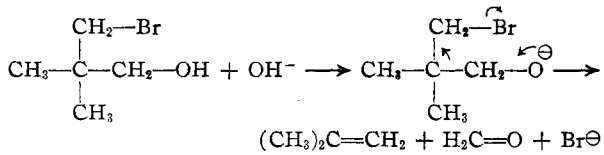
Pyrolysis of I would be expected to give isobutylene and formaldehyde,[7] but this possible source seems untenable in view of the observation that even at 250° I is stable in the presence of potassium hydroxide. Furthermore, the cleavage in 15% potassium hydroxide occurs at a temperature of 100° or less, which is much too low for a pyrolysis. It would appear reasonable, however, that isobutylene and formaldehyde result from a rearrangement of the same alkoxide ion which is the intermediate for the cyclization reaction



$$(CH_3)_2C{=}CH_2 + H_2C{=}O + Br^{\ominus}$$

Thus, this cleavage reaction is an extended chain analog of the usual elimination reaction which generally accompanies substitution, but which is impossible here because of the lack of β-hydrogen atoms. A few other examples of this type of elimination have been reported, as in the cases of β-dimethylpivalophenone methiodide[8] and α-tosyloxy-β,β-dimethyl-γ-butyrolactone,[9] and the reverse aldol reaction is, of course, closely related. The alkali-instability of the bromoalcohol considered here was observed in 1913 by Franke,[10] who reported its decomposition by boiling sodium carbonate solution to an unknown steam volatile oil which reduced Tollens reagent. The nature of the decomposition was not recognized but the latter observation indicated that some cleavage had occurred, since I does not reduce Tollens reagent. On repeating the experiment it was observed that the cleavage reaction proceeds so slowly under these conditions that the steam distillate is principally unreacted bromoalcohol, contaminated with small amounts of I and formaldehyde.

Experimental

Reaction of 3-Bromo-2,2-dimethyl-1-propanol (II) with Alkali. (A).—An intimate mixture of 110 g. of powdered sodium hydroxide and 21.5 g. of II (prepared by the method of Fonteyne and Ticket[4] in 55% yield) was immersed in an oil-bath maintained at 200°. The distillate was collected in two traps kept at 0 and −70°, respectively, and after drying over potassium carbonate was fractionally distilled.

Isobutylene, b.p. −6.5 to −6° (lit. −6°[11]), was obtained in the amount of 1.5 g. (23% yield); m.p. of 2,4-dinitrobenzenesulfenyl chloride adduct,[12] 85–86° (lit. 86–87°[13]). Addition of bromine dissolved in methylene dichloride to a solution of the olefin in methylene dichloride, cooled by an ice–salt bath, gave a 41% yield of 1,2-dibromo-2-methylpropane, b.p. 143–145° (750 mm.), $n^{21.5}D$ 1.5072 and a 12% yield of 1,2,3-tribromo-2-methylpropane, b.p. 111–114° (22 mm.), $n^{21.5}D$ 1.5644, in agreement with the results of Hurd and Spence.[14]

2,2-Dimethyltrimethylene oxide, b.p. 77–79° (752 mm.) was obtained in the amount of 1.3 g. (13% yield) and from a low boiling (66–70°) fraction was obtained 0.5 g. of methyl 3,5-dinitrobenzoate, m.p. 106–107° (lit. 108°[15]). Evidence for the formation of potassium formate was obtained by dissolving the reaction residue in water, acidifying with phosphoric acid and distilling. The distillate was acidic, decolorized potassium permanganate and reduced mercuric oxide to a dark gray precipitate of elemental mercury.

(B).—Dropwise addition of 40 g. of II to a stirred molten mixture of 60 g. of potassium hydroxide and 40 g. of sodium hydroxide at 200°, which is a good reagent for preparing trimethylene oxide from 3-chloropropyl acetate, gave 10 g. of isobutylene (77% yield) and 2.5 g. of 2,2-dimethyltrimethylene oxide (12% yield).

(C).[12]—To 100 g. of 15% potassium hydroxide at 90°, 25 g. of I was added dropwise with stirring over a period of 50 minutes; the bath temperature was then slowly raised to 150° over a period of two hours. The products which distilled off were collected as described in (A), but a water layer in the 0° trap was separated before the remainder was dried over potassium carbonate. Acidification of this water layer with acetic acid and addition of dimedone gave a few milligrams of formaldehyde dimedone, fine needles melting at 187° (lit. 189°[16]). Distillation of the non-aqueous products gave 5 g. (60% yield) of isobutylene and 1.3 g. (10% yield) of 2,2-dimethyltrimethylene oxide.

(7) A. Barbot, *Ann. chim.*, **11**, 519 (1939).
(8) H. R. Snyder and J. H. Brewster, THIS JOURNAL, **71**, 1061 (1949).
(9) H. Bretschneider and H. Hass, *Monatsh.*, **81**, 945 (1950).
(10) A. Franke, *ibid.*, **34**, 1893 (1913).
(11) C. C. Coffin and O. Maass, THIS JOURNAL, **50**, 1483 (1928).
(12) Unpublished work of W. K. Witsiepe, Northwestern University, 1950, which is acknowledged with thanks.
(13) N. Kharasch and C. M. Buess, THIS JOURNAL, **71**, 2724 (1949).
(14) C. D. Hurd and L. U. Spence, *ibid.*, **51**, 3361, 3569 (1929).
(15) W. M. D. Bryant, *ibid.*, **54**, 3760 (1932).
(16) D. Vorlander, *Z. anal. Chem.*, **77**, 247 (1929).

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Condensations of α-Carbethoxy-α-methyl-γ-butyrolactone

BY GLENN S. SKINNER AND R. E. HERBENER

RECEIVED JANUARY 5, 1953

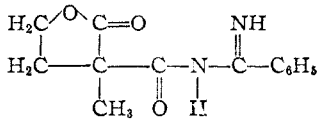
In continuation of the study of the reaction of α-alkyl-α-carbethoxy-γ-butyrolactones[1] with urea and related compounds the methyl homolog has been prepared and condensed with urea, thiourea, guanidine and benzamidine.

The reactions proceeded in the expected manner in all cases. However, the following comparisons should be noted. The condensation of this lactone ester with thiourea required milder temperature conditions to obtain good yields. It was necessary to modify the procedures also on account of the marked differences in the solubilities of the barbituric acid derivatives. The intermediate sodium salt obtained from the condensation with urea is much more insoluble in alcohol and the free acid is so much more soluble in water as to require very specific conditions for its isolation.

This lactone ester was condensed with benzamidine to test the validity of the proposal[2] that the active hydrogen of the unalkylated lactone ester participates in the reaction leading to the tetrahydropyrimidine derivative.

Another possible explanation is that the nonformation of the tetrahydropyrimidine derivative from the alkylated lactone esters is due to steric hindrance. Actually, the substitution of the smaller methyl radical for the active hydrogen led only to the lactone amidine. Within the limits of the possibilities of decreasing the size of the alkyl group it would therefore appear that the hindrance to the cleavage of the lactone ring is not steric in nature.

(1) Last previous report of this series: G. S. Skinner and W. H. Waitz, Jr., THIS JOURNAL, **74**, 498 (1952).
(2) G. S. Skinner, Ethel Anderson and R. F. Bogart, *ibid.*, **71**, 1482 (1949).



Lactone amidine

By mouth in rats (I) at 400 mg./kg., (V) at 400–900 mg./kg., and (VII) at 400–900 mg./kg. gave no hypnosis. When orally administered to rats (III) at 400 mg./kg. gave no protection by either the metrazol or electroshock method, (VI) at 400 mg./kg. gave no protection by electroshock and 40% protection by the metrazol method, and (VII) at 400 mg./kg. gave no protection[3] against either metrazol or electroshock.

BARBITURIC ACID DERIVATIVES $RCH_3C(CONH)_2C{=}X$

	R	X	Yield, %	M.p., °C.	Nitrogen, % Calcd.	Found
I	$HOCH_2CH_2-$	O	72	202–203	15.0	14.9
II	$HOCH_2CH_2-$	S	55	194.5–195.5	13.9	13.7
III	$HOCH_2CH_2-$	NH	58	202–203	22.7	22.5
IV	$BrCH_2CH_2-$	O	72	166–167	11.2	11.2
V	$(H_2NC(=NH_2)-SCH_2CH_2-)^+Br^-$	O	88	265–265.5[a]	17.2	17.1
VI	$H_2NC(=NH)-SCH_2CH_2-$	O	94	197[a]	22.9	22.5
VII	$EtOC(=S)-S-CH_2CH_2-$	O	64	161.5–162.5	9.6	9.5
VIII	$HSCH_2CH_2-$	O	66	145–146	13.9	14.4

[a] Decomposition.

Experimental

α-Carbethoxy-α-methyl-γ-butyrolactone.—This ester was prepared in the usual way from 2.0 moles of powdered sodium, 4.0 moles of diethyl methylmalonate and 4.0 moles of ethylene bromide in one liter of dry benzene. The mixture was heated 13 hours at 75–80°. Conversion of the bromo compound to the lactone ester was effected after removal of the solvent by refluxing 8 hours at 135° (120 mm.); yield 66% (based on sodium), b.p. 146–149° (18 mm.), $n^{20}D$ 1.4430, $d^{20/4}$ 1.1386.

Anal. Calcd. for $C_8H_{12}O_4$: M_R, 40.25; C, 55.8; H, 7.0. Found: M_R, 40.07; C, 55.1; H, 6.9.

Condensations of the Lactone Ester: (a) With Urea.—The previously described general procedure for condensation with urea was employed.[4] The product was isolated as the very insoluble sodium salt by filtration and washing with absolute alcohol. A rubber dam was used for protection against moisture; yield 97%.

Anal. Calcd. for $C_9H_{14}O_5N_2Na_2$: Na, 16.65. Found: Na, 16.47.

After a number of attempts to isolate the acid the following satisfactory procedure was adopted. A mixture of 50 g. of crushed ice and 20 cc. of hydrochloric acid (d. 1.19) was cooled in a freezing bath. With good stirring 27 g. of the salt was added. After one-half hour the product was filtered with suction, washed with ice-cold dilute hydrochloric acid and then sparingly with ice-cold water; yield of crude product 17 g. (91%), m.p. 191–194°. After two recrystallizations from absolute alcohol the melting point was constant at 202–203°.

(b) With Thiourea.—The best result for the reaction with thiourea was obtained by adding to a stirred solution of sodium ethoxide prepared from 4.6 g. of sodium and 92 cc. of absolute alcohol at 2° first 11.4 g. (0.15 mole) of thiourea and then 17.2 g. (0.10 mole) of the lactone ester. After several hours when the temperature had risen to 15° a precipitate began to form. The amount of precipitate reached a maximum after standing 24 hours at 19–24°. The yield of this intermediate was 26 g. but it could not be obtained pure for analysis.

By applying the above treatment with hydrochloric acid this salt yielded 13 g. (65%) of the 2-thiobarbituric acid, m.p. 186–189°. Five recrystallizations from absolute alcohol were necessary to give a pure product, m.p. 194.5–195.5°.

(c) With Guanidine.—By an adaptation of the previously described procedure[2] 18.0 g. (0.10 mole) of guanidine carbonate was added to a solution of sodium ethoxide prepared from 8.0 g. (0.347 mole) of sodium and 125 cc. of absolute alcohol. The lactone ester (8.6 g., 0.050 mole) was added with stirring at 5°. The mixture was allowed to stand 3 hours at 5° and then 24 hours at room temperature. The precipitate was dissolved by stirring with 100 cc. of ice and water. The solution, while cooled in ice, was made just acid to litmus with acetic acid and then cooled in an ice–salt bath. The precipitate was filtered, washed with dilute acetic acid and then with ice-cold water; yield 8.8 g. (95%), m.p. 200–203°. When recrystallized from the minimum amount (500 cc.) of 64% alcohol it had m.p. 202–203°.

To a solution of sodium ethoxide prepared from 5.6 g. (0.243 mole) of sodium and 100 cc. of absolute alcohol there were added with stirring at 22° 13.56 g. (0.0866 mole) of benzamidine hydrochloride and then immediately 11.9 g. (0.0693 mole) of the lactone ester. The temperature was brought rapidly to 45° where it was maintained for 24 hours and then at 70° for 3 hrs. The stirred ice-cold mixture was carefully neutralized to litmus by the addition of hydrochloric acid (1.19) and the salt was filtered with suction. Concentration of the filtrate gave 0.5 g. of product, m.p. 136–138°. Extraction of the precipitate with alcohol gave 4.8 g., m.p. 136.5–138.5°. Recrystallization from absolute alcohol gave a product free from chlorine, m.p. 138–139°.

Anal. Calcd. for $C_{13}H_{14}O_3N_2$: N, 11.4. Found: N, 11.2.

The above lactone amidine (1.0 g.) was converted to the inner salt by dissolving it in the minimum amount (6 cc.) of cold 5% sodium hydroxide and allowing it to stand at room temperature for two hours. The solution was cooled in an ice-bath and made just acid to litmus with hydrochloric acid (d. 1.19). The product did not precipitate at once when cooled in an ice–salt bath, but after standing 36 hours a white crystalline precipitate had formed. This was filtered, washed sparingly with water and dried on porous plate in a desiccator; m.p. 153–155° (dec.). Careful decomposition gave ammonia, and the residue gave the characteristic odor of benzonitrile. It is therefore the expected inner salt.

Anal. Calcd. for $C_{13}H_{16}O_4N_2$: N, 10.6. Found: N, 10.1.

Compounds from 5-(β-Hydroxyethyl)-5-methylbarbituric Acid.—To avoid cleavage of the ring the following modification of the previously described procedure[5] was employed to convert I to IV. Thirty-seven and two-tenths grams (0.20 mole) of I was mixed with 60 cc. of hydrobromic acid (60%), first at 0° and then at room temperature in a bottle capped with a rubber disc, until dissolved. After standing 24 hours at room temperature the solution had set to a solid mass; yield of crude product 43.7 g. (88%), m.p. 164–166°.

(3) Pharmacological tests by Eli Lilly and Co.

(4) G. S. Skinner, Arthur Stokes and George Spiller, THIS JOURNAL, 69, 3083 (1947).

(5) G. S. Skinner, *ibid.*, 59, 322 (1937).

Crystallization from ethyl alcohol gave 36 g., m.p. 166–167°.

The bromide IV was converted successively to V, VI and VIII by procedures that require no further description.[1]

The xanthoethyl derivative VII was also made by an unmodified procedure.[6]

(6) G. S. Skinner and J. B. Bicking, THIS JOURNAL, **72**, 1140 (1950).

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Alkylene Bis-(2-thenylquaternaryammonium) Salts[1]

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RECEIVED JANUARY 24, 1952

During the past few years, bis-quaternary-ammonium salts of a wide variety of types have been prepared and studied for curarimimetic and autonomic drug activity. Peak curarimimetic activity usually is associated with bis-quaternary salts in which ten carbon atoms or equivalent distance separates the quaternary nitrogen atoms and autonomic blockade is maximal in homologs with a five or six carbon atom separation. In the present series of compounds, 2-thenyl substituted quaternary salts of various size were prepared for comparison with one another and with some corresponding isosteric phenyl substituted analogs.

Muscle paralytic activity, as measured in mice according to published procedures,[3] followed the expected sequence. In the bis-thenyldimethylammonium series, activity increased in the following sequence with ED_{50} values of approximately 8 mg. per kg. for the C_6, 2 for C_9 and 1 for the C_{10} homologs; corresponding bis-benzyldimethylammonium derivatives were of the same order of activity as the thenyl analogs. In the C_{10} bis-thenylammonium series, activity decreased with degree of steric hindrance about the nitrogen atoms in the order: dimethyl (1 mg. per kg.), diethyl (2 mg. per kg.) and cyclohexamethylene (10 mg. per kg.). Tests for autonomic activity (in anesthetized dogs) revealed that all of the compounds markedly reduced blood pressure, but for only from five to thirty minutes after intravenous administration of 2 mg. per kg. Mechanism of action varied within the series.[4]

Experimental[5]

2-Thenylamines.—Tertiary 2-thenylamines were prepared by the Leuckart reaction from 2-thienylaldehyde[6] (0.1 mole), formic acid (0.25 mole) and appropriate secondary amine (0.2 mole). The procedure was similar to that of Smith and Macdonald[7]; refluxing was for ten hours or with volatile amines, heating was carried out in a pressure bomb. From dimethylamine, N,N-dimethyl-2-thenylamine[8] was obtained in better than 70% yield and its physical properties agreed with those published. Treatment with methyl iodide yielded a crystalline methiodide, m.p. 167–168°.

Anal. Calcd. for $C_8H_{14}INS$: C, 33.93; H, 4.98; I, 44.82. Found: C, 34.09; H, 5.09; I, 44.20.

N,N-Diethylthenylamine was prepared in similar manner in 65% yield; b.p. 40° at 1.5 mm., $n^{20}D$ 1.5095.

Anal. Calcd. for $C_9H_{15}NS$: N, 8.27. Found: N, 8.18.

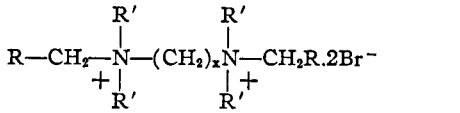
Methiodide, m.p. 156°. *Anal.* Calcd. for $C_{10}H_{18}INS$: C, 38.59; H, 5.79. Found: C, 38.64; H, 5.89.

From hexamethyleneimine there was obtained a 44% yield of N-(2-thenyl)-hexamethyleneimine, b.p., 72–73° at 1.5 mm., $n^{23}D$ 1.5375.

Anal. Calcd. for $C_{11}H_{17}NS$: N, 7.17. Found: N, 6.77.

TABLE I

α,ω-ALKYLENE BIS-QUATERNARYAMMONIUM SALTS



R	R′	x	M.p., °C. (cor.)	Reflux, hr.	Yield, %	Analyses, % Calcd. Carbon	Calcd. Hydrogen	Calcd. Bromine	Found Carbon	Found Hydrogen	Found Bromine
2-C_4H_3S	CH_3	3	219	23	60	42.15	5.83	33.33	42.42	5.98	32.75
2-C_4H_3S	CH_3	4	223	8	85	43.37	6.07	32.07	43.71	6.28	31.65
2-C_4H_3S	CH_3	5	111–114	8	75	44.53	5.70	31.19	44.65	6.26	30.65
2-C_4H_3S	CH_3	6	218–220	3[a]	70	S, 12.18		30.36	S, 11.75		29.90
2-C_4H_3S	CH_3	9	226	35	50	48.59	7.09	28.11	48.40	7.14	28.29
2-C_4H_3S	CH_3	10	200	7[a]	60	49.47	7.26	27.47	49.56	7.23	26.96
2-C_4H_3S	C_2H_5	10	176–180	50	40	52.65	7.87	25.03	52.85	8.04	24.45
2-C_4H_3S	Cyclo(—CH_2—)$_5$[b]	10	201–204	24	45	55.64	7.88	23.14	55.76	8.08	23.36
C_6H_5	CH_3	5	218–220	8	85	55.20	7.25	31.94	55.27	7.26	31.64
C_6H_5	CH_3	6	226	8	90	56.03	7.45	31.07	56.20	7.43	30.72
C_6H_5	CH_3	10	208	8	70	58.94	8.14	28.01	59.08	8.08	27.75

[a] 90 lb. pressure in bomb. [b] Hexamethyleneimonium derivative.

Reaction of Thenylamines with Alkylene Dibromides.—The bis-quaternaryammonium bromide salts were prepared by heating the reagents in *n*-propanol solution in the proportions: 0.05 mole of α,ω-alkylene dibromide, 0.15 mole of tertiary thenylamine, 50 ml. of propanol. Heating time, yields and analyses are summarized in Table I. The bis-quaternary salts were recrystallized from *n*-propanol.

Reaction of Benzyldimethylamine with Alkylene Dibromides.—Benzyldimethylamine (15 g. or 0.11 mole) was re-

(1) Contribution from the Department of Chemistry, James Millikin University, and from the Research Laboratories of Irwin, Neisler & Company.

(2) (a) Phillips Petroleum Co., Waco, Texas; (b) Irwin, Neisler & Company.

(3) C. J. Cavallito, A. E. Soria and J. O. Hoppe, THIS JOURNAL, **72**, 2661 (1950).

(4) Curarimimetic tests by Dr. T. B. O'Dell, autonomic activity measurements by Dr. F. J. Macri, of Irwin, Neisler & Company.

(5) Halogen analyses by Mr. C. F. Duewer of Irwin, Neisler & Company. Microanalyses by Clark Microanalytical Laboratory, Urbana, Illinois.

(6) W. J. King and F. F. Nord, *J. Org. Chem.*, **13**, 635 (1948).

(7) P. A. S. Smith and A. J. Macdonald, THIS JOURNAL, **72**, 1037 (1950).

(8) L. P. Kyrides, F. C. Meyer, F. B. Zienty, J. Harvey and L. W. Bannister, *ibid.*, **72**, 745 (1950).