

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

 α -Iodoketones (Part 2).¹ Reaction of Enol Acetates with N-Iodosuccinimide²BY CARL DJERASSI AND CARL T. LENK³

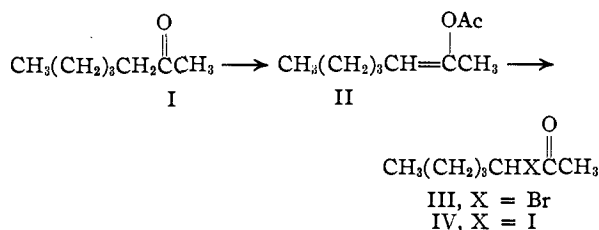
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As illustrated in three instances, enol acetates react with N-iodosuccinimide to yield the corresponding α -iodoketone (or aldehyde) and N-acetylsuccinimide. Iodine monochloride can be substituted for N-iodosuccinimide, but the latter reagent has the advantage of not attacking nuclear double bonds. As an illustration of this selective iodination, Δ^5 -pregnen-3 β -ol-20-one was converted in three steps to Δ^5 -pregnene-3 β -21-diol-20-one diacetate.

In contrast to their chloro or bromo analogs, α -iodoketones (and aldehydes) have been studied infrequently. While this is partly due to their relative instability, it should also be noted that there are only very few satisfactory syntheses available. Of these, the sodium iodide interchange reaction⁴ is the most satisfactory, but it is subject to pronounced steric effects; thus in the steroid series, it has been noted that neither 17-bromo-20-ketones⁴ nor 4-bromo-5 β ,3-ketosteroids¹ react to any appreciable extent with sodium iodide. It appeared of interest, therefore, to develop a synthetic route to such compounds which would not proceed through the bromoketones and which would lend itself, if possible, to the selective introduction of iodine at particular positions in a polyfunctional molecule.

The first method to be investigated and one which is described in this paper involves the reaction of enol acetates with "positive" iodine compounds. Two general methods are available for the preparation of such enol acetates, one involving acetic anhydride⁵ and the other isopropenyl acetate⁶ in the presence of a strong acid catalyst. The latter procedure is generally superior, since it is milder and usually proceeds in higher yield. More importantly, however, in the case of a ketone which can afford two different enols, the two reactions do not necessarily produce the same ratio of the corresponding enol acetates⁷ and it is often possible to obtain exclusively one product or the other depending upon the choice of conditions.^{8,9} As a result, the use of the proper enol acetate should lead to an iodoketone with the halogen atom either on the methyl or methylene group adjacent to the carbonyl function and an example of each reaction will be given.

Heptanone-2 (I) affords the same enol acetate II by either method¹⁰ and this has been confirmed in the present investigation by bromination which yielded the same bromoketone III in each instance.



The bromination could be carried out either with bromine in the standard manner⁵ or with N-bromoacetamide in carbon tetrachloride solution. Subsequent iodide interchange in acetone solution produced 3-iodoheptanone-2 (IV) which was required for comparison purposes with samples prepared by the two methods indicated below. In contrast to the behavior of the bromoketone III, which underwent the usual dehydrobromination with collidine, the iodoketone IV was deiodinated under those conditions, regenerating the saturated ketone I in accordance with the observation made earlier in the steroid series.¹ Treatment of the enol acetate II with iodine monochloride in chloroform solution furnished the above 3-iodoheptanone (IV) in 60% yield with the concomitant formation of acetyl chloride, thus demonstrating that the reaction of a positive iodine carrier with an enol acetate is in principle a satisfactory method for the synthesis of iodoketones. In view of the fact that iodine monochloride also reacts very readily with isolated double bonds,¹¹ this reagent cannot be used for the synthesis of iodoketones which contain additional centers of unsaturation and attention was directed to the use of an alternate "positive" iodine compound, preferably one which is stable, solid and hence easy to handle in small scale experiments. N-Iodosuccinimide has proved to be the reagent of choice.

N-Iodosuccinimide, abbreviated below as NIS, was first prepared by Bunge¹² by iodination of the silver salt of succinimide and a modification of this method, described in the experimental section, was found to be very satisfactory. In contrast to Bunge's report, N-iodosuccinimide was found to be a stable, colorless solid melting at 200°. When NIS was treated with 2-hepten-2-ol acetate (II) with or without a solvent (dioxane), up to 82% of pure 3-iodoheptanone (IV) was obtained. In addition, it was possible to isolate nearly 90% of N-acetylsuccinimide, the structure of which was proved by analysis and by reaction with ammonia and aniline. The isolation of IV and N-acetylsuccinimide strongly suggests that the reaction

(1) Part 1, G. Rosenkranz, O. Mancera, J. Gatica and C. Djerassi, *THIS JOURNAL*, **72**, 4077 (1950).

(2) We are indebted to the Research Corporation of New York for a Frederick Gardner Cottrell grant in support of this work.

(3) Research Corporation Fellow, 1952-1953.

(4) P. L. Julian and W. J. Karpel, *THIS JOURNAL*, **72**, 362 (1950), and leading references cited therein.

(5) P. Z. Bedoukian, *ibid.*, **67**, 1430 (1945).

(6) Cf. H. J. Hagemeyer and D. C. Hull, *Ind. Eng. Chem.*, **41**, 2920 (1949).

(7) Cf. E. H. Man, F. C. Frostick and C. R. Hauser, *THIS JOURNAL*, **74**, 3228 (1952).

(8) R. B. Moffett and D. I. Weisblat, *ibid.*, **74**, 2183 (1952).

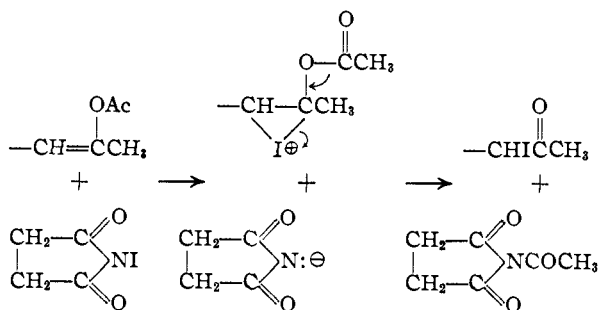
(9) H. Vanderhaeghe, E. R. Katzenellenbogen, K. Dolbriner and T. F. Gallagher, *ibid.*, **74**, 2810 (1952).

(10) F. G. Young, F. C. Frostick, J. J. Sanderson and C. R. Hauser, *ibid.*, **72**, 3635 (1950).

(11) Cf. C. K. Ingold and H. G. Smith, *J. Chem. Soc.*, 2742 (1931).

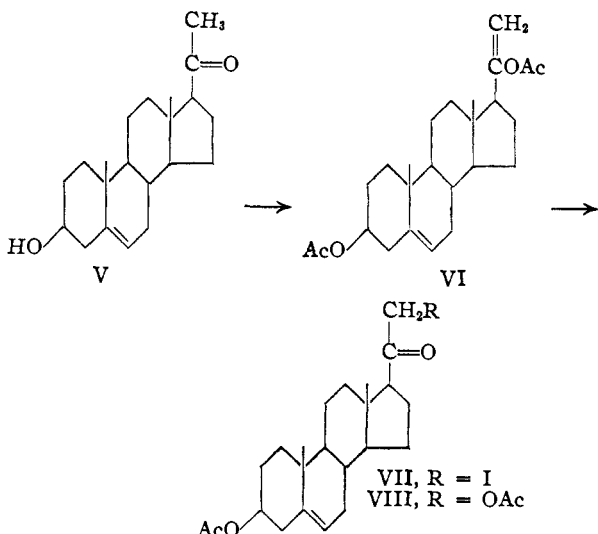
(12) N. Bunge, *Ann.*, **7** (Supplement), 117 (1870).

proceeds by an ionic mechanism, most likely through an intermediate iodonium complex.



NIS showed no free radical reactivity when refluxed for six hours with toluene in carbon tetrachloride solution in the presence of benzoyl peroxide and strong light, conditions under which N-bromosuccinimide¹³ reacts very readily. The only clear-cut reaction of N-bromosuccinimide with an enol acetate reported so far¹⁴ also appears to proceed by a free radical mechanism, thus indicating a fundamental difference in the mechanisms operating with NIS and NBS, respectively.

When examined in the case of butyraldehyde enol acetate, the reaction with NIS proceeded quite smoothly but it was impossible to distill the resulting α -iodobutyraldehyde without decomposition and to obtain a satisfactory analytical sample. In order to test the utility of NIS with an enol acetate which also possesses an isolated double bond, $\Delta^5,20$ -pregnadiene- $3\beta,20$ -diol 3,20-diacetate (VI) was selected, since this crystalline enol acetate can be prepared in good yield^{8,9} with isopropenyl acetate from the abundant Δ^5 -pregnen- 3β -ol-20-one (V) and the resulting 21-iodo-20-ketone VII would be of preparative significance for the elaboration of the ketol side chain characteristic of the adrenal hormone desoxycorticosterone.



In the case of the steroidal enol acetate VI, it was necessary to employ a solvent for the reaction with NIS and dioxane proved satisfactory. The resulting 21-iodopregnenolone acetate VII was

(13) C. Djerassi, *Chem. Revs.*, **43**, 271 (1948).

(14) C. Djerassi and C. R. Scholz, *J. Org. Chem.*, **14**, 660 (1949).

obtained as colorless crystals and the structure was proved by conversion in nearly quantitative yield to Δ^5 -pregnene- $3\beta,21$ -diol-20-one diacetate (VIII). While 21-iodopregnenolone is an important intermediate in a commercial synthesis of desoxycorticosterone,¹⁵ it has only been prepared by iodination of the sodium enolate of the corresponding glyoxalate and it apparently has never been purified. The corresponding acetate VII, obtained in the present work, was isolated by Reichstein¹⁶ in a nearly pure state by treatment of Δ^5 -pregnene- $3\beta,21$ -diol-20-one 3-acetate 21-tosylate with sodium iodide, but such a method is of no preparative significance since it utilizes the desired end-product, the 3,21-diol, as starting material. Addition of bromine to *both* double bonds of the enol acetate VI followed by reaction with sodium iodide is feasible,⁸ but it does not lend itself readily to the isolation of the pure 21-iodo-20-ketone VII. A similar sequence (bromination and acetolysis) has also been carried out with the corresponding saturated pregnane analog.⁹

Taking advantage of the presently described NIS-enol acetate method, it has been possible to synthesize certain hitherto inaccessible iodoketones and their reactions are now under investigation.

Experimental¹⁷

N-Iodosuccinimide.—The following procedure represents a modification of that described by Bunge.¹² To a solution of 392 g. of succinimide in 12 l. of boiling water was added 510 g. of freshly precipitated silver oxide, the mixture was filtered and the silver salt was allowed to crystallize. Filtration and washing with cold water furnished 450 g. of the silver salt of succinimide suitable for the iodination step. The finely powdered salt (49.5 g.) was added in portions with stirring to a solution of 50.8 g. of iodine in 300 cc. of acetone, the temperature being maintained at 5–10°. After decolorization (30 min.), the silver iodide was filtered, the solvent was removed under reduced pressure at room temperature and the residue was washed with ether, yielding 43 g. of N-iodosuccinimide with m.p. 189–191°. The analytical sample (85% recovery) was obtained by dissolving in the minimum quantity of hot dioxane and precipitating with carbon tetrachloride; colorless needles, m.p. 200–201°. Material with m.p. not lower than 197° was used for the subsequent iodinations. Bunge¹² reported m.p. 110–135° with decomposition. Satisfactory N-iodosuccinimide is now available commercially from Arapahoe Chemicals, Boulder, Col.

Anal. Calcd. for $C_4H_4O_2IN$: I, 56.41. Found: I, 56.52 (by titration).

2-Hepten-2-ol Acetate (II).—Heptanone-2 was converted into its enol acetate by two methods: (a) acetic anhydride-*p*-toluenesulfonic acid,⁵ yielding 30% with b.p. 77.5° at 16 mm., n_D^{25} 1.4245, d_4^{25} 0.8839; (b) isopropenyl acetate-sulfuric acid,¹⁰ 60% yield, b.p. 58° at 8 mm., n_D^{25} 1.4240. The identity of the two samples was established by infrared spectroscopy.

3-Bromoheptanone-2 (III).—A mixture of 7.8 g. of the above enol acetate II, 6.9 g. of N-bromoacetamide and 70 cc. of dry carbon tetrachloride was refluxed for 30 min. The initial red color disappeared rapidly with the concomitant formation of a precipitate. After washing with water, sodium carbonate solution, water, drying and evaporating, there was obtained 7.2 g. of crude product which upon fractionation afforded 4.5 g. of the pure bromoketone with b.p.

(15) H. Ruschig, *Angew. Chem.*, **60A**, 247 (1948).

(16) T. Reichstein and W. Schindler, *Helv. Chim. Acta*, **23**, 669 (1940).

(17) Melting points are uncorrected. Rotations were measured in chloroform solution and infrared spectra were obtained with a Baird Associates double beam recording spectrophotometer. We are indebted to Messrs. R. Mullins and M. Pappo for the microanalyses.

49° at 1 mm., n_D^{25} 1.4617; the infrared spectrum was identical with that of a sample prepared by Bedoukian's method.⁸

3-Iodoheptanone-2 (IV). (a) By Sodium Iodide Interchange.—A solution of 30 g. of sodium iodide and 19.3 g. of 3-bromoheptanone-2 (III) in 150 cc. of dry acetone was refluxed for one hour and the precipitated sodium bromide was filtered. After removal of the solvent, taking up in ether and washing in the usual manner, the product was twice distilled through a 6-in. Vigreux column; yield 17.2 g. (72%), b.p. 76° at 1.5 mm., n_D^{25} 1.5010, d_4^{25} 1.483, M_D found 47.86, M_D calcd. 47.35.

Anal. Calcd. for $C_7H_{13}OI$: C, 35.02; H, 5.46. Found: C, 34.93; H, 5.49.

(b) From the Enol Acetate and Iodine Monochloride.—Addition of 16.2 g. of iodine monochloride in 40 cc. of chloroform to a solution of 15.6 g. of 2-hepten-2-ol acetate (II) in 100 cc. of chloroform at 5° produced no change. After 2 hours at room temperature, the mixture was refluxed for one-half hour and a small amount of distillate produced an immediate precipitate with silver nitrate presumably due to the formation of acetyl chloride.¹⁸ The chilled solution was washed well with thiosulfate and water, dried and distilled through a Vigreux column furnishing 13.1 g. (60%) of iodoketone with b.p. 70–72° at 1.5 mm., n_D^{25} 1.5020, d_4^{25} 1.485, M_D found 47.87; the identity of this material with samples prepared according to (a) and (c) was established by infrared spectroscopy.

(c) From the Enol Acetate and N-Iodosuccinimide.—A mixture of 22.5 g. of N-iodosuccinimide and 15.6 g. of 2-hepten-2-ol acetate in 40 cc. of purified dioxane¹⁹ was heated for 1 hour at 80–100° and the solvent was removed *in vacuo*. After dissolving the residue in ether, washing with water and drying, it was fractionated yielding 13.9 g. (58%) of pure iodoketone with b.p. 75° at 1.5 mm., n_D^{25} 1.5005, d_4^{25} 1.479, M_D found 47.95.

The absence of a solvent not only increased the yield in this instance but also made possible the isolation of N-acetylsuccinimide which is formed during the reaction. Equimolar amounts of N-iodosuccinimide (22.5 g.) and the enol acetate II (15.6 g.) were heated for 15 min. at 120°, the resulting reddish, viscous liquid was diluted with an excess of dry ether and left in the refrigerator overnight. After cooling for 30 min. at –60°, the solid was filtered and washed well with ether. Distillation of the ether residue furnished 82% of pure iodoketone IV with b.p. 47–48° at 0.4 mm., n_D^{25} 1.5005. The original solid precipitate after drying weighed 12.6 g. (90%) and exhibited m.p. 36–39°, raised to m.p. 40–41° after recrystallization from ether. The substance was identified as N-acetylsuccinimide²⁰ by elementary analysis and the reactions described below.

Anal. Calcd. for $C_6H_7O_2N$: C, 51.06; H, 5.00. Found: C, 51.28; H, 5.08.

An ether solution of N-acetylsuccinimide was treated with ammonia gas for 2 hours, the ether was evaporated and the residue was distilled directly yielding two fractions: (a) m.p. 77–78° identified as acetamide by a mixture melting point and (b) succinimide, m.p. 122–123°, undepressed upon admixture with an authentic sample of succinimide.

For further characterization, a small amount of N-acetylsuccinimide was mixed with aniline, resulting in liquefaction and an exothermic reaction. Recrystallization

from water followed by sublimation yielded acetanilide, m.p. 113–114°, identified by direct comparison with an authentic sample.

Reaction of 3-Iodoheptanone-2 with γ -Collidine.—A mixture of 15 g. of iodoketone IV and 25 cc. of collidine was heated at 80° for 1 hour, whereupon it turned black. Ether was added, basic material was removed by repeated washing with dilute hydrochloric acid and after washing until neutral and drying, the ether was evaporated and the residue was distilled; yield 3.5 g. of heptanone-2, identified as the yellowish orange 2,4-dinitrophenylhydrazone m.p. 73–74°, undepressed upon admixture with an authentic specimen.²¹

A similar reaction (9 hours refluxing) with 3-bromoheptanone-2 resulted in the formation of 85% of collidine hydrobromide and after working up as above, there was isolated 55% of 3-heptanone-2 with b.p. 54° at 10 mm., n_D^{25} 1.4354. The 2,4-dinitrophenylhydrazone exhibited m.p. 125–126° (lit.²² 125–126°).

Anal. Calcd. for $C_{13}H_{18}O_4N_4$: C, 53.42; H, 5.52. Found: C, 53.36; H, 5.80.

α -Iodobutyraldehyde.—A mixture of 5.7 g. of 1-butenyl acetate,²³ 11.3 g. of N-iodosuccinimide and 10 cc. of dioxane was kept at 75° for 1 hour in an atmosphere of nitrogen. Methylene chloride was then added and the solution was washed well with thiosulfate solution and water, dried and the solvent was evaporated *in vacuo* at room temperature leaving 9.7 g. (98%) of a light yellow, lachrymatory liquid, n_D^{25} 1.4970. Attempts to prepare an analytical sample by distillation failed, since the material distilling at 68–69° and 35 mm. already possessed a strong iodine color due to partial decomposition. Analysis indicated the presence of ca. 85% of iodoaldehyde.

21-Iodo- Δ^5 -pregnene-3 β ,21-diol-20-one Acetate (VII).— Δ^5 ,²⁰-Pregnadiene-3 β ,20-diol diacetate (VI)^{8,9} (2.0 g.) was heated for 45 min. at 85° with 1.18 g. of N-iodosuccinimide in 2 cc. of purified dioxane.¹⁹ The cooled, dark red solution was treated with potassium iodide solution followed by thiosulfate and much water. The precipitate was collected (2.1 g., m.p. 115–123°) and recrystallized from methanol-water (9:1) furnishing 1.31 g. (54%) of iodo ketone with m.p. 135–137°. The analytical sample crystallized as colorless needles with m.p. 140–141°, $[\alpha]_D^{25} +63^\circ$, $\lambda_{max}^{CS_2}$ 5.78 and 5.88 μ ; Reichstein and Schindler¹⁶ reported m.p. 129–131° for a sample prepared from Δ^5 -pregnene-3 β ,21-diol-20-one 3-acetate 21-tosylate.

Anal. Calcd. for $C_{23}H_{32}O_3I$: C, 57.03; H, 6.86. Found: C, 56.54; H, 6.61.

Δ^5 -Pregnene-3 β ,21-diol-20-one Diacetate (VIII).—The above 21-iodoketone (0.73 g., m.p. 135–137°) in 30 cc. of pure acetone was refluxed for 12 hours with a mixture²⁴ (prepared in a mortar) of 3.5 g. of potassium bicarbonate and 2.1 cc. of glacial acetic acid. Dilution with water and filtration produced 0.60 g. (95%) of the diacetate with m.p. 161–163°, raised after one recrystallization from methanol to 165–166°, $[\alpha]_D^{25} +28^\circ$. An authentic sample,²⁵ prepared by acetylation of Δ^5 -pregnene-3 β ,21-diol-20-one 21-acetate (kindly supplied by Syntex, S.A., Mexico City), possessed m.p. 164.5–165.5°, $[\alpha]_D^{25} +27^\circ$, and the identity of the two specimens was proved by mixture melting point determination and coincidence of their infrared spectra.

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 72.09; H, 8.70. Found: C, 71.81; H, 8.71.

DETROIT, MICHIGAN

(21) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948.

(22) S. G. Powell and D. Ballard, *THIS JOURNAL*, **60**, 1914 (1938).

(23) D. Y. Curtin and M. J. Hurwitz, *ibid.*, **74**, 5381 (1952).

(24) Cf. G. Rosenkranz, J. Pataki, S. Kaufmann, J. Berlin and C. Djerassi, *ibid.*, **72**, 4084 (1950).

(25) T. Reichstein and C. Montigel, *Helv. Chim. Acta*, **22**, 1212 (1939).

(18) In a model experiment in which cyclohexanone enol acetate was treated with an equimolar amount of iodine monochloride in carbon tetrachloride solution, careful fractionation yielded 60% of pure acetyl chloride; the presence of additional amounts of the chloride in the higher boiling fractions was demonstrated chemically by reaction with aniline.

(19) L. F. Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., New York, N. Y., 1941, p. 369.

(20) J. Tafel and M. Stern, *Ber.*, **33**, 2224 (1900), obtained this substance by refluxing succinimide in acetic anhydride solution; b.p. 167° at 0.5 mm., solidifying on cooling.