carried out by the method described previously.[3] In contrast to sulfhydryl-containing albumin, which requires a concentration of 1.3% to form a solid coagulum on heating 30 minutes at 100° in 0.1 *M* phosphate buffer of *p*H 7.4, iodoacetamide-treated albumin forms a solid gel under these conditions in a 0.6% concentration. Although the gels formed from iodoacetamide-treated albumin are not entirely clear, they are markedly less turbid and much firmer than those obtained with sulfhydryl-containing albumin. Addition of one mole of mercaptoethanol per mole of protein raises the "least coagulable concentration" to greater than 0.9% and causes the coagula to be opaque, synerizing and typical of the clots formed from sulfhydryl-containing albumin. Even 0.1 mole of mercaptoethanol per mole of iodoacetamide-treated albumin will induce the foregoing effect on the gel characteristics.

Discussion

The foregoing viscosity and sedimentation data support the concept suggested by previous coagulation studies, namely, that during thermal denaturation of plasma albumin aggregation can take place by several mechanisms, and that free sulfhydryl groups promote lateral association of polypeptide chains. The sedimentation patterns indicate that all of the sulfhydryl-containing albumin becomes aggregated at a rapid rate upon heating. The fact that this process does not produce a very large increase in viscosity suggests that this aggregation is predominantly of a side-by-side nature (process B) which decreases rather than increases the asymmetry of the molecule. In view of the ability of a simple mercaptan to restore partially to iodoacetamide-treated albumin the aggregation and coagulation characteristics typical of sulfhydryl-containing albumin, it appears that process B involves a sulfhydryl-disulfide chain reaction similar to that described in the preceding paper[8] for the case of denaturation by urea.

The aggregation of sulfhydryl-free albumin at 100° takes place more slowly than that of sulfhydryl-containing albumin, but that portion which does aggregate forms a larger, or at least a more rapidly sedimenting, unit. This type of aggregation (process A) is accompanied by a large increase in viscosity in dilute solutions and an increased capacity for gel-formation in more concentrated solutions. That the reaction or reactions of process A possess a higher temperature coefficient than the other mechanisms of aggregation is indicated by the data in Fig. 2. Whereas the viscosity of a heated solution of sulfhydryl-containing albumin is influenced more by the protein concentration than by the temperature at which thermal denaturation is effected, the viscosity of silver-treated albumin depends more on the denaturation temperature than on the concentration. The chemical nature of process A as yet is obscure, but apparently it does not involve free amino groups.[3]

Apart from hypotheses, one definite conclusion is evident from the foregoing experimental results. The changes in viscosity and sedimentation characteristics which accompany the thermal denaturation of bovine plasma albumin differ significantly depending on whether or not the protein has been treated first with extremely small amounts of reagents believed to react selectively with sulfhydryl groups.

CHICAGO, ILLINOIS

[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

α,α-Dimethylcholine: Esters and Carbamates[1]

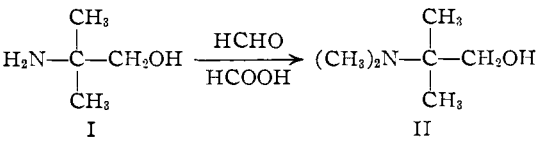
BY WILLIAM B. WHEATLEY

RECEIVED JANUARY 15, 1954

2-Dimethylamino-2-methyl-1-propanol, prepared easily by methylation of 2-amino-2-methyl-1-propanol, provides a convenient route to acetyl-α,α-dimethylcholine and analogs. A number of esters and carbamates of this type are reported herein. A cyclic α,α-disubstituted acetylcholine (III) also has been prepared.

In an attempt to obtain compounds which would act as acetylcholine but be less susceptible to hydrolysis by cholinesterase, we have synthesized a series of esters and carbamates of α,α-dimethylcholine. At the time that this investigation was started, no acyl α,α-dimethylcholines had been reported, although α,α-dimethylcholine itself had been described by Moyer and du Vigneaud[2] and by Alexander.[3] The commercial availability of 2-amino-2-methyl-1-propanol (I) appeared to offer a convenient starting material for the preparation of α,α-dimethylcholine and derivatives thereof.

Methylation of I with methyl iodide and potassium hydroxide gives α,α-dimethylcholine iodide directly[2]; methylation with formaldehyde and formic acid[4] gives 2-dimethylamino-2-methyl-1-propanol (II) in good yield.[5]



I II

α,α-Dimethylcholine iodide also may be prepared by the Cannizzaro reaction on the methiodide of α-

(1) Presented before the Division of Medicinal Chemistry of the American Chemical Society, Kansas City, Mo., March, 1954.

(2) A. W. Moyer and V. du Vigneaud, *J. Biol. Chem.*, **143**, 373 (1942).

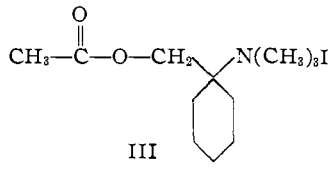
(3) E. R. Alexander, THIS JOURNAL, **70**, 2592 (1948).

(4) H. T. Clarke, H. B. Gillespie and S. Z. Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

(5) V. Rosnati (*Gazz. chim. ital.*, **80**, 663 (1950); *C. A.*, **46**, 429 (1952)) has recently described this same preparation. He quaternized II with methyl iodide, then acetylated to obtain acetyl-α,α-dimethylcholine iodide (*cf.* compound V, Table 1).

dimethylaminoisobutyraldehyde, though in low yield.[3] The aminoalcohol II was esterified by reaction with acid anhydrides or chlorides, or converted to carbamates by one of several methods. The carbamate XIV was prepared by adding II to an excess of phosgene, followed by ammonolysis of the intermediate chlorocarbonate. Phenyl isocyanate and II yielded the N-phenylcarbamate XVI, while N,N-disubstituted carbamyl chlorides gave the N,N-disubstituted carbamates. Quaternization of the esters and carbamates proceeded readily on addition of methyl iodide to an alcohol solution of the base. The facile hydrolysis of choline type esters was observed in an attempted preparation of acetyl-α,α-dimethylcholine iodide (V). 2-Dimethylamino-2-methylpropyl acetate hydrochloride (IV) was shaken at room temperature with dilute alkali and the liberated organic base extracted into ether. Treatment of the ether extract with methyl iodide yielded not V but the methiodide of II. When carbonate was used to liberate the basic ester, hydrolysis did not occur, and the desired ester V was obtained.

An example of an α,α-disubstituted acetylcholine in which the substituents are incorporated in a cyclic structure is the cyclohexane derivative III, which was prepared by a series of reactions starting with nitrocyclohexane. Formaldehyde condensed with nitrocyclohexane in the presence of sodium



III

hydroxide to give 1-nitrocyclohexanemethanol in high yield. While a satisfactory analysis could not be realized on this product, catalytic reduction over Raney nickel yielded the known 1-aminocyclohexanemethanol.[6] A small amount of cyclohexylamine was isolated from this reduction, indicating a partial reversal of the condensation to formaldehyde and nitrocyclohexane. The instability of nitroalcohols in the presence of bases and consequent inconsistent yields of aminoalcohols obtained by reduction has been reported.[7] Methylation of 1-aminocyclohexanemethanol, followed by acetylation and quaternization, yielded III.

Acknowledgment.—The author is indebted to Mr. Richard M. Downing for the microanalyses reported, and wishes to express his appreciation for the advice and encouragement of Dr. Lee C. Cheney throughout this investigation.

Experimental[8]

2-Dimethylamino-2-methyl-1-propanol.—Methylation of 2-amino-2-methyl-1-propanol by means of formaldehyde and formic acid[4] gave the expected tertiary amine, which was isolated in 74% yield as the hydrochloride, m.p. 250° dec.

Anal. Calcd. for $C_6H_{15}NO\cdot HCl$: C, 46.9; H, 10.5; N, 9.2. Found: C, 47.2; H, 10.5; N, 8.9.

The free base, liberated from the hydrochloride by flake sodium hydroxide, is completely miscible with water but dissolves only slightly in ether or benzene. It boils at 61° at 20 mm. (lit.[5] 159–161°), $n^{25}D$ 1.4450.

2-Diethylamino-2-methyl-1-propanol.—The difficulty of dialkylation of 2-amino-2-methyl-1-propanol experienced by Bachman and Mayhew[9] was encountered also by us. The first ethyl group was introduced with ethyl sulfate, the second with ethyl bromide following isolation of the intermediate monoethylamino compound. Sodium–alcohol reduction of ethyl α-diethylaminoisobutyrate gives the same 2-diethylamino-2-methyl-1-propanol.[10]

1-Nitrocyclohexanemethanol.—Nitrocyclohexane (400 g., 3.1 moles) was mixed with a solution of 1 g. of sodium hydroxide in 375 ml. of 95% ethanol. To this solution was added over a period of 1.5 hours 225 ml. of 37% formalin. During this time, the reaction mixture was stirred and maintained at about 55° by application of heat as needed. After three hours more at this temperature, 200 ml. of solvent was distilled under reduced pressure. The residual solution was poured into 2 l. of water and acidified with hydrochloric acid. The oil which settled to the bottom was withdrawn and the aqueous layer extracted three times with benzene. The extracts were added to the oil, and the resulting benzene solution dried over anhydrous sodium sulfate. Distillation of the decanted solution afforded a small amount of recovered nitrocyclohexane, followed by 444 g. (93% yield) of 1-nitrocyclohexanemethanol, b.p. 110–114° at 3 mm., $n^{25}D$ 1.4850. The analysis suggests a high-oxygen impurity.

Anal. Calcd. for $C_7H_{13}NO_3$: C, 52.8; H, 8.2; N, 8.8. Found: C, 51.8; H, 8.3; N, 7.8.

The N-phenylcarbamate, recrystallized from Skellysolve C, melted at 100.0–103.0°.

Anal. Calcd. for $C_{14}H_{18}N_2O_4$: C, 60.4; H, 6.5. Found: C, 60.7; H, 6.3.

1-Aminocyclohexanemethanol.—1-Nitrocyclohexanemethanol (272 g., 1.71 moles) was hydrogenated in 350 ml. of methanol at 600 lb./in.^{2} over 20 g. of Raney nickel (wet paste as obtained from the Gilman Paint and Varnish Works, Chattanooga, Tenn.). At 65° absorption of hydrogen began, and the exothermic reaction carried the temperature to 125°. Shaking was interrupted for 20 minutes in order to allow the bomb to cool somewhat. After an hour of additional shaking, hydrogenation had ceased, with a total hydrogen absorption corresponding to 65% of theory having occurred. The catalyst was removed by filtration and the solvent distilled under reduced pressure. The residual oil was taken up in benzene and extracted with dilute hydrochloric acid. The aqueous acid extract was made strongly basic with potassium hydroxide and subjected to continuous ether extraction for 48 hours. (The solubility of the aminoalcohol in water is so great that simple extraction is not satisfactory.) Distillation of the ether extract gave a forerun of 75.3 g., followed by 95.5 g. (43% yield) of 1-aminocyclohexanemethanol as a rather viscous, colorless liquid, b.p. 114–118° at 14 mm., $n^{20}D$ 1.4964 (lit.[6] b.p. 117–118° at 27 mm., $n^{20}D$ 1.4970). Redistillation of the forerun showed it to be essentially a mixture of water and cyclohexylamine, 29.2 g. (17% yield) of the latter being obtained.

1-Dimethylaminocyclohexanemethanol.—Formaldehyde–formic acid methylation of 1-aminocyclohexanemethanol gave the tertiary amine in 79% yield, isolated and purified as the hydrochloride by recrystallization from isopropyl alcohol–ether, m.p. 185.5–187.0°.

Anal. Calcd. for $C_9H_{19}NO\cdot HCl$: C, 55.8; H, 10.4; N, 7.2. Found: C, 56.2; H, 10.3; N, 6.9.

The free aminoalcohol boiled at 105–109° at 11 mm., and solidified to a low-melting solid.

(1-Hydroxymethylcyclohexyl)-trimethylammonium Iodide.—Ten milliliters of methyl iodide was added to a solution of 8.8 g. of 1-dimethylaminocyclohexanemethanol in 50 ml. of isopropyl alcohol. The solution was heated to reflux, then diluted with an equal volume of ethyl acetate. Scratching induced crystallization, and after chilling the solid was collected by filtration. Recrystallization from isopropyl alcohol–ethyl acetate gave 9.6 g. (58% yield) of the methiodide, m.p. 157.0–160.5°.

Anal. Calcd. for $C_{10}H_{22}INO$: C, 40.1; H, 7.4. Found: C, 40.4; H, 7.5.

(6) H. Adkins and H. R. Billica, THIS JOURNAL, **70**, 3121 (1948).

(7) H. B. Hass and E. F. Riley, *Chem. Revs.*, **32**, 389 (1943).

(8) All melting points are corrected.

(9) G. B. Bachman and R. L. Mayhew, *J. Org. Chem.*, **10**, 243 (1945).

(10) W. B. Burnett, R. L. Jenkins, C. H. Peet, E. E. Dreger and R. Adams, THIS JOURNAL, **59**, 2248 (1937).

TABLE I

	R	R′	Y	Yield, %	Method[a]	M.p., °C.	Recrystallization solvent	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
IV	CH_3	CH_3	HCl	87	A	130.0–131.5	$CHCl_3$–Et_2O	$C_8H_{17}NO_2$·HCl	49.1	48.8	9.3	9.0		
V	CH_3	CH_3	CH_3I	87	B	194.0–195.0[b]	*i*-PrOH							
VI	$ClCH_2$	CH_3	HCl	39	C	126.0–130.0	Me_2CO	$C_8H_{16}ClNO_2$·HCl	41.8	41.9	7.5	7.7	6.1	6.2
VII	$ClCH_2$	CH_3	CH_3I	26	B	231 dec.	*i*-PrOH–H_2O	$C_9H_{19}ClINO_2$·H_2O	30.6	30.5	6.0	6.4	4.5	4.0
VIII	$(C_6H_5)_2CH$	CH_3	HCl	64	D	170.0–171.5	*i*-PrOH–SSB[d]	$C_{20}H_{25}NO_2$·HCl	69.1	69.4	7.5	7.8	4.0	4.4
IX	*p*-$O_2NC_6H_4$	CH_3	HCl	65	D	206.0–207.0	*i*-PrOH	$C_{13}H_{18}N_2O_4$·HCl	51.6	51.6	6.3	6.4	9.3	9.1
X	*p*-$H_2NC_6H_4$	CH_3	HCl	51	E	187.0–189.0	MeOH–*i*-PrOH	$C_{13}H_{20}N_2O_2$·HCl	57.2	57.3	7.8	7.9	10.3	10.5
XI	$(C_6H_5)_2CH$	C_2H_5	HCl	21	C	141.0–143.0	Me_2CO–Et_2O	$C_{22}H_{29}N_2O$·HCl	70.3	70.6	8.4	7.9		
XII	$(C_6H_5)_2CH$	C_2H_5	CH_3I	36	F	169.0–169.5	*i*-PrOH	$C_{23}H_{32}INO_2C_4H_8O$	57.7	58.0	7.5	7.5		
XIII	*p*-$O_2NC_6H_4$	C_2H_5	HCl	55	F	167.0–168.0[c]	*i*-PrOH	$C_{15}H_{22}N_2O_4$·HCl	54.5	54.6	7.0	7.1		
XIV	H_2N	CH_3	HCl	37	G	215.0–218.0	MeOH–*i*-PrOH	$C_7H_{16}N_2O_2$·HCl	42.7	42.9	8.7	8.2	14.2	13.8
XV	H_2N	CH_3	CH_3I	38	G	203.5–205.0	*i*-PrOH–H_2O	$C_8H_{19}IN_2O_2$	31.8	31.9	6.3	6.5	9.3	9.1
XVI	C_6H_5NH	CH_3	HCl	40	H	194.5–196.0	*i*-PrOH	$C_{13}H_{20}N_2O_2$·HCl	57.2	57.1	7.8	7.9	10.3	10.1
XVII	C_6H_5NH	CH_3	CH_3I	87	B	186.0–187.0	*i*-PrOH–MeOH	$C_{14}H_{23}IN_2O_2$	44.4	44.5	6.1	6.4	7.4	7.5
XVIII	$(C_6H_5)_2N$	CH_3	HCl	55	J	204.5–206.5	*i*-PrOH–Et_2O	$C_{19}H_{24}N_2O_2$·HCl	65.4	65.3	7.2	7.4	8.3	7.7
XIX	$(C_6H_5)_2N$	CH_3	CH_3I	45	J	208.5–210.0	*i*-PrOH	$C_{20}H_{27}IN_2O_2$	52.9	52.9	6.0	6.1	6.2	5.8

[a] See Experimental. [b] Rosnati[5] reported m.p. 194–195°. [c] Previously reported as an oil.[10] [d] SSB = petroleum ether, b.p. 60–70°.

Esters and Carbamates of 2-Dialkylamino-2-methyl-1-propanol. (See Table I.) Method A.—A solution of 2-dimethylamino-2-methyl-1-propanol hydrochloride in an excess of acetic anhydride was heated for 5 hours on the steam-bath. Dilution with ethyl acetate and cooling resulted in crystallization of the hydrochloride of the basic ester.

Method B.—An aqueous solution of the ester (or carbamate) hydrochloride was carefully neutralized with sodium carbonate and the liberated organic base extracted into ether or chloroform. The solvent was evaporated, the residual oil taken up in isopropyl alcohol and treated with an excess of methyl iodide. Carbonate is preferable for neutralization, since when sodium hydroxide was used with 2-dimethylamino-2-methylpropyl acetate hydrochloride (IV), the product obtained was not the methiodide of the ester, but that of the alcohol, β-hydroxybutyltrimethylammonium iodide.

Method C.—A 10% excess of the acid chloride was added dropwise to a stirred suspension of the aminoalcohol hydrochloride in chloroform. At the end of the addition, the hydrochloride had dissolved completely. The solution was refluxed for 30 minutes, the solvent evaporated under reduced pressure and the residue crystallized from a suitable solvent.

Method D.—A benzene solution of the acid chloride (1 equiv.) was added dropwise to a stirred suspension of the aminoalcohol hydrochloride (1 equiv.) in chloroform containing pyridine (2 equiv.), cooling intermittently to maintain the mixture at about room temperature. Upon completion of the addition, the mixture was refluxed for one hour, cooled and poured into water. The separated benzene–chloroform layer was shaken with sodium carbonate solution, then dried over sodium sulfate. Evaporation of the solvent left an oil which was taken up in isopropyl alcohol and treated with dry hydrogen chloride.

Method E.—A solution of the *p*-nitrobenzoate ester in 40% ethanol was hydrogenated over 5% palladium-on-carbon at low pressure and room temperature; reduction was complete in one hour. After filtration to remove the catalyst, the solvent was distilled and the residue crystallized.

Method F.—Esterification was carried out as in method C except that the free aminoalcohol was used instead of its hydrochloride.

Method G.—A chloroform solution of 0.2 mole of the hydrochloride of II was added all at once to an ice-cold solution of 0.25 mole of phosgene in chloroform. The mixture was allowed to warm slowly to room temperature, and stood overnight. Solvent and excess phosgene were distilled under reduced pressure and the residue taken up in fresh chloroform. This solution was added dropwise to an ice-cold, stirred solution of about 10 g. of ammonia in chloroform; a white solid separated. After coming to room temperature, the mixture was treated with just enough water to dissolve the solid. The chloroform layer was withdrawn, filtered through anhydrous potassium carbonate and the solvent evaporated. The solid residue was dissolved in isopropyl alcohol and divided into two equal parts; one part was treated with dry hydrogen chloride, the other with methyl iodide.

Method H.—Equivalent amounts of the hydrochloride of II and phenyl isocyanate in diethylacetamide were heated on the steam-bath overnight. The mixture was cooled and the precipitated carbamate hydrochloride collected by filtration.

Method J.—A pyridine solution of equivalent amounts of II and diphenylcarbamyl chloride was heated on the steam-bath for 2 hours. The cooled reaction mixture was poured into water, made strongly basic and the carbamate isolated by extraction with benzene. Evaporation of the benzene from the dried extracts left a residual oil which was taken up in isopropyl alcohol and divided into two parts for preparation of the hydrochloride and methiodide as described in method G.

1-Dimethylaminocyclohexanemethyl Acetate Hydrochloride.—1-Dimethylaminocyclohexanemethanol hydrochloride was esterified with acetic anhydride as in method A above. The product was obtained in

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-Acetoxymethylcyclohexyl)-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]-trimethylammonium Iodide.—Reaction of II and N,N-diethylthiocarbamyl chloride according to method J yielded 2-dimethylamino-2-methylpropyl N,N-diethylthiocarbamate, b.p. 114–118° at 3 mm., $n^{25}D$ 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.

SYRACUSE, NEW YORK

NOTES

8-Basically-substituted Caffeines

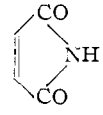
BY F. F. BLICKE AND H. C. GODT, JR.

RECEIVED JANUARY 11, 1954

During a study of substituted xanthines, a few 8-basically substituted caffeines[1] were prepared by amination of 8-chlorocaffeine.

Experimental

General Procedure.—8-Chlorocaffeine[2] (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.



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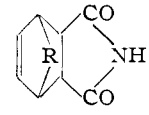
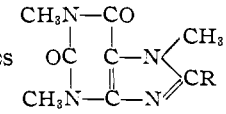


II

8-BASICALLY-SUBSTITUTED CAFFEINES



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

	R	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % 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-Hexamethyleniminо	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

RECEIVED DECEMBER 30, 1953

Maleimide (I), a relatively simple substance, has proved to be remarkably inaccessible. While 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 Cattadori[2] obtained I in small yield by chromic acid oxidation of pyrrole. Prill[3] employed a dienophile exchange reaction in which bicyclic imide adducts of the type II were heated in a gas flow system with excess maleic anhydride, while Tawney[4] 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 described[5] procedure for the preparation of II (R = O) from the readily accessible furan–maleic anhydride adduct (III).

The steps of the sequence III → IV → V → 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.