combined chloroform extracts were washed with 75 ml. of 10% sodium bisulfite solution followed by 75 ml. of water. After drying over anhydrous magnesium sulfate, the chloroform was distilled off in reduced pressure. The oily residue was distilled at 115° (0.5 mm.). Reeve and Sadle[9a] report 143 to 150° at 0.3 and 0.36 mm. The distillate was light yellow; yield 229.6 g., 96%.

A typical procedure for hydrogenolysis of Mannich bases is described in Method D.

Method D. 4-Methoxy-*o*-cresol by Hydrogenolysis of α^2-Dimethylamino-4-methoxy-*o*-cresol.—A solution of 18.1 g. (0.1 mole) of α^2-dimethylamino-4-methoxy-*o*-cresol in 150.0 ml. of absolute ethanol and 2.0 g. of copper chromite catalyst was reduced at 175° and an initial pressure of 1800 lb. for six hours. The catalyst was filtered off and the filtrate was concentrated to about 50 ml. This solution was diluted with 200 ml. of water and acidified with 10% hydrochloric acid. The oil which separated was extracted completely with ether. The combined ether extracts were washed with water until neutral and then dried over calcium chloride. Evaporation of the ether on a steam-bath yielded 13.8 g. of tan solid melting at 66–69°. Recrystallization of this material from petroleum ether gave a white crystalline solid melting at 71–72°. Bamberger[15] reports a melting point of 71.5°; yield 12.9 g., 93%.

A general procedure for hydrogenolysis of acetoxymethyl acetate to phenols is described below.

Method E. 4-Methoxy-2,6-xylenol by Hydrogenolysis of α^2,α^6-Diacetoxy-4-methoxy-2,6-xylenyl Acetate.—A solution of 22 g. (0.071 mole) of α^2,α^6-diacetoxy-4-methoxy-2,6-xylenyl acetate[10] in 200 ml. of absolute ethanol and about 1.0 g. of Raney nickel[16] was placed in a hydrogenation bomb and rocked for 24 hours at 165° and 100 atmospheres pressure. After filtration of the catalyst, the alcohol was concentrated in vacuum to about 40 ml. This solution was diluted with 200 ml. of water and then extracted with ether. The combined ether extracts were washed with sodium bicarbonate and dried over magnesium sulfate. After separation of the drying agent, the ether was distilled off in vacuum. The oily residue was distilled at 91–92° (0.4 mm.). The colorless distillate rapidly solidified in the receiver; yield 8.9 g., 65%; m.p. 76–77°.

4-Methoxy-*o*-cresol.—Ten and two-tenths grams (0.05 mole) of 2-bromohydroquinone monomethyl ether (prepared by method of Irvine and Smith[17]) was dissolved in 50 ml. of anhydrous ethyl ether. Into this solution was added slowly over a period of 45 minutes in an atmosphere of nitrogen 210 ml. of 0.715 *N* butyllithium in ether solution. The reaction mixture warmed up to reflux temperature during the early stages of the addition. This mixture was then allowed to stand for three hours before adding, dropwise, a solution of 21.3 g. of methyl iodide in 50 ml. of anhydrous ether. The mixture was then refluxed for two hours and allowed to stand overnight. The next day, the mixture was poured into 250 ml. of ice-water and acidified with 20% hydrochloric acid. The ether layer was separated and the aqueous portion was extracted completely with ether. The combined ether extracts were washed with water before drying over sodium sulfate. The ether was distilled off in vacuum leaving a brown oil. This oil was dissolved in boiling petroleum ether and after slight cooling, a brown oil settled on the bottom of the flask. The solvent was decanted and after cooling in an ice-box for several hours, white needle crystals separated. This procedure was repeated several times on the brown oil. The crystals from the combined extracts were filtered off and air-dried; yield 3.5 g.; 50.5%, m.p. 70–71°.

4-Methoxy-*o*-cresyl Acetate.—α^2-Acetoxy-4-methoxy-*o*-cresyl acetate[10] was reduced in dioxane by Method E in 94% yield. Saponification of a sample of the distilled 4-methoxy-*o*-cresyl acetate with 10% sodium hydroxide solution produced the known 4-methoxy-*o*-cresol in 90% yield. A mixed melting point of the material with a sample of 4-methoxy-*o*-cresol obtained from hydrogenolysis of α^2-dimethylamino-4-methoxy-*o*-cresol showed no depression.

Acknowledgment.—The authors wish to thank Henry Walton for suggestions relating to this work.

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[15] E. Bamberger, *Ann.*, **390**, 174 (1912).

[16] A. A. Pavlic and H. Adkins, THIS JOURNAL, **68**, 1471 (1946).

[17] F. M. Irvine and J. C. Smith, *J. Chem. Soc.*, 47 (1947).

OAKDALE, LONG ISLAND, NEW YORK

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[CONTRIBUTION FROM THE RESEARCH DIVISION, SMITH, KLINE AND FRENCH LABORATORIES]

Cyclic Quaternary Immonium Compounds Derived from 2,2-Diphenyl-4-pentenoic Acid[1]

BY PAUL N. CRAIG

A mechanism is proposed for the lactonization of 2,2-diphenyl-4-pentenoic acid and its methyl ester with bromine or sulfuric acid. Evidence for the proposed mechanism is given by showing that amides and dialkylamides of the above acid cyclize in an analogous manner to give cyclic quaternary immonium ethers. The structures assigned to these cyclic ethers are substantiated by their properties and conversion to the corresponding lactones and, in one case, to an aminolactone.

A study of the lactonizations of 2,2-diphenyl-4-pentenoic and 2,2-diphenyl-4-methyl-4-pentenoic acids[2] led to the observation that the latter acid was lactonized more readily than the former by both bromine and sulfuric acid. Consideration of the reaction mechanism proposed by Tarbell and Bartlett[3] for the formation of halolactones from 1,2-dimethylfumaric and 1,2-dimethylmaleic acids leads to the proposed reaction scheme given.

In the present case the reaction can proceed to completion due to the availability of the covalent-bonded electron pair joining the hydrogen and oxygen atoms for participation in the reaction sequence as shown. This is in contrast with the reactions studied by Tarbell and Bartlett, where the ring is closed by an electron pair present on the negatively charged carboxyl anion.

When R is methyl (*e.g.*, 2,2-diphenyl-4-methyl-4-pentenoic acid) the methyl group may act by hyperconjugation to favor transformations which may be considered to involve an intermediate carbonium ion.[4] In accordance with this factor, 2,2-diphenyl-4-methyl-4-pentanoic acid lactonizes more readily with bromine or sulfuric acid than does the 2,2-diphenyl-4-pentenoic acid.[2]

Consideration of the course in the reaction which might follow the formation of such a carbonium ion intermediate indicates that a group which is in position to close a five or six-membered ring can attack the carbonium carbon atom, providing that the electron release from the attacking group (in this case the oxygen atom of the carboxyl group) may be compensated for by subsequent electron

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[1] Allyldiphenylacetic acid obtained from General Mills, Inc., Minneapolis, Minnesota.

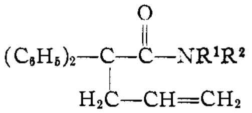
[2] P. N. Craig and I. H. Witt, THIS JOURNAL, **72**, 4925 (1950).

[3] D. S. Tarbell and P. D. Bartlett, *ibid.*, **59**, 407 (1937).

[4] J. W. Baker, *Trans. Faraday Soc.*, **37**, 632 (1941).

TABLE I

AMIDES OF 2,2-DIPHENYL-4-PENTENOIC ACID

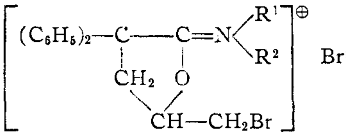


$(C_6H_5)_2-\underset{H_2C-CH=CH_2}{\underset{|}{C}}-\overset{\overset{O}{\|}}{C}-NR^1R^2$

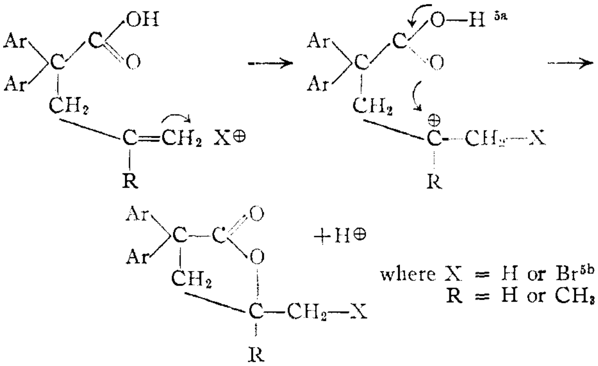
R¹	R²	B.p. °C.	B.p. Mm.	M.p., °C.	Yield, %	Analyses, % Calcd. C	Calcd. H	Found C	Found H
H-	H-	180-181	0.8	77-78	78	Ref. 2	..	...	..
CH_3-	CH_3-	.....	....	110-111	75	81.68	7.58	81.49	7 61
C_2H_5-	C_2H_5-	185-195	3.5	93.5-94.5	70	82.04	8.20	82.10	8.37
$-CH_2CH_2-O-CH_2CH_2-$		200-216	2.5-3.0	96-98	83	78.47	7.21	78.46	7.44

TABLE II

QUATERNARY IMMONIUM SALTS



R¹	R²	M.p., °C. (dec.)	Yield, %	Analyses, % Calcd. C	Calcd. H	Calcd. Br	Found C	Found H	Found Br
H-	H-	247-249	80	49.66	4.17	19.44	49.37	4.00	19.46
CH_3-	CH_3-	194-197	73	51.96	4.82	36.39	51.75	5.08	36.67
C_2H_5-	C_2H_5-	195-196	76	53.98	5.39	34.20	53.89	5.61	33.92
$-CH_2CH_2-O-CH_2CH_2-$		194-195	62	52.41	4.82	33.21	52.52	4.86	32.85



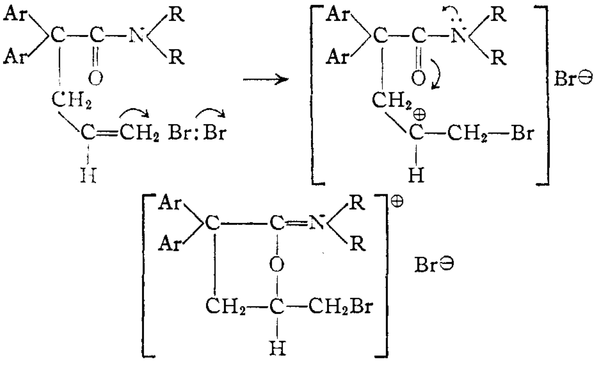
where X = H or Br[5b]
R = H or CH_3

shifts. In the lactonizations of these unsaturated acids the loss of a proton enables such a course to ensue. The methyl esters of these two unsaturated acids also lactonize readily[2] with the elimination of the methyl groups. Evidence has been obtained which indicates that methyl bromide is formed during the reaction of bromine with the methyl ester of 2,2-diphenyl-4-methyl-4-pentenoic acid. The exact mechanism of the release of the methyl group is not yet known.[6]

Since the carboxyl group readily enables these cyclizations to occur, it was planned to extend this study to determine whether groups other than carboxyl might participate in such ring closures. The first to be studied was the carboxamide group. The amide of 2,2-diphenyl-4-pentenoic acid[2] was treated with gaseous hydrogen chloride dissolved in carbon tetrachloride. A crystalline compound resulted which was found to be identical with 3,3-diphenyl-5-methyl-2-iminotetrahydrofuran hydrochloride, prepared by the alkylation of diphenylacetonitrile with propylene oxide.[7]

This reaction was extended to the study of amides prepared from three secondary amines with 2,2-diphenyl-4-pentenoic acid (Table I). In each case a facile ring closure occurred when the amides were treated with bromine in carbon tetrachloride solution.

A mechanism of the reaction leading to the ring closure is proposed below



The resulting quaternary immonium salts (Table II) were characterized by their hydrolysis to the known 2,2-diphenyl-5-bromo-4-valerolactone[2] by treatment with aqueous acids. The cyclic immonium salts are water soluble and react instantly with aqueous silver nitrate to give silver halides. The immonium salts derived from ammonia were

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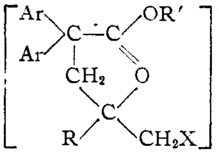
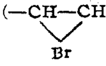
(5) (a) This intermediate may also be written as



in which form it bears a striking resemblance to cyclic intermediates postulated by Winstein, *et al.*, for certain displacement reactions (THIS JOURNAL, **64**, 2780, 2787, 2796 (1942); *ibid.*, **65**, 613 (1943)). (b) Instead of Br^+ one may consider the cyclic brommonium ion



. Compare with I. Roberts and G. E. Kendall, *ibid.*, **59**, 947 (1937).

(6) The mechanism of bromolactone formation from esters of allyldiphenylacetic acid is currently under investigation by Dr. Richard T. Arnold and Mr. Kenneth Lindsay, University of Minnesota (private communication).

(7) N. R. Easton, J. H. Gardner and J. R. Stevens, THIS JOURNAL, **69**, 2941 (1947).

hydrolyzed by water to form the corresponding lactones, whereas the cyclic salts prepared from secondary amines form stable aqueous solutions with an extremely bitter taste.

The reaction of morpholine with 3,3-diphenyl-5-bromomethyltetrahydrofuran - 2 - (N - morpholimmonium) bromide was found to give the same aminolactone, 2,2-diphenyl-5-(4'-morpholino)-4-pentanolactone, which is obtained from 2,2-diphenyl-5-bromo-4-pentanolactone and morpholine.[8]

Ultraviolet spectral data for some of these compounds are given in Fig. 1. Whereas the simple lactones[9] show spectra due to the two phenyl groups, the immonium compounds have such an intense absorption at wave lengths below 275 mμ that only the strong peaks attributable to the aromatic rings are found as mere shoulders on the more intense curve (see Fig. 1). No maximum was found for this peak at the limit of the instrument (210 mμ.)

The pharmacological evaluation of these compounds is in progress.

Acknowledgment.—The author wishes to acknowledge the helpful interest and suggestions shown for this problem by Drs. R. T. Arnold and G. E. Ullyot.

Experimental[10]

Detection of Methyl Bromide.—The reaction of bromine in carbon tetrachloride with methyl 2,2-diphenyl-4-methyl-4-pentenoate was carried out while a current of nitrogen was passed through the reaction flask. The exit gases were washed by passing through a test-tube of water to remove any hydrogen bromide. The purified gases were then run into an alcoholic aqueous silver nitrate solution. A blank was run using 2,2-diphenyl-4-methyl-4-pentenoic acid in place of its ester. Only a trace of clouding appeared when the acid was used, whereas a precipitate of silver bromide was obtained when the methyl ester was used. This is evidence for the formation of methyl bromide during the lactonization.

3,3-Diphenyl-5-methyl-2-iminotetrahydrofuran Hydrochloride.—A solution of 3.0 g. of the amide of 2,2-diphenyl-4-pentenoic acid in 20 ml. of carbon tetrachloride was heated on the water-bath while gaseous hydrogen chloride was slowly introduced beneath the liquid surface. After 15 minutes the solution was cooled, diluted with 50 ml. of ether, and the resultant crystalline precipitate was washed with ether, 0.2 g.; m.p. 215–216° (lit. 220–222°[7]). A sample was hydrolyzed by dissolving it at room temperature in dilute hydrochloric acid to give 2,2-diphenyl-4-valerolactone; m.p. 112–113° alone and mixed with authentic sample.[2,7]

2,3-Diphenyl-5-bromomethyl-2-iminotetrahydrofuran Hydrobromide.—A solution of 1.0 g. of the amide of 2,2-diphenyl-4-pentenoic acid in 10 ml. of carbon tetrachloride was treated dropwise with a 1 to 10 solution of bromine in carbon tetrachloride with shaking. After no more orange colored precipitate formed, 1 ml. of acetone was added to remove the excess bromine. The white precipitate was collected and washed with acetone; m.p. 247–249° dec.

3,3-Diphenyl-5-bromomethyltetrahydrofuran-2-dialkylimmonium Bromides.—The same method was applied for the preparation of the three salts. The dialkylamide was prepared from 2,2-diphenyl-4-pentenoic acid *via* the acid chloride, and was purified either by distillation *in vacuo* or by recrystallization from benzene and petroleum ether. A solution of the amide in carbon tetrachloride was treated with excess bromine or bromine in carbon tetrachloride until no further precipitation occurred. Acetone was added to remove the excess bromine, and the mixture was evaporated *in vacuo* on the steam-bath. The residual crude salt, either crystalline or as a tar, was recrystallized from an appropriate solvent or mixture such as alcohol–ether, isopropyl alcohol (99%)-acetone, etc.

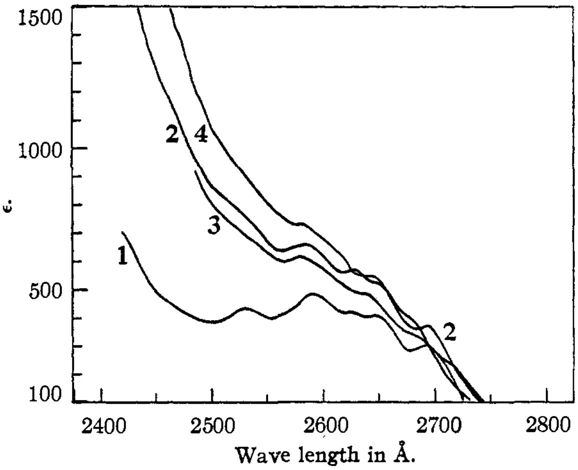


Fig. 1.—(1) is for 2,2-diphenyl-5-bromo-4-pentanolactone; (2) is for 3,3-diphenyl-5-bromomethyl-2-furanoneimmonium bromide; (3) is for 3,3-diphenyl-5-bromomethyltetrahydrofuran-2-dimethylimmonium bromide; (4) is for 3,3-diphenyl-5-bromomethyltetrahydrofuran-2-diethylimmonium bromide.

Hydrolysis of the Quaternary Salts.—The dialkylimmonium salts were hydrolyzed by warming on the steam-bath with dilute hydrochloric acid for varying lengths of time as required. The resulting lactone was recrystallized from alcohol and characterized by melting points and mixed melting points with authentic samples.

Reaction of Morpholine with 3,3-Diphenyl-5-bromomethyltetrahydrofuran-2-dimethylimmonium Bromide.—A solution of 6.0 g. of 3,3-diphenyl-5-bromomethyltetrahydrofuran-2-dimethylimmonium bromide in 20 ml. of morpholine was refluxed for 15 minutes. The solution was diluted to 250 ml. with water, and extracted with 100 ml. of ether. The ether layer was washed five times with water and dried over calcium chloride. On addition of gaseous hydrogen chloride a brown precipitate was obtained, which was recrystallized twice from chloroform, acetone and ether to give 0.3 g. of hydrochloride tan crystals; m.p. 220–222°.

This was converted to the free base by addition of dilute sodium hydroxide to an aqueous solution of the amine hydrochloride. Recrystallization of the free base from alcohol–water gave white crystals of 2,2-diphenyl-5-(4'-morpholino)-4-pentanolactone; m.p. 103–105°.

Anal. Calcd. for $C_{21}H_{23}O_3N$: C, 74.75; H, 6.87. Found: C, 74.68; H, 7.14.

A mixed melting point with the same aminolactone,[11] prepared from 2,2-diphenyl-5-bromomethyl-4-pentanolactone and morpholine, was not depressed.

PHILADELPHIA, PENNA. RECEIVED JUNE 7, 1951

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(8) P. N. Craig, I. H. Witt, J. G. Dacanay, E. Macko, E. J. Fellows and G. E. Ullyot, THIS JOURNAL, 73, 1339 (1951).

(9) P. N. Craig, work to be published.

(10) All melting points are corrected. Analyses by Mrs. Lillian Shreve and the Misses Ruth Savacool and Rita Fox.

(11) Reported as the hydrochloride in Ref. 8; converted to free base by standard procedures.