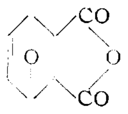
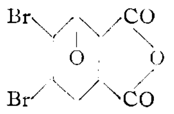
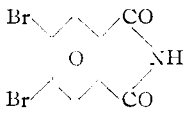


III



IV



V

(R = O) is converted to maleimide (77% yield) and furan. The over-all yield of I from III (55%) is thus comparable to those reported by Prill[3] and by Tawney[4] and superior to that obtained by the pyrrole oxidation (9%[2b]).

In the face of the thermal instability of II (R = O), the report[3] that this substance can be prepared by fusion of the ammonium salt of 3,6-endoxo-Δ^4-tetrahydrophthalamidic acid is surprising. The melting point reported[3] for II (R = O) prepared in this way is 153.5–154°. The two stereoisomers of II (R = O) prepared by diene synthesis or by zinc debromination of the isomers of V melt at 130 and 162°, respectively.[2b,5]

Experimental[6]

Bromination of III.—A mixture of 70 g. of III[7] and 250 cc. of acetic acid was cooled to 20° and treated with a solution of 23 cc. of bromine in 100 cc. of acetic acid during one hour with vigorous stirring. The temperature was kept below 35° with an ice-bath. After being stirred an additional one-half hour, the mixture was cooled to 20° and the crystalline precipitate collected and washed with three 50-cc. portions of carbon tetrachloride. A second crop of crystals was obtained from the filtrate. The yield of *exo-cis*-3,6-endoxo-*trans*-4,5-dibromohexahydrophthalic anhydride (IV), m.p. 157–159°, was 125.7 g. (91%).

Pyrolysis of II (R = O).—Twenty grams of II (R = O)[4] was placed in the sublimation apparatus described by Abrahamson.[8] The charge was heated in an oil-bath at 180–190°, whereupon furan was evolved vigorously. When the evolution of gas had ceased, heating was continued while a gentle stream of nitrogen was admitted to the apparatus. A white solid appeared on the cold finger. After one hour, sublimation had ceased. The sublimate of colorless wedges of maleimide, m.p. 91–93° (reported[2a] m.p. 93°), weighed 9.1 g. (77% of theory).

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[6] Melting points are uncorrected. We are indebted to Mr. Jack Pinkus for checking the procedure.

[7] O. Diels and K. Adler, *Ber.*, **62**, 557 (1929).

[8] E. M. Abrahamson, *Anal. Chem.*, **25**, 203 (1953).

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Decomposition of Quaternary Salts. II. Stereospecificity in the Isomethadone Series

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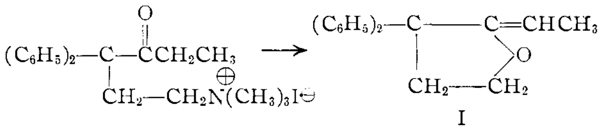
The decomposition of quaternary salts of certain γ-aminoketones has been reported[2] to give compounds with the ethylidenetetrahydrofuran structure (I).



I

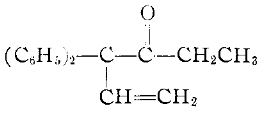
In order to ascertain whether this reaction proceeds through the unsaturated ketone II as an intermediate, a study was made in the isomethadone series. It was first determined that the methiodide of *dl*-isomethadone decomposed to give an ethylidenetetrahydrofuran. This was done by comparing the ultraviolet curves as in Table I.

TABLE I

SPECTRAL DATA

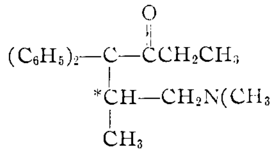
Pyrolysis product of methadone methiodide			Pyrolysis product of isomethadone methiodide	
λ alcohol, max mμ	*E*	Type of peak	λ alcohol, max mμ	*E*
250	930	Shoulder	252	618
259	738	Small peak	259	555
264	580	Shoulder	264	403
270	359	Shoulder	270	248

Since the optically active center (*) of isomethadone (III) is adjacent to the carbon attached to the nitrogen atom any intermediate of the unsaturated ketone type (II) would cause racemization of the optically active forms of isomethadone.



$(C_6H_5)_2\underset{\mathrm{CH{=}CH_2}}{\mathrm{C}}\text{—}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\text{—}CH_2CH_3$

II



$(C_6H_5)_2\underset{\underset{\mathrm{CH_3}}{\mathrm{{}^{*}CH—CH_2N(CH_3)_2}}}{\mathrm{C}}\text{—}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}CH_2CH_3$

III

A study was then made of the decomposition of the methiodides of the optically active forms of isomethadone. It is found that while the *dl* form gives a product melting at 166–168° both the *d* and the *l* forms give products melting at 102–104°. A mixed melting point of these two products was 125–150° and when hot alcoholic solutions were combined the resulting product melted at 166–168°. Since there is no racemization, it is clearly indicated that the reaction cannot have the unsaturated ketone as an intermediate.

The neutral products obtained were of a high degree of purity since after a single recrystallization they gave a product of constant melting point. Since the *dl* product has a higher melting point and is less soluble in ethanol, its presence would be readily ascertained. However, none of it could be detected in either of the optically active compounds.

It is of interest to note that the yields of neutral decomposition products were considerably greater in the case of the active forms. This may be due to the fact that these methiodides melted at a lower temperature than did the methiodide in the *dl* form (Table II).

Since it has been reported[3] that the heating of isomethadone with base required much more drastic conditions to cleave the propionyl group than that required for methadone and it has also been reported[4] that the decomposition of the quaternary hydroxides of methadone gives no neutral product, it was deemed advisable to study the decomposition of the quaternary hydroxide of isomethadone. It was found that the decomposition of the quaternary hydroxide of isomethadone gives the same neutral

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[1] Lilly Research Laboratories, Eli Lilly and Company, Indianapolis 6, Indiana.

[2] N. R. Easton, S. J. Nelson, V. B. Fish and P. N. Craig, THIS JOURNAL, **75**, 3751 (1953).

[3] E. L. May and E. Mosettig, *J. Org. Chem.*, **13**, 663 (1948).

[4] E. L. May and E. Mosettig, *ibid.*, **13**, 459 (1948).

TABLE II

DECOMPOSITION OF QUATERNARY SALTS

Parent cpd.	Derivative	Specific rotation	Product, m.p., °C.	Specific rotation	Yield, %	Solvent of crystaln.	Analyses,[a] % Found	
							Carbon	Hydrogen
dl-Isomethadone	Me I	0	166–168	0	17	Ethyl acetate	86.20	7.74
d-Isomethadone	Me I	+98.1	102–104	+312	30.4	Ethanol	86.20	7.72[b]
l-Isomethadone	Me I	−96.8	102–104	−308	40	Ethanol	86.10	7.78[c]
dl-Isomethadone	Quat. hydrox.	0	166–168	0	53			
d-Isomethadone	Quat. hydrox.		102–104		51.5			
l-Isomethadone	Quat. hydrox.		102–104		67			

[a] Calcd.: C, 86.32; H, 7.63. [b,c] Mixture of these two compounds melted at 125–150°. Combination of hot ethanolic solutions of the two gave a compound identical to that obtained from *dl*-isomethadone.

product as the methiodide and in a much greater yield. The *d* and *l* forms of isomethadone reacted in the same manner but the increase in yield was not as marked.

It has been reported[2] that the ethylidenetetrahydrofurans such as I react with hydroxylamine to form an adduct either by straight addition or by the hydrolysis of the ethylidenetetrahydrofuran and the reaction of hydroxylamine with the hydroxyketone. It is found that the ethylidenetetrahydrofurans in these series undergo the same type of reaction.

It is of interest to note that the ethylidenetetrahydrofurans have the same direction of rotation as the parent compound but the hydroxylamine products give the opposite rotation.

A study of the ultraviolet spectra (Table I) points out the interesting effect of changing the methyl group from position 5 to position 4 of the tetrahydrofuran ring. The molar extinction coefficient is reduced by roughly one third by this change.

Experimental

Decomposition of the Quaternary Iodides.—These decompositions were carried out by heating 10 g. of the methiodide in a Claisen flask under 16–24 mm. pressure, with a free flame until decomposition was complete. The product was dissolved in ether. (A small quantity of material was ether insoluble and sublimed at about 365°; this was undoubtedly tetramethylammonium iodide.) The ether solution was washed with dilute hydrochloric acid, dried over magnesium sulfate and concentrated on a steam-bath.

Decomposition of Quaternary Hydroxides.—A mixture of 10 g. of the methiodide and 5 g. of silver oxide in an ethanol-water mixture was stirred until the solution gave a negative test for the iodide ion. It was filtered and the precipitate was washed with ethanol and then with water. The solution was concentrated at reduced pressure. The optically active compounds were decomposed by heating on a steam-bath. The racemic mixture was transferred to a Claisen flask and decomposed as the methiodides. The products were dissolved in ether, extracted with dilute hydrochloric acid, dried and concentrated. The products were purified as above.

Reaction of Decomposition Products with Hydroxylamine.—The materials obtained by the thermal decomposition of the methiodides of *dl*-, *d*- and *l*-isomethadones reacted with hydroxylamine to give the respective adducts. A typical preparation is as follows: a mixture of 1.5 g. of the ethylidene compound, 1.5 g. of hydroxylamine hydrochloride, 7.5 ml. of ethanol and 7.5 ml. of anhydrous pyridine was refluxed for about three hours. The solvent was evaporated on a steam-bath until the residue became a viscous liquid; then about 5 ml. of ethanol was added to dissolve the residue. The solution was mixed with 100 ml. of water, the precipitate was filtered and dried. The crude product was recrystallized several times from a mixture of neohexane and methylcyclohexane and finally from methanol and water. Table III indicates the melting points and other data found for these adducts.

TABLE III

PHYSICAL CONSTANTS AND ANALYSIS OF THE ADDUCTS WITH HYDROXYLAMINE

Parent cpd.	Yield, %	M.p., °C.	Specific rotation	Analyses,[a] % Found		
				Carbon	Hydrogen	Nitrogen
dl		160–163	0	76.50	7.94	4.72
d	40	140–141	−15.0	76.85	7.97	4.71
l	37	139–141	+14.8	76.75	7.60	

[a] Calcd.: C, 76.80; H, 7.79; N, 4.71.

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