was made neutral to Congo red by the addition of 50 cc. of 2 *N* sodium carbonate which had been diluted to 100 cc. A solution of sodium arsenite was prepared by dissolving 30 g. of arsenious oxide in 300 cc. of 2 *N* sodium carbonate, and to it was added 2 g. of copper sulfate to serve as a catalyst. After this had been cooled to 0°, the tetrazotized diaminodiphenyl solution was siphoned into the arsenite solution during fifteen to twenty minutes. During this procedure there was much gas evolved and there was considerable foaming, which was very difficult to get rid of. An olive-green precipitate was produced, which was filtered by suction and washed with water. The precipitate was extracted with hot 10% hydrochloric acid and the extract was neutralized with ammonia or sodium hydroxide. This gave a precipitate of crude cyclic *o,o'*-azodiphenyl. The yield was 7.5 g. or 45% of the theoretical amount. The crude material melted at 153–154°. It was crystallized from alcohol and gave yellow crystals melting at 155°. A mixed melting point carried out with a sample of the cyclic azo compound prepared according to Täuber,[3] showed no depression of the melting point. It also gave a picrate melting at 191°.

Cyclic Azo Compound from 2,2'-Diamino-4,4'-dimethyldiphenyl.[4]—This compound was prepared in a manner similar to the above, from 2,2'-diamino-4,4'-dimethyldiphenyl. It consisted of yellow needles, soluble in dilute hydrochloric acid, and melted at 184–185°. A mixed melting point carried out with this sample and the compound produced by the sodium amalgam and methanol reduction of 2,2'-dinitro-4,4'-dimethyldiphenyl showed no depression of the melting point.

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Summary

Tetrazotized diaminodiphenyls, when treated with arsenious oxide in sodium carbonate solution, are in part converted into cyclic azo compounds.

(4) Ullmann and Dieterle, *Ber.*, **37**, 24 (1904).

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL CHEMISTRY, COLUMBIA UNIVERSITY]

Carboxymethoxylamine

BY E. BOREK[1] AND H. T. CLARKE

In the course of experiments on the synthesis of canaline and analogous compounds, the need arose for a convenient process for preparing carboxymethoxylamine (hydroxylamineacetic acid). In view of the recent report by Anchel and Schoenheimer[2] of the use of this substance as a reagent for the isolation of ketones from natural sources, an early description of our method of preparation seems advisable.

Carboxymethoxylamine was first prepared by Werner[3,4] by the hydrolysis of ethylbenzhydroximinoacetic acid; it has also very recently been prepared by Kitagawa and Takani[5] by condensation of benzhydroxamic acid and ethyl bromoacetate, with subsequent hydrolysis by hydrochloric acid.

The method here described consists in condensing the sodium derivative of acetoxime with ethyl chloroacetate, followed by successive alkaline and acid hydrolysis of the condensation product. The intermediate acetone carboxymethoxime may also be prepared, though in somewhat smaller yields, by condensing acetoxime with sodium chloroacetate in alkaline solution by a modification of the method of Hantzsch and Wild.[6]

The carboxymethoxylamine is isolated in the form of its hydrochloride, which melts at 151°. This product in our hands has invariably proved to consist of the hemihydrochloride; that prepared by Werner was reported to melt at 147–148°[3] and at 156°[4,5] and to give analytical figures agreeing satisfactorily with the normal hydrochloride. We are unable to account for this discrepancy.

Experimental

A solution of 24.4 g. of acetoxime in 250 cc. of absolute alcohol was added to a solution of 7.7 g. of sodium in 150 cc. of absolute alcohol. The alcohol was removed by distillation under diminished pressure and the white crystalline residue was dried *in vacuo* over phosphorus pentoxide. To the dry salt 100 cc. of ethyl chloroacetate was added and the mixture refluxed for thirty minutes. When cool, the salt was filtered off and well washed with absolute alcohol. The alcohol and the unreacted ethyl chloroacetate were removed under diminished pressure, the fraction distilling up to 52° under 28 mm. being discarded.

The sirupy residue, which consisted mainly of acetone carbethoxymethoxime, together with the corresponding

(1) This report is from a dissertation submitted by Ernest Borek in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University.

(2) Anchel and Schoenheimer, *J. Biol. Chem.*, **114**, 539 (1936).

(3) Werner, *Ber.*, **26**, 1567 (1893).

(4) Werner and Sonnenfeld, *ibid.*, **27**, 3350 (1894).

(5) Kitagawa and Takani, *J. Biochem. (Tokio)*, **23**, 181 (1936).

(6) Hantzsch and Wild, *Ann.*, **289**, 285 (1896).

free acid, acetoxime and other contaminants such as ethyl glycolate, was heated for one hour at 100° with 125 cc. of 11.4% sodium hydroxide. When cool, the alkaline solution was extracted five times with one-fourth its volume of ether; the ether solution, which contained slight amounts of unreacted acetoxime and unsaponified ester, was discarded. The aqueous solution was acidified to Congo red with concentrated hydrochloric acid, saturated with sodium chloride and extracted with three times its volume of ether in six portions. The ether solution was dried with sodium sulfate, and the ether removed by distillation. After the last traces of ether had been removed under diminished pressure, acetone carboxymethoxime crystallized. The weight of the crude preparation was 25 g. (58% of the theoretical).

Acetone carboxymethoxime can also be prepared in aqueous solution: a solution of sodium chloroacetate prepared by neutralizing 212 g. of chloroacetic acid with 450 g. of 20% sodium hydroxide was added to a solution of 146 g. of acetoxime in 450 cc. of water; 200 g. of 40% aqueous sodium hydroxide solution was then added and the whole refluxed for one hour. When cold, the alkaline solution was four times extracted with one-fourth of its volume of ether; the ether solution, which contained some unreacted acetoxime, was discarded. The aqueous layer was acidified with hydrochloric acid to Congo red, saturated with sodium chloride and six times extracted with one-half its volume of ether. The ether solution was dried with sodium sulfate, and the ether removed on the steam-bath, finally under diminished pressure. The crude acetone carboxymethoxime which crystallized weighed 128 g. (49%). By the original method of Hantzsch and Wild[6] the yield was 46%.

The crude acetone carboxymethoxime from either preparation can be purified by distillation; b. p. 110–118° (1 mm.). It solidifies in the receiver in long needles. There is considerable carbonization and hydrogen cyanide is formed. It can be crystallized from a hot concentrated solution of acetone by the addition of ligroin. The resulting plates, the odor of which is not unlike that of phenylacetic acid, melt at 76–76.5° (uncorr.).

Anal. Calcd. for $C_5H_9O_3N$: C, 45.80; H, 6.87; N, 10.69; neut. equiv., 131. Found: C, 46.12; H, 6.49; N, 10.92; neut. equiv., 131.5.

For the preparation of carboxymethoxylamine hemihydrochloride 10 g. of the crude acetone carboxymethoxime in 100 cc. of 6 *N* hydrochloric acid was refluxed for three hours; the solution was then treated with charcoal and concentrated to about 10 cc. under diminished pressure. To the sirup was added 200 cc. of a solution of 1:1 ether and ethyl alcohol, and the cloudy solution was placed in an ice box. Four grams of crystals deposited. The mother liquor was again concentrated to a sirup and ether and alcohol solution added. One gram more of the crystals was thus obtained. The melting point of the crystals after one recrystallization from water, ether–alcohol solution is 151°.[7]

Anal. Calcd. for $(C_2H_5O_3N)_2HCl$: C, 21.95; H, 5.03; N, 12.81; Cl, 16.23. Found: C, 22.26; H, 5.45; N, 12.54; Cl, 16.29.

Acetophenone carboxymethoxime was prepared by adding a solution of 150 mg. of carboxymethoxylamine hemihydrochloride in 4 cc. of water to a solution of 0.2 cc. of acetophenone in 4 cc. of ethyl alcohol. After the solution was made alkaline to litmus with *N* sodium hydroxide, it was warmed on the steam-bath for one hour. The cool, alkaline solution was extracted five times with ether and the ether solution discarded. The aqueous solution was acidified to Congo red and placed in the ice box. The large plates that formed were filtered and recrystallized from alcohol–water solution; colorless plates, m. p. 97–97.5°, soluble in ether and alcohol; almost insoluble in water.

Anal. Calcd. for $C_{10}H_{11}O_3N$: C, 62.15; H, 5.74; N, 7.25. Found: C, 62.07; H, 5.66; N, 7.12.

Benzaldehyde carboxymethoxime was prepared in the same way as the above; it melted at 96°. Hantzsch and Wild,[6] who prepared this compound by condensing sodium chloroacetate with benzaldoxime, report a melting point of 98°.

Pyruvic acid carboxymethoxime was prepared the same way, but since it is water-soluble the solution, after acidification, was five times extracted with one-half its volume of ether, the ether solution dried with sodium sulfate and the ether distilled. The crystals which were obtained were recrystallized from ether and chloroform; m. p. 129° (Hantzsch and Wild[6] report 130–132°).

Summary

Directions are given for the preparation of carboxymethoxylamine hemihydrochloride, a reagent of use for the isolation of ketones.

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(7) As hydroxylamine hydrochloride also melts at 151°, a mixed melting point should be performed.