NOTES

Oxidation of Formazans to Tetrazolium Chlorides with *t*-Butyl Hypochlorite

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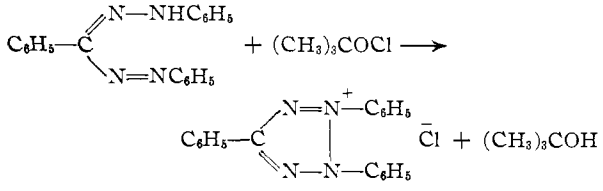
Various reagents have been used in the past for the oxidation of formazans to the corresponding tetrazolium salts. These include yellow mercuric oxide,[1] lead tetraacetate,[2] hydrogen peroxide and hydrochloric acid in the presence of vanadium pentoxide[3] and nitric acid.[4]

While *t*-butyl hypochlorite usually functions as a chlorinating agent, a few oxidation reactions have been reported. Clark[5] found that primary alcohols can be oxidized to the corresponding aldehydes. Similarly, while studying chlorination of various aromatic aldehydes Ginsberg[6] found that certain ring substituents favored conversion of the aldehyde to the corresponding acid chloride rather than ring chlorination.

This note reports the results of several experiments in which *t*-butyl hypochlorite was used as the oxidizing agent in the preparation of tetrazolium chlorides from formazans. Substantially



equimolar quantities of *t*-butyl hypochlorite and formazan are required for the oxidative conversion, which is carried out in an inert solvent. The presence of small amounts of an acidic or basic catalyst appears to increase the reaction rate but is not essential.

Experimental

2,3,5-Triphenyltetrazolium Chloride.—Triphenylformazan (6.0 g., 0.02 mole) is dissolved in 100 ml. of chloroform, a few ml. of alcoholic potassium hydroxide added and the mixture chilled to 5°. *t*-Butyl hypochlorite (8 ml. of 33% material, 0.023 mole) is added dropwise with stirring. The color changes from opaque to a clear red but is not completely discharged. The solution is filtered, evaporated on the steam-bath to about 15 cc., and acetone and ether added. The precipitate formed is filtered off, dissolved in chloroform containing 1 or 2 drops of alcohol and precipitated with a little ether. Four grams of product is obtained (60% yield). *Anal.* Calcd.: N, 16.74; Cl, 10.59. Found: N, 16.6; Cl, 10.7.

5-*n*-Hexyl-2,3-diphenyltetrazolium Chloride.—Impure C-*n*-hexyl-N,N′-diphenylformazan (4 g., 0.013 mole) is dissolved in 50 ml. of chloroform and the mixture chilled to 5°. *t*-Butyl hypochlorite (0.013 mole) is added dropwise with stirring. The solution is evaporated on the steam-bath. Ether and acetone are added and the resulting precipitate filtered off. The product is recrystallized by dissolving in acetone containing a few drops of alcohol and adding ether to precipitate the product; yield 1.5 g., 34%. *Anal.* Calcd.: C, 66.55; H, 6.76; N, 16.34. Found: C, 66.8; H, 7.0; N, 16.6.

5-α-Naphthyl-2,3-diphenyltetrazolium Chloride.—C-α-Naphthyl-N,N′-diphenylformazan (2.1 g., 0.006 mole) is dissolved in 80 ml. of dioxane and 1 ml. of glacial acetic acid is added. After cooling to 7–8°, *t*-butyl hypochlorite (0.0065 mole) in 5 ml. of dioxane is added dropwise with stirring. The solution is heated on the steam-bath for 15 minutes during which time the color became much lighter and a light colored precipitate begins to form. Addition of ether gives more precipitate which is filtered off. The combined gummy precipitates are taken up in the minimum amount of chloroform at room temperature, charcoal is added, the mixture stirred 15 minutes and filtered. Evaporation to a low volume and addition of acetone gives a precipitate which is filtered off; yield 1.4 g., 61%. *Anal.* Calcd.: N, 14.56; Cl, 9.21. Found: N, 14.4; Cl, 9.3.

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(1) H. v. Pechman and P. Runge, *Ber.*, **27**, 2920 (1894).
(2) R. Kuhn and D. Jerchel, *ibid.*, **74**, 941 (1951).
(3) W. Reid, *Angew. Chem.*, **64**, 391 (1952).
(4) F. Fichter and E. Schiess, *Ber.*, **33**, 747 (1900).
(5) B. F. Clark, Jr., *Chem. News*, **143**, 265 (1931).
(6) D. Ginsberg, This Journal, **73**, 702 (1951).

Rauwolfia Alkaloids. IX.[1] Isolation of Yohimbine from *Rauwolfia serpentina* Benth.

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Our investigations of the alkaloids of the Indian plant *Rauwolfia serpentina* Benth. have led to the isolation of yohimbine. An amorphous alkaloidal fraction (50 g.) from which reserpine had been previously removed was used as a source of material.

The weak bases were removed by ether extraction of a solution of the crude alkaloids in dilute acetic acid. Following neutralization of the aqueous layer with concentrated aqueous ammonia, the solution was extracted with ether containing 10% methanol and the solvent evaporated. The amorphous residue (5 g.) was chromatographed on alumina (Activity II/III) eluting first with increasing concentrations of acetone in benzene followed by increasing concentrations of methanol in acetone. Acetone eluted an amorphous material (127 mg., fractions 32 and 33) that yielded crystalline yohimbine (15 mg.), m.p. 224–228°, from the same solvent.

A further confirmation of the presence of yohimbine in *R. serpentina* Benth. is afforded by the earlier isolation in our laboratories (Basle, 1948), of a then unidentified alkaloid. This alkaloid was isolated as the hydrochloride by fractional crystallization of crude ajmaline hydrochloride.[2] The free base and the hydrochloride have now been shown to be identical with yohimbine and yohimbine hydrochloride. The hydrochloride, crystallized from methanol, melted at 300–302°, no depression with yohimbine hydrochloride, $[\alpha]^{22}D$ +92 ± 5° (*c* 0.92 in water). The free base was recrystallized from chloroform–petroleum ether,

(1) L. Dorfman, *et al.*, *Helv. Chim. Acta*, **37**, 59 (1954).
(2) Prepared by a modification of the method of E. Schlittler and H. Schwarz, *ibid.*, **33**, 1463 (1950).

m.p. 234–236°, no depression with yohimbine, $[\alpha]^{22}D$ + 47 ± 4° (*c* 1.26 in ethanol), $[\alpha]^{22}D$ +76 ± 4° (*c* 1.13 in pyridine). *Anal.* Calcd. for $C_{21}H_{26}N_2O_3$: C, 71.17; H, 7.40; N, 7.91; OCH_3, 8.75. Found: C, 70.92; H, 7.58; N, 7.92; OCH_3, 8.37.

Infrared spectra (Nujol) of both the alkaloid isolated by chromatography and the alkaloid isolated by fractional crystallization were identical with the spectrum of yohimbine.

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Formation Constants of Metal Complexes of Tropolone and its Derivatives. II. Some Alkyltropolones[1,2]

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The investigation of metal complexes of tropolone[4] has been extended to include the dissociation constants of methyl- and isopropyltropolones and the formation constants of some complexes of these substances with divalent metal ions.

Experimental

This investigation would not have been possible without the kindness of others in supplying samples of most of the substituted tropolones. To Professor T. Nozoe of Tohoku University, Seudai, Japan, we are indebted for the α-isopropyltropolone (m.p. 33–34°), β-isopropyltropolone (m.p. 52°), and for samples of α- and β-methyltropolone; to Professor A. B. Anderson of the University of California for γ-isopropyltropolone (m.p. 78–79°); and to Professor H. Erdtmann of The Royal Institute of Technology, Stockholm, Sweden, for β-isopropyl-γ-(3-methylbut-2-enyl)-tropolone.

Ring Expansion of 4-Methylcyclohexanone.—Five hundred grams of 4-methylcyclohexanone was allowed to react with diazomethane by the same procedure used by Kohler, Tishler, Potter and Thomson[5] to prepare cycloheptanone from cyclohexanone. Fractionation of the reaction mixture yielded 375 g. (67%) of 4-methylcycloheptanone, $n^{20}D$ 1.4590, distilling at 78° (16 mm.), and 110 g. of unreacted 4-methylcyclohexanone.

Oxidation of 4-Methylcycloheptanone.—A solution of 378 g. (3 moles) of 4-methylcycloheptanone in 700 ml. of absolute ethanol was brought to reflux in a 5-liter flask equipped with a reflux condenser, an efficient stirrer, and a dropping funnel. Over a period of 1.25 hr., a solution of 333 g. (3 moles) SeO_2 in 500 ml. of absolute ethanol and 1600 ml. of 95% ethanol was added *via* the dropping funnel. The solution was refluxed an additional 6 hr., and allowed to stand at room temperature for 18 hr. The precipitated selenium was filtered, and the filtrate boiled with Norit. About 1 liter of ethanol was distilled at atmospheric pressure, and the solution again filtered. Distillation was continued under vacuum. There was obtained 145 g. (55%) of a viscous, yellow material, boiling 79–103° (3 mm.).

Bromination of Diketone.—A solution of 140 g. (1.64 moles) of the diketones in 200 ml. of glacial acetic acid was cooled to 0°, and 520 g. (3.25 moles) of bromine in 200 ml. of glacial acetic acid was added to the cold, stirred solution over a period of 1 hr. The dark orange solution was allowed to stand at room temperature for 16 hr. The solution was was then heated until evolution of HBr ceased (1.5 hr.), and the acetic acid solvent was removed by steam distillation. The dark, tarry residue was extracted with ether. The ethereal extract was filtered and shaken with 6 *N* NaOH. The bright yellow precipitate was filtered and recrystallized from water; yield, 60 g., darkening at 240°, completely melted at 265°.

Apparently some impurity in this material poisoned the palladium catalyst used in catalytic debromination, so the material was dissolved in water and the solution acidified with 2 *N* H_2SO_4. The acidified solution was extracted with ether, and the extract was shaken with 6 *N* NaOH. The butter-yellow precipitate was filtered, washed with cold brine and recrystallized from 95% ethanol. This material was found to darken at *ca.* 240° and melt at 250–260°.

Although a mixture of materials was expected, all attempts to separate the yellow material failed. Paper chromatograms, developed with $FeCl_3$, indicated that only one active compound was present.

β-Methyltropolone.—Five grams of the above material, 1 g. of 10% palladium–charcoal and 200 ml. of 95% ethanol were shaken under H_2 until uptake ceased (1.5 hr.). The ethanol was stripped under vacuum and the residue was extracted with ligroin. The extract yielded 1.6 g. of material, melting 60–63°. Repeated recrystallization yielded 1.3 g. of material, m.p. 69–70°. A sample of β-methyltropolone furnished by Professor T. Nozoe was found to melt 73–74°. A mixture of the two samples melted 69–70°. *Anal.* Calcd. C, 70.6; H, 5.88. Found: C, 70.0; H, 5.92.

2-Methylcycloheptanone.—From 129 g. of cyclohexanone, 40 g. (27.4%) of 2-methylcycloheptanone, b.p. 36° (2 mm.), $n^{20}D$ 1.4534, was prepared in a manner similar to that previously mentioned[5] by the generation *in situ* of diazoethane from nitrosoethylurethan. The low yield, compared to that reported for a different method[6] can be explained by the fact that the nitrosoethylurethan was used without purification.

3-Methylcycloheptane-1,2-dione.—In a manner analogous to the SeO_2 oxidation described above, 127 g. of 2-methylcycloheptanone yielded 30 g. (17.3%) of 3-methylcycloheptane-1,2-dione, b.p. 65° (3 mm.), $n^{20}D$ 1.4787.

α-Methylbromotropolone.—Thirty grams of the above diketone in 30 ml. of glacial acetic acid was cooled to 0°, and 78 g. of bromine in 30 ml. of glacial acetic acid was added to the cold, stirred solution dropwise over a period of 4 hr. The temperature was maintained at 0° throughout addition of bromine. The dark solution was allowed to stand for 16 hr. at room temperature. The major portion of the acetic acid was then removed under reduced pressure and the residue was steam distilled. The distillate deposited cream-colored needles which were separated, and the distillate was extracted with toluene. The toluene was evaporated and the residue was recrystallized from 95% ethanol; fine, cream-colored needles, m.p. 121°, yield 8 g. (17%).

α-Methyltropolone.—The bromo compound was dissolved in ether and shaken with 6 *N* NaOH to yield the **sodium salt of α-methylbromotropolone**, brilliant yellow powder, darkening at *ca.* 265°, completely black at 295° but failing to melt below 300°. Ten grams of the salt was dissolved in 270 ml. of 95% ethanol and 1 g. of 10% Pd–charcoal was added. The solution was shaken under H_2 until hydrogen absorption ceased. The catalyst was filtered and the alcohol was removed from the red solution at room temperature under reduced pressure. The residual red oil was extracted with ligroin. The extract deposited light cream-colored plates upon chilling in acetone–Dry Ice. The crystals were filtered and the same ligroin used for extraction until chilling failed to induce further crystallization. Repeated recrystallization from ligroin yielded 3.0 g. (59%) of cream-colored plates, m.p. 48–50°. An authentic sample, supplied by T. Nozoe melted 49–51°. A mixture of the samples melted 48–50°.

Titrations were performed as described previously[4] with the exception that it was generally found necessary to evaluate the first formation constants of the Be, Pb and Zn complexes by a modified procedure. In the presence of excess chelating agents it was found that coördination was so far

(1) Taken in part from a dissertation presented by Burl E. Bryant in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1952.

(2) Presented in part before the Fifth Annual Meeting-in-miniature of the Philadelphia Section of The American Chemical Society, January 29, 1953.

(3) Public Health Service Research Fellow of the National Institutes of Health, 1953–1954.

(4) B. E. Bryant, W. C. Fernelius and B. E. Douglas, THIS JOURNAL, **75**, 3784 (1953).

(5) E. P. Kohler, M. Tishler, H. Potter and H. T. Thomson, *ibid.*, **61**, 1057 (1939).

(6) A. P. Giraitis and J. L. Bullock, *ibid.*, **59**, 951 (1937).