirup. Fresh methanol, 200 ml., was added and the solution again concentrated in the same way to a total volume of 100 ml. The solution crystallized rapidly to a mass of white granular crystals. The mixture after storage for 36 hours at −20° was filtered and washed with a little cold methanol to give 46 g. of product, dec. 100° (preheat 95°). An additional 3.5 g. of material was obtained from the mother liquor to give a total yield of 76%. A third fraction, 1–2 g., was obtained which proved to be unreacted fructose. Methanol solutions of the compound should be kept cold at all times, since the compound rearranges and turns brown rapidly in this solvent. The crystalline compound should be stored at 0° or lower. The product could be recrystallized with a 75% recovery by dissolving in 300 ml. of warm methanol (not more than five minutes at 55°) followed by rapid cooling to 0° and storing at −20° for several days. The pure compound is obtained as coarse granular crystals. It colors and shrinks at 97° and decomposes at 100–101° when preheated to 95°. *Specific Rotations:* In 0.1 *N* hydrochloric acid, $[\alpha]^{25}D$ −4.4° (5 min.) → −77.2° (3 hours) (*l* 2, *c* 1.27); calcd. for complete hydrolysis to D-fructose, equil. $[\alpha]^{25}D$ −88.8°. Extrapolation from the equation of Vosburgh[10] for fructose solutions gives $[\alpha]^{25}D$ −88.7°. That fructose was probably the only reducing substance present was demonstrated by paper chromatography[11] and its identity was confirmed by the preparation of the 2,4-dinitrophenylhydrazone[11] and microscopic observation. In pyridine, $[\alpha]^{26}D$ +30.8° (18 min.) → +16.1° (1.5 hr.) → +10.2° (48 hours) (*l* 2, *c* 1.46). The solution turned a pale yellow in 10 hours and progressively darkened on standing; in methanol, $[\alpha]^{25}D$ +10° (10 min.) → +5.9° (23 min.) → +12.5° (48 hr.) (*l* 2, *c* 1.1). This is not an equilibrium value as the solution turned yellow in 48 hours and progressively darkened.

(10) W. C. Vosburgh, THIS JOURNAL, **42**, 1696 (1920).

(11) I am indebted to Mr. L. M. White for paper chromatography and for the preparation and identification of fructose 2,4-dinitrophenylhydrazone.

Anal. Calcd. for $C_8H_{17}NO_5$: C, 46.36; H, 8.27; N, 6.76. Found: C, 46.6; H, 8.29; N, 6.78.

2-Ethylamino-2-deoxy-α-D-glucose.—A solution of 5 g. of fructosylethylamine in 250 ml. of methanol containing 0.2 ml. of acetic acid was allowed to stand for 24 hours at 24–26°. The solution, originally colorless, turned yellow in eight hours and amber in 24 hours. The solution was concentrated *in vacuo* to 15 ml., 45 ml. of acetone was added and the solution allowed to crystallize at 0° for several days. The product, 1.8 g. of yellow semi-crystalline material, was recrystallized from a mixture of 20 ml. of methanol and 50 ml. of acetone to yield 1.0 g. (20%) of colorless elongated prisms, dec. 136–137°. In the absence of acetic acid, the reaction solution requires about 72 hours to develop the same degree of color and a comparable yield of isolable crystalline product. Conducting the experiment for a longer period of time leads to a decrease in isolable crystalline product probably as a result of increased formation of dark resinous material. The pure compound is isolated in the form of white granular crystals, dec. 138–139° (preheat to 125°). *Specific Rotations:* In pyridine, $[\alpha]^{25.5}D$ +146.4° (20 min.) → +106.9° (7 hr.) (*l* 2, *c* 1.0). In 0.1 *N* hydrochloric acid, $[\alpha]^{25}D$ +108° (0) → +101.7° (2 hr.) (*l* 2, *c* 1.27) (calc. as the hydrochloride, equil. $[\alpha]D$ +86.5°). In CO_2-free water, $[\alpha]^{25}D$ +64° (0) → +49° (175 hours) (*l* 2, *c* 1.16).

Anal. Calcd. for $C_8H_{17}NO_5$: C, 46.36; H, 8.27; N, 6.76. Found: C, 46.6; H, 8.41; N, 6.70.

2-Ethylamino-2-deoxy-α-D-glucose Hydrochloride.—This salt was prepared by the same procedure as for the other hydrochlorides and was recrystallized from ethanol–acetone (1:1), sheathes of jagged needles, dec. 180–181° (preheat to 155). In water, *p*H 5.1, $[\alpha]^{25}D$ +93.6° (0) → +87.0° (2 hr.).

Anal. Calcd. for $C_8H_{18}NO_5Cl$: N, 5.75; Cl, 14.55. Found: N, 5.75; Cl, 14.5.

2-*n*-Butylamino-2-deoxy-D-gluconic Acid.—A suspension of 6 g. of red mercuric oxide[12] in a solution of 1.5 g. of 2-*n*-butylamino-2-deoxy-α-D-glucose in 250 ml. of water was heated in a hot water-bath at 97–99° for 25 minutes. When refluxing was attempted, the solution foamed severely. The solution was filtered, mercuric ion removed with hydrogen sulfide, and the solution, after removal of hydrogen sulfide by aeration, was filtered through carbon. The solution was concentrated *in vacuo* to 10 ml., 80 ml. of absolute ethanol added and the solution again concentrated to 10 ml. when crystallization took place. The suspension was diluted with 20 ml. of ethanol and stored at 0° overnight. A yield of 540 mg. of acid was obtained. The pure acid was obtained by recrystallization from 12 ml. of water plus 35 ml. of absolute ethanol as tiny fibrous crystals. Dec. 205–207° (gas), preheat 190°. *Specific Rotations:* in 0.1 *N* sodium hydroxide, $[\alpha]^{25.5}D$ +24.5° (*l* 2, *c* 1.37). Acidified with normal hydrochloric acid to *p*H 1.2, $[\alpha]^{26}D$ +6.5° (4 min.) → +19.8° (125 hours).

Anal. Calcd. for $C_{10}H_{21}NO_6$: C, 47.80; H, 8.42; N, 5.57. Found: C, 47.9; H, 8.48; N, 5.45.

(12) Procedure of F. A. Kuehl, Jr., E. H. Flynn, F. W. Holly, R. Mozingo and K. Folkers, THIS JOURNAL, **69**, 3032 (1947).

ALBANY 10, CALIFORNIA

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, CHEMICAL DIVISION, MERCK & CO., INC.]

Neopinone[1]

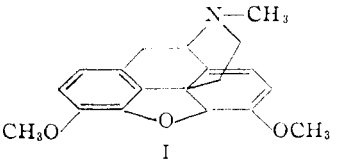
BY HAROLD CONROY

RECEIVED APRIL 29, 1955

Neopinone, the ketone corresponding to the opium alkaloid neopine, has been prepared by catalytic reduction of 14-bromocodeinone. The reduction of neopinone, its reactions with aqueous acids and alkali and the unusual course of degradation of its methiodide are described in detail.

The direct hydrolysis[2] of thebaine (I) with dilute sulfuric acid provides little more than a trace of codeinone (II); most of the product is alkali soluble and contains one or more of the known rearranged derivatives,[3] thebenine, morphothebaine and the metathebainone precursor.[4] Since it was a matter of practical interest to develop a preparative method for the conversion of thebaine to codeine (III), an alternative route for the change I → II,[5] was investigated.

The bromination of thebaine in acetic acid as solvent gives a substance[6,7] for which two structures (IV and V) have been considered,[8] that of 14-bromocodeinone (IV) having been generally favored. The ultraviolet spectrum does not permit any distinction to be made,[9] but the infrared spectrum of this compound contains a strong peak at 1679 cm.$^{-1}$, as does that of codeinone itself, so that



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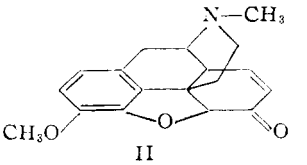

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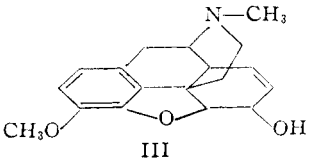

III

(1) Paper presented at the Sixth Summer Seminar in the Chemistry of Natural Products, University of New Brunswick, Fredericton, N. B., Canada, August 17–21, 1954.

(2) L. Knorr and H. Hörlein, *Ber.*, **39**, 1409 (1906).

(3) For excellent summaries of the chemistry of thebenine and morphothebaine, *cf.* L. F. Small, "Chemistry of the Opium Alkaloids," U. S. Government Printing Office, Washington, D. C., 1932, pp. 321, 327; K. W. Bentley, "The Chemistry of the Morphine Alkaloids," Oxford University Press, London, 1954, pp. 314, 326.

(4) G. Stork, in "The Alkaloids," Vol. II, edited by R. H. F. Manske and H. L. Holmes, Academic Press, Inc., New York, N. Y., 1953, pp. 193–197; K. W. Bentley, ref. 3, p. 319.

(5) The sodium borohydride reduction of codeinone to codeine proceeds stereospecifically in high yield (M. Gates, THIS JOURNAL, **75**, 4340 (1953)).

(6) M. Freund, *Ber.*, **39**, 844 (1906).

(7) E. Speyer and K. Sarre, *ibid.*, **57**, 1404 (1924).

(8) L. F. Small, ref. 3, pp. 248, 255; E. A. Kollontay, Austrian Patent 162,928 (1949); K. W. Bentley, ref. 3, p. 251.

(9) The product shows high intensity absorption, but no well-defined maximum in the 230 mμ region [λ_{max} (for the guaicol nucleus) 280 mμ, log ε 3.35 (CH_3OH)], while codeinone gives an indistinct shoulder at 227 mμ, log ε 4.16 [λ_{max} 280 mμ, log ε 3.14 (C_2H_5OH)].