isolated after acidification of the alkaline hydrolysate. The reactions of gliotoxin with potassium sulfide, potassium thioglycollate, and alkaline plumbite solution indicate the presence of a disulfide linkage.

Reduction of gliotoxin by amalgamated aluminum under mild conditions eliminated the sulfur atoms quantitatively as hydrogen sulfide and gave a colorless, crystalline, optically-active compound of the formula $C_{13}H_{16}N_2O_4$, which has been designated as desthiogliotoxin. The action of hot alcoholic alkali on desthiogliotoxin yields as the principal product the same C_{13} amino acid previously obtained from the hydriodic reduction product of gliotoxin, namely, N-2-indolecarbonyl-N-methylalanine. There is formed concurrently a small quantity of a crystalline compound corresponding to the empirical formula $C_{13}H_{12}N_2O_2$.

On the basis of the available evidence, provisional structural formulas for desthiogliotoxin and for gliotoxin have been proposed.

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

A Plan for Distinguishing between Some Five- and Six-membered Ring Ketones

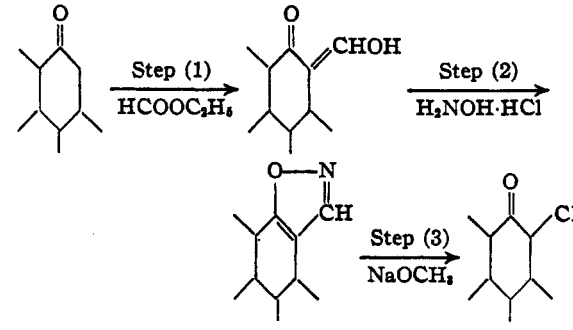
BY WILLIAM S. JOHNSON AND WESLEY E. SHELBERG

The importance of a method for the accurate discrimination between five- and six-membered ring ketones is strikingly illustrated by the classical problem of the structure of the sterols, in which the application of the Blanc rule[1] served as the means of determining ring size.[2] The Blanc rule, however, is not general,[3] and erroneous conclusions resulting from its failure led to an incorrect structure of the sterol nucleus. The position of prominence which this rule, nevertheless, has since occupied in the study of structure apparently is due to the lack of other methods.

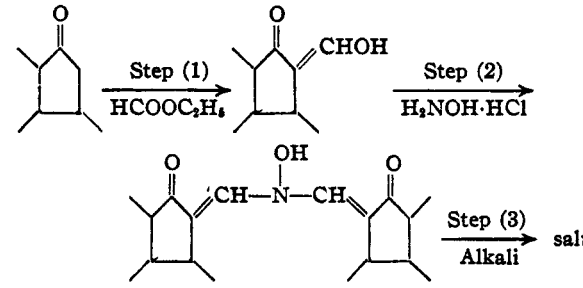
During the course of a study of the reaction of α-hydroxymethylene ketones with hydroxylamine we have observed a striking difference in behavior between cyclohexanone and cyclopentanone derivatives. This difference suggested a possible plan for distinguishing between five- and six-membered ring ketones which are capable of conversion to the hydroxymethylene derivatives, *e. g.*, ketones containing at least one reactive (α) methylene group. The ketones involved in the proof of structure of the steroid nucleus fall into this class and should afford interesting examples for testing the generality of the plan.

The scheme consists of: (1) condensation of the ketone with ethyl formate, (2) treatment of the resulting hydroxymethylene ketone with hydroxylamine hydrochloride in acetic acid, and (3) examination of the condensation products, particularly as to their behavior toward alkali. In the cases which have been studied it has been found that the cyclohexanone derivatives reacted according to the conventional scheme A, giving rise to isoxazoles at step (2). These substances were non-acidic, but were readily cleaved with sodium methoxide (step 3) to the acidic β-ketonitriles. In sharp contrast the cyclopentanone derivatives did not give isoxazoles, but condensed to form di-substituted hydroxylamine derivatives (see scheme B). These substances, unlike the isoxazoles, were colored and weakly acidic. They were conclusively distinguished from the isoxazoles by analysis for nitrogen.

SCHEME A FOR SIX-MEMBERED RINGS



SCHEME B FOR FIVE-MEMBERED RINGS



Cyclohexanone Derivatives

The formation of isoxazoles from open chain α-hydroxymethylene ketones and hydroxylamine is well-known.[4] That the generality of this reaction extends to cyclohexanone derivatives is indicated by previous work. For example, v. Auwers, Bahr and Frese[5] have thoroughly investigated the

(1) Blanc, *Compt. rend.*, **144**, 1356 (1907).

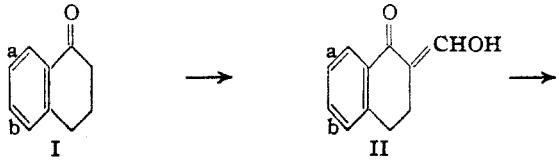
(2) For a review see Fieser, "The Chemistry of Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1937.

(3) *Cf.* the failure of the Blanc rule in the case of ring C; Wieland, *Z. physiol. Chem.*, **108**, 306 (1920).

(4) For early work see Claisen (a) *Ber.*, **36**, 3664 (1903), and (b) *ibid.*, **42**, 59 (1909).

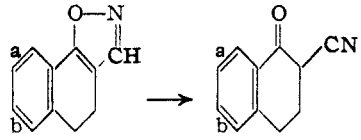
(5) v. Auwers, Bahr and Frese, *Ann.*, **441**, 54 (1925).

formation of isoxazoles from the hydroxymethylene derivatives of cyclohexanone and *o*-methylcyclohexanone. In the present work tetralone-1, I, 4-keto-1,2,3,4-tetrahydrophenanthrene, Ia, and 1-keto-1,2,3,4-tetrahydrophenanthrene, Ib, have been studied. The hydroxymethylene derivatives, II, IIa and IIb were all obtained in over 90% yields by the procedure for the condensation of 5-methoxyhydrindone-1 with ethyl formate described in a previous communication.[6]



I II

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



III IV
IIIa IVa
IIIb IVb

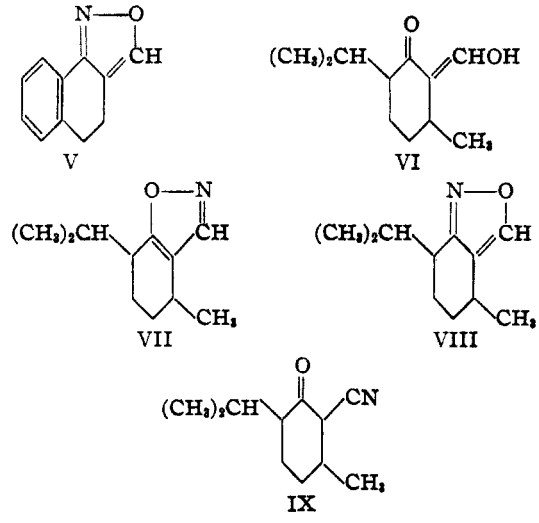
From the phenanthrene derivatives the crystalline isoxazoles IIIa and IIIb each were obtained in 95% yield. These were cleaved to the cyano ketones IVa and IVb in 90 and 85% yields, respectively. The isoxazole III has been reported by v. Auwers and Nold[7] to be the sole product obtained by the condensation of 2-hydroxymethylenetetralone-1, II, with hydroxylamine hydrochloride. No yield was reported. In the present investigation the crude alkali-insoluble fraction from the condensation amounted to 97% of the theoretical and consisted of a mixture of III and the isomer V. The latter type of isoxazole has been encountered previously in the cyclohexanone series.[5] It is stable in the presence of sodium methoxide, and treatment of the mixture with this reagent consequently effects a ready separation by conversion of the unstable isoxazole into the alkali-soluble nitrile.[4a,5] In this way we obtained a 9% yield of the isoxazole V, and a 79% yield of 2-cyanotetralone-1, IV. None of the isoxazoles of the type stable to sodium methoxide was encountered in the phenanthrene series.

In order to test an optically active natural product the behavior of *l*-menthone was examined. The hydroxymethylene derivative VI which was obtained in 85% yield condensed with hydroxylamine hydrochloride to give 84–90% yields of isoxazole fraction.[8] Although the boiling point was fairly constant this proved to be a mixture of VII and VIII as shown by the sodium methoxide

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

(7) v. Auwers and Nold, *J. prakt. Chem.* [2] **150**, 57 (1938).

(8) *Cf.* Swiss Patent 118,177 (1926), *Chem. Zentr.*, **98**, I, 2688 (1927).



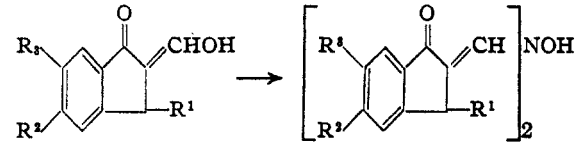
V VI

VII VIII

IX

treatment. The stable isoxazole VIII remained unchanged (yield 21%) and VII was converted to the cyano ketone IX[8] in 51% yield. The latter was not homogeneous, and was separated by fractional distillation into a solid and a liquid diastereoisomer, an operation which, however, is obviously unnecessary in testing the size of the ring.

Cyclopentanone Derivatives

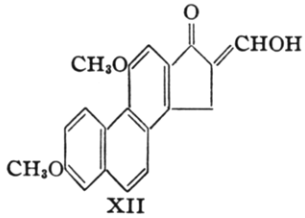


X	($R^1 = R^2 = R^3 = H$)	XI
Xa	($R^1 = R^2 = H$, $R^3 = OCH_3$)	XIa
Xb	($R^1 = R^3 = H$, $R^2 = OCH_3$)	XIb
Xc	($R^1 = C_6H_5$, $R^2 = R^3 = H$)	XIc

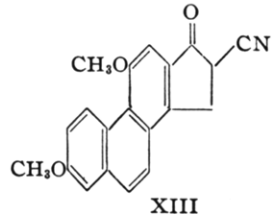
In a previous communication[6] the condensation of 2-hydroxymethylene-5-methoxyhydrindone-1, Xa, with hydroxylamine was described. The product which was formed in 90% yield was a sparingly soluble orange substance to which was assigned the structure XIa. The reaction now appears to be general for hydrindones. Thus in the present work the hydroxymethylene derivatives, X, Xb and Xc, of hydrindone-1, 6-methoxyhydrindone-1 and 3-phenylhydrindone-1 each were found to give analogous condensation products, XI, XIb and XIc, in good yields. Like XIa these were orange compounds which reacted with dilute alkali to give intensely purple-colored salts. The presence of a replaceable hydrogen was shown also by the formation of a monoacetyl derivative of XI. The procedure which was used for the above condensations was essentially the same as that employed by Robinson and Rydon[9] for the condensation of the hydroxymethylene ketone XII with hydroxylamine. The product which they presumed to be the nitrile XIII "gave a brilliant violet colour with alcoholic alkali; it could not

(9) Robinson and Rydon, *J. Chem. Soc.*, 1394 (1939).

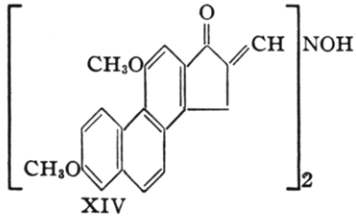
be purified for analysis." The nitriles XV[6] and XVa have been prepared by the action of sodium cyanide on the 2-bromohydrindones and they differ from the condensation products XIa and XI in being relatively low-melting, soluble, colorless compounds which are practically colorless in alkaline solution. It therefore seems likely that



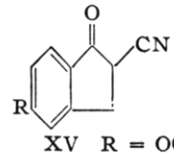
XII



XIII



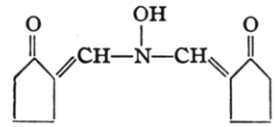
XIV



XV R = OCH_3
XVa R = H

the material of Robinson and Rydon was largely the condensation product XIV. The behavior of their substance on alkaline hydrolysis is consistent with this structure.[10] It likewise seems probable that the condensation product (from 2-hydroxymethylene-4-methylhydrindone-1) described by Chakravarti[11] as the nitrile was also a di-substituted hydroxylamine derivative.

Formation of intermolecular condensation products of type XI is not limited to fused ring systems as was shown by a study of the parent five-membered ring ketone. Cyclopentanone was found to respond typically to the test reactions to produce the red bis-(ketocyclopentylidenemethyl)-hydroxylamine, XVI. Although the yield of crystalline material at the condensation step (2) was low (36%), all but a trace of the total product was alkali-soluble indicating that little, if any, isoxazole was formed.



XVI

The reaction of a hydroxymethylene ketone with hydroxylamine most probably involves the initial formation of an oxime, A, (*cf.* the case of camphor which is considered below). The fate of this intermediate would seem to depend upon at least two competing reactions: (1) intramolecular dehydration to give the isoxazole (B), and (2) condensation with unreacted hydroxymethylene ketone to form (C). The former appears to take

(10) *Cf.* the alkaline hydrolysis of XIa, ref. 6.
(11) Chakravarti, *J. Ind. Chem. Soc.*, **20**, 393 (1943).

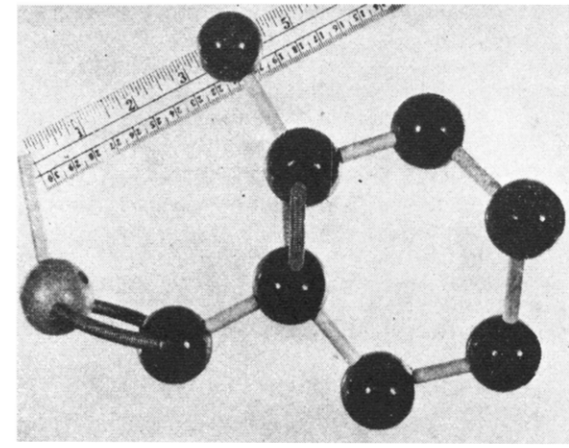


Fig. 1.

precedence when the cyclization is unhindered as in the case of open-chain and six-membered ring ($n = 2$) ketones. With five-membered ring derivatives ($n = 1$), however, the intermolecular reaction (2) seems to predominate to produce (C). An examination of simple molecular models of the isoxazoles in which the nitrogen to oxygen bond is unformed provides a rationalization of the facts. With the model of the cyclohexanone derivative (Fig. 1) the heterocyclic ring can be closed with little resulting strain. In the case of the cyclopentanone system (Fig. 2), however,

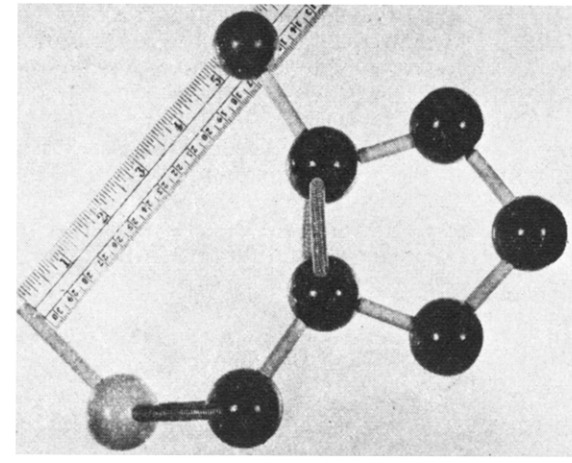
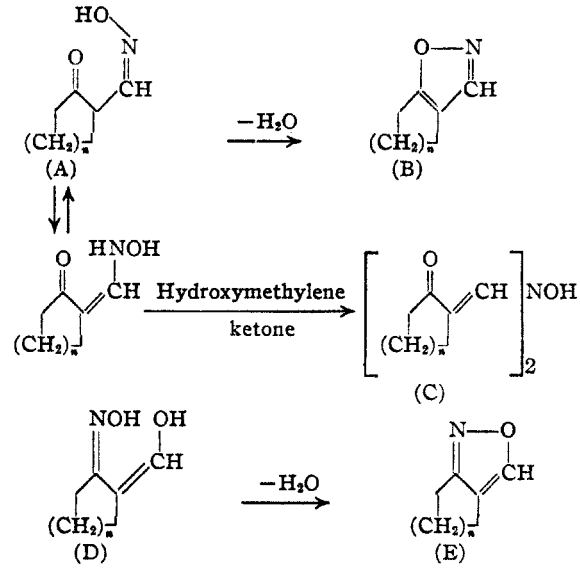


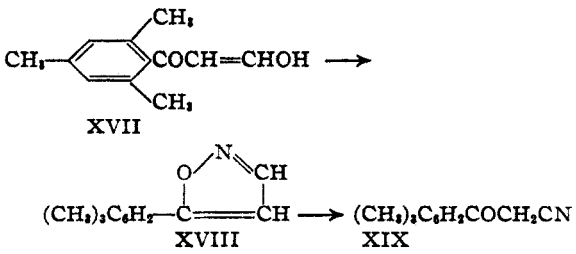
Fig. 2.

the ring cannot be closed without introducing considerable strain owing to the spread in the extracyclic bond angles (at the ethylenic linkage) brought about by the reduction in the size of the homocyclic ring. This observation suggests that a structure of the type (B) ($n = 1$) would be less readily formed than one like B ($n = 2$). Indeed to our knowledge a compound having a structure of the former type has never been prepared. If

these theoretical considerations are correct it is reasonable to expect, moreover, that strainless cyclic ketones of more than six members ($n > 2$) would give rise to isoxazoles (B), while cyclic ketones of less than five members would behave like the cyclopentanone derivatives giving the intermolecular condensation product (C).



Theoretically it is possible to have a situation in which the carbonyl group of an oxime (type A), even though derived from an open-chain or six-membered ring ketone, would be so unreactive that the expected intramolecular reaction (1) would give way to reaction (2) and a condensation product type C would be formed. This would lead to the wrong conclusion regarding ring size. In order to test for such limitations hydroxymethyleneacetomesitylene (XVII) was examined. In spite of the highly hindered nature of the ketone group, an isoxazole was obtained in 94% yield. The structure XVIII was established by conversion to cyanoacetomesitylene XIX in 90% yield.



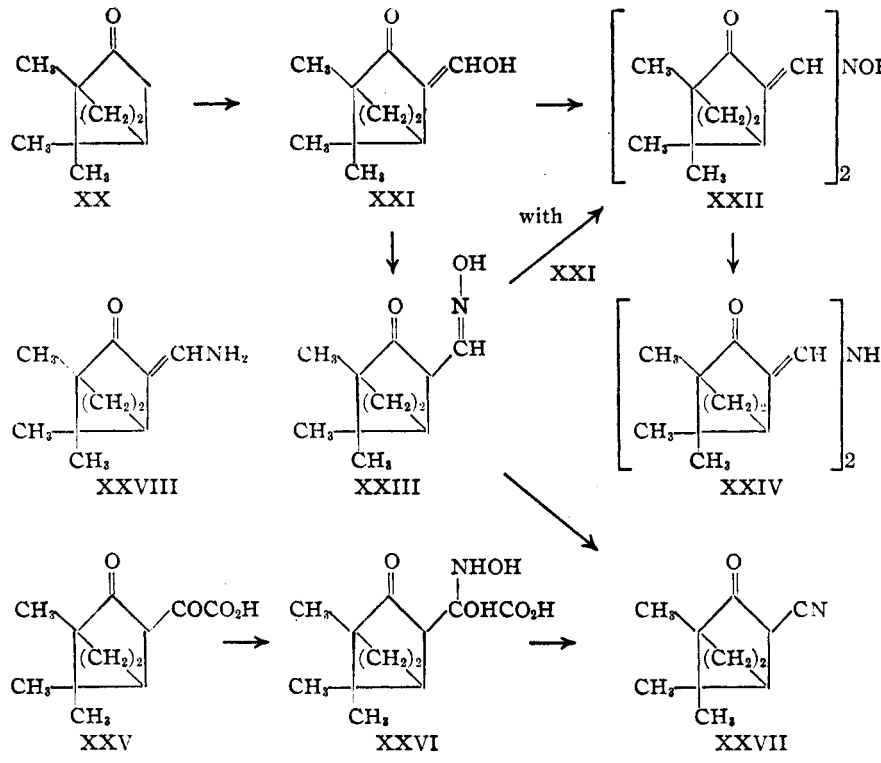
Another competing reaction which is operating at least in the case of the cyclohexane derivatives, is the formation of isoxazoles of the type (E) stable to sodium methoxide. These must arise from the initial reaction of the hydroxylamine with the ketone carbonyl group presumably involving the intermediate oxime (D). Even though no cyclopentane type isoxazole E ($n = 1$) yet has been isolated, models indicate that such a structure would be practically strainless. It seems likely that a cyclopentanone derivative having a sufficiently hindered hydroxymethylene group could give this type of isoxazole. Evidently this situation is not realized to any appreciable extent with 2-hydroxymethylene-3-phenylhydrindone-1, Xc, which in spite of the phenyl substituent adjacent to the hydroxymethylene group gave the condensation product XIc in good yield. Apparently no conclusions could be reached regarding ring size if an isoxazole of type E should be the only product isolated, although its isolation along with either B or C would not invalidate the proposed scheme.

Of particular interest is the case of camphor which is a cyclopentanone as well as a cyclohexanone derivative (formula XX). According to the theoretical considerations discussed above it was expected that the influence of the five-membered ring would inhibit isoxazole formation and that a condensation product XXII would be formed. It is reported[12] that an isoxazole can be prepared from the addition product XXVI of camphorglyoxalic acid XXV and hydroxylamine. The structure assigned to the product is indeed an isoxazole of the strained type B ($n = 1$), but on repeating the work of Tingle, we have found that his so-called "camphylisoxazole," reported to melt at 124–125°, is identical with the previously described[13] isomeric cyanocamphor XXVII melting at 127–128°. Bishop, Claisen and Sinclair[13] have reported that the condensation of hydroxymethylene camphor XXI with hydroxylamine hydrochloride in refluxing acetic acid gave cyanocamphor (XXVII). We also have obtained XXVII in poor yield using these conditions which differ from those used for the formation of the disubstituted hydroxylamine derivatives only in the reaction temperature. This is a critical factor inasmuch as the expected *bis-(2-keto-3-camphylidenemethyl)-hydroxylamine (XXII) was obtained in over 60% yields* when the reaction was carried out at room temperature. It was a sparingly soluble yellow substance which dissolved in alkali giving a yellow solution. It could be formed also by the interaction of the oxime XXIII with XXI. This affords evidence in support of the assumption that the oxime serves as the intermediate in the other condensations described in this paper. Some evidence, in addition to analyses, has been produced in favor of the structure XXII for the yellow condensation product. Reduction with zinc and acetic acid gave the colorless amine derivative XXIV identical with the product obtained by the condensation of hydroxymethylenecamphor (XXI) with 2-keto-3-camphylidenemethyl amine XXVIII.[14] The substance XXIV was obtained also when the condensation product XXII was sublimed under reduced pressure, a treatment

(12) Tingle, *Am. Chem. J.*, **19**, 393 (1897).
(13) Bishop, Claisen and Sinclair, *Ann.*, **281**, 314 (1894).
(14) Singh and Bhaduri, *J. Ind. Chem. Soc.*, **9**, 109 (1932).

which apparently promoted disproportionation; and by the reaction of hydroxymethylenecamphor with ammonium chloride in acetic acid.

In agreement with the observations of Bishop, Claisen and Sinclair[13] all efforts to prepare an isoxazole from camphor have failed. When the oxime XXIII was heated in acetic acid containing hydrogen chloride, cyanocamphor XXVII was formed. This suggests that the oxime may be the intermediate in the formation of the nitrile from XXI and hydroxylamine (Claisen's procedure). It was found however, that under similar conditions the condensation product XXII hydrolyzed to give cyanocamphor also in comparable yields.



Although as yet we have found no exceptions, proof of the generality of the reaction schemes described in this paper must await further application It should be pointed out that the cyclopentanone derivatives which have been studied gave rise to condensation products which were insoluble in the reaction medium and were, therefore, easily isolated. Preliminary experiments with some 2-alkylcyclopentanones indicate, however, that in some instances the reaction products may be soluble and very difficult to purify. It is recommended that when used as a diagnostic test, the reaction between a hydroxymethylene ketone and hydroxylamine be conducted at room temperature.

Experimental Part[15,16,17,18]

Tetralone-1 Series

2-Hydroxymethylenetetralone-1 (II).—v. Auwers and Wiegand[19] have prepared this compound in 70-75% yield by the condensation of tetralone-1 with ethyl formate in the presence of metallic sodium. By the modified procedure[16] better yields have now been realized. From 12.22 g. of tetralone-1 and 12.45 g. of ethyl formate there was obtained 13.75 g. (94% yield) of crude alkali-soluble condensation product. Sodium methoxide from 3.86 g. of sodium and a total of 200 cc. of benzene were used in the reaction. The crude hydroxymethylenetetralone was satisfactory for the next step, and gave better over-all yields, because distillation was attended by some decomposition. Rapid distillation of the crude product gave, usually in about 90% recovery, a light yellow oil, b. p. 176-180° (27-28 mm.). The reported b. p. is 153.5-154° (10 mm.).[19] In agreement with the reported properties,[19] this material gave a red color with ferric chloride and dissolved in aqueous bicarbonate solution.

The Reaction of 2-Hydroxymethylenetetralone-1 with Hydroxylamine.—A solution of 14.3 g. of crude 2-hydroxymethylenetetralone-1 in 100 cc. of glacial acetic acid was stirred for eight hours at 70 to 80° with 11.4 g. of powdered hydroxylamine hydrochloride. The acetic acid was largely removed under reduced pressure (at 40-50°), and the residue was diluted with water and extracted with ether. The ether solution was washed with dilute sodium bicarbonate solution to remove acetic acid and any unreacted hydroxymethylenetetralone, and then with water followed by saturated salt solution. Evaporation of the dried (over anhydrous sodium sulfate) solution afforded 13.6 g. of a reddish oil which was insoluble in dilute sodium hydroxide and which therefore consisted of a mixture of the isomeric isoxazoles III and V as shown by the experiment described directly below.

The above mixture was dissolved in dry ether and treated with about 15 to 20 cc. of a cold concentrated solution of sodium in methanol. After one hour water was added, and the ether layer was separated and washed thoroughly with 5% potassium hydroxide solution. The combined alkaline extracts were acidified, and the liberated cyanotetralone was taken up in ether, treated with Norit, and again extracted with 5% potassium hydroxide solution. Acidification of the chilled alkaline solution with cold hydrochloric acid gave 11.08 g. (79% yield) of tan, crystalline 2-cyanotetralone-1, m. p. 68-70°. Recrystallization from methanol gave golden crystals, m. p. 77-78° (reported,[7] 79°).

(15) All melting points are corrected.

(16) Unless otherwise indicated the condensations between the ketones and ethyl formate (step 1) were carried out according to the procedure which has been previously described in detail for the preparation of 2-hydroxymethylene-5-methoxyhydrindone-1; ref. 6.

(17) The reactions between the hydroxymethylene ketones and hydroxylamine hydrochloride (step 2) were conducted essentially by the procedure already described for the preparation of bis-(5-methoxy-1-keto-2-hydrindylidenemethyl)-hydroxylamine; ref. 6.

(18) We wish to thank Mr. E. Shelberg for performing a number of the micro analyses.

(19) v. Auwers and Wiegand, *J. prakt. Chem.*, [2] **134**, 82 (1932).

The neutral material remaining in ether solution after the sodium methoxide treatment was washed with saturated salt solution and dried over anhydrous sodium sulfate. Evaporation gave 1.31 g. (9% yield) of crude liquid 4,5-dihydronaphth[1,2-*c*]isoxazole, V, which largely distilled at 114–117° (0.3–0.4 mm.) to yield a straw-colored product; $n^{26}D$ 1.5968; d^{26}_4 1.178; M_D (found) 49.52; M_D (calcd.)[20] 48.97. This material gradually darkened on standing, but was unaffected by further treatment with sodium methoxide.

Anal. Calcd. for $C_{11}H_9ON$: N, 8.18. Found: N, 8.24.

The above experiment was repeated except that the reaction was carried out at room temperature for fifteen hours.[17] From 15.0 g. of hydroxymethylenetetralone there was obtained 14.0 g. (95% yield) of crude isoxazole mixture. When 11.95 g. of this material was treated with sodium methoxide there was obtained 9.11 g. (76% yield) of cyanotetralone, m. p. 75–77°, and 1.98 g. (17% yield) of crude isoxazole, V. The higher proportion of stable isoxazole V obtained at the lower temperature suggests that the conditions of reaction may be critical factors. This may explain why v. Auwers and Nold[7] did not encounter any of the stable isoxazole, since they used alcohol as a solvent for the reaction. It is possible, on the other hand, that this isoxazole was removed by the mercuric chloride purification step.

4-Keto-1,2,3,4-tetrahydrophenanthrene Series

3-Hydroxymethylene-4-keto-1,2,3,4-tetrahydrophenanthrene (IIa) has been prepared recently by Meyer and Reichstein[21] using potassium in *t*-amyl alcohol as the condensing agent. They obtained the product in 79% yield as an oil which crystallized after standing for some time. The recrystallized material melted at 41°. In the present work from 5.40 g. of 4-keto-1,2,3,4-tetrahydrophenanthrene, 4.12 g. of ethyl formate, sodium methoxide (from 1.28 g. of sodium) and a total of 150 cc. of benzene there was obtained[16] 5.93 g. (a 96% yield) of crystalline hydroxymethylene ketone, m. p. 41–42°, directly on acidification of the alkaline washings. A pure sample was prepared by crystallization from dilute alcohol; thin yellow plates, m. p. 41.5–42.2°. It gave an intense brown color with dilute alcoholic ferric chloride solution.

Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.32; H, 5.40. Found: C, 80.55; H, 5.41.

Carl Djerassi has recently observed that the condensation proceeds in consistently excellent yields with 1-keto-1,2,3,4-tetrahydrophenanthrene (see below) if the reaction mixture is allowed to reflux for one-half hour instead of standing at room temperature for four hours.

4,5-Dihydrophenanthro[3,4-*d*]isoxazole (IIIa).—A solution of 4.97 g. of 3-hydroxymethylene-4-keto-1,2,3,4-tetrahydrophenanthrene in 200 cc. of acetic acid was stirred with 2.30 g. of powdered hydroxylamine hydrochloride for eight hours at 70–80°. The solution was then diluted with water and cooled to 5°, whereupon 4.66 g. (95% yield) of crystalline isoxazole separated, m. p. 94–94.5°. A sample recrystallized from dilute alcohol was obtained as long colorless needles, m. p. 94–95°.

Anal. Calcd. for $C_{15}H_{11}ON$: C, 81.42; H, 5.01; N, 6.33. Found: C, 81.60; H, 5.00; N, 6.29.

3-Cyano-4-keto-1,2,3,4-tetrahydrophenanthrene (IVa).—The isozazole IIIa was cleaved with sodium methoxide according to the procedure described above in the tetralone series except that xylene was used instead of ether as the solvent. Thus from 3.74 g. of isoxazole there was obtained 3.38 g. (90% yield) of alkali-soluble, cream-colored cyano ketone, m. p. 118–120°. Recrystallization from dilute alcohol gave colorless plates and needles, m. p. 122–123°.

Anal. Calcd. for $C_{15}H_{11}ON$: C, 81.42; H, 5.01; N, 6.33. Found: C, 81.48; H, 5.10; N, 6.46.

(20) The value used for the oximino-N was 3.90. See v. Auwers and Ottens, *Ber.*, **57**, 456 (1924).

(21) Meyer and Reichstein, *Pharm. Acta Helv.*, **19**, 128 (1944).

1-Keto-1,2,3,4-tetrahydrophenanthrene Series

2-Hydroxymethylene-1-keto-1,2,3,4-tetrahydrophenanthrene (IIb) has been prepared recently by Meyer and Reichstein[21] in 67% (crude) yield. In the present work practically pure hydroxymethylene ketone has been obtained in 94% yield.[16] Thus from the same weights of materials as were used above with the 4-keto isomer, there was obtained 5.82 g. of pale-yellow crystalline material, m. p. 82–83° (reported,[21] 86°). This m. p. was unaltered by recrystallization from dilute alcohol which gave thin, pale-yellow plates; intense purple-brown color with aqueous ferric chloride.

Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.32; H, 5.40. Found: C, 80.62; H, 5.40.

10,11-Dihydrophenanthro[2,1-*d*]isoxazole (IIIb).—From 3.39 g. of 2-hydroxymethylene-1-keto-1,2,3,4-tetrahydrophenanthrene and 1.55 g. of hydroxylamine hydrochloride stirred with 130 cc. of acetic acid for eight hours at 70–80° there was obtained, on dilution with water and cooling, 3.17 g. (95% yield) of colorless crystals, m. p. 107–108°. Recrystallization from dilute alcohol raised the m. p. to 109.8–110.5°

Anal. Calcd. for $C_{15}H_{11}ON$: C, 81.42; H, 5.01; N, 6.33. Found: C, 81.71; H, 4.90; N, 6.48.

2-Cyano-1-keto-1,2,3,4-tetrahydrophenanthrene (IVb).—The sodium methoxide isomerization of the above isoxazole (0.850 g.) was carried out according to the procedure described above in the tetralone series except that dry benzene (50 cc.) was used as the solvent. The alkali-soluble keto nitrile amounted to 0.721 g. (85% yield), m. p. 125–126°. Recrystallization from dilute alcohol gave colorless plates, m. p. 128–129°.

Anal. Calcd. for $C_{15}H_{11}ON$: C, 81.42; H, 5.01; N, 6.33. Found: C, 81.68; H, 4.96; N, 6.39.

l-Menthone Series

The menthone used in the following experiments was prepared by the oxidation of *l*-menthol.[22]

Hydroxymethylene-*l*-menthone (VI).—Bishop, Claisen and Sinclair[13] have prepared this substance in 45–50% yields by the condensation of *l*-menthone and amyl formate in the presence of sodium. Using sodium amide instead of sodium Rupe and Gubler[23] later obtained somewhat better yields (55–65%). By the modified procedure[16] yields of over 80% now have been consistently realized. For example from 50.0 g. of *l*-menthone, 50.0 g. of ethyl formate and sodium methoxide (from 14.9 g. of sodium) there was obtained 50.0 g. (85% yield) of alkali-soluble, light-yellow hydroxymethylene-*l*-menthone. Distillation gave 48.3 g. (82% yield) of colorless material; b. p. 120–122° (13 mm.), 138–140° (30–31 mm.). The reported b. p. is 121° (12.5 mm.).[13] As this condensation proceeded the mixture became very viscous, and additional benzene (300 cc. total), therefore, was used.

The Reaction of Hydroxymethylene-*l*-menthone with Hydroxylamine.—When the reaction was carried out at 80–90° according to the procedure described above under the tetralone series the mixture of isoxazoles VII and VIII was obtained in 84–90% yields. For example from 25.35 g. of distilled hydroxymethylene-*l*-menthone in 150 cc. of acetic acid, and 19.4 g. of hydroxylamine hydrochloride there was obtained 21.02 g. (84% yield) of crude reddish oily isoxazole fraction. A sample on distillation gave a colorless oil having the constant b. p. 78° (0.5–0.6 mm.).[8]

Anal. Calcd. for $C_{11}H_{17}ON$: C, 73.70; H, 9.56. Found: C, 73.46; H, 9.45.

That this was a mixture of the isomeric isoxazoles VII and VIII follows from the succeeding experiment. The above undistilled product (21.02 g.) in 200 cc. of ether was treated with sodium methoxide according to the procedure described above under the tetralone series. The material

(22) Sandborn, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., p. 340.

(23) Rupe and Gubler, *Helv. Chim. Acta*, **9**, 582 (1926).

which was alkali-insoluble after this treatment amounted to 4.31 g. (17% crude yield) of reddish liquid **7-isopropyl-4-methyl-4,5,6,7-tetrahydrobenz[1,2-*c*]isoxazole (VIII).** Distillation gave a colorless product; yield 3.2 g. (75% recovery); b. p. 76–77° (0.45–0.55 mm.), 85–86° (1.0–1.4 mm.); $n^{26}D$ 1.4848; d^{26}_4 0.997; M_D (found) 51.50; M_D (calcd.)[30] 52.57.

Anal. Calcd. for $C_{11}H_{17}ON$: C, 73.70; H, 9.56. Found: C, 73.66; H, 9.65.

The negative exaltation of the molecular refractivity (−1.07) is in fair agreement with the values reported for some other stable type isoxazoles derived from cyclohexanone derivatives. For example v. Auwers[24] observed the negative exaltation −1.21, for 4,5,6,7-tetrahydrobenz[1,2-*c*]isoxazole and −1.25 for 7-methyl-4,5,6,7-tetrahydrobenz[1,2-*c*]isoxazole.

The alkali-soluble fraction produced by the above sodium methoxide treatment amounted to 15.19 g. (61% yield) of crude reddish liquid 2-cyano-*l*-menthone (IX). That this was a mixture of isomers was shown by distillation through a modified Widmer column: fraction (1), 4.9 g., b. p. 87–96° (0.7–1.0 mm.); fraction (2), 3.5 g., b. p. 96–112° (0.7–1.0 mm.); fraction (3), 3.0 g., b. p. 112–113° (0.7–1.0 mm.).

Fraction (1) solidified in the receiver, m. p. 73–76°. Crystallization from ethanol followed by recrystallization from benzene–petroleum ether (b. p. 40–60°) gave colorless plates, m. p. 78–79.2°. This product may be designated as α-2-cyano-*l*-menthone.

Anal. Calcd. for $C_{11}H_{17}ON$: C, 73.70; H, 9.56. Found: C, 73.61; H, 9.64.

Fraction (2) consisted of a colorless mixture of the solid and liquid isomer (see below).

Fraction (3) apparently was homogeneous and remained as a colorless liquid. It may be called β-2-cyano-*l*-menthone.

Anal. Calcd. for $C_{11}H_{17}ON$: C, 73.70; H, 9.56. Found: C, 74.12; H, 9.54.

As in the tetralone series the reaction of 2-hydroxymethylene-*l*-menthone (40.00 g.) with hydroxylamine hydrochloride was repeated at room temperature for sixteen hours. The yield of crude stable isoxazole VIII was 8.30 g. (21%) and of crude mixture of cyanomenthones was 20 g. (51%).

Hydrindone-1 Series

2-Hydroxymethylenehydrindone-1, X, has been prepared in unspecified yield by Ruhemann and Levy.[25] By the modified procedure[16] there was obtained from 5.00 g. of hydrindone-1, 6.0 cc. of ethyl formate and sodium methoxide (from 1.90 g. of sodium) a yield of 5.37 g. (89%) of material melting at 111–112° (reported,[25] 112–113°). This product was sufficiently pure for the subsequent steps.

Bis-(1-keto-2-hydrindylidenemethyl)-hydroxylamine (XI).—From 2.00 g. of 2-hydroxymethylenehydrindone-1 and 1.08 g. of hydroxylamine hydrochloride in 80 cc. of acetic acid there was obtained[17] 1.91 g. (96% yield) of crude orange condensation product, m. p. 193–196° (dec.). Comparable yields were obtained when the reaction was conducted at 70° according to the procedure of Robinson and Rydon.[9] Recrystallization from pyridine gave orange microscopic plates, m. p. 244–246° (dec., introduced in bath at 243°). This substance dissolves in dilute alkali to give a deep-purple solution.

Anal. Calcd. for $C_{20}H_{15}O_3N$: C, 75.69; H, 4.77; N, 4.41. Found: C, 76.12; H, 4.80; N, 4.11.

The **acetate of XI** was prepared by heating a solution of XI (500 mg.) in 35 cc. of pyridine with 9 cc. of acetic anhydride for nine minutes on the steam-bath. The yellow precipitate which formed on dilution with crushed ice was separated and triturated rapidly with 100 cc. of cold 3% potassium hydroxide solution. The acetate which remained undissolved was washed with water and recrystallized from chloroform (Norit); yield 123 mg.; pale-yellow, short needles, m. p. 159–160°. This derivative is slowly hydrolyzed by cold dilute alkali as evidenced by the gradual development of the characteristic purple color.

Anal. Calcd. for $C_{22}H_{17}O_4N$: C, 73.52; H, 4.77. Found: C, 73.73; H, 5.00.

2-Bromohydrindone-1.—Kipping[26] has prepared this substance in unspecified yield by the bromination of hydrindone-1 in acetic acid solution. Later Ishiwara[27] described a two-step synthesis of the bromo ketone starting with indene dibromide; over-all yield about 45%. Using the excellent procedure of Wilds[28] for the bromination of 1-keto-1,2,3,4-tetrahydrophenanthrene we have prepared 2-bromohydrindone-1 from hydrindone-1 in practically quantitative yield. Thus from 4.83 g. of hydrindone-1 in 200 cc. of ether and 2.10 cc. of bromine there was obtained without recrystallization 7.66 g. (99% yield) of colorless bromo ketone, m. p. 36–37° (reported, 38–39°,[26] and 38.5°[27]).

2-Cyanohydrindone-1 (XVa).—Mitchell and Thorpe[29] have described the preparation of this compound by the hydrolysis of 2-cyano-1-iminohydrindone which was obtained by a Thorpe cyclization. The yields were not given. In the present work the metathetical reaction between 2-bromohydrindone-1 and potassium cyanide afforded the cyano ketone in 52% yield.

To a solution of 7.65 g. of 2-bromohydrindone-1 in 50 cc. of ethanol was added 9.0 g. of potassium cyanide followed by just enough water to make the mixture homogeneous. After refluxing on the steam-bath for fifteen minutes the dark brown solution was worked up by the procedure previously described for the preparation of 2-cyano-5-methoxyhydrindone-1.[6] The alkali-soluble material amounted to 2.95 g., m. p. 64.5–67.5°. Crystallization from alcohol gave almost colorless plates, m. p. 68–69° (reported,[29] 73°).

6-Methoxyhydrindone-1 Series

2-Hydroxymethylene-6-methoxyhydrindone-1 (Xb).—From 5.00 g. of 6-methoxyhydrindone-1,[30] 4.57 g. of ethyl formate and sodium methoxide (from 1.42 g. of sodium) there was obtained[16] 5.84 g. (100% yield) of cream-colored hydroxymethylene ketone, m. p. 147–148°. Crystallization from dilute alcohol gave small, pale-yellow plates, m. p. 150–151° (introduced in bath at 140°) with gas evolution and formation of a deep-red melt. This substance gives an intense purple color with aqueous ferric chloride.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.66; H, 5.28.

The red product formed by thermal decomposition of 2-hydroxymethylene-6-methoxyhydrindone-1 is most probably **2-(6-methoxy-1-keto-2-hydrindylidenemethyl)-6-methoxyhydrindone-1.**[31] It was obtained after heating Xb for one hour at 160–165°, as bright red needles from acetic acid, m. p. 240–243° (dec., introduced in bath at 236°).

Anal. Calcd. for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43. Found: C, 75.41; H, 5.47.

Bis-(6-methoxy-1-keto-2-hydrindylidenemethyl)-hydroxylamine (XIb).—From 2.78 g. of 2-hydroxymethylene-6-methoxyhydrindone and 1.02 g. of hydroxylamine hydrochloride in 100 cc. of acetic acid there was obtained[17] 1.76 g. (64% yield) of the crude insoluble orange condensation product, m. p. 200–213° (dec.). Recrystallization from pyridine gave small orange crystals, m. p. 234–236° (dec., introduced in bath at 225°). The compound dissolves in dilute alkali giving a deep-purple solution.

Anal. Calcd. for $C_{22}H_{19}O_5N$: C, 70.01; H, 5.07; N, 3.71. Found: C, 70.00; H, 5.17; N, 3.62.

(24) v. Auwers, *Ber.*, **57**, 461 (1924).

(25) Ruhemann and Levy, *J. Chem. Soc.*, 2542 (1912).

(26) Kipping, *ibid.*, 480 (1894).

(27) Ishiwara, *J. prakt. Chem.*, [2] **108**, 194 (1924).

(28) Wilds, THIS JOURNAL, **64**, 1421 (1942).

(29) Mitchell and Thorpe, *J. Chem. Soc.*, 2261 (1910).

(30) Johnson and Shelberg, THIS JOURNAL, **67**, 1853 (1945).

(31) *Cf.* the thermal decomposition of 2-hydroxymethylenehydrindone-1, ref. 25.

3-Phenylhydrindone-1 Series

3-Phenylhydrindone was prepared by the cyclization of β,β-diphenylpropionic acid[32] according to the procedure for the cyclization of β-*p*-methoxyphenylpropionic acid.[30] The yield of unrecrystallized ketone, m. p. 74–75° (reported,[32] 78°), was 96%. This material was satisfactory for preparation of the hydroxymethylene derivative.

2-Hydroxymethylene-3-phenylhydrindone-1, Xc, was prepared[16] from 10.00 g. of 3-phenylhydrindone-1, 6.9 g. of ethyl formate and sodium methoxide (from 2.21 g. of sodium). The yield after standing eight hours was 10.55 g. (93%) of cream-colored solid, m. p. 130–132°. The pure compound crystallized from ethyl acetate as colorless crystals, m. p. 132–133.2° (introduced in bath at 127°). In dilute alcoholic solution it gives an intense purple color with ferric chloride.

Anal. Calcd. for $C_{16}H_{12}O_2$: C, 81.33; H, 5.12. Found: C, 81.09; H, 5.28.

Bis-(1-keto-3-phenyl-2-hydrindylidenemethyl)-hydroxylamine (XIc).—From 2.00 g. of 2-hydroxymethylene-3-phenylhydrindone-1 and 1.18 g. of hydroxylamine hydrochloride in 15 cc. of acetic acid there was obtained[17] 1.58 g. (79.5% yield) of crude orange condensation product, m. p. 222–229° (dec.). An additional 0.396 g. of crude condensation product was obtained from the acetic acid solution, m. p. (after recrystallization from pyridine) 224–228° (dec.). The analytical sample of XIc was obtained by recrystallization from pyridine; orange crystals; m. p. 239–241° (dec., introduced in bath at 230°). It dissolved in dilute alkali to give the characteristic deep-purple solution.

Anal. Calcd. for $C_{32}H_{23}O_3N$: C, 81.85; H, 4.94; N, 2.98. Found: C, 81.71; H, 4.89; N, 3.02.

Cyclopentanone Series

2-Hydroxymethylenecyclopentanone.—The best yields which have been reported for the preparation of this substance were obtained when metallic sodium was used to promote the condensation.[33] Thus Thompson[33b] obtained 15 to 20% yields of material melting at 73°. v. Auwers and Nold[33c] have reported the m. p. 77° and have shown that some 2,4-di-hydroxymethylene-cyclopentanone also is formed. Using the sodium methoxide procedure,[16] but lowering the proportion of ethyl formate in order to minimize di-condensation, we have obtained the pure monohydroxymethylene derivative in 10 to 20% yields. For example from 41.5 g. of cyclopentanone, 36.5 g. of ethyl formate, sodium methoxide (from 11.4 g. of sodium) and 200 cc. of benzene there was obtained after nine hours at room temperature about 26 g. of alkali-soluble material. On cooling about 0.7 g. of the di-hydroxymethylene derivative crystallized, m. p. 113.5–114° (reported,[33c] 115.5–116.5°). The oil was distilled rapidly at 0.5–1.5 mm. giving a pale yellow, semi-solid product (17.8 g.). Crystallization from petroleum ether afforded 5.5 g. (10% yield) of colorless material, m. p. 76–77°. This substance gradually decomposes on standing at room temperature.

Bis-(1-keto-2-cyclopentylidenemethyl)-hydroxylamine, XVI.—A solution of 5.00 g. of freshly prepared 2-hydroxymethylenecyclopentanone in 15 cc. of glacial acetic acid was stirred with 3.1 g. of powdered hydroxylamine hydrochloride. After ten to fifteen minutes a dark brown precipitate appeared, and after thirty minutes this material was separated. After trituration with water it amounted to 1.76 g. (36% yield) of light tan condensation product, m. p. 158–159° (dec.) with previous softening. The analytical sample crystallized from alcohol as light orange needles, m. p. 168–169.5° (dec., introduced in bath at 165°). It dissolves in alkali to give a purple solution.

Anal. Calcd. $C_{12}H_{13}O_3N$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.36; H, 6.94; N, 6.40.

No additional condensation product could be isolated from the acetic acid solution. The material contained therein was practically all alkali-soluble, indicating that little, if any, isoxazole was formed. When the condensation reaction was allowed to proceed for several hours the condensation product which originally precipitated gradually went back into solution from which it was not isolable.

Acetomesitylene Series

Hydroxymethyleneacetomesitylene (XVII).—Fuson, Fugate and Fisher[34] have obtained this substance in 33% yield by the interaction of the bromomagnesium derivative of acetomesitylene with ethyl formate. By the sodium methoxide procedure[16] yields as high as 99% of alkali-soluble material have been realized. Thus from 25 g. of ketone, 22.5 g. of ethyl formate and sodium methoxide (from 7.1 g. of sodium) there was obtained 29.1 g. of crude hydroxymethylene derivative. Distillation was attended by considerable decomposition so that at best the recovery of material b. p. 158–163° (28–30 mm.) was 80% (23.1 g. in the above experiment).

5-Mesitylisoxazole (XVIII).—A solution of 10.00 g. of distilled hydroxymethyleneacetomesitylene in 100 cc. of acetic acid was treated with 5.5 g. of powdered hydroxylamine hydrochloride with stirring at 70–80° for eight hours. On dilution with water 9.25 g. (94% yield) of pale yellow isoxazole precipitated, m. p. 102–104.5°. A pure sample was obtained by crystallization from alcohol; pale yellow needles, m. p. 109–111°.

Anal. Calcd. for $C_{12}H_{13}ON$: C, 76.97; H, 7.00; N, 7.48. Found: C, 77.08; H, 6.90; N, 7.37.

Cyanoacetomesitylene (XIX).—The isoxazole XVIII was cleaved with sodium methoxide according to the procedure described under the tetralone series except that benzene instead of ether was used as the solvent. Thus from 4.00 g. of isoxazole there was obtained 3.6 g. (90% yield) of alkali-soluble, pale yellow cyano ketone, m. p. 103–105°, depressed to 74–76° on admixture with the isoxazole XVIII. Recrystallization from dilute alcohol gave almost colorless crystals, m. p. 107.5–108° (reported,[35] 108–109°). Fuson and Beveridge[35] have prepared this substance in 50–60% yields from chloroacetomesitylene.

Camphor Series

Attempts to prepare hydroxymethylenecamphor (XXI) by the sodium methoxide condensation gave only traces of the desired material. It was therefore prepared essentially by the method of Bishop, Claisen and Sinclair[13] which employs metallic sodium. Ethyl instead of amyl formate was used.

Bis-(2-keto-3-camphylidenemethyl)-hydroxylamine (XXII). (*a*) *From d-Camphor.*—A solution of 6.0 g. of hydroxymethylene-*d*-camphor in 12 cc. of acetic acid was stirred for twenty hours with 2.3 g. of powdered hydroxylamine hydrochloride. The yellow precipitate was separated and triturated with water; yield 3.58 g. (60%); m. p. 197–199° (dec.). Crystallization from glacial acetic acid gave bright yellow crystals, m. p. 202–204° (dec.). The condensation product is sparingly soluble in dilute aqueous alkali, but nevertheless imparts a yellow color to the solution. It dissolves readily in Claisen alkali.[36]

Anal. Calcd. for $C_{22}H_{31}O_3N$: C, 73.91; H, 8.74; N, 3.92. Found: C, 73.79; H, 8.76; N, 3.88.

The filtrate from the reaction mixture was diluted with water and neutralized. The organic material was taken up in ether, and washed with 5% potassium hydroxide solution. This removed very little of the condensation product which was found to be largely in the ether solution. Evaporation gave 0.324 g. of crude material which

(32) Prepared according to the procedure described by Pfeiffer and Waal, *Ann.*, **520**, 185 (1935).

(33) (a) Wallach and Steindorff, *ibid.*, **329**, 109 (1904); (b) Thompson, THIS JOURNAL, **53**, 3160 (1931); (c) v. Auwers and Nold, *Ann.*, **536**, 97 (1938).

(34) Fuson, Fugate and Fisher, THIS JOURNAL, **61**, 2362 (1939).

(35) Fuson and Beveridge, *ibid*, **53**, 1985 (1931).

(36) Claisen, *Ann.*, **418**, 96 (1919): 35 g. of potassium hydroxide in 25 g. of water diluted to 100 cc. with methanol.

was shown to consist, at least in part, of the condensation product XXII by sublimation at 215–230° (0.1–0.5 mm.). This treatment as is shown below converts XXII into **bis-(2-keto-3-camphylidenemethyl)-amine, XXIV.** After three recrystallizations of the sublimate from methanol it was obtained as colorless crystals, m. p. 221–223.2°.

Anal. Calcd. for $C_{22}H_{31}O_2N$: C, 77.36; H, 9.17; N, 4.10. Found: C, 77.43; H, 9.16; N, 4.18.

(*b*) *From d,l-Camphor.*—From 9.0 g. of hydroxymethylene-*d,l*-camphor there was obtained by the procedure described above under (a), a yield of 5.30 g. (59%) of the condensation product, m. p. 200–202° (dec.). The recrystallized material melted at 208–210° (dec.).

(*c*) *From l-Camphor.*—The condensation of hydroxymethylene-*l*-camphor with hydroxylamine proceeded just as described above under (a) for the *d*-camphor derivative. The recrystallized material melted at 202–204° (dec.) and a mixture with an equal amount of the condensation product derived from *d*-camphor melted at 208–210° (dec.). Such a mixture is not necessarily stereochemically identical with the condensation product from *d,l*-camphor since the latter can exist in a *meso* modification.

(*d*) *From the Condensation of Hydroxymethylenecamphor with the Monoxime of Hydroxymethylenecamphor.*[37]—To a solution of 2.00 g. of hydroxymethylene-*d,l*-camphor in 25 cc. of acetic acid was added 2.1 g. of the *d,l*-monoxime XXIII (prepared by the procedure of Bishop, Claisen and Sinclair[13]). A homogeneous solution was obtained on stirring, and after twenty hours at room temperature a yellow precipitate of the condensation product XXII had formed; yield 1.75 g. (45.5%) after trituration with water; m. p. 202–204°. Recrystallization from acetic acid gave material with the m. p. 208–210°, not depressed on mixing with the product described above under (b).

Bis-(2-keto-3-camphylidenemethyl) Amine (XXIV). (*a*) *By Reduction of XXII with Zinc and Acetic Acid.*[37]—A solution of 1.00 g. of bis-(2-keto-3-camphylidenemethyl)-hydroxylamine (from procedure (b) above) in 40 cc. of acetic acid was heated with 5 g. of zinc dust on the steam-bath for eight minutes. After cooling, the mixture was diluted with water and extracted with ether. The ether solution was washed with Claisen alkali[36] to remove unchanged di-substituted hydroxylamine, and then with water followed by saturated salt solution. Evaporation of the dried (over anhydrous sodium sulfate) solution gave 0.53 g. of the crude colorless di-substituted amine, m. p. 202–211° (with previous softening). Recrystallization from methanol gave material melting at 220–221.5°. A sample of XXIV prepared by the method of Bishop, Claisen and Sinclair[13] involving the action of hydrochloric acid on 2-keto-3-camphylidenemethyl amine, melted at 220–221.5° (reported m. p. 216–218°[14]) and showed no m. p. depression on admixture with the material described above.

(*b*) *By Sublimation of XXII.*—Five-tenths of a gram of the condensation product (from procedure (b) above) was sublimed at 220–240° (0.1–0.5 mm.). Vigorous evolution of gas was noted as the material melted. The sublimate amounted to 0.413 g., m. p. about 175–205°. Crystallization from methanol gave 0.173 g. of pale yellow material, m. p. 214–216°. An additional 0.084 g., m. p. 209–214°, was obtained from the filtrate making the total yield 54%. After three more recrystallizations the m. p. was 220–221.5°, undepressed on admixture with the products described above under (a).

A similar experiment was performed with the di-substituted hydroxylamine prepared from *d*-camphor. The sublimate after two recrystallizations from methanol melted at 221–223.2° (reported m. p. 220–221°,[13] 216–218°[14]). The m. p. was not depressed on admixture with the material obtained as a by-product in the preparation of bis-(2-keto-3-camphylidenemethyl)-hydroxylamine from *d*-camphor (see above).

(*c*) *By the Reaction of Hydroxymethylenecamphor with Ammonium Chloride.*—A solution of 2.38 g. of hydroxymethylene-*d*-camphor in 8 cc. of acetic acid was stirred with 0.70 g. of ammonium chloride for twelve hours at room temperature. The mixture was made alkaline in the cold and extracted with ether. The ether solution was washed thoroughly with 5% sodium hydroxide solution, water, and saturated salt solution. Evaporation of the dried solution left 0.070 g. of crude material which after sublimation and recrystallization from methanol melted at 221–223.2°. No m. p. depression was observed on admixture with the sample prepared from *d*-camphor in the preceding experiment. The low yield is possibly due in part to the low solubility of ammonium chloride in acetic acid.

(*d*) *By the Condensation of 2-Keto-3-camphylidenemethyl Amine (XXVIII) with Hydroxymethylenecamphor.*[37,14]—A solution of 1.5 g. of 2-keto-3-*d,l*-camphylidenemethyl amine (prepared by the procedure of Bishop, Claisen and Sinclair[13]) and 1.5 g. of hydroxymethylene-*d,l*-camphor in 10 cc. of glacial acetic acid was allowed to stir at room temperature for twenty hours. After dilution with water and neutralization, the mixture was extracted with ether. The ether solution was washed with 200 cc. of Claisen alkali,[36] then with water followed by saturated salt solution. Evaporation of the dried solution gave 2.07 g. of crude yellow di-substituted amine, m. p. 200–210°. Once recrystallized the material was almost colorless; m. p. above 210°; total yield 58%. Further crystallization gave the colorless product, m. p. 220–221.5°, undepressed on admixture with the product described above under (a).

Cyanocamphor (XXVII). (*a*) *From Hydroxymethylenecamphor and Hydroxylamine.*—The procedure of Bishop, Claisen and Sinclair[13] was followed with certain modifications. A solution of 2.00 g. of hydroxymethylene-*d*-camphor in 10 cc. of acetic acid was boiled with 0.77 g. of hydroxylamine hydrochloride for five minutes; some hydrogen chloride was evolved. After standing at room temperature for one and one-half hours the acetic acid was removed in a current of air, and the residue was steam distilled. Colorless cyanocamphor crystallized in the distillate; yield 0.17 to 0.47 g. (9 to 24%); m. p. 125–127° (reported,[13] 127–128°).

(*b*) *From the Monoxime of Hydroxymethylenecamphor.*—A solution of 2.2 g. of the crude monoxime of hydroxymethylene-*d*-camphor[13] in 10 cc. of acetic acid containing approximately 0.4 g. of hydrogen chloride was boiled for five minutes and worked up just as was the reaction mixture under (a) above. The colorless cyanocamphor amounted to 0.10 to 0.15 g. (5 to 7.5% yield), m. p. 124–127°.

(*c*) *From Bis-(2-keto-3-camphylidenemethyl)-hydroxylamine and Hydroxylamine Hydrochloride.*—A solution of 2.0 g. of the di-substituted hydroxylamine (derived from *d*-camphor) in 10 cc. of acetic acid was treated with 0.39 g. of hydroxylamine hydrochloride by the procedure described above under (a). The cyanocamphor amounted to 0.012 g., m. p. 122–124°. When the amount of hydroxylamine hydrochloride was doubled, yields as high as 0.30 g. (15%) were realized; m. p. 125–127°.

The Identity of Tingle's[12] "Camphylisoxazole" with Cyanocamphor.—Following the reported procedures for the preparation of "camphylisoxazole" from camphorglyoxalic acid (XXV) we have been able to duplicate the experimental results described by Tingle. The product obtained by us melted at 127–128.5° (reported m. p. 124–125°[12]) after recrystallization from benzene. It dissolved in cold 1% sodium hydroxide and was reprecipitated only on acidification. Authentic cyanocamphor was prepared by the procedure of Lapworth[38]; it melted at 127–128° and on admixture did not depress the m. p. of the product prepared by Tingle's procedure. For further comparison the crystalline bromocyanocamphor was prepared. The product of bromination (in carbon bisulfide solution) of Tingle's substance melted at 73–74° after crystallization from dilute alcohol. Bromocyanocamphor prepared by the method of Lapworth[38] melted at 74–75° (reported m. p. 74–75°[38]) and showed no m. p. depression on admix-

(37) All reagents derived from *d,l*-camphor.

(38) Lapworth, *J. Chem. Soc.*, **77**, 1053 (1900).

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.

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

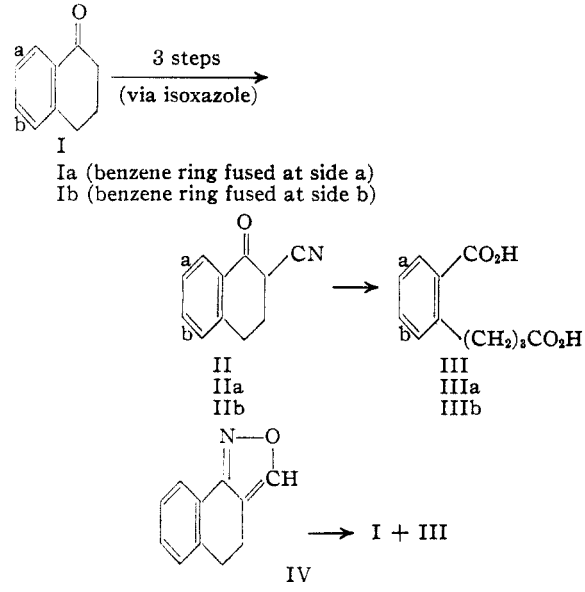
Studies on Opening the Rings of Cyclic Ketones

BY WILLIAM S. JOHNSON AND WESLEY E. SHELBERG

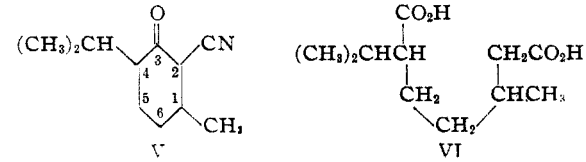
In connection with a study of the reaction of hydroxylamine hydrochloride with the α-hydroxymethylene derivatives of some cyclic ketones,[1] it was shown that the cyclohexanone derivatives behaved like open-chain hydroxymethylene ketones giving rise to isoxazoles which could be isomerized by sodium methoxide 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.

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]



(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).