Assignment of the Olefinic Position in Unsaturated Acids by Means of the Iodolactonization Reaction

By Eugene E. van Tamelen and Maurice Shamma

By means of infrared spectrophotometric methods certain β,γ- and γ,δ-unsaturated acids have been shown to yield five-membered iodolactones on treatment with iodine–potassium iodide in bicarbonate solution at room temperature. The single δ,ϵ-unsaturated acid studied, δ,ϵ-hexenoic acid, yields (probably) δ-iodomethyl-δ-valerolactone, whereas acids with double bonds farther removed from the carboxyl function lead to unstable, poorly-defined products.

In an endeavor to locate the position of a double bond relative to a carboxyl group in a certain sesquiterpenoid, we have applied to advantage the reaction in which certain unsaturated acids are converted by iodine–potassium iodide and bicarbonate in aqueous medium to *iodolactones*. The possibility that others may be faced with similar structural problems prompts us to detail the results obtained in a study of this readily executed reaction.

Iodolactonization was first reported in 1908 by Bougault,[1] whose fairly comprehensive report may be summarized by stating that (i) α,β-unsaturated acids do not give iodolactones, (ii) β,γ- as well as γ,δ-unsaturated acids do afford iodolactones, (iii) δ,ϵ-acids or acids with the unsaturation farther removed from the carboxyl group yield only the poorly characterized unsaturated acid iodohydrins, and (iv) α-keto-β,γ-alkenoic acids and α,β-γ,δ-acids are exceptional in that no iodolactones are obtained from them. Bougault surmised correctly that the β,γ-acids lead to β-iodo-γ-lactones(I), but incorrectly—as we shall demonstrate later—that the γ,δ-isomers result in γ-iodo-δ-lactones (II). The cyclization method has been utilized more re-

cently by Linstead[2] and others[3] to distinguish α,β-unsaturated acids from the β,γ-isomers. Arnold[4] has shown that iodolactones can be obtained by the use of cyanogen iodide in place of iodine and bicarbonate.
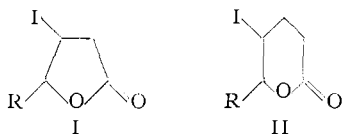
Our first aim was extension of the series of lactones derived from β,γ-acids as well as confirmation of the lactone ring size. Toward this end, β,γ-butenoic acid, β,γ-pentenoic acid (III) and Δ^1-cyclohexeneacetic acid (IV) were treated with the iodine–bicarbonate reagent. Surprisingly enough, β,γ-*butenoic acid* (an example not previously reported), *even on long standing, deposited no iodolactone*. The other two acids rapidly afforded iodolactones, which, like the subsequent members in this study, were analyzed by iodine determination. Both iodolactones exhibited strong absorption in the 5.6 μ region[5,6] of the infrared (Table I), thereby

revealing the five-membered nature of the lactone rings.

$$CH_3CH{=}CHCH_2{-}COOH \longrightarrow I \ (R = -CH_3)$$

III

IV   V
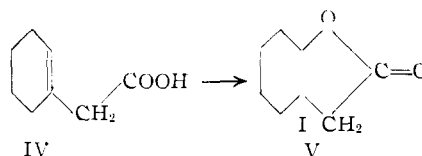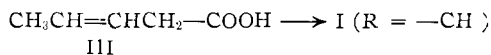
It is readily apparent that for lactones derived from γ,δ-unsaturated acids there are two structural possibilities: δ-iodo-γ-lactones (*e.g.*, VI) and γ-iodo-δ-lactones, the latter being favored, as mentioned above, by Bougault. Infrared analysis (Ta-

VI
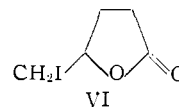
ble I) indicated that both γ,δ-pentenoic acid (VII) and Δ^2-cyclohexeneacetic acid (VIII) gave rise to the γ-lactones VI and IX, rather than the δ-isomers. The latter type would be expected, like

$$CH_2{=}CHCH_2CH_2COOH \longrightarrow VI$$

VII

VIII   IX
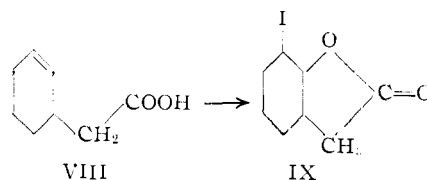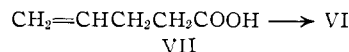
other δ-lactones, to absorb at about 5.75 μ in the infrared,[5] whereas absorption actually lay in the 5.6 μ area.

As a representative of the Δ^5-unsaturated acid class, δ,ϵ-hexenoic acid was selected for study. In the light of Bougault's report, we were surprised to observe the ready formation of a crystalline product, which analysis showed to be the iodolactone. Although the 5.74 μ band in the infrared excluded the unlikely γ-lactone possibility, the spectroscopic technique cannot reliably distinguish the δ- and ϵ-lactone structures (X and XI); of course the precedent for assigning the δ-structure is overwhelming.

X   XI

(1) J. Bougault, *Ann. chim. phys.*, **14**, 145 (1908); **15**, 296 (1908).

(2) R. P. Linstead and C. J. May, *J. Chem. Soc.*, 2565 (1927).

(3) (a) A. W. Schrecker, G. Y. Greenberg and J. L. Hartwell, This Journal, **74**, 5669 (1952); (b) A. W. Schrecker and J. L. Hartwell, *ibid.*, **74**, 5676 (1952).

(4) R. T. Arnold and K. L. Lindsay, *ibid.*, **75**, 1048 (1953).

(5) R. S. Rasmussen and R. R. Brattain, *ibid.*, **71**, 1073 (1949).

(6) G. S. Skinner and R. deV. Huber, *ibid.*, **73**, 3321 (1951).
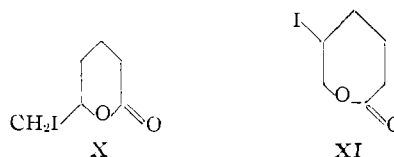
Because of the success in the Δ⁵-series, we were interested in learning whether ε,ζ-heptenoic acid should conform to the lactonization pattern. It, as well as ω-undecylenic acid, did slowly form a viscous, dark-colored oil in the iodine–bicarbonate reaction medium. These unstable, intractable materials gave variable iodine analyses which in no case corresponded to those expected for the iodolactones. Apparently lactonization to stable seven- (or more) membered rings is unfavorable here; the nature of the product formed is obscure.

TABLE I

| Acid	Lactone	Infra-red, μ	M.p.,[a] °C.	Analyses, I, % Calcd.	Found
β,γ-Pentenoic	I (R = CH₃)	5.59	Liquid	56.15	55.64
Δ¹-Cyclohexeneacetic	V	5.59	56–58²	...	...
γ,δ-Pentenoic	VI	5.63	Liquid	56.15	56.15
Δ²-Cyclohexeneacetic	IX	5.62	65–66	47.17	47.22
δ,ε-Hexenoic	X (or XI)	5.74	39–40	52.92	52.86

[a] All melting points are corrected.

On the basis of these results, we have concluded that the appearance of carbonyl absorption at about the 5.6 μ region in an iodolactone indicates that the starting acid was probably β,γ- or γ,δ-unsaturated. Adsorption at about 5.75 μ demonstrates the probable presence of a δ,ε-double bond. Furthermore, our experience with ε,ζ-heptenoic and undecylenic acids emphasizes that mere precipitation of an oil in the attempted iodolactonization has limited significance and that purification and analysis are prerequisites for reliable deductions regarding the position of a double bond.

In terms of modern theory, it seems likely that iodolactonization proceeds by way of an initial positive iodine attack on the double bond, followed by carboxylate anion displacement on the resulting iodonium ion portion of the intermediate zwitterion. This view does not differ fundamentally from that
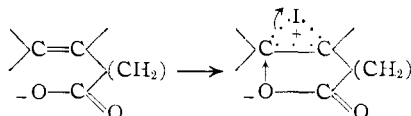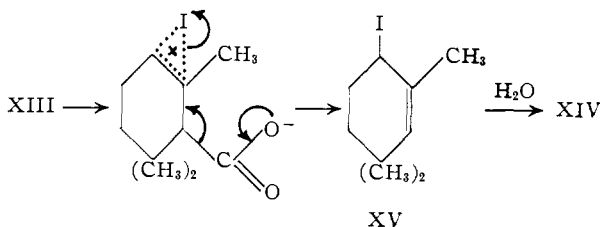

of Linstead (and Robinson),² who proposed that the addition of iodine gives rise to the acyclic intermediate (XII), which subsequently lactonizes.
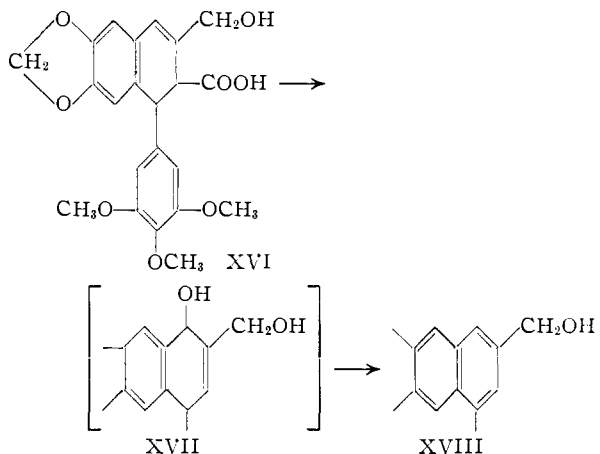

XII
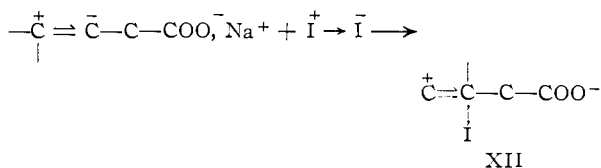
In any case, the success of the reaction seems to depend, first of all, on the ability of the system to form either a five- or six-membered ring. Furthermore, the double bond must be isolated¹; conjugation, as in an α-keto-β,γ-acid or α,β-γ,δ-acid, apparently decreases the electron density on the olefin link to such an extent that attack by positive iodine becomes ineffectual, and no iodolactone is produced. An abnormal course of reaction⁷ which appears to depend on more subtle structure features is the conversion of α-cyclogeranic acid (XIII) to 2,4,4-

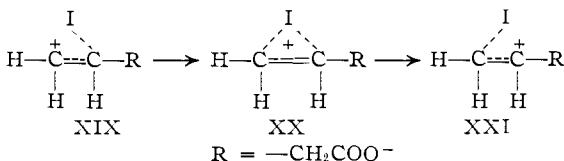(7) J. Bougault, Ann. chim. phys., 22, 125 (1911).
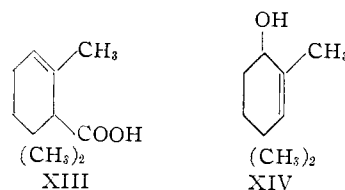
trimethyl-2-cyclohexenol (XIV). It appears possible that the normal iodonium ion is formed, but that the rate of lactonization may be sensibly diminished because of the steric nature of the system, particularly the methyl group attached to the iodo-

nium ring; decarboxylative β-elimination may then supervene, affording the cyclohexenyl iodide (XV), which finally undergoes solvolysis to the observed alcohol. That the aforementioned methyl group may play a decisive role is indicated by the observation³ᵃ that 1,2-dihydronaphthalene-2-carboxylic acid gives the expected iodolactone, whereas α-apopodophyllic acid³ᵇ (XVI) leads to the hydroxymeth-

ylnaphthalene XVIII, possibly via the intermediate XVII.³ᵇ So far we have not developed a completely satisfactory explanation for the inertness of β,γ-butenoic acid toward iodolactonization, a finding particularly enigmatic in view of the successful result with β,γ-pentenoic acid and γ,δ-pentenoic acid. It is possible, however, that, of the canonical forms XIX, XX and XXI, the first, which would logically lead to γ-lactonization, may contribute

R = —CH₂COO⁻

comparatively slightly because the carbonium ion is primary; in all successful cases studied herein

the positive charge may be placed on a secondary carbon either γ or δ to the carboxyl function.

Experimental

β,γ-**Butenoic Acid.**—The substance was obtained by the acid hydrolysis[8] of the corresponding nitrile, which was in turn produced by the reaction[9] of allyl bromide with cuprous cyanide.

β,γ-**Pentenoic Acid.**—Crotyl bromide[10] was converted to crotononitrile by treatment with cuprous cyanide[11]; hydrolysis of the nitrile, which was separated from the isomeric methallyl cyanide by fractionation, was carried out according to the directions of Lane, et al.[12]

Δ^1-**Cyclohexeneacetic Acid.**—Cyclohexanone was subjected to a Reformatsky reaction,[13] and the resulting β-hydroxyester was dehydrated[14] with dry hydrogen chloride and subsequently hydrolyzed[2] under acidic conditions.

γ,δ-**Pentenoic Acid.**—The material was obtained by the hydrolysis and decarboxylation of diethyl allylmalonate.[15]

Δ^2-**Cyclohexeneacetic Acid.**—Sodium diethyl malonate was alkylated with 3-bromocyclohexene[16,17]; the resulting diester was hydrolyzed and decarboxylated.

(8) R. P. Linstead, E. G. Noble and E. J. Boorman, *J. Chem. Soc.*, 560 (1933).

(9) R. Breckpot, *Bull. soc. chim. Belg.*, **39**, 465 (1930).

(10) L. Fieser, THIS JOURNAL, **49**, 861 (1927).

(11) H. L. Goering, S. J. Cristol and K. Dittmer, *ibid.*, **70**, 3314 (1948).

(12) J. F. Lane, J. Fentress and L. T. Sherwood, *ibid.*, **66**, 547 (1944).

(13) S. Natelson and S. P. Gottfried, *ibid.*, **61**, 970 (1939).

(14) E. Schwenk and D. Papa, *ibid.*, **67**, 1432 (1945).

(15) R. Fittig and A. Messerschmidt, *Ann.*, **208**, 92 (1881).

(16) J. F. Eijkman, *Chem. Weekblad*, **6**, 699 (1909).

(17) K. Ziegler, A. Späth, E. Schaaf, W. Schuman and E. Winkelmann, *Ann.*, **551**, 80 (1942).

δ,ϵ-**Hexenoic Acid.**—Allyl bromide, after conversion to the Grignard reagent, was treated with gaseous formaldehyde[18]; the resulting 3-butenol was transformed into butenyl bromide, which was in turn used to alkylate sodium diethyl malonate. Hydrolysis and decarboxylation of the substituted product led to the desired acid.

ϵ,ζ-**Heptenoic Acid.**—The procedure used for δ,ϵ-hexenoic acid was modified[19,20] by using ethylene oxide instead of formaldehyde.

Preparation of Iodolactones.—A solution of 5 mmoles of the acid in 30 cc. of 0.5 N sodium bicarbonate and a solution of 10 mmoles of iodine and 30 mmoles of potassium iodide in 15 cc. of water were mixed and allowed to stand in the dark for 24 hours. The dark precipitate which had separated was washed with water and then shaken with chloroform and aqueous thiosulfate until two almost colorless phases were obtained. The aqueous layer was extracted with chloroform, and the combined extracts were washed successively with aqueous bicarbonate and with water and finally dried over anhydrous sodium sulfate. The oil remaining after evaporation of the solvent was dried *in vacuo* for several hours, and the product (*ca.* 40% yield) was then analyzed.[21] In case the product solidified, it was recrystallized from ethanol–petroleum ether. Iodolactones are unstable, and therefore every attempt was made to purify, analyze and obtain the infrared spectrum of the lactone as soon as possible after the preparation was complete. The infrared spectra were obtained using matched sodium chloride cells with the lactone dissolved in chloroform. A Baird Automatic Infrared Spectrophotometer with a sodium chloride prism was used for the determination.

(18) R. P. Linstead and H. N. Rydon, *J. Chem. Soc.*, 1995 (1934).

(19) M. S. Kharasch and C. F. Fuchs, *J. Org. Chem.*, **9**, 370 (1944).

(20) P. Gaubert, R. P. Linstead and H. N. Rydon, *J. Chem. Soc.*, 1971 (1937).

(21) C. W. Bacon, THIS JOURNAL, **31**, 49 (1909).

MADISON, WISCONSIN

The Preparation of Basic Alcohols and Basic Alkyl Chlorides which Contain a 1-Hexa-, 1-Hepta- or 1-Octamethylenimino Radical

BY F. F. BLICKE AND N. J. DOORENBOS[1,2]

The preparation of eighteen basic alcohols and eighteen basic alkyl chlorides which contain a 1-hexamethylenimino, 2-methyl-1-hexamethylenimino, 4-methyl-1-hexamethylenimino, 1-heptamethylenimino or a 1-octamethylenimino radical has been described.

Basic alcohols and basic alkyl chlorides, which contain dialkylamino as well as polymethylenimino radicals (pyrrolidino and piperidino) as the basic substituents, have been used extensively for the preparation of such synthetic drugs as local anesthetics, antispasmodics, antihistaminics, analgesics and antimalarials. It seemed desirable to extend the series of basic alcohols and chlorides which contain polymethylenimino groups to include compounds which contain seven-, eight- and nine-membered rings, *i. e.*, hexa-, hepta- and octamethylenimino radicals. This project became feasible only after methods had been found by means of which hepta- and octamethylenimine could be obtained readily in relatively large amounts.

The five cyclic imines, used as intermediates, were synthesized by reduction of the required lac-

tam with lithium aluminum hydride. Thus, ϵ-caprolactam yielded hexamethylenimine. 2-Methyl- and 4-methylcyclohexanone, treated with sodium azide and hydrochloric acid, produced 2-methyl-7-keto- and 4-methyl-2-ketohexamethylenimine, respectively, and these keto compounds yielded 2-methyl- and 4-methylhexamethylenimine. Cycloheptanone, sodium azide and hydrochloric acid produced 2-ketoheptamethylenimine which was reduced to heptamethylenimine. Cyclooctanone was treated with sodium azide and hydrochloric acid to produce 2-ketooctamethylenimine which was reduced to octamethylenimine.

Incidentally, the N-formyl and methyl derivatives of heptamethyleimine was prepared and hexa-, hepta- and octamethylenimines were allowed to react with carbon disulfide to form polymethylenammonium polymethylenedithiocarbamates. Mannich reactions were carried out with the hydrochlorides of hepta- and octamethylenimine.