Anal. Calcd. for $C_{12}H_{13}Cl_2NO_2$: C, 52.56; H, 4.78; Cl, 25.86. Found: C, 52.30; H, 4.81; Cl, 26.45.

N-(2,4-Dichlorobenzyl)-6-methyl-3-morpholone.—Prepared as above in 41% yield, m.p. 68–70°. *Anal.* Calcd. for $C_{12}H_{13}Cl_2NO_2$: C, 52.56; H, 4.78; Cl, 25.86. Found: C, 52.70; H, 4.88; Cl, 25.74.

N-(4-Aminobenzyl)-3-morpholone.—4-(4-Nitrobenzyl)-3-morpholone (9.0 g.) in 500 ml. of absolute ethanol was reduced catalytically with palladium-on-charcoal at an initial hydrogen pressure of 45 pounds per square inch. The reduction was complete after five hours. The catalyst was filtered off and the filtrate was distilled *in vacuo* leaving a solid residue. The product, 7.0 g. (89%), was recrystallized first from benzene and then from isopropyl alcohol, m.p. 111–112°.

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.04; H, 6.84; N, 13.53. Found: C, 63.91; H, 6.90; N, 13.35.

N-Chloroacetoxyethyl-4-ethoxybenzylamine Hydrochloride.—A solution of 42 g. of N-(4-ethoxybenzyl)-ethanolamine hydrochloride in boiling ethylene dichloride was treated with 21 g. of chloroacetyl chloride with stirring. Refluxing was continued for about 30 minutes until the evolution of hydrogen chloride ceased. During this time some of the hydrochloride of the N-chloroacetoxyethyl-4-ethoxybenzylamine crystallized. Crystallization was completed by cooling to 20°. The product was collected, washed with cold ethylene dichloride and petroleum ether and dried at 70°; yield 47 g. (85%), m.p. 168–170°.

Anal. Calcd. for $C_{13}H_{19}Cl_2NO_3$: N, 4.54. Found: N, 4.66.

When the mother liquor was evaporated an oil remained which could not be induced to crystallize. This oil appeared to be the O,N-bis-(chloroacetyl)-4-ethoxybenzylethanolamine since treatment of it in 50% alcohol with excess sodium hydroxide solution gave an 80% yield of N-(4-ethoxybenzyl)-3-morpholone.

N-(4-Ethoxybenzyl)-3-morpholone.—To a solution of 195 g. (1 mole) of N-(4-ethoxybenzyl)-ethanolamine in 2 l. of 50% ethyl alcohol was added 100 ml. of 35% sodium hydroxide solution and then while keeping the temperature between 15° and 20° by means of an ice-bath there was added simultaneously with strong stirring 350 ml. of 35% sodium hydroxide solution and 290 g. (2.5 moles) of chloroacetyl chloride during about 1 hour. Stirring was continued for another 30 minutes at about 20° whereupon the solution was made acid to litmus with hydrochloric acid, concentrated *in vacuo* to a volume of about 2 l. and diluted with two liters of ice-water. The crystalline precipitate was collected, washed with cold water and dried *in vacuo* yielding 191 g. (81%) of N-(4-ethoxybenzyl)-3-morpholone, m.p. 69–72°, which after recrystallization from isopropyl alcohol melted at 70–72.5°.

N-(2,4-Dichlorobenzyl)-3-morpholone.—A solution of 11 g. (0.05 mole) of N-(2,4-dichlorobenzyl)-ethanolamine in 100 ml. of 50% ethanol was treated with 12.5 ml. of 35% sodium hydroxide solution and then at 15–20° with strong stirring 12.5 ml. of 35% sodium hydroxide and 15 g. of chloroacetyl chloride were added simultaneously. After another half-hour at 20° the solution was worked up as described above yielding 10.5 g. (80%) of N-(2,4-dichlorobenzyl)-3-morpholone, m.p. 92.5–96°, which after recrystallization from isopropyl alcohol melted at 94–96°.

The same over-all yields of morpholones were obtained when the substituted ethanolamines were first converted to the O,N-bis-(chloroacetyl) derivatives by treating with 2.2 equivalents of chloroacetyl chloride in ethylene dichloride solution (finishing with a one-hour reflux) and the total oil residue from this acylation was added to excess alkali in 50% ethanol solution.

N-Benzyl-3-hydroxypropylamines (Table III).—The following two procedures were employed for the preparation of the N-benzyl-3-hydroxypropylamines. A. This method was used with the chloro- and dichlorobenzyl chlorides. One mole of the latter was added dropwise with stirring to 3 moles of 3-aminopropanol over a period of about 45 minutes. After stirring for two hours longer the mixture was treated with an excess of 35% sodium hydroxide and the product was extracted with ethylene dichloride and distilled. B. Equimolar quantities of the benzaldehyde and 3-aminopropanol were heated *in vacuo* on a steam-bath for one hour. The product was then dissolved in alcohol and reduced catalytically with palladium-on-charcoal.

N-Benzyl-3-homomorpholones (Table IV).—The procedure described above for the preparation of the 3-morpholones was employed for the preparation of these compounds. In most cases the crude N-benzyl-N-(3-hydroxypropyl)-chloroacetamides were dissolved in absolute ethanol and treated directly with powdered potassium hydroxide.

RENSSELAER, NEW YORK

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE AND THE RENSSELAER POLYTECHNIC INSTITUTE]

A New Method for the Preparation of 3-Substituted-2-oxazolidones

BY GEORGE Y. LESHER[1a] AND ALEXANDER R. SURREY[1b]

RECEIVED AUGUST 31, 1954

It has been found that N-benzyl-2- and 3-hydroxyalkylamines react with methyl or ethyl trichloroacetate to yield N-benzyl-2-oxazolidones and N-benzyl-2-pentoxazolidones, respectively. With N-benzyl-4-hydroxybutylamine and methyl trichloroacetate an N-substituted pyrrolidine was obtained. Possible mechanisms for these reactions are presented.

In our investigation of potential amebacidal agents we had planned to prepare some N-benzyl-N-(2-hydroxyalkyl)-monochloroacetamides (R = CH_2Cl), -dichloroacetamides (R = $CHCl_2$) and -trichloroacetamides (R = CCl_3). The first two types presented no difficulties. The monochloro-

$$R'—C_6H_4CH_2N(—CO—R)—CH_2CH_2OH$$

acetamides were formed in the usual manner from the reaction of N-benzylethanolamines with chloroacetyl chloride in the presence of aqueous sodium hydroxide.[2] For the dichloroacetamides it was found that acylation of the N-benzylethanolamines could be brought about with methyl or ethyl dichloroacetate as well as with dichloroacetyl chloride.[3] It seemed reasonable, therefore, to expect similar acylations with methyl or ethyl trichloroacetate, or with trichloroacetyl chloride. However, this did not prove to be the case.

When N-(2,4-dichlorobenzyl)-ethanolamine and ethyl trichloroacetate were warmed at 50–60° for two hours, a product was formed whose analysis indicated a loss of a mole of chloroform as well as a mole of ethanol. In a repetition of this experi-

(1) (a) This paper is constructed from part of a dissertation to be presented to the Rensselaer Polytechnic Institute by George Y. Lesher in partial fulfillment of the requirement for the degree of Doctor of Philosphy. (b) Adjunct Professor, Rensselaer Polytechnic Institute.

(2) A. R. Surrey, S. O. Winthrop, M. K. Rukwid and B. F. Tullar, THIS JOURNAL, **77**, 633 (1955).

(3) A. R. Surrey, *ibid.*, **76**, 2214 (1954).

TABLE I

N-(BENZYL)-HYDROXYALKYLAMINES[a] R—C$_6$H$_4$—CH$_2$NH(CH$_2$)$_n$OH

R	n	Yield, %	B.p., °C.	Mm.	n^{25}D	Formula	Nitrogen, % Calcd.	Found
4-CH_3	2	55	105–110	0.3[b]		$C_{10}H_{15}NO$	8.49	8.28
4-OH	2	60	[c]			$C_9H_{13}NO_2$		
3,4-$(CH_3O)_2$	2	60	148–152	.06[d]		$C_{11}H_{17}NO_3$	6.67	6.62
H	3	58	110–115	.7	1.5370	$C_{10}H_{15}NO$	8.50	8.27
4-$(CH_3)_2CH$	3	58	135–138	.6	1.5230	$C_{14}H_{21}NO$	6.76	6.56
2-Cl	3	50[e]	130–135	.8	1.5445	$C_{10}H_{14}ClNO$	7.01	7.03
4-CH_3O	3	62	140–145	.7	1.5390	$C_{11}H_{17}NO_2$	7.19	6.52
4-C_2H_5O	3	88	130–135	.05[f]		$C_{12}H_{19}NO_2$	6.70	6.60
3,4-CH_2O_2	3	59	147–151	.7	1.5500	$C_{11}H_{15}NO_3$	6.70	6.63
H	4	72	120–125	.6	1.5310	$C_{11}H_{17}NO$	7.82	7.70
4-$(CH_3)_2CH$	4	48	145–150	.5	1.5180	$C_{14}H_{23}NO$	6.34	6.07

[a] Several of the N-benzylhydroxyalkylamines used in this work have been described previously.[3] [b] Solidified on standing, melted at 56–59°. [c] The hydrochloride melted at 144–145°. *Anal.* Calcd.: Cl^-, 17.41. Found: Cl^-, 17.51. [d] The hydrochloride melted at 115–116°. *Anal.* Calcd.: Cl^-, 14.32. Found: Cl^-, 14.31. [e] Prepared from 2-chlorobenzyl chloride and 3-hydroxypropylamine.[3] [f] Solidified on standing, recrystallized from Skellysolve B, melted at 44–47°.

ment the chloroform was collected and identified by its odor, boiling point and color reaction with pyridine and sodium hydroxide solution.[4] In a similar experiment with ethyl trichloroacetate and N-benzylethanolamine a halogen-free compound

$$C_6H_5CH_2NHCH_2CH_2OH + CCl_3COOC_2H_5 \longrightarrow C_6H_5CH_2N\begin{matrix}CH_2CH_2\\ |\\ CO\text{–}O\end{matrix} + CHCl_3 + C_2H_5OH$$

was obtained which was identified as 3-benzyl-2-oxazolidone by its analysis and by direct comparison with a sample prepared from N-benzylethanolamine and ethyl carbonate according to the method of Homeyer.[5]

Further investigation of this new reaction indicated that it is a general one. Both N-substituted-2- and 3-hydroxyalkylamines could be employed successfully.[6] In the latter case, 3-substituted-2-pentoxazolidones (tetrahydro-1,3,2H-oxazin-2-ones) are formed. The present paper reports the preparation of some 3-benzyl-2-oxazolidones and 3-benzyl-2-pentoxazolidones by this new method. The results are summarized in Tables II and III. Several of these compounds have been found to possess interesting mild analgesic and antipyretic activities.

A review of the literature indicated that although a variety of methods have been described for the preparation of 2-oxazolidones, only a few references have been found dealing with 2-pentoxazolidones.[7] Some of the more commonly used methods for the synthesis of 2-oxazolidones have been evaluated by Close,[8] and Newman and Kutner.[9] These include the reaction of ethanolamine or one of its derivatives with ethyl carbonate, urea or phosgene, and the Curtius reaction with β-hydroxy acids. The present procedure employing a trichloroacetic acid ester offers a very simple and convenient method for the preparation of N-substituted-2-oxazolidones as well as 2-pentoxazolidones. No catalysts or high temperatures are required. In fact, the reaction may be run at room temperature by simply allowing a mixture of the reactants to stand for several days. Good yields of product are obtained in most cases. In those experiments which were repeated the initial yields were usually increased to 80–90%. The use of trichloroacetyl chloride, instead of the ester, usually resulted in much poorer yields of the 2-oxazolidones. For example, with N-(2,4-dichlorobenzyl)-ethanolamine and the acid chloride, the yields of 3-(2,4-dichlorobenzyl)-2-oxazolidone in two runs were 9 and 22% as compared with 79% using the ester. In one of these two cases some of the N,O-bis-trichloroacetyl derivative of the ethanolamine also was isolated.

The reaction of other trihaloesters also has been studied. With ethyl tribromoacetate and N-(2,4-dichlorobenzyl)-ethanolamine a 41% yield of the 2-oxazolidone was obtained along with a small amount of the hydrobromide salt of the starting amine. None of the expected 2-oxazolidone was obtained with ethyl trifluoroacetate. Instead, a 75% yield of the trifluoroacetic acid salt of N-(2,4-dichlorobenzyl)-ethanolamine was formed.

In the preparation of 2-oxazolidones and 2-pentoxazolidones from 2-hydroxy- and 3-hydroxyalkylamines with methyl trichloroacetate, methyl alcohol and chloroform are formed. However, when this procedure was applied to the homologous 4-hydroxyalkylamines a reaction occurred in which methyl alcohol, chloroform and carbon dioxide were liberated and an N-substituted-pyrrolidine was obtained. For example, with N-benzyl-4-hydroxybutylamine and methyl trichloroacetate

(4) "Merck Index," 5th Ed., Merck and Co., Inc., Rahway, N. J., 1940, p. 889.

(5) A. H. Homeyer, U. S. Patent 2,399,118; *C. A.*, **40**, 4084 (1946).

(6) This reaction is restricted apparently to N-substituted-hydroxyalkylamines. All attempts to prepare cyclic compounds with simple hydroxyalkylamines were unsuccessful. In a very recent paper, M. M. Joullié and A. R. Day, THIS JOURNAL, **76**, 2990 (1954), also have shown that ethyl trichloroacetate reacts in distinctly different ways with primary and secondary amines. With the former, N-substituted-trichloroacetamides were obtained.

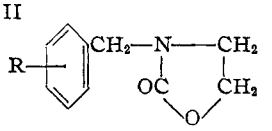
(7) A. P. N. Franchimont and A. Lublin, *Rec. trav. chim.*, **21**, 45 (1902); M. Kohn, *Monatsh.*, **26**, 939 (1905); M. Kohn and J. Giaconi, *ibid.*, **28**, 470 (1907); K. Hess and Cl. Uibrig, *Ber.*, **48**, 1974 (1915); M. Kohn, *ibid.*, **49**, 250 (1916); A. M. Paquin, *Z. Naturforsch.*, **1**, 518 (1946); *C. A.*, **42**, 123 (1948); American Cyanamid New Product Bulletin, Coll. Vol. III, 72 (1954).

(8) W. J. Close, THIS JOURNAL, **73**, 95 (1951).

(9) M. S. Newman and A. Kutner, *ibid.*, **73**, 4199 (1951).

TABLE II

N-(BENZYL)-2-OXAZOLIDONES[a]

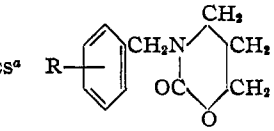


R	M.p., °C.[b]	Yield, %	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found
H	78.3–79.2	40[c]	$C_{10}H_{11}NO_2$	67.76	68.00	6.26	5.92	7.91	7.92
4-CH_3	[d]	92	$C_{11}H_{13}NO_2$	69.09	69.09	6.85	6.52	7.33	7.27
4-$(CH_3)_2CH$	47.5–49.1	59[e]	$C_{13}H_{17}NO_2$	71.16	71.35	7.81	7.88	6.38	6.46
2-Cl	70.0–72.1	75	$C_{10}H_{10}ClNO_2$	56.74	56.84	4.76	4.98	6.64	6.56
4-Cl	72.1–73.5	48	$C_{10}H_{10}ClNO_2$	56.74	57.00	4.76	4.80	16.75[h]	16.72[h]
2,6-Cl_2	115.8–118.1	57	$C_{10}H_9Cl_2NO_2$	48.82	48.68	3.68	3.60	5.69	5.68
3,4-Cl_2	68.0–69.6	84	$C_{10}H_9Cl_2NO_2$	48.82	48.95	3.68	3.75	5.69	5.68
2,4-Cl_2	72.2–74.3	79	$C_{10}H_9Cl_2NO_2$	48.82	48.80	3.68	3.66	5.69	5.69
4-NO_2	148.0–150.3	90	$C_{10}H_{10}N_2O_4$	54.05	54.26	4.54	4.68	6.30[g]	6.28[g]
4-NH_2·HCl	190.9–192.1	43[e]	$C_{10}H_{12}N_2O_2$·HCl	52.52	52.70	5.73	5.77	15.50[i]	15.69[i]
4-HO	128.2–129.2	52	$C_{10}H_{11}NO_3$	62.16	62.44	5.74	5.83	7.25	7.22
4-C_2H_5O	63.4–66.1	68	$C_{12}H_{15}NO_3$	65.13	65.16	6.83	6.78	6.33	6.27
4-$CH_3(CH_2)_3O$	[f]	87	$C_{14}H_{19}NO_3$	67.45	67.77	7.68	7.41	5.62	5.66
3,4-$(CH_3O)_2$	94.1–96.8	80	$C_{12}H_{15}NO_4$	60.74	60.90	6.37	6.48	5.91	5.90
3,4-CH_2O_2	59.3–62.2	63	$C_{11}H_{11}NO_4$	59.72	59.83	5.01	5.20	6.33	6.32

[a] The 4- and 5-substituted-2-oxazolidones that were prepared are described in the Experimental section. [b] Melting points are corrected. [c] Prepared by the method of Homeyer.[5] [d] Product obtained as a low-melting waxy solid which was distilled, b.p. 160–162° (0.03 mm.), $n^{25}D$ 1.5385. [e] Yield is for the reduction of the corresponding nitro compound. [f] Product obtained as a low-melting waxy solid which was distilled, b.p. 170–175° (0.04 mm.), $n^{25}D$ 1.5263. [g] Determination of nitrogen by titration with titanous chloride. [h] Cl analysis. [i] Cl^- analysis.

TABLE III

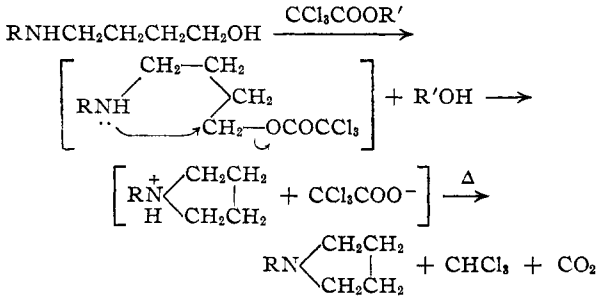
N-(BENZYL)-2-PENTOXAZOLIDONES[a]



R	M.p., °C.[b]	Yield, %	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found
H	38.4–42.4[c]	38	$C_{11}H_{13}NO_2$	69.17	69.15	6.85	7.12	7 33	7 31
4-$(CH_3)_2CH$	72.7–73.9[d]	69	$C_{14}H_{19}NO_2$	72.09	71.78	8.21	8.50	6.01	5.97
2-Cl	75.6–76.8[d]	44	$C_{11}H_{12}ClNO_2$	58.54	58.98	5.36	5.52	Cl, 15.71	15.90
3,4-Cl_2	[f]	54	$C_{11}H_{11}Cl_2NO_2$	50.78	50.30	4.26	4.50	Cl, 27.27	28.66
2,4-Cl_2	108.8–111.1[e]	46	$C_{11}H_{11}Cl_2NO_2$	50.78	50.54	4.26	4.24	5.39	5.54
4-CH_3O	62.5–66.1[d]	52	$C_{12}H_{15}NO_3$	65.15	65.15	6.83	7.14	6.63	6.33
4-C_2H_5O	89.8–92.8[e]	86	$C_{13}H_{17}NO_3$	66.36	66.40	7.28	7.02	5.95	5.95
3,4-CH_2O_2	99.7–100.7[d]	51	$C_{12}H_{13}NO_4$	61.28	61.57	5.55	5.74	5.95	5.93

[a] The 6-substituted-2-pentoxazolidones that were prepared are described in the Experimental section. [b] Melting points are corrected. [c] Recrystallized from ether. [d] Recrystallized from benzene–Skellysolve A. [e] Recrystallized from isopropyl alcohol. [f] Obtained as an impure oil, b.p. 175–180° (0.05 mm), $n^{25}D$ 1.5720.

the product was N-benzylpyrrolidine. The course of this reaction may be illustrated as



The initial step probably involves O-acylation followed by a displacement of the trichloroacetoxy ion by nitrogen to yield the 5-membered nitrogen heterocycle.[10] The trichloroacetic acid thus formed decomposes to give chloroform and carbon dioxide.[11] The scope and usefulness of this novel reaction is being investigated.

Evidence for the initial formation of an O-acyl derivative has been reported previously[3] in the reaction of N-benzylethanolamines with methyl dichloroacetate. There seems to be no doubt that the formation of dichloroacetamides in this reaction is facilitated by the presence of the hydroxy group. An analogous mechanism appears to apply in the present work with ethyl or methyl trichloroacetate.[12] The formulation of this reaction involving a cyclic intermediate[13] (III) as in the

(10) A similar reaction has been reported with the *p*-toluenesulfonic acid ester, D. D. Reynolds and W. O. Kenyon, THIS JOURNAL, **72**, 1597 (1950); see also, H. Meerwein, *Ann.*, **453**, 16 (1927).

(11) Trichloroacetic acid has been reported to react vigorously at 60° in the presence of dimethylaniline to give chloroform, V. M. Rodionov and A. M. Fedorova, *Bull. acad. sci. U.R.S.S., Classe sci. chim.*, 330 (1946); *C. A.*, **43**, 5361 (1949).

(12) An alternative path, however, involving an initial split of chloroform rather than methyl alcohol also is a possibility.

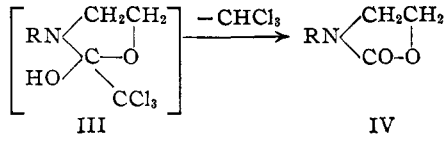
(13) A somewhat similar cyclic intermediate may be involved in the reaction of phenyl biguanide with ethyl trichloroacetate reported recently by S. L. Shapiro and C. G. Overberger, THIS JOURNAL, **76**, 97 (1954).

O ⇄ N acyl migration may be pictured as

$$\underset{\text{I}}{RNHCH_2CH_2OH} + CCl_3COOR' \longrightarrow$$

$$[RNHCH_2CH_2OCOCCl_3] + R'OH \longrightarrow$$

II



III IV

Apparently, either the starting amine I or the O-acyl compound II acts as a basic catalyst in effecting a split of chloroform from the cyclic intermediate III. With a 1,2-glycol, an analogous cyclic compound has been reported[14] which loses chloroform on treatment with pyridine to give a cyclic carbonate. In the present work, when ethylene glycol was heated with methyl trichloroacetate in the presence of pyridine, ethylene carbonate was obtained. Propylene carbonate also was prepared in a similar manner.

In an effort to obtain evidence for the proposed mechanism the reaction of N-(2-hydroxyethyl)-acetamide (V) with methyl trichloroacetate was studied. It was hoped that some intermediates resembling those in the above sequence could be obtained. When this reaction was carried out at steam-bath temperatures three products were isolated, two of which have been identified as known compounds, 3-acetyl-2-oxazolidone[5] (VI) and 2-methyloxazoline[15] (VII). The formation of these two compounds may be explained on the basis of the above suggested mechanisms. In both cases an initial O-trichloroacetylation may be involved.

$$\underset{\text{V}}{CH_3CONHCH_2CH_2OH} + CCl_3COOCH_3 \longrightarrow \underset{\text{VI}}{CH_3CON\langle CH_2CH_2 / CO{-}O\rangle} + \underset{\text{VII}}{CH_3C\langle N{-}CH_2 / O{-}CH_2\rangle}$$

So far, all efforts to isolate the N-benzyl-N-(2-hydroxyethyl)-trichloroacetamides have been unsuccessful. Attempts to effect selective hydrolysis of an N-benzyl-N,O-bis-(trichloroacetyl)-ethanolamine[16] with 0.2 *N* sodium hydroxide solution in acetone led only to the 2-oxazolidone derivative. Apparently the presence of base results in a loss of chloroform after O-deacylation occurs. Heating the N,O-bis-trichloroacetyl derivative with *p*-toluenesulfonic acid and methanol was equally ineffective in bringing about selective deacylation. Only a small amount of the N-benzylethanolamine as its *p*-toluenesulfonic acid salt and starting material were isolated from the reaction mixture.

Acknowledgment.—The authors wish to thank Mr. M. E. Auerbach and Mr. K. D. Fleisher and staffs for the analytical data and corrected melting points and Miss Marcia K. Rukwid for her technical assistance. Mild analgesic and antipyretic screening were carried out by Dr. J. R. Lewis.

(14) H. Hibbert and M. E. Greig, *Can. J. Research*, **4**, 254 (1931); see also H. Meerwein and H. Sönke, *Ber.*, **64**, 2375 (1931).

(15) The picrate of this product was recrystallized from ordinary isopropyl alcohol and found to be identical with a product obtained after the recrystallization of the picrate of 2-methyloxazoline from wet isopropyl alcohol. See S. Gabriel, *Ber.*, **22**, 2220 (1889).

(16) The preparation of N-benzyl-N,O-bis-(acyl)-ethanolamines is the subject of a forthcoming publication.

Experimental

N-(4-Hydroxybenzyl)-ethanolamine.—The preparation of the N-benzylethanolamines listed in Table I is illustrated by the following examples.

To a solution of 24.2 g. (0.2 mole) of 4-hydroxybenzaldehyde in 250 ml. of absolute ethanol was added with stirring 12.2 g. (0.2 mole) of ethanolamine. The mixture was cooled and the solid (20 g.) which separated was collected on a filter. Evaporation of the filtrate left an oily residue which on crystallization from ethanol gave an additional 4.5 g. of the 4-hydroxybenzylidene-ethanolamine (total yield 75%). After two recrystallizations from absolute ethanol it melted at 165–167°.

Anal. Calcd. for $C_9H_{11}NO_2$: N, 8.50. Found: N, 8.27.

Reduction of 8.3 g. (0.05 mole) of this Schiff base in 250 ml. of absolute ethanol was accomplished with Raney nickel in a Parr hydrogenator. After the theoretical amount of hydrogen was taken up the catalyst was removed by cautious filtration and the solvent distilled under reduced pressure. The red oily residue, 6.7 g. (80%), could not be crystallized. The hydrochloride melted at 144–145°.

N-(2,4-Dichlorobenzyl)-3-hydroxybutylamine.—To 54 g. (0.6 mole) of 3-hydroxybutylamine was added slowly with stirring 29 g. (0.15 mole) of 2,4-dichlorobenzyl chloride. The mixture was stirred for two hours and then poured into water. The oil that separated was dried by dissolving in chloroform and removing the chloroform under reduced pressure. The product, 34 g. (91%), was characterized as its hydrochloride, m.p. 152.4–154.2° (cor.).

Anal. Calcd. for $C_{11}H_{15}Cl_2NO\cdot HCl$: C, 46.42; H, 5.66; Cl^-, 12.46. Found: C, 46.14; H, 5.97; Cl^-, 12.44.

N-(2,4-Dichlorobenzyl)-5-methyl-2-oxazolidone.—The general procedure for the preparation of the 2-oxazolidones (Table II) is illustrated by the following example. A mixture of 21 g. (0.09 mole) of N-(2,4-dichlorobenzyl)-2-hydroxypropylamine and 20 g. (0.105 mole) of ethyl trichloroacetate (or 18.5 g. of methyl trichloroacetate) was heated on a steam-bath for four hours. The resulting clear red liquid was taken up in ethylene dichloride and washed with 2 *N* hydrochloric acid and then with water. After drying with anhydrous potassium carbonate the ethylene dichloride solution was treated with charcoal, filtered and the solvent distilled under reduced pressure. An orange oil was obtained, 12.5 g. (48%), which was crystallized by trituration with Skellysolve C. After two recrystallizations from this same solvent a colorless product was obtained which melted at 75.4–77.6° (cor.).

Anal. Calcd. for $C_{11}H_{11}Cl_2NO_2$: C, 50.80; H, 4.27; Cl, 27.27. Found: C, 50.82; H, 4.50; Cl, 27.50.

All the other 2-oxazolidones were recrystallized from either isopropyl alcohol or benzene–Skellysolve A.

3-(β-Phenethyl)-2-oxazolidone.—This compound was prepared according to the above procedure from N-(β-phenethyl)-ethanolamine in 55% yield. After recrystallization from benzene–Skellysolve A it melted at 64.5–66.2° (cor.).

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.78; H, 6.89; N, 7.20.

N-(4-Aminobenzyl)-2-oxazolidone Hydrochloride.—A mixture of 26.5 g. (0.12 mole) of N-(4-nitrobenzyl)-2-oxazolidone, 120 g. of iron filings, 5 ml. of acetic acid, 100 ml. of water and 400 ml. of ethanol was refluxed with good stirring for two hours. The acid was neutralized with solid sodium carbonate and the mixture filtered while still hot. Removal of the ethanol by distillation gave an oil which was taken up in chloroform. This chloroform solution was washed with water, dried and the solvent was removed under reduced pressure to give a pink solid (11.5 g., 50%), m.p. 127.5–129°. The product was dissolved in acetone and treated with alcoholic hydrogen chloride. The resulting hydrochloride salt, 11.5 g. (85%), melted at 190.9–192.1° (cor.) after recrystallization from ethanol.

Preparation of 2-Oxazolidones at Room Temperature.—A mixture of 13.5 g. (0.06 mole) of N-(3,4-dichlorobenzyl)-ethanolamine and 12.5 g. (0.07 mole) of methyl trichloroacetate was stirred at room temperature until solution was complete. After two weeks of standing the mixture had

almost completely solidified. It was taken up in ethylene dichloride and worked up in a manner similar to that for the other N-benzyl-2-oxazolidones. After trituration with Skellysolve C, 12.5 g. (84%) of the colorless 3-(3,4-dichlorobenzyl)-2-oxazolidone was obtained, m.p. 68–70°.

Reaction of N-(2,4-Dichlorobenzyl)-ethanolamine with Trichloroacetyl Chloride.—A mixture of 11 g. (0.05 mole) of N-(2,4-dichlorobenzyl)-ethanolamine, 50 ml. of 1 *N* sodium hydroxide solution and 100 ml. of ethylene dichloride was stirred and cooled below 5° while a solution of 8.2 g. (0.045 mole) of trichloroacetyl chloride in 50 ml. of ethylene dichloride was added. When the addition was complete stirring was continued while the mixture was allowed to warm to room temperature. The organic layer was separated, washed twice with 2 *N* hydrochloric acid and once with water. After the solution was dried and treated with charcoal the solvent was removed under reduced pressure. The oily residue, 3 g. (16% based on unrecovered amine), was crystallized from ethanol–water. After a recrystallization from Skellysolve B the melting point was 102–103°. The analysis indicated the compound to be the N-(2,4-dichlorobenzyl)-N,O-bis-(trichloroacetyl)-ethanolamine.

Anal. Calcd. for $C_{13}H_9Cl_8NO_3$: C, 30.56; H, 1.78; Cl,[17] 41.64. Found: C, 30.45; H, 1.68; Cl,[17] 41.44.

Concentration of the ethanol–water mother liquor, above, gave 1 g. (9%) of a solid that melted at 65–70°. A mixed melting point determination with 3-(2,4-dichlorobenzyl)-2-oxazolidone was not depressed.

The original aqueous acid extracts were combined, made basic with an excess of 35% sodium hydroxide solution and extracted with ethylene dichloride. After removal of the solvent from this organic layer, 3 g. of unreacted amine was obtained.

Reaction of Ethyl Tribromoacetate with N-(2,4-Dichlorobenzyl)-ethanolamine.—A mixture of equimolar quantities of carefully dried N-(2,4-dichlorobenzyl)-ethanolamine and redistilled ethyl tribromoacetate was left at room temperature for one week. The solid that formed was collected on a filter and identified as N-(2,4-dichlorobenzyl)-ethanolamine hydrobromide (15%), m.p. 178–180°. A mixed melting point with an authentic sample was not depressed.

Anal. Calcd. for $C_9H_{11}Cl_2NO \cdot HBr$: Br^-, 26.55. Found: Br^-, 26.43.

From the above filtrate an acid insoluble solid was obtained, m.p. 67–70°, (41%), that was identical with 3-(2,4-dichlorobenzyl)-2-oxazolidone.

A similar experiment with methyl dibromoacetate and the same N-(2,4-dichlorobenzyl)-ethanolamine also gave the hydrobromide salt (30% yield) along with the expected N-(2,4-dichlorobenzyl)-N-(2-hydroxyethyl)-dibromoacetamide.[8]

Reaction of Ethyl Trifluoroacetate with N-(2,4-Dichlorobenzyl)-ethanolamine.—The ethyl trifluoroacetate was redistilled; the fraction boiling at 60° was collected, $n^{25}D$ 1.3066.

A mixture of 11 g. (0.05 mole) of ethyl trifluoroacetate and 7.1 g. (0.05 mole) of N-(2,4-dichlorobenzyl)-ethanolamine was warmed until solution was complete. After two weeks at room temperature a crystalline solid had formed. This solid was collected and washed with Skellysolve A, 12.5 g. (75%). After recrystallization from benzene the product melted at 99–99.5°. A mixed melting point determination with an authentic sample of the trifluoroacetic acid salt of N-(2,4-dichlorobenzyl)-ethanolamine was not depressed.

Anal. Calcd. for $C_9H_{11}Cl_2NO \cdot C_2HF_3O_2$: N, 4.19. Found: N, 4.15.

N-Benzyl-2-pentoxazolidones.—The procedure here is generally the same as for the N-benzyl-2-oxazolidones. Equal molar quantities of the N-benzyl-3-hydroxypropylamine and ethyl (or methyl) trichloroacetate were heated together on a steam-bath for two to five hours and worked up in the usual manner. In general, the purification of the 2-pentoxazolidones (Table III) was more difficult than with the 2-oxazolidones. The reaction mixtures were quite discolored and the products did not crystallize as readily. These difficulties may be obviated by carrying out the reaction at room temperature. For example, with N-(4-ethoxybenzyl)-3-hydroxypropylamine and methyl trichloroacetate the yield of the corresponding 2-pentoxazolidone was 86% when the reaction was run at room temperature for two weeks.

3-(2,4-Dichlorobenzyl)-6-methyl-2-pentoxazolidone was prepared in 46% yield from N-(2,4-dichlorobenzyl)-3-hydroxybutylamine. After recrystallization from Skellysolve C it melted at 96.9–99.0° (cor.).

Anal. Calcd. for $C_{12}H_{13}Cl_2NO_2$: C, 52.56; H, 4.78; N, 5.11. Found: C, 52.24; H, 4.51; N, 5.14.

Reaction of Methyl Trichloroacetate with N-(2-Hydroxyethyl)-acetamide.—Equivalent quantities of N-(2-hydroxyethyl)-acetamide and methyl trichloroacetate were heated together on the steam-bath for an hour and a half. During this time approximately the theoretical amount of methanol and chloroform distilled from the reaction.

Distillation of the residue gave a low-boiling fraction (b.p. 87–90°, $n^{25}D$ 1.4321, 20% yield) having a strong piperidine-like odor. The picrate of this basic material was prepared and recrystallized from isopropyl alcohol, m.p. 163–165°. 2-Methyloxazoline was prepared essentially according to the method of Wenker[18] (b.p. 108–109°, $n^{25}D$ 1.4314) and the picrate of this material, recrystallized from absolute ethanol, melted at 151–153° (lit. 147–149°).[15] This product was recrystallized from wet isopropyl alcohol and a picrate melting at 162.5–166° (lit. 167–169°)[15] was obtained. A mixed melting point determination with our product melting at 163–165° was not depressed. The latter differs from the picrate of 2-methyloxazoline by the elements of water.[15]

Anal. Calcd. for $C_4H_9NO_2 \cdot C_6H_3N_3O_7$: C, 36.15; H, 3.64; neut. equiv., 332.24. Found: C, 36.91; H, 3.61; neut. equiv., 333.4.

A second fraction was collected (b.p. 110–114° (2 mm.), 8% yield) that solidified on standing. After recrystallization from isopropyl alcohol it melted at 67.5–68.5°. A mixed melting point with an authentic sample of 3-acetyl-2-oxazolidone[5] was not depressed.

A third fraction containing chlorine also was collected. This has not been identified as yet (b.p. 145–150° (2 mm.), $n^{25}D$ 1.4676).

N-Benzylpyrrolidine.—A mixture of 8 g. (0.045 mole) of N-benzyl-4-hydroxybutylamine and 9 g. (0.05 mole) of methyl trichloroacetate was warmed in a water-bath at 50–60° for about 2 hours. A vigorous evolution of gas commenced almost immediately and gradually subsided. During the distillation of the resulting mixture a low-boiling fraction, 3 g., was obtained that proved to be chloroform. The major fraction, 4.4 g. (61%), boiled at 116–122° (22 mm.), $n^{25}D$ 1.5195, and was identified as N-benzylpyrrolidine. The melting point of the hydrochloride salt was 154–155° and was not depressed when mixed with an authentic sample prepared *via* alkylation of pyrrolidine with benzyl chloride.

During a similar experiment the gas evolved was bubbled through a standard sodium hydroxide solution. A little more than the theoretical amount of carbon dioxide was found on titration.

Reaction of Ethylene Glycol with Methyl Trichloroacetate.—A mixture of 6.2 g. (0.1 mole) of ethylene glycol, 17.7 g. (0.1 mole) of methyl trichloroacetate and 6 drops of pyridine was heated on a steam-bath for 45 minutes. During this time 13.5 g. of distillate (methanol and chloroform) was collected. The oily residue which solidified on cooling was sucked dry on a Büchner funnel, 5.5 g. (69%), m.p. 35–37°. A mixed melting point determination with an authentic sample of ethylene carbonate[19] was not depressed.

Propylene Carbonate.—This cyclic carbonate was prepared in a similar manner as above with triethylamine as the basic catalyst, yield 59%. About 40% of unreacted glycol was recovered. The product boiled at 112–114° (2 mm.), $n^{25}D$ 1.4197, (commercial sample[19] $n^{25}D$ 1.4190).

Hydrolysis of N-(2,4-Dichlorobenzyl)-N,O-bis-(trichloroacetyl)-ethanolamine. A.—An ice-cooled 0.2 *N* sodium hydroxide solution (100 ml.) was added to an ice-cooled solution of 5.1 g. (0.01 mole) of N-(2,4-dichlorobenzyl)-N,O-bis-(trichloroacetyl)-ethanolamine in 100 ml. of acetone. After 90 minutes the cooled solution was neutralized with 10 ml. of 2 *N* hydrochloric acid and concentrated under reduced pressure to about 10 ml. and then extracted with ethylene dichloride. The ethylene dichloride solution was

(17) Determination of readily hydrolyzable chlorine.

(18) H. Wenker, THIS JOURNAL, **57**, 1079 (1935).

(19) Jefferson Chemical Co., Inc.

dried and the solvent removed under reduced pressure. The residual oil was crystallized from isopropyl alcohol, 1.75 g. (71%), m.p. 68–71°. A mixed melting point determination with authentic 3-(2,4-dichlorobenzyl)-2-oxazolidone was not depressed.

B.—A solution of 5.1 g. (0.01 mole) of N-(2,4-dichlorobenzyl)-N,O-bis-(trichloroacetyl)-ethanolamine and 0.5 g. (0.003 mole) of anhydrous *p*-toluenesulfonic acid in 50 ml. of anhydrous methanol was refluxed for six hours. The resulting solution was concentrated to about 10 ml. and cooled. The solid which separated was collected, washed with ether and recrystallized from isopropyl alcohol, 1.1 g. (94%), m.p. 145–146.5°. The product was identified as the *p*-toluenesulfonic acid salt of N-(2,4-dichlorobenzyl)-ethanolamine by a mixed melting point determination with an authentic sample.

Anal. Calcd. for $C_9H_{11}Cl_2NO \cdot C_7H_8SO_3$: Cl, 18.08. Found: Cl, 18.35.

The filtrate and ether washings from above yielded 3.5 g. (68%) of the starting amine.

RENSSELAER, NEW YORK

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

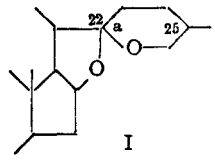
The C-25 Isomerism of Smilagenin and Sarsasapogenin[1]

BY IRVING SCHEER, ROBERT B. KOSTIC AND ERICH MOSETTIG

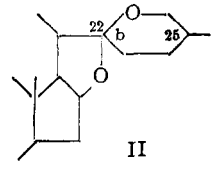
RECEIVED MAY 26, 1954

It is shown that pseudosmilagenin and pseudosarsasapogenin are different compounds. In acidic media they are recyclized to the original genins, smilagenin and sarsasapogenin, respectively. Contrary to previous reports in the literature, dihydrosmilagenin and dihydrosarsasapogenin, and tetrahydrosmilagenin and tetrahydrosarsasapogenin are not identical. The oxidation of pseudosmilagenin and pseudosarsasapogenin yielded the side chain fragments (−)-α-methylglutaric acid and (+)-α-methylglutaric acid, respectively. By the reduction of both dihydrosmilagenin 26-tosylate and dihydrosarsasapogenin 26-tosylate 16,22-epoxycoprostan-3β-ol is obtained. By these experiments it is established that smilagenin and sarsasapogenin are isomeric at C-25.

The so-called "iso" (I) and "normal" (II) ("22a" and "22b") epimeric steroidal sapogenins differ, according to Marker's concepts,[2] in their



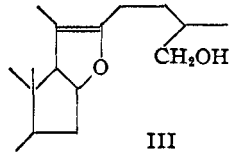
I



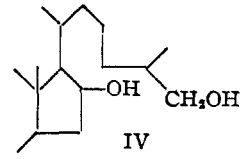
II

configuration at the asymmetric C-22 position. The "22b"-sapogenins can be converted irreversibly to the "22a" epimers by refluxing with alcoholic hydrochloric acid.

The main support for the assumption that the configurational differences accounting for the epimeric "22a" and "22b" series are located at C-22 was the observation that smilagenin and sarsasapogenin gave, with acetic anhydride at 200°,[3] the same pseudosapogenin[4] (III) and, in the Clemmensen reduction, the same tetrahydrosapogenin[5] (IV). In both procedures the asymmetric center at C-22 was destroyed.



III



IV

While preparing a number of pseudosapogenins by rearrangement in acetic anhydride we observed that smilagenin (V) and sarsasapogenin (VI) gave different compounds, a pseudosmilagenin (VII) and a pseudosarsasapogenin (VIII), respectively. This was established by the direct comparison (melting points, rotations, infrared spectra) of the alcohols and the diacetates and the di-3,5-dinitrobenzoates. In acidic media pseudosmilagenin (VII) was recyclized to smilagenin (V), and pseudosarsasapogenin (VIII) gave sarsasapogenin (VI),[6] in quantitative yields. The large positive shift in rotation[7] from $[\alpha]^{20}D$ −66° of V to $[\alpha]^{20}D$ +24° of VII and the ease of recyclization of VII to the original structure V indicated that VII was a pseudosapogenin. The presence of a band of moderate intensity at 1695 cm.$^{-1}$ in the infrared spectrum of VII was a further indication of its pseudosapogenin nature, for it has been shown[8] that the appearance of a band in this region is a characteristic of pseudosapogenins and does not occur with the sapogenins or their derivatives which do not have a C-20—C-22 double bond. The chromic acid oxidation and subsequent hydrolysis of VII and VIII led to the same product, Δ^{16}-pregnene-3,20-dione (IX),[8] and the oxidation of the acetates of VII and VIII, followed by catalytic reduction and hydrolysis, gave the same triol, pregnane-3β,16β,20β-triol (X).[9] The results of these oxidations furnished strong evidence that the pseudosapogenins VII and VIII were epimeric at C-25. Reduction (PtO_2, acetic acid, 25°) of VII and VIII yielded a dihydropseudosmilagenin (XI) and a dihydropseudosarsasapogenin[10] (XII), respectively. The direct comparison (melting points, mixed melting points, rotations, infrared spectra) of the alcohols and the diacetates, and the dibenzoates showed that XI and XII were different.

In view of these findings it appeared pertinent

(1) A preliminary report of this work has appeared earlier; I. Scheer, R. B. Kostic and E. Mosettig, THIS JOURNAL, **75**, 4871 (1953).

(2) R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith and C. H. Ruof, *ibid.*, **68**, 2167 (1947).

(3) R. E. Marker and E. Rohrmann, *ibid.*, **62**, 518 (1940).

(4) R. E. Marker, E. Rohrmann and E. M. Jones, *ibid.*, **62**, 648 (1940).

(5) R. E. Marker and E. Rohrmann, *ibid.*, **61**, 846 (1939).

(6) R. E. Marker and E. Rohrmann, *ibid.*, **62**, 896 (1940).

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(8) A. Hayden, P. Smeltzer and I. Scheer, *Anal. Chem.*, **26**, 550 (1954).

(9) R. E. Marker, D. L. Turner, R. B. Wagner, P. R. Ulshafer, H. M. Crooks, Jr., and E. L. Wittle, THIS JOURNAL, **63**, 779 (1941)

(10) R. E. Marker and E. Rohrmann, *ibid.*, **62**, 521 (1940).