ture with the substance in question. Tingle reported that his "camphylisoxazole" dissolved in warm aqueous alkali and reprecipitated on cooling. It seems probable that the material which precipitated was actually the sodio derivative of cyanocamphor which has been previously observed to crystallize from strongly alkaline solutions.[13]

Summary

A striking difference has been observed between certain cyclohexanone and cyclopentanone derivatives in regard to the manner in which their α-hydroxymethylene derivatives react with hydroxylamine hydrochloride in the presence of acetic acid. The six-membered ring derivatives behaved normally giving rise to isoxazoles which could be isomerized readily to α-cyano ketones. In sharp contrast the hydroxymethylenecyclopentanone derivatives which were studied did not form isoxazoles, but condensed to produce derivatives of bis-(1-keto-2-cyclopentylidenemethyl)-hydroxylamine. This difference in behavior, which can be rationalized on theoretical grounds, suggests a plan for distinguishing between five- and six-membered ring ketones.

MADISON, WISCONSIN RECEIVED JULY 2, 1945

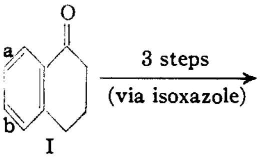
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Studies on Opening the Rings of Cyclic Ketones

BY WILLIAM S. JOHNSON AND WESLEY E. SHELBERG

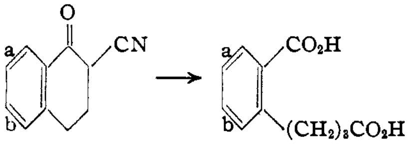
In connection with a study of the reaction of hydroxylamine hydrochloride with the α-hydroxymethylene derivatives of some cyclic ketones,[1] it was shown that the cyclohexanone derivatives behaved like open-chain hydroxymethylene ketones giving rise to isoxazoles which could be isomerized by sodium methoxide to α-cyano ketones (II, IIa, IIb, V). The cyclopentanone derivatives, on the other hand, condensed to produce derivatives of bis-(1-keto-2-cyclopentylidenemethyl)-hydroxylamine (X, XI, VIIIa-d). The present communication deals with the alkaline hydrolysis of these cyano ketones and disubstituted hydroxylamines.

Since it is known that the alkaline hydrolysis of α-cyano derivatives of cyclic ketones effects a ring fission with the formation of dibasic acids,[2] it was expected that the cyano ketones II, IIa, IIb and V would behave similarly. This indeed was realized.



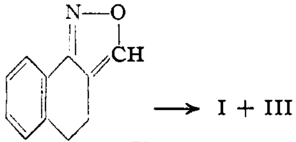
I

Ia (benzene ring fused at side a)
Ib (benzene ring fused at side b)



II
IIa
IIb

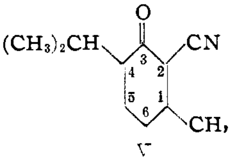
III
IIIa
IIIb



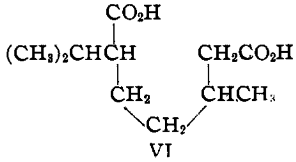
IV

2-Cyanotetralone, II, which has been obtained in 74% yield from tetralone-1, I,[1] was cleaved with boiling 30% potassium hydroxide solution to γ-(2-carboxyphenyl)-butyric acid, III, in 77% yield. 4,5-Dihydronaphth[1,2-*c*]isoxazole, IV, which is formed concomitantly with the [2,1-*d*] isomer (the precursor of II) but is stable to sodium methoxide,[1] was found to undergo alkaline cleavage, also to give the dibasic acid III, but in poor (18%) yield.[3] For the preparation of III, therefore, it was unnecessary to separate the isoxazole IV. The sodium methoxide treatment, moreover, could be eliminated, and direct alkaline hydrolysis of the crude isoxazole mixture thus afforded the dibasic acid III in 80% over-all yield from tetralone-1, I. Hückel and Goth[4] have prepared this acid in about 11% over-all yield from tetralone-1 through the alkaline cleavage of 2-carbethoxytetralone-1.

Alkaline hydrolysis of 3-cyano-4-keto-1,2,3,4-tetrahydrophenanthrene, IIa, which has been obtained in 82% yield from the ketone Ia,[1] afforded γ-(1-carboxy-2-naphtyl)-butyric acid, IIIa, in 57% yield. Similarly γ-(2-carboxy-1-naphthyl)-butyric acid, IIIb, was obtained in 46% yield from 2-cyano-1-keto-1,2,3,4-tetrahydrophenanthrene, IIb. The latter substance has been prepared from 1-keto-1,2,3,4-tetrahydrophenanthrene, Ib, in 76% yield.[1]



V



VI

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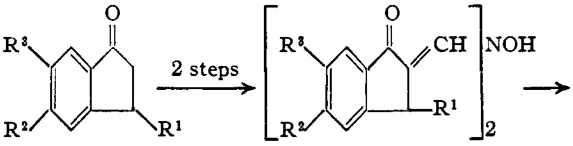
(1) Johnson and Shelberg, THIS JOURNAL, **67**, 1745 (1945).

(2) For an early example *cf.* the hydrolysis of cyanocamphor to homocamphoric acid; see Lapworth, *J. Chem. Soc.*, 1053 (1900).

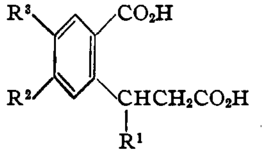
(3) This course of cleavage is consistent with the behavior of the corresponding open-chain isoxazoles on alkaline hydrolysis; see Claisen, *Ber.*, **36**, 3664 (1903).

(4) Hückel and Goth, *Ber.*, **57**, 1285 (1924).

Two stereoisomeric forms of 2-cyanomenthone, V, have been described previously.[1] Alkaline hydrolysis of the α(crystalline) isomer gave in excellent yield a form of 2-isopropyl-5-methylpimelic acid, VI, melting at 66–67°. The same treatment of the β(liquid) isomer of V gave a good yield of oily acidic material from which the 66–67° acid VI was isolated in 20% yield.[5] For the preparation of the acid VI the crude mixture of isomers of cyanomenthone can be hydrolyzed directly. The 66–67° acid thus was obtained in 74% yield.

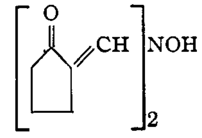


VIIa (R^1 = R^2 = R^3 = H) VIIIa
VIIb (R^1 = R^3 = H, R^2 = OCH_3) VIIIb
VIIc (R^1 = R^2 = H, R^3 = OCH_3) VIIIc
VIId (R^1 = C_6H_5, R^2 = R^3 = H) VIIId

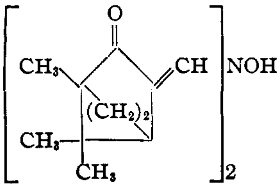


IXa
IXb
IXc
IXd

In a previous communication[6] we described the alkaline hydrolysis of bis-(5-methoxy-1-keto-2-hydrindylidenemethyl)-hydroxylamine, VIIIb, in the presence of hydroxylamine to give β-(2-carboxy-5-methoxyphenyl)-propionic acid, IXb, in 61% yield. The over-all yield for the ring-opening process VIIb → IXb was 54%. In the present work we have investigated the cleavage of three additional hydrindone derivatives. The parent substance VIIa, which has been converted into the di-substituted hydroxylamine VIIIa in 85% yield,[1] thus afforded β-(2-carboxyphenyl)-propionic acid, IXa. The yield for the hydrolytic step VIIIa → IXa was 44%. Similarly the condensation product VIIIc derived from 6-methoxyhydrindone-1 (in 64% yield)[1] was cleaved to β-(2-carboxy-4-methoxyphenyl)-propionic acid, IXc, in 66% yield. A 46% yield of β-(2-carboxyphenyl)-β-phenylpropionic acid, IXd, was similarly realized by the cleavage of the condensation product VIIId derived (in 73% yield) from 3-phenylhydrindone-1.[1] This behavior now appears to be general for hydrindones, and a similar interpretation involving the di-substituted hydroxylamines as intermediates[1] may be applied to the opening of the five-membered ring both of 3′-keto-4,7-dimethoxy-1,2-cyclopentenophenanthrene described by Robinson and Rydon[7] and of 4-methylhydrindone-1 reported by Chakravarti.[8]



X



XI

Behavior similar to that described above for the hydrindone derivatives was exhibited in the cyclopentanone and camphor series. Bis-(1-keto-2-cyclopentylidenemethyl)-hydroxylamine, X,[1] thus was cleaved by alkaline hydrolysis in the presence of hydroxylamine to give adipic acid in 72% yield. The condensation product XI derived from camphor,[1] was similarly cleaved to homocamphoric acid in 54% yield.

The cleavage of the five-membered ring of 5-methoxyhydrindone-1, VIIb, has been investigated also according to the procedure of Bardhan[9] for opening ring D of estrone. This involves condensation of the hydroxymethylene ketone with hydroxylamine in aqueous alkaline medium. In the estrone series this was reported to give a "pasty mass" which on prolonged hydrolysis afforded the desired dibasic acid in unspecified yield. When the method was applied to VIIb, the dibasic acid IXb was obtained in only 34% yield. It is not certain if the di-substituted hydroxylamine type of product is involved as an intermediate in Bardhan's procedure. The only substance which was isolated after the alkali-catalyzed condensation of 2-hydroxymethylene-5-methoxyhydrindone-1 with hydroxylamine proved to be the oxime of 5-methoxyhydrindone-1. This derivative, moreover, was isolated in about 40% yield, and evidently resulted from alkaline cleavage of the hydroxymethylene ketone. It is possibly due to this type of undesirable competitive reaction that Bardhan's method has been found to fail in other instances.[7,10]

When the di-substituted hydroxylamines (A) are submitted to alkaline hydrolysis in the absence of hydroxylamine, the yields of dibasic acids are lower. For example, the yield for the cleavage VIIIb → IXb was 61% in the presence of hydroxylamine,[6] but was only 36% in the absence of this reagent. Some of the steps involved during the latter treatment are shown in the accompanying flow sheet. Since the primary cleavage products, *e. g.*, the cyano ketone B and the

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[5] Even though a mixture of acids was produced, it is, nevertheless, possible that the so-called β-isomer is stereochemically homogeneous having the opposite configuration from the α-isomer at C_4 (and perhaps also at C_3 which, however, loses its asymmetry upon hydrolysis). The formation of the 67° acid would then be explained by a partial inversion (through the active hydrogen atom) of C_4 during the hydrolysis.

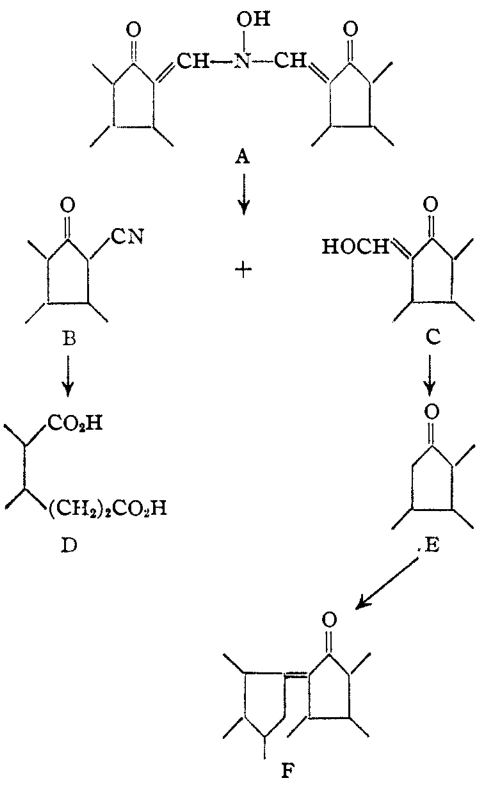
[6] Johnson, Anderson and Shelberg, THIS JOURNAL, **66**, 218 (1944).

[7] Robinson and Rydon, *J. Chem. Soc.*, 1394 (1939).

[8] Chakravarti, *J. Ind. Chem. Soc.*, **20**, 393 (1943).

[9] Bardhan, *J. Chem. Soc.*, 1848 (1936).

[10] Robinson and Walker, *ibid.*, 183 (1938).



hydroxymethylene ketone C, are themselves very susceptible to alkaline cleavage, their isolation was not easy. However, when a solution of the condensation product VIIIb in aqueous alkali was heated for a short period until the deep purple color (due to VIIIb) was discharged, it was possible to isolate a small yield of 2-cyano-5-methoxyhydrindone-1 (B) which was identified by comparison with an authentic specimen previously synthesized *via* 2-bromo-5-methoxyhydrindone-1.[6] Since it is known that this cyano ketone is cleaved by alkali to the dibasic acid IXb in 88% yield,[6] it seems reasonable to postulate this substance as the precursor of the dibasic acid in the cleavage of VIIIb. The alkaline hydrolysis of 2-cyanohydrindone-1 has now been found to give the acid IXa also in good (80%) yield.[11]

The direct isolation of the hydroxymethylene ketone C by mild hydrolysis of the condensation product A was successful only in the camphor series. Mild hydrolysis of the condensation product VIIIa from hydrindone-1, however, afforded an oil which on treatment with aniline gave the anil of (C) 2-hydroxymethylenehydrindone-1.

When the condensation product VIIIb was heated for forty-five minutes with dilute alkali, a 47% yield of 5-methoxyhydrindone-1 was isolated from the neutral fraction. Camphor was also isolated in the experiment (described above) on the hydrolysis of XI to homocamphoric acid. These products evidently resulted from the cleavage of the hydroxymethylene ketone (C → E), a hypothesis which is supported by the observation that pure 2-hydroxymethylene-5-methoxyhydrindone-1 underwent alkaline hydrolysis readily and almost quantitatively to the ketone. A number of the other hydroxymethylene ketones involved in this work have been found to be similarly susceptible to alkaline cleavage. On prolonged alkaline hydrolysis of the di-substituted hydroxylamine VIIIb as in the actual synthesis of the dibasic acid IXb, 2-(5-methoxy-1-hydrindylidene)-5-methoxyhydrindone-1 (F) was isolated instead of the ketone VIIb. It was shown further that this product (F) of aldol condensation could be prepared also from the hydroxymethylene ketone or from 5-methoxyhydrindone-1 by prolonged heating with alkali, thus substantiating the source of this product obtained upon hydrolysis of VIIIb.

It now becomes apparent why the addition of hydroxylamine increases the yield of dibasic acid D obtained on alkaline hydrolysis of the condensation product A. Some of the hydroxymethylene ketone C, which would otherwise be cleaved to the ketone E, reacts with the hydroxylamine to produce additional dibasic acid probably *via* the Bardhan scheme (see above).

Experimental Part[12]

Tetralone-1 Series

γ-(2-Carboxyphenyl)-butyric Acid (III): (*a*) *Hydrolysis of 2-Cyanotetralone-1*.—A solution of 0.92 g. of crude cyano ketone II[1] in 200 cc. of 30% potassium hydroxide was boiled under reflux for sixty hours. Ammonia was evolved slowly. The cooled solution was washed with ether, acidified with hydrochloric acid, and extracted with ether. The dibasic acid was then extracted from the ether solution with dilute potassium hydroxide solution, acidification of which afforded 0.865 g. (77% yield) of colorless γ-(2-carboxyphenyl)-butyric acid, m. p. 138.5–139°. Recrystallization from water gave material melting at 139–140° (reported m. p., 139–140°[4]).

(*b*) *Hydrolysis of 4,5-Dihydronaphth[1,2-c]isoxazole (IV)*.—The pure isoxazole[1] (1.15 g.) was hydrolyzed in 100 cc. of alcohol, with 60 g. of potassium hydroxide in 100 cc. of water. After refluxing for forty-eight hours, ammonia was no longer evolved, and the mixture was extracted with ether. The aqueous portion was worked up as described under (a) above. The yield of almost colorless dibasic acid, m. p. 135–136°, was 0.250 g. (18%). After recrystallization from water the m. p. was 138–139° and was not depressed on admixture with the specimen prepared from cyanotetralone (see (a) above).

The dried ether solution of neutral material from the original hydrolysis mixture afforded on evaporation 0.43 g. of a dark liquid which possessed the characteristic odor of tetralone-1 and formed a semicarbazone melting at 217.4–218.4°. The m. p. was not depressed on admixture with an authentic sample of tetralone-1 semicarbazone.

(*c*) *Direct Preparation from 2-Hydroxymethylenetetralone-1*.—A solution of 1.67 g. of undistilled hydroxymethyl-

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[11] This reaction now completes the ring-opening of hydrindone-1 by the scheme: ketone $\xrightarrow{(99\%;\ \text{ref. } 1)}$ α-bromo ketone $\xrightarrow{(52\%;\ \text{ref. } 1)}$ α-cyano ketone $\xrightarrow{80\%}$ dibasic acid. The over-all yield (41%) is comparable to that (37%) obtained *via* the di-substituted hydroxylamine. Similar results have been realized in the 5-methoxyhydrindone-1 series (ref. 6), the over-all yield *via* the bromo ketone being 61% (compared to 54%). Such a scheme, therefore, promises to be generally useful for opening ring ketones and warrants further study.

[12] All melting points are corrected.

enetetralone[1] in 20 cc. of acetic acid was stirred for two hours at 70-80° with 0.77 g. of hydroxylamine hydrochloride. A solution of 114 g. of potassium hydroxide in 300 cc. of water was then added, and the mixture was boiled under reflux for three days. The colorless dibasic acid was isolated as described under (a) above; yield 1.69 g. (85%); m. p. 136-138°. Since the 2-hydroxymethylenetetralone-1 used in this experiment was prepared from tetralone-1 in 94% yield,[1] the over-all yield of the dibasic acid was 80%. A sample of the acid was recrystallized from water; m. p. 139-140°, not depressed on admixture with the specimens obtained under (a) and (b) above.

Ketotetrahydrophenanthrene Series

γ-(1-Carboxy-2-naphthyl)-butyric Acid (IIIa).—The hydrolysis of 3-cyano-4-keto-1,2,3,4-tetrahydrophenanthrene[1] (2.18 g.) was carried out with 1000 cc. of 30% potassium hydroxide solution. The potassio derivative of the cyano ketone, which formed an insoluble precipitate at room temperature, dissolved on boiling. After refluxing for four days, ammonia was no longer evolved, and the mixture was washed with ether, acidified, and extracted with ether. The acid was isolated from the ether extracts by extraction with 5% sodium bicarbonate solution. Acidification gave 1.46 g. (57% yield) of colorless dibasic acid IIIa, m. p. 190-190.5°. Recrystallization from dilute alcohol gave colorless thin plates, m. p. 190.5-191.5°.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.94; H, 5.49.

γ-(2-Carboxy-1-naphthyl)-butyric Acid (IIIb).—The hydrolysis of 2-cyano-1-keto-1,2,3,4-tetrahydrophenanthrene[1] (1.16 g.) was carried out according to the procedure described above for the isomeric cyano ketone. A total of 400 cc. of 30% potassium hydroxide solution was used, and the mixture was heated for one week. The yield of colorless dibasic acid IIIb was 0.630 g. (46%), m. p. 174-175°. Recrystallization from dilute alcohol gave short colorless needles, m. p. 174.5-176°.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.64; H, 5.55.

Hydrolysis of 3-Hydroxymethylene-4-keto-1,2,3,4-tetrahydrophenanthrene.—The light-orange solution of 400 mg. of the hydroxymethylene ketone[1] in 10 cc. of 2% aqueous sodium hydroxide was boiled for forty-five minutes. The yellow oil which had separated, solidified on cooling; yield 335 mg. (96%) of 4-keto-1,2,3,4-tetrahydrophenanthrene, m. p. 65-66°. Recrystallization from dilute alcohol gave colorless plates, m. p. 67-68.5° (reported, 69°[13]), not depressed on admixture with an authentic specimen, m. p. 65-67.5°.

Hydrolysis of 2-hydroxymethylene-1-keto-1,2,3,4-tetrahydrophenanthrene[1] (400 mg.) was carried out according to the preceding procedure. The yield of crude 1-keto-1,2,3,4-tetrahydrophenanthrene was 325 mg. (93%), m. p. 89-90°, after recrystallization 95-96° (reported, 95-96°[13]).

Menthone Series

2-Isopropyl-5-methylpimelic Acid (VI): (*a*) *Hydrolysis of the Crude Mixture of α- and β-2-Cyanomenthone* (*V*).—A solution of 8.00 g. of undistilled cyanomenthone[1] in 300 cc. of 30% aqueous potassium hydroxide was allowed to reflux for four days. The acid was isolated according to procedure (a) above for the preparation of γ-(2-carboxyphenyl)-butyric acid. It was obtained as an oil which was taken up in ether. Evaporation gave 9.54 g. of oily dibasic acid VI which solidified on standing. Crystallization from 40-60° petroleum ether gave 7.15 g. (74% yield) of colorless crystals, m. p. 66-67.5°. Further recrystallization did not raise the m. p.

Anal. Calcd. for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.42; H, 9.45.

The di-amide was obtained by the action of ammonia on the acid chloride of VI (prepared with phosphorus pentachloride). It crystallized from water in the form of colorless rods, m. p. 211.5-213°.

Anal. Calcd. for $C_{11}H_{22}O_2N_2$: N, 13.07. Found: N, 13.08.

(*b*) *Hydrolysis of α-2-Cyanomenthone.*—A 0.84-g. sample of recrystallized α-2-cyanomenthone, m. p. 73-75°,[1] was hydrolyzed with potassium hydroxide solution according to the procedure (a) described above for the mixture of isomeric cyanomenthones. The crude solid product amounted to 0.94 g. (93% yield), m. p. 57-64°. Recrystallization of a sample from 40-60° petroleum ether gave material melting at 66-68°. The mixed m. p. with the specimen described under (a) above showed no depression.

(*c*) *Hydrolysis of β-2-Cyanomenthone.*—A 1.65-g. sample of β-2-cyanomenthone, b. p. 112-113° (0.7-1 mm.),[1] was hydrolyzed with potassium hydroxide solution according to procedure (a) above. The crude acid amounted to 1.80 g. of oily material which did not solidify even on seeding with the 67° acid. This material was dissolved in about 35 cc. of 40-60° petroleum ether, treated with Norit, seeded with the 67° acid from (a) above, and kept overnight at 5°. There was obtained, after drying on a porous plate, 0.30 g. of colorless crystals, m. p. 61-67° with previous softening. An additional 0.09 g. of material, m. p. about 50-60°, was all that could be obtained crystalline from the mother liquors. Recrystallization of these products afforded material with the m. p. 66-67.5° not depressed on admixture with the specimens described under (a) and (b) above.

Hydrindone-1 Series

Hydrolysis of Bis-(1-keto-2-hydrindylidenemethyl)-hydroxylamine (VIIIa): (*a*) *In the Absence of Hydroxylamine.*—A purple solution of 1.06 g. of unrecrystallized di-substituted hydroxylamine VIIIa[1] in 200 cc. of 2% aqueous potassium hydroxide was boiled under reflux for thirty hours. The solution, which contained some suspended material, was filtered, acidified and extracted with ether. The acid was extracted from the ether solution with 5% potassium hydroxide solution. Acidification gave 0.456 g. (35% yield[14]) of β-(2-carboxyphenyl)-propionic acid (IXa), m. p. 163-164° with softening at 150°. Recrystallization from water gave a colorless product, m. p. 165-167.5° (reported, 166-167°[15]).

(*b*) *In the Presence of Hydroxylamine.*—The above procedure was repeated exactly as described except that 0.20 g. of hydroxylamine hydrochloride was added to the hydrolysis mixture. The yield of crude dibasic acid IXa was 0.57 g. (44%), m. p. mainly at 163-165°, but starting at 155° with softening around 150°.

(*c*) *Under Mild Conditions. Isolation of 2-Hydroxymethylenehydrindone-1 as the Anil.*—A solution of 0.675 g. of the di-substituted hydroxylamine in 175 cc. of 2% aqueous potassium hydroxide was warmed on a hot-plate just until (ten to fifteen minutes) the deep purple color was discharged. The red solution was cooled and washed with ether. Acidification liberated an oil which was isolated by ether extraction. Treatment of a solution of this oil in 6 cc. of hot alcohol with 1.0 cc. of acetic acid followed by 1.0 cc. of aniline gave a bright-yellow precipitate of the anil of 2-hydroxymethylenehydrindone-1; yield 0.220 g.; m. p. about 217°. Recrystallization from alcohol gave yellow needles, m. p. 218.5-219.5° (reported, 217-218°[16]). The mixed m. p. with an authentic specimen of the anil (m. p. 221-222°) prepared directly from 2-hydroxymethylenehydrindone-1 was 219-220°.

Hydrolysis of 2-Cyanohydrindone-1.—A clear red solution of 1.50 g. of the cyano ketone[1] in 250 cc. of 5% aqueous

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[13] Haworth, *J. Chem. Soc.*, 1125 (1932).

[14] This yield is calculated for one molecule of di-substituted hydroxylamine giving two molecules of dibasic acid as required for determining the over-all yield in the ring-opening process. The value should be doubled in order to represent the yield according to the actual mechanism of hydrolysis in the absence of hydroxylamine (*cf.* flow sheet).

[15] Straus and Lemmel, *Ber.*, **46**, 232 (1913).

[16] Ruhemann and Levy, *J. Chem. Soc.*, 2542 (1912).

potassium hydroxide was boiled under reflux for forty-eight hours. The product was worked up by the procedure described above for the hydrolysis of 2-cyanotetralone-1. The yield of β-(2-carboxyphenyl)-propionic acid was 1.49 g. (80%), m. p. 165–167.5°. Recrystallization from water gave colorless needles, m. p. 168–168.5°, not depressed on admixture with the samples of IXa prepared as described above.

6-Methoxyhydrindone-1 Series

β-(2-Carboxy-4-methoxyphenyl)-propionic Acid (IXc).—A 0.700-g. sample of unrecrystallized bis-(6-methoxy-1-keto-2-hydrindylidenemethyl)-hydroxylamine (VIIIc)[1] was hydrolyzed for forty-eight hours with 200 cc. of 5% aqueous potassium hydroxide and 0.265 g. of hydroxylamine hydrochloride. A procedure already described was followed.[17] The yield of dibasic acid was 0.551 g. (66%), m. p. 185–187°. Sublimation under reduced pressure afforded (in 90% recovery) colorless material melting at 192.5–193.5°, which crystallized from water as colorless plates, m. p. 194–195.5° (introduced in bath at 180°).

Anal. Calcd. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40. Found: C, 58.83; H, 5.38.

Hydrolysis of 2-Hydroxymethylene-6-methoxyhydrindone.—A solution of 0.300 g. of the hydroxymethylene ketone[1] in 7 cc. of 2% aqueous potassium hydroxide was boiled for forty-five minutes. The crude 6-methoxyhydrindone-1 which precipitated amounted to 0.228 g., m. p. 90–95°. Recrystallization from alcohol gave needles, m. p. 107–108°, not depressed on admixture with an authentic specimen of the same melting point.[18]

3-Phenylhydrindone-1 Series

β-(2-Carboxyphenyl)-β-phenylpropionic Acid (IXd).—A 1.76-g. sample of unrecrystallized bis-(1-keto-3-phenyl-2-hydrindylidenemethyl)-hydroxylamine (VIIId),[1] was hydrolyzed for three days with 200 cc. of 15% aqueous potassium hydroxide, 20 cc. of pyridine (to aid solution of the sparingly soluble di-substituted hydroxylamine), and 1.0 g. of hydroxylamine hydrochloride. The pyridine was allowed to steam distill out of the mixture after one day of refluxing. On working up the mixture according to a procedure already described[17] 0.923 g. (46% yield) of crude dibasic acid, m. p. 130–132°, was obtained. Crystallization from benzene (Norit) gave colorless material melting at 135–138°. On recrystallization the m. p. rose suddenly to 155–157° with previous softening (polymorphism ?), and was not altered by further recrystallization.

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.24; H, 5.33.

Hydrolysis of 2-hydroxymethylene-3-phenylhydrindone-1[1] (0.50 g.) with 15 cc. of 2% potassium hydroxide solution for thirty minutes (refluxing) gave 0.425 g. (96%) of crude 3-phenylhydrindone-1, m. p. 71–73°. Recrystallization from alcohol gave material melting at 74–75° (reported m. p., 78°[19]).

Cyclopentanone and Camphor Series

Hydrolysis of Bis-(1-keto-2-cyclopentylidenemethyl)-hydroxylamine (X).—A purple-red solution of 1.50 g. of the di-substituted hydroxylamine[1] and 0.50 g. of hydroxylamine hydrochloride in 200 cc. of 20% aqueous potassium hydroxide was allowed to reflux for forty-eight hours. Soon after heating was started the color of the solution faded to a pale yellow. After the hydrolysis the solution was washed with ether, acidified with hydrochloric acid, and evaporated to dryness on the steam-bath. After drying for two hours at 100° the residue was extracted with hot ethanol which on evaporation yielded 1.42 g. (72%) of crude adipic acid, m. p. 143–147° with previous softening. Sublimation under reduced pressure gave 1.14 g. (58% yield) of colorless material, m. p. 150–152°, not depressed on admixture with an authentic specimen having the same m. p.

Hydrolysis of Bis-(2-keto-3-camphylidenemethyl)-hydroxylamine (XI): (*a*) *In the Presence of Hydroxylamine. Formation of Homocamphoric Acid.*—The orange solution of 1.03 g. of the unrecrystallized di-substituted hydroxylamine derived from *d*-camphor[1] and 0.40 g. of hydroxylamine hydrochloride in 200 cc. of 30% aqueous potassium hydroxide was boiled under reflux for two days. As the hydrolysis progressed, *d*-camphor collected in the condenser. A sample was identified by m. p. (176–177°) and mixed m. p.

The acidic material which was isolated according to a previously described procedure[17] amounted to 0.673 g. (54% yield) of colorless homocamphoric acid, m. p. 234–236.5° (reported, 234°[2]). Recrystallization from dilute alcohol raised the m. p. to 235.5–238.5°.

(*b*) *Under Mild Conditions. Isolation of Hydroxymethylenecamphor.*—A solution of 1.00 g. of the di-substituted hydroxylamine derived from *d,l*-camphor[1] in 100 cc. of 2% aqueous potassium hydroxide was boiled for thirty minutes. On acidification with hydrochloric acid followed by steam distillation, a small amount (0.05 g.) of colorless hydroxymethylenecamphor was obtained. It gave the characteristic purple color with ferric chloride and melted at 79–81° (reported m. p., 80–81°[20]).

Hydrolysis of Bis-(2-keto-3-camphylidenemethyl) Amine.—This experiment shows that the di-substituted amine is not an intermediate in the hydrolysis of the (easily reduced[1]) di-substituted hydroxylamine.

A mixture of 1.00 g. of recrystallized di-substituted amine derived from *d,l*-camphor,[1] 200 cc. of 30% potassium hydroxide solution and 150 cc. of alcohol was boiled under reflux for fifty-six hours. Solution was gradually effected, and ammonia was evolved. The acidic material which was obtained according to the usual procedure[17] amounted to 0.47 g. of oil which solidified on standing. The m. p. (76–80°) and the ferric chloride test (deep-purple) showed that this was without much doubt hydroxymethylenecamphor. No homocamphoric acid was obtained.

5-Methoxyhydrindone-1 Series

β-(2-Carboxy-5-methoxyphenyl)-propionic Acid (IXb) by Bardhan's[9] Procedure.—To a solution of 0.50 g. of 2-hydroxymethylene-5-methoxyhydrindone-1[6] and 0.23 g. of sodium hydroxide in 1.3 cc. of water was added 0.23 g. of hydroxylamine hydrochloride dissolved in the minimum amount of water. The solution was boiled for five minutes. A solution of 3.0 g. of potassium hydroxide in 9.0 cc. of water was then added, and the mixture was allowed to reflux for forty-eight hours during which ammonia was gradually evolved. The acid IXb was isolated according to the usual procedure[17]; yield 0.200 g. (34%), m. p. 191–196°. Sublimation under reduced pressure followed by recrystallization from water gave colorless material, m. p. 203–204°, not depressed on mixing with an authentic specimen (m. p. 203.5–204°).[6]

The first part of the above experiment was repeated. After the five-minute refluxing period the solution was cooled and crystals separated; weight 0.188 g. (40% yield), m. p. about 140–145°. Crystallization from dilute methanol followed by sublimation gave colorless needles of the oxime of 5-methoxyhydrindone-1, m. p. 155–157° (reported, 151°[21]). The mixed m. p. with a sample (m. p. 155–157°) prepared directly from 5-methoxyhydrindone-1 was not depressed.

Anal. Calcd. for $C_{10}H_{11}O_2N$: C, 67.77; H, 6.27; N, 7.91. Found: C, 67.97; H, 6.38; N, 8.00.

Hydrolysis of Bis-(1-keto-5-methoxy-2-hydrindylidenemethyl)-hydroxylamine (VIIIb). (*a*) *In the Absence of Hydroxylamine.*[22] *Isolation of 2-(5-Methoxy-1-hydrindyli-*

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[17] *Cf.* the preparation of β-(2-carboxy-5-methoxyphenyl)-propionic acid from VIIIb; ref. 6.

[18] Johnson and Shelberg, THIS JOURNAL, **67**, 1751 (1945).

[19] Pfeiffer and Waal, *Ann.*, **520**, 185 (1935).

[20] Pope and Read, *J. Chem. Soc.*, 444 (1913).

[21] Ingold and Piggott, *ibid.*, 1469 (1923).

[22] *Cf.* ref. 6 for hydrolysis in the presence of hydroxylamine: yield of IXb, 61%.

dene)-5-methoxyhydrindone-1.—A solution of 1.00 g. of the di-substituted hydroxylamine in 200 cc. of 2% aqueous potassium hydroxide was allowed to reflux for forty-eight hours. The insoluble material was separated and crystallized from alcohol; yield 23 mg.; m. p. 185–186.4°. The mixed m. p. with authentic 2-(5-methoxy-1-hydrindylidene)-5-methoxyhydrindone (m. p. 185.5–186.5°) described below showed no depression.

Anal. Calcd. for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.22; H, 6.13.

The dibasic acid was isolated from the alkaline solution according to the usual procedure[17]; crude yield 0.432 g. (36%[14]); m. p. 184–192° with previous softening. Crystallization from water gave material melting at 200–202°.

(*b*) *Under Mild Conditions. Isolation of 2-Cyano-5-methoxyhydrindone-1 and of 5-Methoxyhydrindone-1.*—A solution of 2.00 g. of the di-substituted hydroxylamine in 300 cc. of water containing 2.0 g. of potassium hydroxide and 6 cc. of alcohol was boiled for forty-five minutes by the end of which time the deep-purple color had changed to red. The cooled solution was washed with ether, acidified, and extracted with ether. The ether solution was washed thoroughly with 1% sodium bicarbonate solution, and then extracted with 5% potassium hydroxide solution which removed the cyano ketone. Acidification gave a brown suspension which was extracted with ether, dried, and purified by sublimation at 130–170° (0.1–0.5 mm.). Trituration of the sublimate with ether gave 0.065 g. of 2-cyano-5-methoxyhydrindone, m. p. 87–89°. Recrystallization from alcohol gave an almost colorless product, m. p. 94.5–95.5°, not depressed on admixture with authentic material, m. p. 96–96.5°.[6]

In another experiment 0.50 g. of di-substituted hydroxylamine was hydrolyzed for forty-five minutes with 160 cc. of 3% potassium hydroxide solution. The solution was cooled, filtered and extracted with ether. Evaporation of the dried (over anhydrous sodium sulfate) ether solution gave 0.10 g. (47% yield) of 5-methoxyhydrindone, m. p. 102–104°. After sublimation the m. p. was 108–109° and was not depressed on admixture with an authentic specimen.[6]

2-(5-Methoxy-1-hydrindylidene)-5-methoxyhydrindone-1. (*a*) *From 5-Methoxyhydrindone-1.*—5-Methoxyhydrindone-1[6] (1.0 g.) was boiled under reflux with 450 cc. of 10% potassium hydroxide solution for twenty-four hours. The golden suspension was separated and crystallized from methanol; yield 0.340 g. (36%); golden crystals, m. p. 185.5–186.5°. Further recrystallization did not change the melting point.

Anal. Calcd. for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.35, 78.44; H, 6.12, 6.14.

(*b*) *From 2-Hydroxymethylene-5-methoxyhydrindone-1.*—A solution of 0.199 g. of the hydroxymethylene ketone[6] in 70 cc. of 2% aqueous sodium hydroxide was treated according to the preceding procedure. The yield of recrystallized product was 0.024 g. (15%), m. p. 185.5–186.5°.

Hydrolysis of 2-hydroxymethylene-5-methoxyhydrindone-1[6] (282 mg.) in 7 cc. of 2% sodium hydroxide solution was carried out by refluxing for two hours. 5-Methoxyhydrindone-1 was obtained from the cooled mixture; yield 224 mg. (93%); m. p. 105–107°. Recrystallization from alcohol gave colorless needles, m. p. 109–110°, not depressed on admixture with an authentic specimen of the same m. p.[6]

Summary

The alkaline hydrolysis of some 2-cyanocyclohexanone derivatives and of some bis-(1-keto-2-cyclopentylidenemethyl)-hydroxylamine derivatives has been studied. Both of these types, which are readily available from the six- and five-membered ring ketones, respectively, are cleaved to dibasic acids. The over-all effect, therefore, is the opening of the ring of a cyclic ketone to produce a dibasic acid having one more carbon atom.

The mechanism of, and the effect of hydroxylamine on, the alkaline cleavage of the di-substituted hydroxylamines have been studied.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

The Catalytic Glycosylation of Benzene with Sugar Acetates

BY CHARLES D. HURD AND WILLIAM A. BONNER[1]

The reaction between aromatic hydrocarbons and tetraacetylglucosyl chloride in the presence of large quantities of anhydrous aluminum chloride was described in an earlier communication.[2] From this reaction were isolated two unique carbohydrate products, each representing an entirely new class of carbohydrate derivative. Either product could be made predominant by varying the quantity of catalyst employed. Thus 1,1-diphenyl-1-desoxyglucitol pentaacetate was obtained as the sole product when the theoretical eight equivalents of catalyst were utilized, whereas tetraacetylglucopyranosylbenzene in the presence of about 20% of the diphenyl derivative could be isolated when only five equivalents of catalyst were present.

Previous studies have indicated that aluminum chloride, either alone[3] or in the presence of phosphorus pentachloride,[4] chlorinates the acylal function[5] of fully acetylated aldoses to yield the acetylated glycosyl chlorides. In view of this, it seemed likely that the glycosylation reaction might be accomplished by starting with the fully acetylated sugar rather than the chloride. Such a scheme assumes that the glycose acetate would undergo chlorination first at the acylal function, and that the intermediate chloride would then react with the aromatic hydrocarbon in the usual way, as illustrated below.

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[1] Corn Products Refining Company Fellow, 1941–1944.

[2] Hurd and Bonner, THIS JOURNAL, **67**, 1664 (1945).

[3] Kunz and Hudson, *ibid.*, **48**, 1978, 2435 (1926); Hudson, *ibid.*, **48**, 2002 (1926).

[4] Von Arlt, *Monatsh.*, **22**, 144 (1901); Skraup and Kremann, *ibid.*, **22**, 375 (1901); Hudson and Johnson, THIS JOURNAL, **38**, 1223 (1916); Brauns, *ibid.*, **44**, 401 (1922); Richtmyer and Hudson, *ibid.*, **57**, 1716 (1935).

[5] Hurd and Cantor, *ibid.*, **60**, 2678 (1938); Hurd and Green, *ibid.*, **63**, 2201 (1941).