[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

Synthetic Support for the α-Erythroidine Structure. The Conversion of α- to β-Erythroidine[1]

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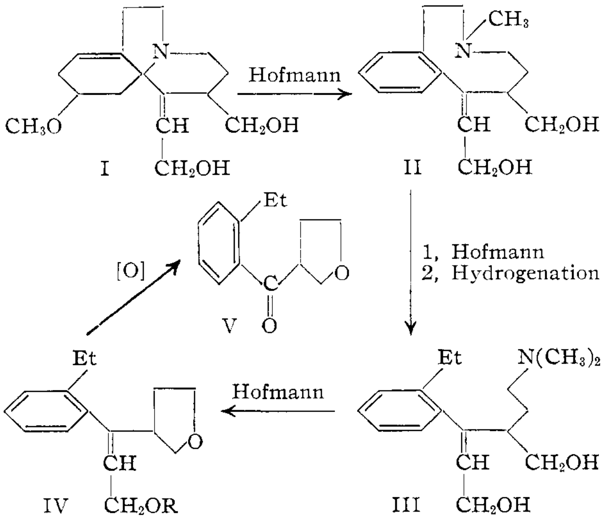
RECEIVED MARCH 7, 1958

The deductions regarding the structure of α-erythroidine made in a previous study of the Hofmann degradation of this alkaloid have been confirmed through the synthesis of V, the final degradation product. In addition, α-erythroidine has been isomerized to β-erythroidine showing that both have the same carbon skeleton and the same stereochemistry at C_3 and C_5. Therefore, the correct structure for the complete α-erythroidine molecule is X.

In a previous communication on α-erythroidine,[3] the Hofmann degradation of dihydro-α-erythroidinol was described. The properties of the products so obtained were interpreted on the basis that dihydro-α-erythroidinol possessed structure I and the chief degradation products had the structures shown in Chart I. To confirm these deductions it was important that the degradation products be established through synthesis. In the present paper the syntheses of IV and V are described and the identity of the synthetic and natural substances establishes the correctness of the formulations given in Chart I.

CHART I

HOFMANN DEGRADATION OF α-ERYTHROIDINE



The synthesis of *o*-ethylphenyl tetrahydro-3-furanyl ketone (V) was undertaken first and, although the molecule is a relatively simple one, a number of obvious routes were tried without success before a satisfactory scheme was developed. The chief difficulty lay in obtaining β-substituted tetrahydrofuranyl derivatives in a convenient fashion. Recently, Korte and Machleidt[4] found that γ-butyrolactone could be converted smoothly and in good yield to 3-carbomethoxy-4,5-dihydrofuran (VI). Although catalytic reduction of furan derivatives over platinum usually leads to rupture of the heterocyclic ring,[5] we found that hydrogenation of VI over Raney nickel gave the desired 3-carbomethoxytetrahydrofuran (VII) in 82% yield. Likewise, the reduction of 3-furoic acid with Raney nickel and alkali gave mainly tetrahydro-3-furoic acid (VIII),[6] although it was accompanied by some of the cleavage product, 2-methyl-γ-butyrolactone.

When tetrahydro-3-furoic acid (VIII) was treated with an excess of *o*-ethylphenyllithium, the desired ketone (V) formed in 50% yield as a clear, mobile liquid. Spectral comparison of the synthetic racemate with the optically active ketone obtained from the degradation showed a close correspondence in both the infrared (liquid film) and ultraviolet.

Even though the identity of the two materials was strongly indicated, it seemed desirable to make the comparison with crystalline substances. For this purpose, since the usual carbonyl derivatives do not form with V, presumably because of steric hindrance, the only readily-available, crystalline substance in the degradative series was the *p*-phenylazobenzoate of IV ($R = -\overset{\overset{O}{\|}}{C}C_6H_4N_2C_6H_5$). The obvious path for extending the synthesis of V to the precursor IV was the addition of acetylene to V followed by hydrogenation and rearrangement of the resulting allyl alcohol. However, just as V failed to give carbonyl derivatives, it also failed to add acetylene. In view of the report by Normant that vinyl bromide forms a normal Grignard in tetrahydrofuran,[7] we investigated the addition of vinylmagnesium bromide. This proceeded normally and in excellent yield to give the carbinol IX. In our experience it is more convenient to prepare vinylmagnesium bromide using anhydrous ether as solvent than tetrahydrofuran. The ease with which vinylmagnesium bromide can be prepared would suggest that in many cases it would be advantageous to use this reagent instead of the addition of acetylene followed by hydrogenation.

Rearrangement of the carbinol IX was tried with various acids, but the most satisfactory reagent proved to be a mixture of acetic anhydride and acetic acid. The course of the rearrangement could be followed by the disappearance in the in-

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[1] Paper XIV in this series; for the preceding communication see W. G. Gall, B. D. Astill and V. Boekelheide, *J. Org. Chem.*, **20**, 1538 (1955).

[2] American Cyanamid Predoctoral Fellow, 1956–1957.

[3] J. C. Godfrey, D. S. Tarbell and V. Boekelheide, THIS JOURNAL, **77**, 3342 (1955).

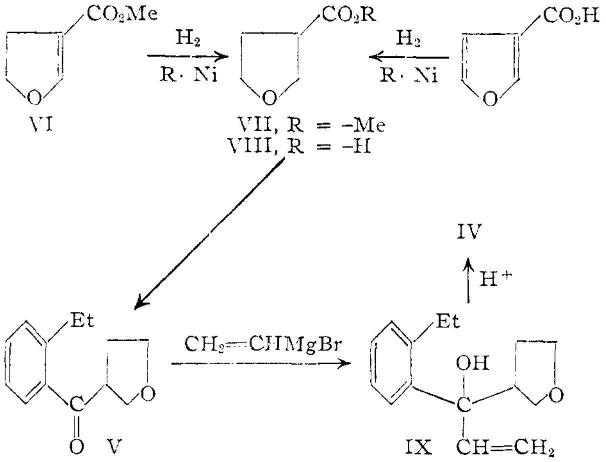
[4] F. Korte and H. Machleidt, *Ber.*, **88**, 1684 (1955).

[5] H. Smith, J. Conley and W. King, THIS JOURNAL, **73**, 4633 (1951).

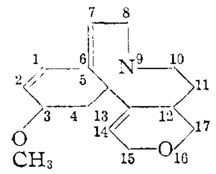
[6] A. Ghosh and C. Raha (*ibid.*, **76**, 282 (1954)) have claimed the preparation of tetrahydro-3-furoic acid, but we were unable to repeat their procedure and the properties which they assign to 3-tetrahydrofuroic acid are not in accord with those which we found for this substance.

[7] H. Normant, *Compt. rend.*, **239**, 1510 (1954).

frared of the absorption bands at 10.1 and 10.9 μ corresponding to the vinyl group (—CH=CH_2). The resulting acetate was hydrolyzed and the rearranged carbinol IV converted directly to the corresponding p-phenylazobenzoate. Since the rearrangement would be expected to yield both geometrical isomers of IV, it was anticipated and found that the p-phenylazobenzoate derivative was a mixture of isomers. By careful chromatography over alumina, separation eventually was achieved and the desired racemate of IV ($R = -\overset{O}{\overset{\|}{C}}C_6H_4N_2C_6H_5$) was obtained in a pure crystalline state. Comparison of the infrared spectrum of the synthetic racemate in chloroform solution with that of the optically active sample of IV ($R = -\overset{O}{\overset{\|}{C}}C_6H_4N_2C_6H_5$) derived from α-erythroidine showed them to be identical. Thus, the structures of the final degradation products IV and V are established and the interpretation given in Chart I can be accepted with assurance.

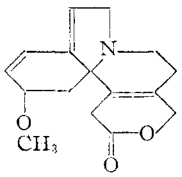


As discussed previously,[3] if dihydro-α-erythroidinol has structure I, the structure of α-erythroidine must be either X or XI. On spectral grounds, it was proposed that XI was the more probable structure. This was based primarily on the fact that α- and β-erythroidine hydrochlorides show the same carbonyl absorption (5.85 μ) in the infrared. Since it is known that β-erythroidine has structure XII,[8] containing an unconjugated δ-lactone, it was presumed that the δ-lactone in α-erythroidine would also not be conjugated and thus XI, rather than X, would be the correct structure.



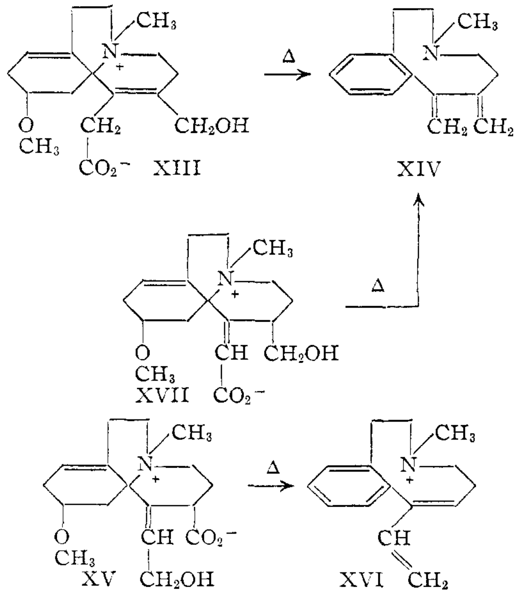
X, $-\overset{O}{\overset{\|}{C}}-$ at C_{15}

XI, $-\overset{O}{\overset{\|}{C}}-$ at C_{17}



XII

To gain chemical evidence revealing the position of the carbonyl group in α-erythroidine, it was decided to subject dihydro-α-erythroidine to a Hofmann degradation. Previously it had been shown that the betaine XIII, derived from dihydro-β-erythroidine, on heating undergoes an "abnormal" Hofmann reaction with loss of the elements of water, methanol and carbon dioxide to give a diene (XIV).[8,9] If structure XI were correct for α-erythroidine, it would be expected that the corresponding betaine XV would decompose in a similar fashion to give XVI. On the other hand, if X were correct, the betaine XVII should lead to the same diene (XIV) as that obtained in the β-erythroidine series. To decide between the two dienes should be relatively simple from spectral data.



When dihydro-α-erythroidine was converted to the corresponding betaine and this was thermally decomposed, the product obtained in low yield was the diene XIV. Its identity was established by comparison of its picrate with an authentic sample of the picrate of XIV. This result requires the precursor betaine to have structure XVII and places the carbonyl function in α-erythroidine at C_{15}. The fact that α- and β-erythroidine hydrochlorides show the same carbonyl absorption in the infrared, even though one has conjugate unsaturation and the other does not, remains an anomalous observation for which we have no explanation. It should be noted, though, that the absorption spectra in the infrared of some other simple lactones recently have been found to show anomalous absorption.[10]

If X is then accepted as the correct structure for α-erythroidine, it is seen that the only difference between α- and β-erythroidine, apart from possible stereochemical differences, is the position of the aliphatic double bond in the lactone ring. Attention was then turned to the possibility of interconverting the two alkaloids. From the extensive studies that have been done on the base-catalyzed

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(8) V. Boekelheide, J. Weinstock, M. F. Grundon, G. L. Sauvage and E. J. Agnello, THIS JOURNAL, **75**, 2550 (1953).

(9) V. Boekelheide and E. J. Agnello, *ibid.*, **73**, 2286 (1951).

(10) R. N. Jones, T. Ito and C. L. Angell, *Angew. Chem.*, **69**, 645 (1957).

equilibrium between α, β- and β,γ-unsaturated acids,[11] it could be predicted that α-erythroidine on heating with base would be largely converted to the non-conjugated, β,γ-unsaturated system. This was in fact found to be the case. Heating α-erythroidine in 10% aqueous sodium hydroxide for three hours gave, on work-up of the reaction mixture, only β-erythroidine. Similarly, dihydro-α-erythroidine was isomerized by alkali to dihydro-β-erythroidine. In this case an attempt was made to determine the amount of dihydro-α-erythroidine remaining after equilibration and from infrared spectral analysis it must be less than 5%.

The isomerization of α- to β-erythroidine establishes that both have the same stereochemistry at C_3 and C_5 and the only point of difference between the two is the position of the double bond in the lactone ring.

Experimental[12]

3-Carbomethoxytetrahydrofuran (VII).—A mixture of 17.0 g. of 3-carbomethoxy-4,5-dihydrofuran[4] and 3 g. of Raney nickel catalyst in 40 ml. of methanol was subjected to hydrogenation at room temperature and 3 atm. pressure of hydrogen. After the hydrogen uptake was complete (2 hr.), the catalyst and solvent were removed. Distillation of the residue gave 15.0 g. (82%) of a colorless oil, b.p. 80° at 15 mm., $n^{25}D$ 1.4370.

Anal. Calcd. for $C_6H_{10}O_3$: C, 55.37; H, 7.75. Found: C, 55.17; H, 7.80.

For characterization, the ester VII was converted to the corresponding anilide by treatment with anilinomagnesium bromide. After recrystallization from water followed by sublimation, the anilide was obtained as white crystals, m.p. 98–99°.

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85. Found: C, 69.10; H, 6.87.

Tetrahydro-3-furoic Acid (VIII). (A) By Hydrolysis of VII.—A mixture of 15.0 g. of 3-carbomethoxytetrahydrofuran in 40 ml. of a 10% aqueous sodium hydroxide solution was boiled under reflux for one hour. The solution was then acidified and extracted continuously with methylene chloride for two days. Concentration of the methylene chloride extract followed by distillation of the residue gave 9.5 g. (70%) of a colorless oil, b.p. 140° at 15 mm., $n^{25}D$ 1.4600.

Anal. Calcd. for $C_5H_8O_3$: C, 51.72; H, 6.90. Found: C, 51.41; H, 7.01.

The anilide of tetrahydro-3-furoic acid was prepared using the procedure of Blicke, Wright and Zienty[13] to make the intermediate acid chloride. After chromatography over alumina followed by sublimation, it was obtained as white crystals, m.p. 98–99°, undepressed by admixture of the anilide prepared from the ester above.

(B) By Hydrogenation of 3-Furoic Acid.—To a solution of 3.2 g. of 3-furoic acid[14,15] in 30 ml. of a 3% solution of aqueous sodium hydroxide there was added 3 g. of Raney nickel catalyst and the mixture was subjected to hydrogenation at room temperature and 3 atm. pressure of hydrogen. Hydrogen uptake was complete in 15 hours. After removal of the catalyst, the solution was acidified and extracted five times with ether. The combined ether extracts were dried and concentrated. Distillation of the residual oil gave 0.3 g. (9%) of a colorless forerun and 1.0 g. (30%) of tetrahydro-3-furoic acid, b.p. 127° at 7 mm., $n^{25}D$ 1.4576. The identity of the tetrahydro-3-furoic acid was proved through conversion, as before, to the anilide, m.p. 98–99°, undepressed by admixture of samples of the anilides previously described.

The identity of the forerun was established as 2-methyl-γ-butyrolactone from its physical properties (b.p. 77° at 9 mm., $n^{25}D$ 1.4285; lit.[16] gives b.p. 70° at 8 mm., $n^{25}D$ 1.4282) and through the preparation of the corresponding hydrazide, m.p. 90–91° (lit.[16] gives 91°).

***o*-Ethylphenyl Tetrahydro-3-furanyl Ketone (V).**—To a stirred mixture of 1.38 g. of lithium wire in 50 ml. of ether there was added dropwise 23.3 g. of *o*-ethyliodobenzene in 50 ml. of ether. To complete the formation of the *o*-ethylphenyllithium the mixture was boiled under reflux and then a solution of 5.8 g. of tetrahydro-3-furoic acid in 25 ml. of ether was added dropwise with stirring. The mixture was boiled under reflux for an additional hour and then poured onto a mixture of 5% sulfuric acid and ice. The ether layer was separated, washed successively with dilute acid, water, bicarbonate solution and again with water. Then it was dried over sodium sulfate and concentrated. Distillation of the residue gave 5.1 g. (50%) of a colorless oil, b.p. 90° at 0.05 mm., $n^{25}D$ 1.5372. The infrared spectrum of a liquid film was essentially superimposable on that of V obtained from the degradation of dihydro-α-erythroidinol.[3] Likewise, the ultraviolet spectrum showed the same maxima as the natural material.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.53; H, 7.79.

Attempted Addition of Acetylene to *o*-Ethylphenyl Tetrahydro-3-furanyl Ketone.—As a model for this reaction, the addition of acetylene to isobutyrophenone was carried out. To 2.4 g. of sodium acetylide[17] in excess liquid ammonia there was added dropwise over a period of 30 min. 6.55 g. of isobutyrophenone. After the ammonia had evaporated, 20 ml. of water was added and the solution was acidified by addition of a 50% sulfuric acid solution. The mixture was then extracted with ether, the ether layer was washed with water, and the ether extracts were dried and concentrated. Distillation of the residue gave in good yield a colorless oil, b.p. 130–133° at 0.05 mm. The infrared spectrum and the composition (*Anal.* Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.27; H, 8.10) of the oil are in accord with that to be expected for phenylisopropylethynylcarbinol.

When the above experiment was repeated using *o*-ethylphenyl tetrahydro-3-furanyl ketone (2.18 g.), none of the desired carbinol was isolated but instead 1.9 g. (86%) of the starting ketone was recovered.

***o*-Ethylphenyltetrahydro-3-furanylvinylcarbinol (IX).**—The vinylmagnesium bromide was prepared in the usual manner for preparing Grignard reagents except that the condenser was cooled by circulating ice-water. To a mixture of 1.70 g. of magnesium in 25 ml. of ether there was added 1.0 g. of vinyl bromide. The spontaneous reaction which occurred caused the ether solution to boil and boiling was maintained at a gentle rate by continued addition of 15% solution of vinyl bromide in ether until all of the magnesium had dissolved. To establish the purity of the vinylmagnesium bromide an aliquot portion was decomposed by addition of ethanol and the evolved gas was analyzed by infrared spectroscopy. The ethylene produced appeared to be quite pure and acetylene was not present in a detectable quantity. A solution of 7.8 g. of *o*-ethylphenyl tetrahydro-3-furanyl ketone in 200 ml. of ether was added slowly and the resulting mixture was boiled under reflux for one hour. The reaction mixture was poured onto a mixture of ice and 5% sulfuric acid and then extracted with ether. After the ether layer was washed with water, it was dried over sodium sulfate and concentrated. Distillation of the residue using a short-path still gave 7.0 g. (80%) of a colorless oil, b.p. (pot temp.) 100–110° at 0.05 mm., $n^{25}D$ 1.5441.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.60; H, 9.03.

1-(*o*-Ethylphenyl)-1-(tetrahydro-3-furanyl)-1-propen-3-ol (IV).—A solution of 2.15 g. of IX, 2.0 g. of acetic acid and 2.0 g. of acetic anhydride was boiled under reflux for 65 hours. After removal of the solvent under reduced pressure, the residue was taken up in hexane and chromatographed over alumina. The main fraction, corresponding to the rearranged acetate, weighed 1.33 g. A second fraction of

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[11] J. W. Baker, "Hyperconjugation," Clarendon Press, Glasgow, 1952, p. 65.

[12] All melting points are corrected. Analyses by Miss A. Smith and by Micro-Tech Laboratories.

[13] F. Blicke, W. Wright and M. Zienty, THIS JOURNAL, **63**, 2488 (1941).

[14] K. Alder and H. Rickert, *Ber.*, **70**, 1354 (1937).

[15] T. Reichstein, A. Grussner, K. Schindler and E. Hardmeier, *Helv. Chim. Acta*, **16**, 276 (1933).

[16] C. Cavallito and T. Haskell, THIS JOURNAL, **68**, 2332 (1946).

[17] E. Horning, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 417.

0.70 g. was shown by infrared analysis to be the starting alcohol IX.

The main fraction from the column was then dissolved in 13 ml. of 5% methanolic potassium hydroxide and boiled under reflux for 3 hours to effect hydrolysis. The solution was then diluted with water and extracted with ether. After the ether solution was washed with water, it was dried over sodium sulfate and concentrated. The residue was taken up in hexane and chromatographed over alumina. The first fraction from the column gave 460 mg. of a colorless oil whose infrared spectrum showed the absence of a hydroxyl and the presence of a vinyl group. Presumably this was a diene fraction resulting from dehydration. The second fraction, consisting of 460 mg. (32% based on unrecovered IX) of a colorless oil, had an infrared spectrum in accord with IV but appeared to be a mixture of isomers. This was dissolved in 8 ml. of pyridine and heated with 600 mg. of *p*-phenylazobenzoyl chloride for 10 min. The mixture was poured into water with stirring and the supernatant liquid decanted from the insoluble gum. After the residue had been washed again with aqueous carbonate and separated by decanting, it was taken up in hexane and passed onto an alumina column. Development of the column was done first with hexane–benzene mixtures and finally with pure benzene. A number of fractions were taken and from one of these there was obtained an oil which, on prolonged standing, gave large orange crystals, m.p. 68–70°. The infrared spectrum of a solution of these crystals in chloroform was superimposable with that obtained from the *p*-phenylazobenzoate of IV derived from α-erythroidine.

Anal. Calcd. for $C_{26}H_{28}N_2O_3$: C, 76.34; H, 6.41; N, 6.36. Found: C, 76.07; H, 6.44; N, 6.79.

Hofmann Degradation of Dihydro-α-erythroidine.—A solution of 2.0 g. of the methiodide of dihydro-α-erythroidine[3] in 30 ml. of water was passed over an ion exchange column (Dowex 2-X4). When the eluate was concentrated, it gave the betaine XVII as a crystalline solid. The betaine was then decomposed by heating it in a short-path still at 175–185° at 25 mm. to give 350 mg. of distillate as a colorless oil. From previous experience in the β-erythroidine series,[9] it was anticipated that the distillate would be a mixture of the "normal" and "abnormal" Hofmann products. Therefore, the oil was taken up in pentane and chromatographed over alumina. From the pentane eluate there was obtained 90 mg. (9%) of "abnormal" Hofmann product. Changing the eluent to ether gave a second fraction of 240 mg. (17%) of a colorless oil which is presumed to be the "normal" Hofmann product.

The picrate of the "abnormal" Hofmann product formed readily in ethanol and was obtained after recrystallization from ethanol in good yield as yellow crystals, m.p. 166–167° dec. A mixture of these crystals with those of the picrate (m.p. 164–167°) from the "abnormal" product (XIV) in the β-erythroidine case[9] showed no depression of melting point. Also, the infrared spectra of the two samples were identical.

Isomerization of Dihydro-α-erythroidine to Dihydro-β erythroidine.—A solution of 2.85 g. of dihydro-α-erythroidine in 14.3 ml. of a 10% aqueous sodium hydroxide solution was boiled under reflux in a nitrogen atmosphere for three hours. The reaction mixture was cooled in an ice-bath and concentrated hydrochloric acid added until the *p*H was below 2.0. After the solution had stood for three hours, sodium bicarbonate was added carefully until the *p*H was just above 7. The solution was then extracted five times with chloroform and the combined extracts were dried and concentrated. The resulting yellow oil, when seeded with a crystal of authentic dihydro-β-erythroidine, immediately crystallized to give 2.60 g. (91%) of white crystals, m.p. 73–78°. The corresponding hydrobromide was prepared by dissolving 2.30 g. of these crystals in ethanolic hydrobromic acid.. There deposited 2.40 g. (84%) of light tan crystals, m.p. 228–229°. One recrystallization from ethanol gave the hydrobromide of dihydro-β-erythroidine as white crystals, m.p. 231–232°, $\alpha^{30}\text{D}$ +109° (1% solution in water).[18]

Regeneration of the free base from the hydrobromide gave white crystals (93% yield), m.p. 80–82°, undepressed by admixture of an authentic sample of dihydro-β-erythroidine. Also, the infrared spectrum of the base was identical with that of dihydro-β-erythroidine and showed the complete absence of the characteristic absorption bands of dihydro-α-erythroidine.

Isomerization of α-Erythroidine to β-Erythroidine.—A solution of 1.20 g. of α-erythroidine hydrochloride in 12 ml. of a 10% aqueous sodium hydroxide solution was boiled under reflux for 3 hours. When the reaction mixture was worked up as described in the previous experiment, there was obtained 700 mg. (67%) of white crystals, m.p. 94–98°, undepressed by admixture of authentic β-erythroidine (m.p. 97–99°). Also, the infrared spectrum of the base was identical with that of β-erythroidine and showed the absence of absorption bands peculiar to α-erythroidine.

The corresponding hydrochloride was prepared in 83% yield as white crystals, m.p. 230.5–231.5° dec., undepressed by admixture of an authentic sample of β-erythroidine hydrochloride. Again, the infrared spectra of the two hydrochlorides were identical.

Rochester, N. Y.

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[18] K. Folkers and F. Koniuszy (U. S. Patent 2,370,651, March 6, 1945) give for dihydro-β-erythroidine hydrobromide, m.p. 231–231.5°, $\alpha^{25}\text{D}$ +107.5° (in water).

[Contribution from the Organic Chemistry Branch, Chemistry Division, U. S. Naval Ordnance Test Station]

An Improved Synthesis of 5-Substituted Tetrazoles

By William G. Finnegan, Ronald A. Henry and Robert Lofquist[1]

Received March 5, 1958

An improved synthesis of 5-substituted tetrazoles has been devised. Alkyl- or arylnitriles and inorganic azides react readily in solvents such as dimethylformamide and diethyl sulfoxide. Relatively low reaction temperatures and short reaction times are effective, and the need for pressure equipment is eliminated. The effects caused by varying the solvent, the electronegativity of the substituent on the nitrile and the nature of the azide salt have been studied and a tentative mechanism for the reaction is advanced.

The previously described syntheses of 5-alkyl- and aryltetrazoles, although generally capable of giving good yields, are not all adaptable to larger scale use. In several instances they suffer the disadvantage of requiring the independent preparation of non-aqueous solutions of hydrazoic acid. Multi-step reaction sequences[2,3] proceeding *via* imino ethers, hydrazides and azides, result in only modest yields. Reactions using solutions of hydrazoic acid in benzene, toluene or xylene, or sodium azide and acetic acid in butanol either in glass[4] or pressure equipment[5] at high temperatures require extended reaction times of four to seven days. The recently described synthesis of 5-substituted tetrazoles by the reaction of aluminum

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[1] University of Michigan, Ann Arbor, Mich.

[2] W. Oberhummer, *Monatsh.*, **63**, 285 (1933).

[3] A. Pinner, *Ber.*, **27**, 984 (1894).

[4] R. M. Herbst and K. R. Wilson, *J. Org. Chem.*, **22**, 1142 (1957).

[5] J. S. Mihina and R. M. Herbst, *ibid.*, **15**, 1082 (1950).