

[CONTRIBUTION FROM THE NATIONAL RESEARCH INSTITUTE OF CHEMISTRY, ACADEMIA SINICA]

Synthesis of 1-Phenyl-2-methyl-4-ethylpyrazol-5-one

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This short paper describes a method for synthesizing 1-phenyl-2-methyl-4-ethylpyrazol-5-one, a compound similar in constitution to the well-known antipyretic, antipyrine, and which may prove to have similar physiological action. Starting with ethyl formylbutyrate, the sodium salt of which was prepared by Johnson and Menge² and Chi and Tien,³ the writers were able to synthesize this pyrazolone in a good yield by reaction of the aldo-ester with phenylhydrazine to form 1-phenyl-4-ethylpyrazol-5-one, followed by treatment of the latter with methyl iodide in methyl alcoholic solution.

Experimental Part

Ethyl Formylbutyrate.—Twenty-three grams of sodium (1 mole) in wire form was suspended in anhydrous ether, and a mixture of 127.6 g. of ethyl butyrate (1.1 mole) and 81.4 g. of ethyl formate (1.1 mole) dissolved in anhydrous ether were added slowly. For the completion of the reaction, it required about forty hours at ordinary temperature. The mixture was then shaken with ice water, to dissolve the sodium salt of ethyl formylbutyrate. The ethereal solution containing the unreacted esters assumed a red color, and was separated from the aqueous solution containing the sodium salt of the required aldo-ester. This aqueous solution, cooled in ice mixture, was acidified with the calculated amount of acetic acid, whereupon the free aldo-ester separated as a brownish-yellow oil. It was then extracted with ether, washed with sodium carbonate solution, and with water and lastly dried over sodium sulfate. After the solvent had been removed, it was fractionated under vacuum several times. The ester boiled at 37–38° at 2 mm. pressure, and the yield was 16 g.

Anal. Calcd. for $C_7H_{12}O_3$: C, 58.29; H, 8.39. Found: C, 57.90, 58.01; H, 8.35, 8.55.

Semicarbazone.—The aldo-ester and semicarbazide interacted normally in alcohol solution at ordinary temperature to give the semicarbazone. This was recrystallized from boiling water and melted at 108–108.5°.

Anal. Calcd. for $C_8H_{15}O_3N_2$: C, 47.73; H, 7.52; N, 20.89. Found: C, 47.75; H, 7.63; N, 21.22, 21.08.

4-Ethylisoxazol-5-one.—Five grams of ethyl formylbutyrate was added to an aqueous solution of hydroxylamine prepared by treating 7.4 g. of hydroxylamine hydrochloride dissolved in water with 3.25 g. of aniline. After heating on a water-bath for two hours water was added and

the isoxazol extracted with ether and the solution dried with sodium sulfate. The isoxazol boiled at 113–114° at 2 mm. pressure. The yield was 2.1 g.

Anal. Calcd. for $C_8H_{11}O_2N$: N, 12.39. Found: N, 12.1, 12.11.

1-Phenyl-4-ethylpyrazol-5-one. Method A.—One gram of the aldo-ester was treated with 0.75 g. of phenylhydrazine, and the mixture heated on a water-bath for about two hours. After cooling, the reaction mixture solidified to a crystalline mass of the required pyrazol. This crystallized from 95% alcohol or from benzene-petroleum ether in colorless prisms, melting at 99–99.5°. The yield was 70%.

Anal. Calcd. for $C_{11}H_{12}ON_2$: C, 70.17; H, 6.43; N, 14.90. Found: C, 69.76; H, 6.52; N, 15.3, 15.07.

Method B.—Ethyl formylbutyrate was treated with an aqueous solution of the required amount of phenylhydrazine hydrochloride, and then acidified with a few drops of concentrated hydrochloric acid. The mixture was shaken occasionally, and allowed to stand for about eight to nine days. The ester gradually dissolved and finally a yellowish oil appeared suspended in the solution. This was separated and the filtrate was exactly neutralized with 25% ammonia, when the pyrazolone separated. On account of its amphoteric character an excess of ammonia was avoided. It was recrystallized from benzene-petroleum ether in prisms and melted at 99.5°. The yield was poor.

Anal. Calcd. for $C_{11}H_{12}ON_2$: N, 14.90. Found: N, 14.94, 15.13.

1-*p*-Nitrophenyl-4-ethylpyrazol-5-one.—One gram of the aldo-ester interacted at water-bath temperature with *p*-nitrophenylhydrazine to form this pyrazolone compound. It was purified by recrystallization from 95% alcohol, and melted at 212–214° with slight decomposition.

Anal. Calcd. for $C_{11}H_{11}O_3N_3$: N, 18.03. Found: N, 18.15, 18.33.

1-*p*-Bromophenyl-4-ethylpyrazol-5-one.—By action of the aldo-ester on *p*-bromophenylhydrazine for one and one-half hours. After purification by recrystallization from benzene-petroleum ether, it melted at 170–171°.

Anal. Calcd. for $C_{11}H_{11}ON_2Br$: Br, 29.93. Found: Br, 29.81.

1-Phenyl-2-methyl-4-ethylpyrazol-5-one.—Fifteen tenths gram of 1-phenyl-4-ethylpyrazol-5-one and 0.38 g. of methyl iodide were dissolved in a small quantity of methyl alcohol and heated at 100–110° in a bomb tube for about eight hours. After the completion of the reaction the solvent was removed and the residue, after decolorizing with sulfurous acid, was treated with dilute sodium hydroxide solution to dissolve unchanged pyrazolone. The fraction insoluble in alkali solution was extracted with benzene. From the benzene solution the above pyrazolone separated in crystalline form. The yield was 0.2 g. It was purified by recrystallization from benzene-petroleum ether, and melted at 121–121.5°.

(1) The writers wish to thank Mr. Yao-Tseng Huang for his assistance in making the micro-analyses. They also desire to express appreciation of the help given by Professor Treat B. Johnson of Yale University in organizing this paper for publication.

(2) Johnson and Menge, *J. Biol. Chem.*, **2**, 105 (1906).

(3) Chi and Tien, *This Journal*, **57**, 215 (1935).

Anal. Calcd. for $C_{12}H_{14}ON_2$: C, 71.25; H, 6.98; N, 13.86. Found: C, 70.96; H, 6.99; N, 13.84.

Summary

1. The preparation of pure ethyl formylbutyrate is described.

2. This aldo-ester reacted with phenylhydrazine, nitrophenylhydrazine and bromophenylhy-

drazine to give the corresponding pyrazolone compounds.

3. The aldo-ester reacted with hydroxylamine to give 4-ethylisoxazol-5-one.

4. The methylation of 1-phenyl-4-ethylpyrazol-5-one gave 1-phenyl-2-methyl-4-ethylpyrazol-5-one.

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Kinetics of the Trivalent Vanadium-Iodine Reaction

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In oxidations by iodine in aqueous solutions, usually containing iodide, several possible oxidizing molecular species exist: namely, iodine molecules, triiodide ions, hypiodite ions and hypiodous acid molecules. That iodine atoms may be involved under ordinary conditions in the dark seems improbable, although such an interpretation is warranted in the photochemical oxidation of oxalate.¹ Iodine molecules have been shown to be a reacting species in several oxidations, among them, that of phosphorous acid,² of trivalent titanium³ and of ferrous iron.⁴ The oxidation of arsenious acid by iodine⁵ is an outstanding historical example of those reactions in which hypiodous acid molecules are involved in the rate determining step. Triiodide ion is at least one of the reacting molecular species in the oxidations of phosphorous acid,² of ferrous iron,⁴ and of hypophosphorous acid.⁶ It seems probable that some relation may be found between the molecular species of iodine involved and the nature of the reducing species or of its transformation, after a larger number of kinetic studies has been made.

The more immediate interest in this reaction is due to its possible importance in the interpretation of the induced catalysis of the autoxidation of hydriodic acid by vanadic acid.⁷ In a general qualitative survey of the reactions of vanadium in its different valence states Rutter⁸ observed that

(1) Griffith and McKeown, *Trans. Faraday Soc.*, **28**, 752 (1932).

(2) Mitchell, *J. Chem. Soc.*, **123**, 2241 (1923).

(3) Yost and Zabaró, *THIS JOURNAL*, **48**, 1181 (1926).

(4) Unpublished work of Bray and Hershey, presented at the San Francisco meeting of the American Chemical Society, Aug. 20, 1935.

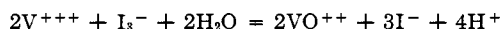
(5) (a) Roebuck, *J. Phys. Chem.*, **6**, 365 (1902); **9**, 727 (1905); (b) Liebhaufsky, *ibid.*, **95**, 1648 (1931).

(6) Mitchell, *J. Chem. Soc.*, **117**, 1322 (1920).

(7) Bray and Ramsey, *THIS JOURNAL*, **55**, 2279 (1933).

(8) Rutter, *Z. anorg. Chem.*, **52**, 368 (1907).

the trivalent vanadium-iodine reaction proceeded at a moderate rate. The stoichiometry of the reaction may be represented by the following equation.



Preparation and Standardization of Stock Solutions.—All chemicals were of C. P. grade. The sodium perchlorate and sodium iodide were shown free from possible impurities by methods recommended by Murray.⁹ Sodium oxalate from the Bureau of Standards was the primary standard. Known solutions of each of the following substances were obtained as indicated: potassium permanganate, with sodium oxalate; sodium thiosulfate, by the Volhard method, under conditions recommended by Bray and Miller;¹⁰ sodium triiodide and potassium iodate, with the sodium thiosulfate; perchloric acid, with potassium iodate by the method of Kolthoff;¹¹ sodium iodide and sodium perchlorate, from accurately weighed quantities which had been dried carefully (the former checked by the method of Andrews¹²); ammonium vanadate, iodometrically.¹³

The stock solutions of vanadic perchlorate, $V(ClO_4)_3$, were prepared by electrolytic reduction of vanadyl perchlorate, VO_2ClO_4 . The latter was formed by mixing vanadium pentoxide, from thermal decomposition of pure ammonium vanadate, with perchloric acid. The oxide dissolved as the reduction progressed. A platinized platinum cathode and a platinum anode were used. The reduction was followed analytically (by a method

(9) Murray, "Standards and Tests for Reagents and C. P. Chemicals," D. Van Nostrand Co., N. Y., 1927.

(10) Bray and Miller, *THIS JOURNAL*, **46**, 2204 (1924).

(11) Kolthoff, *ibid.*, **48**, 1447 (1926).

(12) Andrews, *ibid.*, **25**, 756 (1903).

(13) Ramsey, *ibid.*, **49**, 1138 (1927).