Experimental Part

γ-Ethoxybutyronitrile, $EtOC_3H_6CN$.—γ-Ethoxypropyl alcohol and γ-ethoxypropyl bromide were made essentially as described by Noyes.[4] Forty grams of ethoxypropyl bromide was refluxed for three and one-half hours on a water-bath with 28 g. of potassium cyanide, 6 cc. of water and 40 cc. of alcohol. The liquid was then decanted from the precipitated salts, which were washed with ether. The combined solution was diluted with water and extracted several times with ether. After removal of the solvent from the dried ether extract, the product was fractionated under reduced pressure: wt., about 16 g.; b. p. (716 mm.) 175°. The reported b. p. (750 mm.) is 181.2–181.5°.

δ-Ethoxybutylamine, $EtOC_4H_8NH_2$.—Ten grams of ethoxybutyronitrile and 200 cc. of absolute methanol were placed in a flask under an efficient reflux condenser. Twenty-six grams of sodium, cut into small pieces, was added as rapidly as possible through the condenser. When all the sodium had reacted, steam was passed through the mixture, the distillate being caught in a receiver containing 8 cc. of concd. hydrochloric acid. At the conclusion of the steam distillation the slightly acid distillate was evaporated to a small volume, first over a free flame, finally under reduced pressure using an oil-bath. The evaporation was interrupted upon appearance of a solid residue. This residue was treated with 60% potassium hydroxide solution and extracted with ether. The extract was dried with solid potassium hydroxide, the ether removed by distillation, and the resulting oil again dried with solid potassium hydroxide: yield, about 7 g.; b. p. (730 mm.) 155–156°. The recorded b. p. (746 mm.) is 153–154°.

δ-Ethoxybutyl Urea, $EtOC_4H_8NHCONH_2$.—Two grams of ethoxybutylamine was mixed with 1.5 g. of potassium cyanate in 3 cc. of water. The solution was cooled with ice and stirred while 0.95 cc. of a 1:1 solution of concd. sulfuric acid in water was added in small drops from a capillary pipet. When all the acid had been added the mixture was warmed to 55–60° for five minutes, then 25 cc. of acetone was added. After being cooled in an ice-bath the mixture was filtered by suction. The filtrate was warmed to 55–60° until the odor of acetone was lost, then for one hour to 60–65°. Upon cooling a solid was obtained. This was treated with 6 cc. of acetone; the mixture was filtered, 6 cc. of dry ether added, and the solution placed in ice. The urea soon appeared as a heavy precipitate of oblong microscopic platelets: weight, 1.0 g. of m. p. 68–69°.

The compound is freely soluble in water, ethanol, acetone, chloroform and benzene and practically insoluble in ether. When the compound is tasted a cooling sensation is felt on the tip of the tongue, followed (with most observers) by a faint bitter taste. A 2% water solution was faintly bitter (one observer reported a slight sweet taste).

Anal. Calcd. for $C_7H_{16}N_2O_2$: C, 52.50; H, 10.0; N, 17.50. Found: C, 52.92, 52.35; H, 10.28, 9.61; N, 17.52, 17.71.

Summary

The preparation of *d*-ethoxybutyl urea is described. The compound is faintly bitter, showing that the sweet taste of Dulcin depends upon the presence of the benzene ring. β-Hydroxyethyl urea is also not sweet, while *o*-hydroxyphenyl urea is very sweet.

FAYETTEVILLE, ARK. RECEIVED DECEMBER 22, 1933

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[4] Noyes, *Am. Chem. J.*, **19**, 767 (1897).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ILLINOIS]

Trihalomethylketonic Acids of the Naphthalene Series

BY BENTON A. BULL AND REYNOLD C. FUSON

The retardation of the cleavage phase of the haloform reaction in the case of diortho substituted aryl methyl ketones appears to depend partly on the steric hindrance involved and partly on the solubility of the trihalomethyl ketone in the alkaline medium employed for the cleavage.[1] The separate influence of each of these factors would be clearly demonstrated by a comparison of the reactions of methyl aryl ketones in which (1) the *solubility factor* was changed while the steric factor remained constant, and (2) the *steric factor* was changed while the solubility factor remained constant.

Such a comparison is satisfactorily afforded by a study of the three ketones 1-aceto-2-naphthyl methyl ether (I), 1-aceto-2-naphthoxyacetic acid (II) and 2-aceto-1-naphthoxyacetic acid (III).

Both I and II gave trihalomethyl ketones when treated with hypohalites, but the trihalomethyl ketones from II were cleaved by alkalies (to V) in approximately one-eighth of the time required for the cleavage of the trihalomethyl ketones from I.[2] Hence the cleavage of these two types of trihalomethyl ketones possessing approximately equal steric factors[3] indicates that the introduction of a solubilizing group leads to an increase in the ease of cleavage.

On the other hand, II and its position isomer, III, have approximately the same solubility. The

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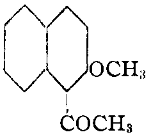
[1] Bull and Fuson, THIS JOURNAL, **55**, 3424 (1933).

[2] See Fuson, Farlow and Stehman, *ibid.*, **53**, 4097 (1931).

[3] The molecular volume of the acetoxy group, while unknown, would certainly not be less than that of the methoxyl group.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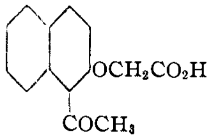
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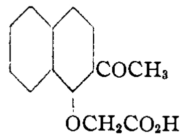
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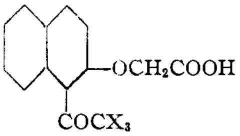
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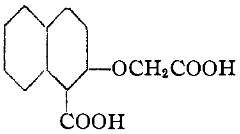
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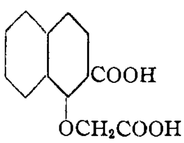
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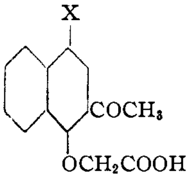
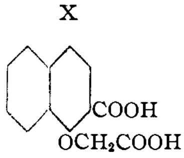

VII


VIII

degree of steric hindrance may therefore be assumed to constitute the essential difference between them. Here the significance of the steric factor was clearly demonstrated by the fact that the unhindered ketone (III) was quantitatively cleaved to the dibasic acid (VI) when treated with hypohalites. This result was observed not only under conditions identical with those obtaining when the trihalomethyl ketones (IV) were prepared, but even when the reaction time was reduced to five minutes, and when in addition an attempt was made to salt out any trihalomethylketonic acid which might have been formed.[4] In sharp contrast with this behavior is the fact that the hindered trihalomethylketonic acids (IV) are readily prepared in cold dilute alkaline hypohalite solutions, and, indeed, can be recovered unchanged from dilute alkali at room temperature.

In an attempt to prepare a trihalomethyl derivative of an unhindered ketone, III was treated with solutions of halogen in sodium carbonate. Halogenation, however, took place only in the nucleus, yielding the 4-bromo (VII, X = Br) and the 4-chloro (VII, X = Cl) derivatives.[5] That the halogen atoms in these compounds were not in the side chain was established by converting them to the corresponding halo dibasic acids (VIII) by the action of hypohalites. The dibasic acids were also prepared by direct halogenation of VI in glacial acetic acid.

Experimental Part

1-Aceto-2-naphthol.—The method of Fries[6] was used. By extending the period of reaction from five to about eleven hours the yield was increased to 70–85% of the theoretical amount, or nearly twice that obtained by the original method.

1-Aceto-2-naphthoxyacetic Acid.—By the method of Fries this acid was obtained in yields of 80% of the theoretical amount.

1-Trichloroacetyl-2-naphthoxyacetic Acid.—A solution of the keto acid (II) in 10% sodium hydroxide solution was cooled, and crushed ice was added to it. To this solution was added an ice-cold solution of sodium hypochlorite. After a few minutes a yellow, gummy precipitate formed; it redissolved when the mixture was shaken. After the reaction mixture had stood for fifteen minutes, an ice-cold solution of sodium bisulfite was added, and immediately thereafter the mixture was acidified. The resulting mixture was extracted with ether and the ether was evaporated; fine needles (from alcohol), melting at 163–165° (with decomposition), were obtained.

The compound was dissolved in a mixture of 10 cc. of alcohol and 24 cc. of 0.01 *N* sodium hydroxide solution at room temperature and, after five minutes, acidification precipitated the ketone unchanged. An attempt to determine the neutral equivalent by titration with 0.01 *N* alkali failed because a distinguishable end-point could not be obtained.

Anal. Calcd. for $C_{14}H_9O_4Cl_3$: C, 48.3; H, 2.6; Cl, 30.6. Found: C, 48.5; H, 2.7; Cl, 30.4.

1-Tribromoacetyl-2-naphthoxyacetic Acid.—By a procedure similar to that outlined above for the trichloro derivative the corresponding tribromo compound was obtained. It melted at 171–172°.

Anal. Calcd. for $C_{14}H_9O_4Br_3$: C, 34.9; H, 1.9; Br, 50.0. Found: C, 35.0; H, 2.0; Br, 50.1.

The tribromoketonic acid was found to show a stability to 0.01 *N* alkali similar to that described for the corresponding trichloro compound.

1-Carboxy-2-naphthoxyacetic Acid.—The acid was prepared by heating a mixture of sodium hypochlorite and 1-aceto-2-naphthoxyacetic acid for one hour. After recrystallization from petroleum ether the product melted at 189°, with decomposition.

Anal. Calcd. for $C_{13}H_{10}O_5$: C, 63.3; H, 4.1; neut. eq., 123. Found: C, 63.4; H, 4.1; neut. eq., 125.

The same acid was obtained by use of a solution of hypobromite but in this case it was necessary to boil the reaction mixture for two hours in order to cause the cleavage to go to completion.

Finally the dibasic acid was prepared from both the trichloro and the tribromo keto acids when these were heated for thirty minutes with 10% sodium hydroxide solution.

2-Aceto-1-naphthol.—By the method of Witt and Braun[7] this compound was obtained in yields of 85% of the theoretical amount.

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(4) In this connection, it is interesting to note that none of the trihalomethylketonic acids prepared in this Laboratory are appreciably soluble in dilute alkalies, and are usually "salted-out" of the alkaline hypohalite solutions during preparation. Indeed, the isolation of the relatively insoluble sodium salt has been used as a convenient method of purification.

(5) Zincke has prepared several hindered and unhindered trihalomethyl ketones by this procedure. See Zincke and Günther, *Ann.*, **272**, 243 (1893).

(6) Fries, *Ber.*, **54**, 711 (1921).

(7) Witt and Braun, *ibid.*, **47**, 3219 (1914).

2-Aceto-1-naphthoxyacetic Acid (V).—The general method of Koelsch[8] was used. By heating an alkaline solution of the naphthol and chloroacetic acid for twelve hours a yield of 45% of the theoretical amount was obtained. The product melted at 130–131°.[9]

2-Carboxy-1-naphthoxyacetic Acid (VI).—When V was treated with hypohalites according to the procedure used for the preparation of the hindered trihaloacetyl compounds (IV), the unhindered ketone was converted quantitatively to the dibasic acid, not only when the procedure was identical with that previously used, but also when the reaction time was reduced to five minutes and the sodium salt of the dibasic acid was "salted out" by reducing the temperature to −10°. The dibasic acid was recrystallized from water; melting point 206–207°.

Anal. Calcd. for $C_{13}H_{10}O_5$: C, 63.3; H, 4.1; neut. eq., 123. Found: C, 63.4; H, 4.1; neut. eq., 124.

4-Chloro-2-aceto-1-naphthoxyacetic Acid (VII, X = Cl).—An ice-cold 20% solution of sodium carbonate was saturated with chlorine, and the excess halogen was removed by the addition of a little additional carbonate solution. To this solution was added a solution of the keto acid (V) in sodium carbonate. After the mixture had stood for fiteen minutes it was treated with cold aqueous sodium bisulfite, and then immediately acidified with dilute sulfuric acid. The product was extracted with chloroform, from which it was precipitated by the addition of low-boiling petroleum ether. After several recrystallizations the compound melted at 184–185°, with decomposition.

Anal. Calcd. for $C_{14}H_{11}O_4Cl$: C, 60.3; H, 4.0; Cl, 12.8. Found: C, 60.5; H, 4.0; Cl, 12.8.

The dibasic acid (VIII, X = Cl) was obtained from the aqueous layer. When purified by recrystallization from water it melted at 245–246°. This acid was also prepared from 4-chloro-2-aceto-1-naphthoxyacetic acid by the action of hypobromite and from VI by treatment with chlorine.

Anal. Calcd. for $C_{13}H_9O_5Cl$: C, 55.6; H, 3.2; Cl, 12.7. Found: C, 55.7; H, 3.3; Cl, 12.6.

4-Bromo-2-aceto-1-naphthoxyacetic Acid (VII, X = Br).—This acid resulted from the action of a solution of bromine in sodium carbonate on V. The procedure was similar to that described for the preparation of the corresponding chloro compound. The bromo compound melted at 195–196°, with decomposition.

Anal. Calcd. for $C_{14}H_{11}O_4Br$: C, 52.0; H, 3.4; Br, 24.8. Found: C, 52.2; H, 3.5; Br, 24.7.

The corresponding dibasic acid (VIII, X = Br) was obtained by the action of hypobromite on the bromoketonic acid and by direct bromination of VI. When purified by recrystallization from water it melted at 242–243°, with decomposition.

Anal. Calcd. for $C_{13}H_9O_5Br$: C, 48.0; H, 2.8; Br, 24.6. Found: C, 48.2; H, 2.9; Br, 24.5.

Summary

1-Trichloroacetyl-2-naphthoxyacetic acid has been prepared by the interaction of 1-aceto-2-naphthoxyacetic acid and sodium hypochlorite in 10% sodium hydroxide solution. The trichloromethyl ketone is stable to alkali in the cold but is cleaved rapidly at higher temperatures.

1-Tribromoacetyl-2-naphthoxyacetic acid has been prepared in an analogous manner. It is likewise stable to alkali in the cold, but at higher temperatures is cleaved somewhat less readily than the trichloro derivative.

Similar methods converted 2-aceto-1-naphthoxyacetic acid to the corresponding dibasic acid. No intermediate products could be isolated.

These results show that the ease with which a trihalomethyl ketone is cleaved by aqueous alkalies is diminished by the introduction of steric hindrance and enhanced by an increase of the solubility of the ketone.

URBANA, ILLINOIS RECEIVED DECEMBER 26, 1933

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[8] Koelsch, THIS JOURNAL, **53**, 304 (1931).

[9] Kostanecki and Tambor [*Ber.*, **42**, 907 (1909)] give the melting point as 130°.