

54% yield, and melted at 153.5–155.0° after recrystallization from acetone.

Anal. Calcd. for $C_{11}H_{21}NO_2 \cdot HCl$: C, 56.0; H, 9.4; N, 5.9. Found: C, 56.1; H, 9.3; N, 5.7.

(1-Acetoxyethylcyclohexyl)-trimethylammonium Iodide (III).—The methiodide was prepared from the hydrochloride as described in method B above; m.p. 169.0–170.0° (recrystallized from isopropyl alcohol), 81% yield.

Anal. Calcd. for $C_{12}H_{24}INO_2$: C, 42.2; H, 9.1. Found: C, 42.2; H, 9.0.

[β -(N,N-Diethylthiocarbamyloxy)-*t*-butyl]-trimethylam-

monium Iodide.—Reaction of II and N,N-diethylthiocarbamyloxy chloride according to method J yielded 2-dimethylamino-2-methylpropyl N,N-diethylthiocarbamate, b.p. 114–118° at 3 mm., n_D^{20} 1.5002.

Anal. Calcd. for $C_{11}H_{24}N_2OS$: C, 56.8; H, 10.4; N, 12.1. Found: C, 57.5; H, 10.6; N, 11.4.

The methiodide melted at 187.5–189.0° after recrystallization from isopropyl alcohol–ethyl acetate.

Anal. Calcd. for $C_{12}H_{27}IN_2OS$: C, 38.5; H, 7.3. Found: C, 39.4; H, 7.6.

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NOTES

8-Basically-substituted Caffeines

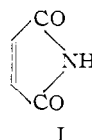
By F. F. BLICKE AND H. C. GODT, JR.

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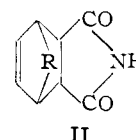
During a study of substituted xanthenes, a few 8-basically substituted caffeines¹ were prepared by amination of 8-chlorocaffeine.

Experimental

General Procedure.—8-Chlorocaffeine² (11.4 g., 0.05 mole), 0.1 mole of the required amine and 75 cc. of absolute ethanol were heated in a citrate bottle at 150° for 6 hours. After refrigeration for 12 hours, the precipitate was filtered and recrystallized.



I



II

various N- and C-substituted derivatives of I have been prepared by straightforward methods,¹ only two practical procedures for the preparation of I itself have been reported. Plancher and Cattadori² obtained I in small yield by chromic acid oxidation of pyrrole. Prill³ employed a dienophile exchange reaction in which bicyclic imide adducts of



All compounds were recrystallized from absolute ethanol except 3 which was recrystallized from 50% methanol.

	R	M.p., °C.	Yield, %	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
1	Pyrrolidino	184–186	76	$C_{12}H_{17}O_2N_5$	54.74	54.54	6.51	6.51	26.60	26.48
2	Piperidino	141–143 ^a	75
3	1-Hexamethylenimino	114–116	69	$C_{14}H_{21}O_2N_5$	57.71	57.97	7.27	7.42	24.04	24.32
4	Morpholino	166–167	66	$C_{12}H_{17}O_3N_5$	51.60	51.41	6.14	6.15	25.08	25.28
5	β -Phenylethylamino	219–221	74	$C_{16}H_{19}O_2N_5$	61.33	61.59	6.11	6.39	22.35	22.39

^a Ref. 1c, m.p. 142°.

Three of the products listed in the table were tested for diuretic activity in the Lilly Research Laboratories. Compound 1, administered orally, produced only slight diuresis in two of six dogs (200 mg. dose). Tested in the same manner, compound 3 (400 mg. dose) and compound 4 (100 mg. dose) did not produce diuresis.

(1) Other 8 basically-substituted caffeines, in which the basic nitrogen atom is attached directly to the 8-carbon atom, have been described by (a) E. Fischer (*Ann.*, **215**, 253 (1882)), (b) L. Cramer (*Ber.*, **27**, 3098 (1894)), (c) A. Einhorn and E. Baumeister (*ibid.*, **31**, 1138 (1898)) and (d) M. Gomberg (*Am. Chem. J.*, **23**, 51 (1900)).

(2) L. M. Long, *THIS JOURNAL*, **69**, 2939 (1947).

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A Synthesis of Maleimide

By JEROME A. BERSON AND RONALD SWIDLER

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Maleimide (I), a relatively simple substance, has proved to be remarkably inaccessible. While

the type II were heated in a gas flow system with excess maleic anhydride, while Tawney⁴ effected similar decompositions without the use of an added diene acceptor.

The present synthesis of I takes advantage of the particularly facile retrogression of the Diels–Alder reaction in the furan series and of our recently described⁵ procedure for the preparation of II (R = O) from the readily accessible furan–maleic anhydride adduct (III).

The steps of the sequence III \rightarrow IV \rightarrow V \rightarrow II (R = O) proceed in yields of 91, 89 and 88%, respectively. Upon being heated at 180–190°, II

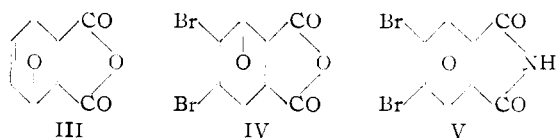
(1) (a) A. Piutti and E. Giustiniani, *Gazz. chim. ital.*, **26**, I, 435 (1896); (b) J. Gottlieb, *Ann.*, **77**, 274 (1851); (c) G. Ciamician and M. Dennstedt, *Gazz. chim. ital.*, **12**, 501 (1882).

(2) (a) G. Plancher and V. Cattadori, *Atti della Reale Acad. dei Lincei*, **13**, I, 490 (1904); (b) H. Kwart and I. Burchuk, *THIS JOURNAL*, **74**, 3094 (1952).

(3) E. J. Prill, U. S. Patent 2,524,136 (1950).

(4) P. O. Tawney, U. S. Patent 2,524,145 (1950). We are indebted to a referee for pointing out this reference.

(5) J. A. Berson and R. Swidler, *THIS JOURNAL*, **76**, in press.



(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 Prill³ and by Tawney⁴ and superior to that obtained by the pyrrole oxidation (9%^{2b}).

In the face of the thermal instability of II (R = O), the report³ that this substance can be prepared by fusion of the ammonium salt of 3,6-endoxo- Δ^4 -tetrahydrophthalamic acid is surprising. The melting point reported³ 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}

Experimental⁶

Bromination of III.—A mixture of 70 g. of III⁷ 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).

(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).

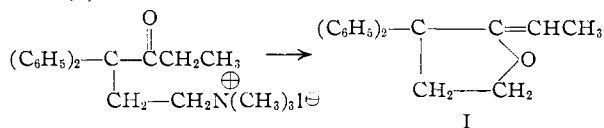
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Decomposition of Quaternary Salts. II. Stereospecificity in the Isomethadone Series

BY NELSON R. EASTON¹ AND VELMER B. FISH

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The decomposition of quaternary salts of certain γ -aminoketones has been reported² to give compounds with the ethylenetetrahydrofuran structure (I).



In order to ascertain whether this reaction pro-

(1) Lilly Research Laboratories, Eli Lilly and Company, Indianapolis 6, Indiana.

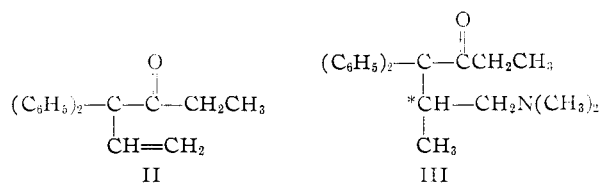
(2) N. R. Easton, S. J. Nelson, V. B. Fish and P. N. Craig, *This Journal*, **76**, 3751 (1953).

ceeds 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 ethylenetetrahydrofuran. This was done by comparing the ultraviolet curves as in Table I.

TABLE I
SPECTRAL DATA

Pyrolysis product of methadone methiodide		Type of peak	Pyrolysis product of isomethadone methiodide	
λ alcohol, max $m\mu$	<i>E</i>		λ alcohol, max $m\mu$	<i>E</i>
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.



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 reported³ 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 reported⁴ 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

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

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