the class of enol acetates and one of the acetyl groups in dihydrorotenonic acid is of this type.

Dihydrorotenone monoacetate is reduced by catalytic hydrogen to dihydrodesoxyrotenone.

WASHINGTON, D. C.

DEGUELIN. IV. THE STRUCTURE OF DEGUELIN AND TEPHROSIN

BY E. P. CLARK

On the basis of information now available it may be stated with a considerable degree of assurance that the structure of deguelin is represented by formula I.
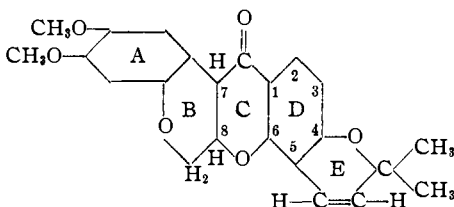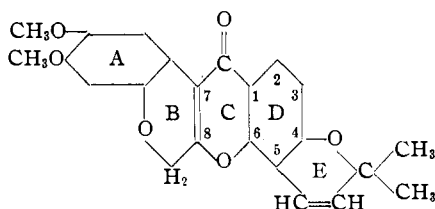

I. Deguelin, $C_{23}H_{22}O_6$

This statement is based upon facts concerning reactions of deguelin previously published together with certain new information which will be presented at this time and also upon the important observation previously made relative to relationships existing between deguelin and rotenone.

As the reactions principally involved in establishing that portion of the structure of deguelin represented by rings A, B, C and D have been recorded[1] and an interpretation of these reactions has been made in establishing the same structures in toxicarol,[2] it will be necessary only to refer to these facts briefly.

Deguelin, like rotenone and toxicarol, contains two hydrogen atoms which are readily removed by mild oxidation. In their place a double bond is introduced into the molecule, and the oxidation product, dehydrodeguelin (formula II), undergoes reactions which establish the fact that the position of the new double bond is between the carbon atoms common to rings B and C (designated in the formula as carbon atoms 7 and 8). The facts supporting the last statement are as follows: first, permanganate oxidation of dehydrodeguelin yields three products, namely, 2-hydroxy-4,5-dimethoxybenzoic acid, risic acid (2-carboxy-4,5-dimethoxyphenoxyacetic

[1] Clark, THIS JOURNAL, (a) 53, 313 (1931); (b) 53, 2369 (1931); (c) 53, 3431 (1931); (d) 53, 2007 (1931).

[2] Clark, ibid., 54, 2537 (1932).

II. Dehydrodeguelin, $C_{23}H_{20}O_6$

acid) and a new tricarboxylic acid, $C_{12}H_{12}O_8$, which has been designated as nicouic acid. Second, hydrolysis of dehydrodeguelin with alcoholic potassium hydroxide yields deguelic acid, $C_{23}H_{24}O_8$, which upon oxidation with potassium permanganate gives risic acid. If, however, the oxidizing agent is alkaline hydrogen peroxide, derric acid (2-carboxymethyl-4,5-dimethoxy-phenoxyacetic acid) is formed. Disregarding for the moment nicouic acid, the interpretation of these facts is the same as was presented in developing that portion of the structure of toxicarol which is identical with rings A, B and C in the deguelin formula presented above.[2] It follows, therefore, that deguelin, having no free hydroxyl as is the case with toxicarol, undoubtedly possesses the structure represented by rings A, B, C and D. There then remain only the elements C_5H_6O to be accounted for.

Available information concerning this grouping is purely of an analytical character, but the evidence is fairly conclusive that the structure represented by ring E in formulas I and II is correct.

Deguelin has been shown to be optically inactive[1a] and it also possesses a double bond capable of reduction to a dihydro derivative. Except for the configurations of carbon atoms 7 and 8 which are assumed to be racemized in the process of preparing deguelin, as was also suggested as being the case with toxicarol,[2] formula I satisfies the two conditions just mentioned. It has further been shown that permanganate oxidation of dehydrodeguelin yields besides 2-hydroxy-4,5-dimethoxybenzoic and risic acids, nicouic acid. to which reference was made above.

Nicouic acid is a tricarboxylic acid, as shown by combustion, titration and the methoxyl content of its methyl ester. It decomposes at its melting point with the evolution of gas and at the same time gives as one of its decomposition products α-hydroxyisobutyric acid. It also gives the fluorescein reaction for resorcinol,[3] and it may be decomposed in boiling aniline solution to give resorcinol. When considered in conjunction with the structure of that portion of the dehydro-deguelin molecule represented by rings A, B and C in formula II and also the manner in which permanganate attacks the molecule, these facts indicate that nicouic acid has the structure represented by III.
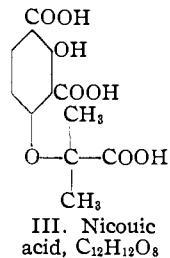

III. Nicouic acid, $C_{12}H_{12}O_8$

[3] Mulliken, "Identification of Pure Organic Compounds," 1905, Vol. I, p. 110.

Further evidence bearing upon the nature of ring E has been obtained through another source. It has been shown that tephrosin, $C_{23}H_{22}O_7$, is a hydroxydeguelin[4,5] and that the hydroxyl group replaces one of the easily oxidizable hydrogen atoms attached to carbon atoms 7 or 8 in deguelin. It has also been shown that tephrosin is oxidized by potassium permanganate to a dicarboxylic acid, $C_{23}H_{22}O_{11}$ (IV),[4] in which process the ring containing the double bond (ring D) is split and four atoms of oxygen are added. No loss of carbon or hydrogen occurs.

Tephrosin dicarboxylic acid, when dissolved in hot diphenyl ether and then heated a short time to the boiling point of the solvent, loses the elements $C_4H_8O_3$ and yields a phenolic monocarboxylic acid, $C_{19}H_{14}O_8$ (V), to which the name tephrosin monocarboxylic acid has been given. In this process the hydrogen atom and the hydroxyl group attached to carbon atoms 7 and 8 are removed as water with the generation of a double bond, so that tephrosin monocarboxylic acid belongs to the dehydro series of derivatives. This fact is shown not only by the insolubility of the product, a characteristic of dehydro derivatives of the rotenone group of fish poisons, but also because of its composition and its ability, when treated with alcholic potassium hydroxide solution, to undergo hydrolysis with the formation of a new carboxyl and phenolic hydroxyl group (deguelic or derrisic acid reaction).

The remaining portion of the $C_4H_8O_3$, namely, $C_4H_6O_2$, which is lost by tephrosin dicarboxylic acid, consists of α-hydroxyisobutyric acid. Evidence of this was obtained by isolating the α-hydroxyisobutyric acid as a decomposition product of the reaction. Because α-hydroxyisobutyric acid is removed from the original acid with the simultaneous generation of a hydroxyl group in ring D, demonstrated by a positive ferric chloride test and the formation of an acetyl derivative, it is obvious that the process is one of hydrolysis and may be represented as follows

IV. Tephrosin dicarboxylic
acid, $C_{23}H_{22}O_{11}$

V. Tephrosin monocarboxylic
acid, $C_{19}H_{14}O_8$
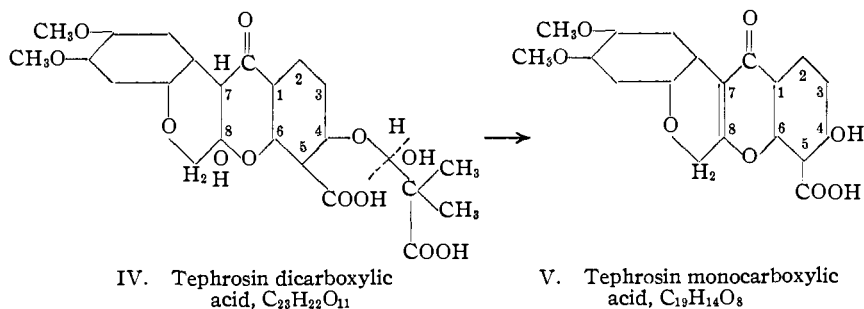
[4] Clark, THIS JOURNAL, **53**, 729 (1931).

[5] Besides acetic anhydride or a mixture of acetic and sulfuric acids other dehydrating agents convert tephrosin into dehydrodeguelin. An acetyl derivative of tephrosin has also been prepared (see experimental part).

The reaction is important, however, aside from showing the nature of the C_4 group, in that tephrosin monocarboxylic acid undergoes the Dakin reaction, yielding risic acid, and therefore restricts the possible positions of the hydroxyl group in tephrosin monocarboxylic acid and consequently the oxygen linkage of ring E in deguelin and tephrosin. The Dakin reaction has been discussed recently in connection with its application to the structure of toxicarol,[2] and from that discussion it follows that the hydroxyl group in ring D of tephrosin monocarboxylic acid is either at position 2 or 4.

From the facts presented relative to nicouic and tephrosin dicarboxylic acids it follows that the grouping C_5H_6O in deguelin and tephrosin consists of an optically inactive unsaturated pyran ring, which can be represented only as indicated by ring E.

In the data thus far presented only two facts bear upon the attachment of ring E to ring D. This of course refers to the application of the Dakin reaction to tephrosin monocarboxylic acid and the evidence that nicouic acid is a resorcinol derivative. However, another approach to this problem is available as a result of the observation that dihydrodehydrodeguelin and dihydrodeguelic acid are respectively identical with dehydro-β-dihydrorotenone and dehydrodihydroxy-β-dihydrorotenonic acid.[1b]

It has recently been demonstrated by LaForge and Haller[6] that rotenone may be represented by formula VI, and in the course of this work it was
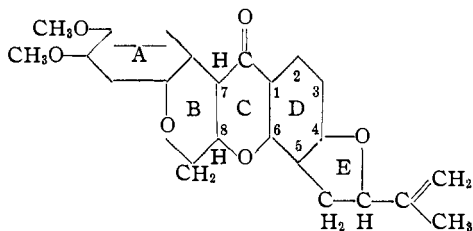
VI. Rotenone

shown that rotenonic acid is formed from rotenone by opening the furan ring (E) by hydrogenation.

Haller[7] also found that in attempting to isomerize rotenonic acid to isorotenonic acid with glacial acetic and sulfuric acids, ring closure occurred in a measure analogous to the formation of a saturated lactone from an unsaturated acid and yielded an alkali-insoluble compound which he designated as β-dihydrorotenone. Mild oxidation of this compound removed the readily oxidizable hydrogen atoms on carbon atoms 7 and 8 in formula VI and yielded dehydro-β-dihydrorotenone. Hydrolysis of the dehydro-β-dihydrorotenone with alcoholic alkali yielded what was called dehydrodi-
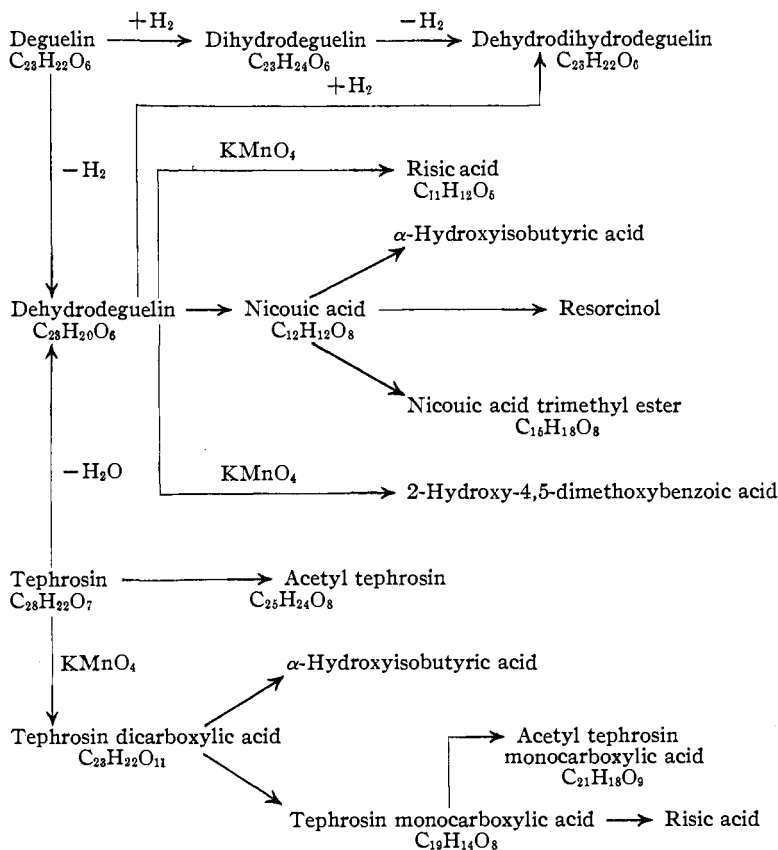
[6] LaForge and Haller, THIS JOURNAL, 54, 810 (1932).
[7] Haller, ibid., 53, 733 (1931).

hydroxy-β-dihydrorotenonic acid. These β-dihydrorotenone compounds, as stated before, were the same as dehydrodihydrodeguelin and dihydrodeguelic acid, respectively. From the way in which the β-dihydrorotenone derivatives were prepared it follows that no shift of points of attachment of ring E to ring D in rotenone occurred, and therefore ring E in deguelin and tephrosin is attached to ring D as indicated in formula I.

The relationships existing between the β-dihydrorotenone and deguelin derivatives are also verification of that portion of the structure of deguelin represented by rings A, B, C and D which was developed upon evidence relating to independent reactions of deguelin and its derivatives.

The reactions involved in the foregoing discussion which have been presented for the first time are summarized in the accompanying chart.

NEW REACTIONS OF DEGUELIN AND TEPHROSIN AND SOME OF THEIR DERIVATIVES

Deguelin $C_{23}H_{22}O_6$ $\xrightarrow{+H_2}$ Dihydrodeguelin $C_{23}H_{24}O_6$ $\xrightarrow{-H_2}$ Dehydrodihydrodeguelin $C_{23}H_{22}O_6$

$+H_2$

$-H_2$

KMnO$_4$ $\longrightarrow$ Risic acid $C_{11}H_{12}O_5$

α-Hydroxyisobutyric acid

Dehydrodeguelin $C_{23}H_{20}O_6$ $\longrightarrow$ Nicouic acid $C_{12}H_{12}O_8$ $\longrightarrow$ Resorcinol

Nicouic acid trimethyl ester $C_{15}H_{18}O_8$

$-H_2O$ KMnO$_4$ $\longrightarrow$ 2-Hydroxy-4,5-dimethoxybenzoic acid

Tephrosin $C_{23}H_{22}O_7$ $\longrightarrow$ Acetyl tephrosin $C_{25}H_{24}O_8$

KMnO$_4$ α-Hydroxyisobutyric acid

Tephrosin dicarboxylic acid $C_{23}H_{22}O_{11}$

Acetyl tephrosin monocarboxylic acid $C_{21}H_{18}O_9$

Tephrosin monocarboxylic acid $\longrightarrow$ Risic acid $C_{19}H_{14}O_8$

Experimental

Dihydrodeguelin.—A solution of 5 g. of deguelin in 150 cc. of hot acetic acid was reduced at atmospheric pressure and 75° with hydrogen and the platinum catalyst of

Voorhees and Adams.[8] The catalyst was removed, and the solution was concentrated *in vacuo* to a sirup, which was dissolved in 35 cc. of methanol and allowed to crystallize. Three and six-tenths grams of colorless crystals separated which melted at 153–155°. This material when recrystallized from various solvents gave products which appeared to be uniform but which did not melt sharply. The melting points of the various preparations also differed from each other over the range from 153° to 163°, and combustion analysis gave carbon and hydrogen results which, while uniform, were too high to warrant the assumption that the material was pure.

A portion of the reduced material dissolved in ethyl acetate was then treated for two hours with hydrogen and the platinum catalyst at a pressure of 375 pounds. The resulting product obtained as outlined above was recrystallized by dissolving it in the necessary quantity of chloroform and adding an excess of methanol. It melted sharply at 173–174° and gave satisfactory analysis.

Anal. Calcd. for $C_{23}H_{24}O_6$: C, 69.67; H, 6.10; OCH$_3$, 15.66. Found: C, 69.31; H, 6.08; OCH$_3$, 15.6.

To further identify the compound as dihydrodeguelin it was oxidized to dehydrodihydrodeguelin with potassium ferricyanide in the manner in which dehydrodeguelin was prepared from deguelin.[1a] The product was shown to be the material expected by comparison with an authentic sample of dehydrodihydrodeguelin.

Risic Acid by Permanganate Oxidation of Dehydrodeguelin.—The mother liquors from which the 2-hydroxy-4,5-dimethoxybenzoic acid was obtained by oxidizing 50 g. of dehydrodeguelin with permanganate[1c] were thoroughly extracted with ether. The extract was dried with sodium sulfate and concentrated to a volume of approximately 50 cc. As the operation proceeded a small quantity (150–160 mg.) of risic acid separated. It was purified according to the directions previously recorded[9] and then was shown to be pure risic acid by comparison with an authentic sample of this material.

Nicouic Acid.—After removing the risic acid from the above ether extract, the mother liquors were concentrated to a sirup and dissolved in 150 cc. of boiling chloroform. Upon standing, 8.2 g. of nicouic acid separated as groups of irregularly shaped salmon-colored rods and plates. Upon spontaneous evaporation the mother liquors left a mass of highly colored sticky crystals. These were dissolved in a large excess of boiling 5% potassium hydroxide solution and treated with small quantities of 30% hydrogen peroxide until the color of the liquid became light yellow. The solution was then acidified with sulfuric acid, filtered through norit and extracted with ether. The purified acid was recovered from the ethereal solution as outlined above. The yield was 2 g., making in all 10.2 g. of nicouic acid from 50 g. of dehydrodeguelin.

For analysis the acid was purified by treatment with hydrogen peroxide as outlined above and then recrystallized once from boiling chloroform. Thus obtained it consisted of colorless rods which melted at 196° with decomposition. They showed inclined extinction (crossed nicols), double refraction was extremely strong and only partial biaxial interference figures were shown in convergent polarized light; α, 1.455; β, indeterminate and $\gamma > 1.740$.[10]

It gave a wine red color with ferric chloride and when it was condensed with phthalic anhydride a yellow-green fluorescent solution (fluorescein) was obtained showing that the acid was a resorcinol derivative.[3]

Anal. Calcd. for $C_{12}H_{12}O_8$: mol. wt., 284.2; C, 50.69; H, 4.26. Found: mol. wt., titration calcd. as a tricarboxylic acid, 291; C, 50.23; H, 4.44.

[8] Voorhees and Adams, THIS JOURNAL, **44**, 1397 (1922).

[9] Clark, *ibid.*, **54**, 1600 (1932).

[10] The optical data here recorded were determined by Geo. L. Keenan of the Food and Drug Administration, U. S. Department of Agriculture.

Nicouic Acid Methyl Ester.—A solution of 1 g. of nicouic acid in 25 cc. of 5% methanolic hydrochloric acid solution was refluxed for two hours and then allowed to stand at room temperature overnight. The liquid was then poured into crushed ice, and after the ice had melted, the liquid was extracted with ether. The ethereal solution was thoroughly washed with water and then dried. The extract was freed from ether and dissolved in methanol and sufficient water was added to cause a slight turbidity. Crystallization soon began, yielding colorless plates which melted at about 90°. The yield was 280 mg. The material was recrystallized from dilute methanol until its melting point rose to 120–121°.

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 55.20; H, 5.56; OCH_3 (3), 28.5. Found: C, 55.12; H, 5.81; OCH_3, 27.5.

α-Hydroxyisobutyric Acid from Nicouic Acid.—Approximately 0.1 g. of nicouic acid was carefully heated in a large test-tube until the material melted and the resultant effervescence subsided. The test-tube was then connected to a high vacuum, and the melt was subjected to distillation as long as any material condensed on the cool portion of the tube.

During the entire process of heating and distilling, a sublimate of long, beautiful crystals collected on the cool portion of the test-tube. This was α-hydroxyisobutyric acid. After purification by sublimation it melted at 79° and when mixed with an authentic sample of α-hydroxyisobutyric acid the melting point was not depressed.

Another product of the decomposition of nicouic acid by this treatment was a water-soluble acid which gave a deep blue color reaction with ferric chloride and melted at 162°. As this material has not been completely investigated it will not be reported upon at this time.

Resorcinol from Nicouic Acid.—A solution of 1 g. of nicouic acid in 4 cc. of aniline was heated to its boiling point and maintained at this temperature until gas was no longer evolved.

The resultant liquid was then mixed with 25 cc. of water, and the mixture was steam distilled until the aniline was completely removed. The residual aqueous solution was cooled in ice, filtered through a little norit, treated with approximately 2 g. of sodium bicarbonate and extracted with ether. The ethereal solution was dried, evaporated to dryness and dissolved in chloroform. After standing for some time the solution crystallized. The product was resorcinol, melting point 110°. The identification consisted of comparing the product with a known sample of resorcinol as to melting point, mixed melting point and optical properties, all of which were in agreement. The crystals were also nitrated according to the directions of Mulliken,[3] and the product was shown by comparison with an authentic sample to be trinitroresorcinol.

Acetyl Tephrosin.—A solution of 2 g. of tephrosin in a mixture of 12 cc. of pyridine and 12 cc. of acetic anhydride was allowed to stand at room temperature for two days. Two volumes of methanol were then added to the reaction mixture and, after the resulting liquid was cooled, water was added until a slight turbidity was produced. Crystallization began at once, and yielded 1.85 g. of acetyl tephrosin. Upon recrystallization from dilute methanol it melted at 200°. When mixed with pure tephrosin (melting point 198°), the melting point was depressed (165–175°).

Anal. Calcd. for $C_{25}H_{24}O_8$: C, 66.35; H, 5.35; OCH_3 (2), 13.72. Found: C, 66.36; H, 5.42; OCH_3, 14.2.

Tephrosin Monocarboxylic Acid.—A mixture of 0.5 g. of tephrosin dicarboxylic acid and 5 cc. of diphenyl ether was heated to its boiling point for approximately one-half minute. During the process the liquid rapidly acquired a bright yellow color as a result of dehydro formation. The solution was then cooled and quickly diluted with three volumes of methanol, causing crystallization to take place immediately. The product

(250 mg.) consisted of bright yellow rods whose melting point was 269° with decomposition.

For analysis, 250 mg. of the acid was dissolved in the necessary quantity of alkali, the solution was diluted with water to 2 liters and then acidified with acetic acid. The material separated as pale yellow hair-like crystals which began to sinter and darken at 250° and melted with decomposition at 268–269°. A saturated alcoholic solution of the material gave a pink color with ferric chloride.

Anal. Calcd. for $C_{19}H_{14}O_8$: mol. wt., 370.2; C, 61.61; H, 3.81; OCH_3 (2), 16.76. Found: mol. wt., acid titration, 370; C, 61.71; H, 3.95; OCH_3, 16.8.

α-Hydroxyisobutyric Acid from Tephrosin Dicarboxylic Acid.—The methanol-diphenyl ether mother liquor from the experiment above was diluted with water, made strongly alkaline and extracted with ether. The aqueous solution was then acidified and again extracted with ether. This extract was dried, the ether was removed and the residue, contained in a test-tube, was gently heated under reduced pressure. A very small quantity of α-hydroxyisobutyric acid sublimed upon the cool portion of the tube. There was, however, a sufficient quantity to identify it by its melting point and its characteristic property of subliming at approximately 50°.

Acetyl Tephrosin Monocarboxylic Acid.—A solution of 0.2 g. of tephrosin monocarboxylic acid in a mixture of 2 cc. of acetic anhydride and 2 cc. of pyridine was allowed to stand at room temperature for two days. During the process 0.2 g. of the acetyl derivative separated. It was dissolved in the necessary quantity of boiling butanol, and this solution was diluted with 5 volumes of ethanol. In a short time the material separated as aggregates of small extremely thin yellow rods, which when rapidly heated began to melt at approximately 230° and decomposed at 250–255°. It gave no color reaction with ferric chloride.

Anal. Calcd. for $C_{21}H_{16}O_9$: C, 61.16; H, 3.91; OCH_3 (2), 15.06. Found: C, 60.75; H, 4.07; OCH_3, 15.7.

Risic Acid from Tephrosin Monocarboxylic Acid.—A solution of 0.5 g. of tephrosin monocarboxylic acid in 10 cc. of 10% potassium hydroxide solution was treated with 3 cc. of 30% hydrogen peroxide, according to the directions for the preparation of derric acid.[1b] When the reaction was completed the solution was diluted to 50 cc. and acidified with sulfuric acid. Two hundred and fifty mg. of risic acid (melting point, 256°) separated and was identified by comparison with an authentic sample of the acid.

Tephrosic Acid from Tephrosin Monocarboxylic Acid.—Tephrosic acid was prepared by hydrolyzing tephrosin monocarboxylic acid with 10% alcoholic potassium hydroxide, according to the directions recorded for the preparation of deguelic acid.[1a] Acidification of the resultant solution caused the separation of tephrosic acid as beautiful colorless crystals which melted at 196°. Their solution gave a brownish pink color with ferric chloride but because of lack of material[11] the study of this compound has not been concluded. A complete description of its properties, therefore, cannot be presented at this time. For the purpose at hand, however, the fact that the compound is formed is sufficient evidence to indicate that tephrosin monocarboxylic acid is a dehydro derivative.

Summary

Evidence has been presented to indicate that deguelin may be represented by formula I in the text.

[11] Our last shipment of cubé roots, upon which we depend for tephrosin and its derivatives, was unusual in that its rotenone content was very high (11%) and the deguelin obtained from the rotenone mother liquors was almost chemically pure. The extract, however, contained no tephrosin. It is therefore necessary to await a satisfactory supply of cubé root from South America before completing the study of tephrosic acid.

It has also been shown that tephrosin is a hydroxydeguelin and that the hydroxyl group in tephrosin occupies the position of one of the hydrogen atoms attached to either carbon atom 7 or 8 in the deguelin formula.

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NOTES

The Decomposition of n-Valerolactone

BY RALPH W. THOMAS AND H. A. SCHUETTE

Proof has already been presented[1] in support of the statement that n-valerolactone will not withstand distillation at atmospheric pressure—reports to the contrary notwithstanding—since it undergoes partial decomposition as it approaches its boiling point. The nature of this decomposition has now been traced to the formation, in the main, of a polymerization product, and an explanation has been found for the discrepancies in the vapor pressure curves of this compound when obtained by two different methods of procedure, a dynamic[2] and a static.[3] How the former conclusion has been arrived at is summarized in this communication.

In order to fix a point of departure in the study of this problem, the assumption was made that the decomposition in question is accompanied by the evolution of carbon dioxide and the formation of a butene (2:3 or 1:2). The set-up in which the decomposition studies were carried out closely simulated the conditions which obtain in the determination of pressure–temperature relationships. To that end the lactone was heated under thermostatically controlled conditions in a 2.5-cc. bulbous glass decomposition chamber to which had been sealed an 8-mm. delivery tube provided with a short upright side arm which was later to serve the dual purpose of introducing or removing samples and as an aid in sweeping out the air from the apparatus with nitrogen. At a distance of about 25 mm. from this side arm, the tube was bent at an angle of 45°; beyond that, as a precautionary measure against loss of material during heating, it took the form of a spiral condenser. A delivery tube leading from the latter to an inverted, mercury-filled buret completed the system.

That the reaction herein involved is not wholly due to a decarboxylation with the formation of a butene was shown by the fact that a 3.16-g. sample yielded only about 1 cc. of gas on heating for 530 hours at $202 \pm 0.5°$, which is four degrees below the alleged boiling point of this compound at atmospheric pressure. Although this gas was found to contain some carbon dioxide, yet no evidence could be secured that ethylenic hydrocarbons had been formed in the decomposition. A repetition of the

[1] Schuette and Thomas, THIS JOURNAL, **52**, 2028 (1930).

[2] Ramsay and Young, J. Chem. Soc., **47**, 42 (1885).

[3] Smith and Menzies, THIS JOURNAL, **32**, 1412 (1910).