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The Conversion of Certain Pyrroles to α,δ-Alkanedioximes

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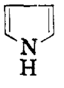
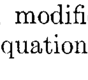
Contrary to the general report, hydroxylamine alone does not convert pyrrole to succindialdoxime. Hydroxylamine hydrochloride alone is likewise ineffective. However, equivalent amounts of these substances (Lossen's hydroxylamine hemichloride) do effect the conversion. The action of these substances on 2,5-dimethylpyrrole is similar. An improved procedure for the preparation of succindialdoxime and certain of its properties are described.

In connection with the synthesis of derivatives of tropinone by the Robinsonian biological method,[1] succindialdoxime has been here employed as the source of succindialdehyde.[1-6] The most convenient laboratory synthesis of this dioxime appears to lie in pyrrole which, as first reported by Ciamician and his associates,[7,8] is thereto converted by the action of hydroxylamine hydrochloride and anhydrous sodium carbonate in boiling alcohol. This reaction was later employed by Harries who, like the discoverers of the reaction, also obtained a yield of about 35% and found that the low yield was partly owing to the failure of all the pyrrole to react.[2] Still later Willstätter and Heubner, following assertions made earlier[3] that hydroxylamine was the active agent, recommended proportions of the reactants required by the ideality of Equation I and differing somewhat from those used by the earlier investigators.[9] However, later investigators[5,6] obtained by this method yields which varied between 35 and 40% and hence were not conspicuously superior to Ciamician and Zanetti's.[8,10]

(I)


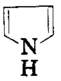
$$+ 2\,H_2NOH\cdot HCl + Na_2CO_3 \longrightarrow -(CH_2-CH{=}NOH)_2 + NH_3 + 2\,NaCl + H_2O + CO_2$$

Repetition of Willstätter and Heubner's procedure in this laboratory resulted in yields of the dioxime considerably lower than those reported.[5,6] A modification of this procedure as specified by Equation II then was tried. Only a trace of product was obtained.

(II)


$$+ 2\,H_2NOH\cdot HCl + 2NaHCO_3 \not\longrightarrow -(CH_2-CH{=}NOH)_2 + NH_3 + 2\,NaCl + 2\,H_2O + 2\,CO_2$$

It was found also that, in the absence of any carbonate, hydroxylamine hydrochloride converts pyrrole solely to dark, polymeric material. However, an alcoholic mixture containing two moles of hydroxylamine hydrochloride and one of sodium bicarbonate for each of pyrrole furnished crude succindialdoxime in 43% yield (Equation III).

(III)


$$+ 2\,H_2NOH\cdot HCl + NaHCO_3 \longrightarrow -(CH_2-CH{=}NOH)_2 + NH_4Cl + NaCl + H_2O + CO_2$$

The stoichiometry of Equation III amounts to the reaction of pyrrole with Lossen's hydroxylamine hemichloride, $(NH_2OH)_2\cdot HCl$,[11,12,13] and it was indeed found that this substance alone converts pyrrole to succindialdoxime in a yield of approximately 45%. Accordingly a procedure was developed in which the carbonate of this equation was replaced by potassium hydroxide and by which a 60% yield of the crude dioxime is obtainable.

Applied to 2,5-dimethylpyrrole, this procedure gives crude acetonylacetone dioxime in a yield of 93–96%,[14] and presumably it will therefore facilitate the conversion of all substituted pyrroles re-

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[1] R. Robinson, *J. Chem. Soc.*, **111**, 762 (1917).

[2] C. Harries, *Ber.*, **35**, 1183 (1902).

[3] R. Willstätter, O. Wolfes, and H. Mäder, *Ann.*, **434**, 121 (1923).

[4] C. Mannich and H. Budde, *Archiv. Pharm.*, **270**, 283 (1932).

[5] C. Schöpf and H. Lehmann, *Ann.*, **518**, 1 (1935).

[6] L. C. Keagle and W. Hartung, *J. Am. Chem. Soc.*, **68**, 1608 (1946).

[7] G. L. Ciamician and M. Dennstedt, *Ber.*, **17**, 533 (1884).

[8] G. L. Ciamician and C. U. Zanetti, *Ber.*, **22**, 1968 (1889).

[9] R. Willstätter and W. Heubner, *Ber.*, **40**, 3871 (1907).

[10] An allusion to the unsatisfactory status of this reaction has recently been made. J. Meinwald, S. L. Emerman, N. C. Yang, and G. Büchi, *J. Am. Chem. Soc.*, **77**, 4401 (1955).

[11] W. Lossen, *Ann.*, **160**, 242 (1871).

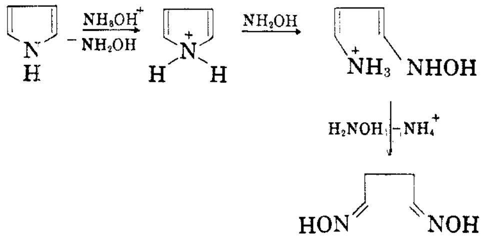
[12] J. W. Mellor, *A Comprehensive Treatise on Inorganic and Theoretical Chemistry*, Vol. VIII, Longmans, Green & Co., New York, 1928, p. 301.

[13] The precise nature of the bonding in hydroxylamine hemichloride has apparently not been established. Such similar types as $(NH_2OH)_3\cdot 2HCl$,[11] $(NH_2OH)_2HI$, and $(NH_2OH)_3\cdot HI$ [W. R. Dunstan and E. Goulding, *J. Chem. Soc.*, **69**, 839 (1896)], and $(NH_2NH_2)_3\cdot 2HI$ (ref. 12, p. 324) have also been reported. In view of the ready loss of hydroxylamine from solutions of the hemichloride and of the analytical data obtained in this work, it is probable that few or none of the foregoing formulae represent stoichiometric necessity.

[14] G. Ciamician and C. U. Zanetti, *Ber.*, **22**, 3176 (1889).

ported to be transformed by the action of hydroxylamine to dioximes.[15] Under similar conditions hydroxylamine alone gives acetonylacetone dioxime in a yield of only about 20%. The importance of hydroxylamine hydrochloride to these reactions is thus apparent. Its function is no doubt to effect the initial step in the reaction sequence (perhaps IV). Presumably hydroxylamine is sufficiently

(IV)

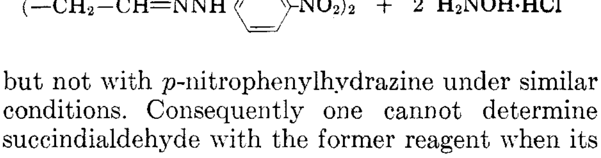


acidic by itself to cleave slowly the more reactive nucleus of 2,5-dimethylpyrrole.

The formation of succindialdoxime by Willstätter and Heubner's procedure is evidently due to incomplete neutralization of hydroxylamine hydrochloride by sodium carbonate. This incompleteness is no doubt owing to mechanical factors, perhaps incrustation of the carbonate by sodium chloride, and in this connection it is noteworthy that hydroxylamine hydrosulfate is reported to give less satisfactory results than hydroxylamine hydrochloride.[6]

Pure succindialdoxime is scarcely soluble in cold water, the 'not inconsiderable' solubility reported by Willstätter and Heubner being really due to the water-soluble impurities, ammonium chloride and hydroxylamine hemichloride, which contaminate the crude product. No care was exercised to protect the reaction mixture from light which, according to Schöpf and Lehmann, causes darkening of the product. Whatever the effect of light may be, that of too much hydroxylamine hydrochloride is considerably more powerful in producing a dark product.

Succindialdoxime combines quantitatively and nearly instantaneously with *p*-nitrophenylhydrazine hydrochloride in aqueous alcohol (Equation V),[16]



but not with *p*-nitrophenylhydrazine under similar conditions. Consequently one cannot determine succindialdehyde with the former reagent when its oxime derivatives are also present. It is converted in small yield to succinimide by polyphosphoric acid[17] and it dissolves in aqueous sodium bisulfite.[18] Succindialdoxime in Nujol absorbs strongly at 5.98–5.99 μ.

EXPERIMENTAL[19]

Materials. Distillation of Du Pont pyrrole (199 g.) afforded 191 g. (96%), b.p. 124–127°/760 mm., n_D^{20} 1.5097. Eastman Kodak pyrrole (500 g.), similarly purified, gave a distillate (454 g., 91%) of the same properties. Eastman Kodak hydroxylamine hydrochloride (sulfate-free) was used without further purification. Union Carbide and Carbon 2,5-dimethylpyrrole was redistilled and the portion boiling at 163–166° was employed.

Pyrrole, hydroxylamine hydrochloride, and sodium carbonate. Pyrrole was converted to succinaldoxime according to the procedure of Willstätter and Heubner.[9] For the two experiments performed the yields were 10 and 26%.

Pyrrole and hydroxylamine. Hydroxylamine hydrochloride (70 g., 1.0 mole) and alcohol (550 ml.) were refluxed until the salt had dissolved, the solution was cooled somewhat, and sodium bicarbonate (90.0 g., 1.07 moles) was added cautiously. Pyrrole (33.5 g., 0.500 mole) was added immediately, and refluxing was resumed and maintained 24 hours. No perceptible color change occurred during this period. The hot solution was filtered with suction from insoluble inorganic material and was concentrated *in vacuo* to dryness. Scarcely any non-volatile material was recovered.

Pyrrole, hydroxylamine, and hydroxylamine hydrochloride. (a) The foregoing procedure was followed except that only half the specified quantity of sodium bicarbonate was used. The crude product recovered from the vacuum concentration was worked up as described in the next section: 24.8 g. (43%) of pure succindialdoxime, m.p. 169°, was obtained. When one-third the specified quantity of sodium bicarbonate was used, the reaction mixture became quite dark, and much insoluble pyrrole polymer was collected with the inorganic salts. After recrystallization the product was still brown and was obtained in only 33% yield.

(*b*) *Recommended Procedure.* Hydroxylamine hydrochloride (90.5 g., 1.30 moles) was pulverized and stirred 30 minutes at room temperature with alcohol (400 ml.). A solution of potassium hydroxide (44.8 g., 0.800 mole) in water (50 ml.) and alcohol (50 ml.) was added. To the thick mixture pyrrole (34.5 ml., 0.500 mole) was admitted and the whole was refluxed gently for 23 hours, during which period it gradually turned orange-brown and gave off ammonia. No crystalline deposit [$(NH_4)_2CO_3$] collected in the condenser as in the experiments where carbonate was used. Alcohol (100 ml.) was added, refluxing continued another hour, and the mixture was filtered hot with suction. The inorganic residue was washed white with hot alcohol (100 ml.), and the dark filtrate and washings were concentrated *in vacuo* to a tan semi-solid which was collected and washed with a little alcohol: 56 g. When treated with 18 *N* sulfuric acid, the vacuum distillate turned bluish-green and deposited hydroxylamine hydrosulfate (1.8 g.). The filtrate and washings, which had an odor reminiscent of indole, contained tarry impurities and hydroxylamine hemichloride (~8 g.).

The tan residue (56 g.) was mixed with an equal weight of water (endothermicity!) and, after a half hour, the water-

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[15] G. Ciamician and C. U. Zanetti, *Ber.*, **23**, 1787 (1890).

[16] *Cf.*, F. Just, *Ber.*, **19**, 1205 (1886); H. von Pechmann, *Ber.*, **20**, 2543 (1887); G. Ciamician and C. U. Zanetti, *Ber.*, **22**, 1974 (1889).

[17] *Cf.*, E. C. Horning and V. L. Stromberg, *J. Am. Chem. Soc.*, **74**, 2680 (1952).

[18] H. v. Pechmann, *Ber.*, **20**, 2904 (1887).

[19] All melting points herein recorded are corrected and were observed in Pyrex capillaries.

soluble impurities (ammonium chloride and hydroxylamine hemichloride) were filtered off leaving 35.5 g. (61%). This product was recrystallized by addition to six times its weight of boiling water, swirling occasionally until dissolved, adding Darco (4 g.), and filtering after 2 minutes through Super-Cel with suction. The yellow filtrate soon deposited crystals and, after storing 2 days at 5°, the dioxime was collected: 30.4 g. (52%) of pale yellow crystals, m.p. 169–170°.

Anal. Calc'd for $C_4H_8N_2O_2$: C, 41.37; H, 6.94. Found: C, 41.22; H, 7.15.

A mixture of hydroxylamine hydrochloride (104 g., 1.50 moles), alcohol (500 ml.), sodium bicarbonate (84.0 g., 1.00 mole), and pyrrole (35.4 ml., 0.500 mole), refluxed gently 40 hours and worked up in similar manner, gave 34.3 g. (59%), m.p. 167–168°, of crude dioxime. After recrystallization as directed above the dioxime was obtained as pale yellow material: 29.9 g. (51%), m.p. 168.5°.

Acetonylacetone dioxime. 2,5-Dimethylpyrrole was converted to acetonylacetone dioxime according to the preceding paragraph, except that refluxing was maintained only 24 hours. The initially reddish reaction mixture was colorless after the first hour of heating. The crude, white dioxime was obtained in 86% yield, m.p. 134–135.5°, and an additional 7–10%, which was lost in washing out water-soluble inorganic impurities, was recovered (reported yield: 90%[14]).

2,5-Dimethylpyrrole and hydroxylamine. This reaction was conducted in the same way as the analogous one of pyrrole and hydroxylamine. Crude acetonylacetone dioxime was isolated in 18% yield.

Pyrrole and hydroxylamine hydrochloride. Hydroxylamine hydrochloride (7.0 g., 0.10 mole) was dissolved in alcohol (50 ml.) by heating to the reflux temperature, and pyrrole (3.5 ml., 0.050 mole) was added. The initially water-white solution underwent a progressive change in coloration during the subsequent refluxing from pale yellow to dark orange. Finely divided material began to precipitate 30 mins. after the addition of pyrrole. This product was reddish-orange, but the precipitate grew darker as it accumulated. After refluxing for 5 hrs. the mixture was cooled to 0°, stored 1 hour, and filtered. The purplish-red residue aggregated 5.7 g., and the material from the alcoholic filtrate was 4.65 g.: total recovery 10.35 g. (100%). By leaching the purple residue with boiling alcohol (2 × 50 ml.) the polymer was reduced successively to 3.67 g. and 3.10 g. The latter portion was a fine black powder which retained some chlorine.

Anal. Calc'd for $(C_4H_5N)_x$: C, 71.6; H, 7.5; N, 20.9. Found: C, 60.82; H, 6.82; N, 14.00.

The alcohol-soluble material appeared to be largely ammonium chloride. It sublimed and liberated ammonia when treated with strong base.

Anal. Calc'd for NH_4Cl: H, 7.54; N, 26.2. Found: C, 1.65; H, 7.13; N, 26.5.

Hydroxylamine hemichloride. Hydroxylamine hydrochloride (34.75 g., 0.500 mole) was dissolved in absolute methanol (175 ml.) by heating the mixture nearly to boiling. A solution of sodium hydroxide (10.0 g., 0.250 mole) in absolute methanol (70 ml.) was added. The solution was warmed briefly and filtered by gravity. The salt residue was washed with a little hot methanol and the combined filtrates were stored at 5°. Some free hydroxylamine was lost during the filtration by co-evaporation with methanol (litmus test). The hemichloride which separated as long, white needles was collected and washed with absolute methanol: 12 g., which melted to a white, foamy liquid at 87° (reported: 85°[11]), was obtained.

Anal. Calc'd for $H_6N_2O_2 \cdot HCl$: N, 27.32; Cl, 34.58. Found: N, 26.80; Cl, 37.42.

Pyrrole and hydroxylamine hemichloride. Hydroxylamine hemichloride (10.3 g., 0.100 mole) was boiled with alcohol (95 ml.) and when most had dissolved pyrrole (7.10 ml., 0.100 mole) was added. The mixture was refluxed 24 hours during which period it slowly became dark red. Removal of the volatile materials *in vacuo* afforded an orange residue: 14.3 g. This was purified as described above. After one crystallization the product (5.2 g. (45%), m.p. 168–169°) was orange.

Physical properties of succindialdoxime. For complete dissolution one part of succindialdoxime requires about six of boiling water. It is much less soluble in boiling alcohol and appears to be slowly volatilized from such solutions. The water-soluble impurities normally present in the crude dioxime cause polymerization at or near its melting point to dark, high-melting products. Both the well washed crude material and recrystallized material melted quickly and entirely. Recrystallized from water with the aid of Darco to constant melting point, succindialdoxime was obtained as small, stellate aggregates of minute, white prisms, m.p. 172–173° (reported: 175.5°,[7] 173°,[20] 172°,[5] and 169°[21]). Darker samples of the dioxime, melting at 169–170°, were analytically as pure as the white product. The darkening action of light on the reaction mixture was not noticed.

Both the light and the darker specimens in Nujol mulls had a strong band at 5.98–5.99 μ and had elsewhere nearly identical absorption. By way of comparison acetoxime and acetonylacetone dioxime in Nujol were measured and found to have strong absorption at 5.95 μ and 5.96 μ, respectively.[22]

Chemical properties of succindialdoxime. (*a*) *Beckmann rearrangement.* Finely divided succindialdoxime (2.0 g.) was suspended in polyphosphoric acid (58 g.) and heated to 100°. The mixture quickly turned black and foamed somewhat. The mixture was worked up approximately as directed by Horning and Stromberg,[17] continuous chloroform extraction being used to isolate the product. The recovered crude material (0.1 g.) was recrystallized from ethyl acetate: m.p. 119–120°; mixture m.p. with succinimide (m.p. 123–125°), 123–125°.

(*b*) *Succinaldehyde bis-p-nitrophenylhydrazone.* Succindialdoxime (1.16 g., 0.0100 mole) was dissolved in alcohol (80 ml.) by careful warming and stirring, care being taken to boil no solvent from the flask. To this mixture was added all at once a filtered solution of *p*-nitrophenylhydrazine hydrochloride (4.2 g.) in water (60 ml.). The resulting clear orange solution solidified almost at once. It was stirred, stored overnight at 5°, mixed with 50% aqueous alcohol (25 ml.), and collected with the aid of more aqueous alcohol on a Büchner funnel. After drying in air 4 days: 3.88 g. It was dried to constant weight *in vacuo* over potassium hydroxide at room temperature: 3.56 g. (100%), m.p. 155–162°. This material absorbs moisture (~7%) when exposed to the atmosphere (changing from yellow to orange in the process) and, like the bis 2,4-dinitrophenylhydrazone,[6] electrifies readily. Although its melting point is low (*vide infra*) it is pure.

Anal. Calc'd for $C_{16}H_{16}N_6O_4$: C, 53.93; H, 4.53. Found: C, 53.98; H, 4.48.

Recrystallized from alcohol, it was obtained as an orange precipitate consisting of minute, yellow blades and prisms, many having bushy ends: m.p. 175–176.5°.[5]

A hot solution of *p*-nitrophenylhydrazine (1.53 g., 0.010 mole) in alcohol (50 ml.) was added to succindialdoxime (0.58 g., 0.0050 mole) in hot alcohol (40 ml.). No precipitate separated even after keeping several days at room temperature.

(*c*) *Reaction with sodium bisulfite.* Succindialdoxime (4.64 g., 0.0400 mole) was stirred with a solution of sodium bisulfite (16.64 g., 0.160 mole) in water (60 ml.). After about 10 minutes, the temperature rose slowly to ~50°, and the dioxime dissolved to give a pale yellow solution. Concentra-

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(20) J. von Braun and W. Sobecki, *Ber.*, **44,** 2526 (1911).

(21) J. Fakstorp, D. Raleigh, and L. E. Schniepp, *J. Am. Chem. Soc.*, **72,** 869 (1950).

(22) *Cf.*, J. Goubeau and I. Fromme, *Chem. Abstr.*, **43,** 6016 (1949); F. Mathis, *Chem. Abstr.*, **45,** 7542 (1951); G. Duyckaerts, *Chem. Abstr.*, **47,** 2601 (1953).

tion *in vacuo* gave a yellow gum which was insoluble in alcohol. Treatment of another such solution with sodium bisulfate monohydrate (11.04 g., 0.0800 mole) resulted in the copious evolution of sulfur dioxide. The solution was concentrated *in vacuo* until crystallization began, alcohol was added, and sodium sulfate (8.9 g.) was filtered off. The filtrate was further concentrated *in vacuo* to a pale pink gum which did not crystallize on keeping several days *in vacuo*. Heated with a mixture of acetic anhydride and acetic acid containing a trace of sulfuric acid, the gum polymerized with the evolution of more sulfur dioxide to granular, chocolate-colored material.

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