stirred overnight, then filtered. The filtrates were evaporated to dryness, and oxidized with a large excess of chromium trioxide–pyridine reagent at 25° overnight. Crystallization of the product from ethyl acetate–methanol gave the 7-ketone (II, 2.07 g.), plates m.p. 252–256°, $[\alpha]_D$ −6°, λ_{max}^{MeOH} 237 mμ (ε 11,000), λ_{max}^{Nujol} 2.92, 5.73, 5.88, 5.96, 6.10, 8.1, 9.08, 9.58 μ.

Anal. Calcd. for $C_{21}H_{36}O_6$: C, 64.27; H, 7.19. Found: C, 64.25; H, 7.02.

7-Methyl-4,6-pregnadiene-17α,21-diol-3,11,20-trione 21-acetate (III). A solution of 3.0 g. of II in tetrahydrofuran (150 ml.) was added dropwise to an ethereal solution of methyllithium (from 3.45 g. of lithium and 14 ml. of methyl iodide in 300 ml. of ether), with stirring under nitrogen. The addition took 45 min., and the reaction mixture was then stirred under nitrogen for 20 hr. at 25°. The mixture was then poured slowly, with stirring, into iced 6% ammonium sulphate solution (1 l.). The product, isolated by extraction with ether, then methylene chloride, was an oil [λ_{max}^{MeOH} 243; 294 mμ (ε 6000; 5000)]. This material was dissolved in 0.27 *N* methanolic perchloric acid (175 ml.)[5] and left at room temperature for 19 hr., yielding 1.83 g. of a substance showing λ_{max}^{MeOH} 293 (ε 21,000). After acetylation (pyridine and acetic anhydride overnight at room temperature) and chromatography on Florisil, there was obtained, in the benzene ether eluates, 7-methyl-4,6-pregnadiene-17α,21-diol-3,11,20-trione 21-acetate (III; 466 mg.) as needles (acetone-hexane) m.p. 199–204°, $[\alpha]_D$ +362°, λ_{max}^{MeOH} 293 (ε 25,000). λ_{max}^{Nujol} 2.95, 5.72, 5.79, 5.84, 6.05, 6.19, 6.32, 8.15 μ.

Anal. Calcd. for $C_{24}H_{30}O_6.0.5(CH_3)_2CO$: C, 69.05; H, 7.50. Found: C, 69.20; H, 7.90.

7β-Methylcortisone acetate (IV). 7-Methyl-4,6-pregnadiene-17α,21-diol-3,11,20-trione 21-acetate (III; 620 mg.) was hydrogenated in benzene (80 ml.) with palladized strontium carbonate (300 mg.) at room temperature until 1 mole of hydrogen had been absorbed. Chromatography of the product over Florisil afforded, in the benzene ether (3:2) eluates, 7β-methylcortisone acetate (IV; 173 mg.), m.p. 206–208° (from acetone-hexane), $[\alpha]_D$ +168°, λ_{max}^{MeOH} 239 mμ (ε 13,800); λ_{max}^{Nujol} 2.94, 5.78, 5.86, 6.02, 6.18, 8.12 μ.

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.00; H, 7.60.

7β-Methylhydrocortisone acetate (V). A solution of 7β-methylcortisone acetate (125 mg.) in methanol (5 ml.), pyridine (0.15 ml.), and water (1.25 ml.) containing semicarbazide hydrochloride (207 mg.) was refluxed for 15 hr. The solution was then concentrated *in vacuo*, diluted with water, and filtered, giving 130 mg. of 3,20-bissemicarbazone. Extraction of the filtrate with ether gave an additional 14 mg. (total yield 144 mg.). The bissemicarbazone (144 mg.) was dissolved in tetrahydrofuran (5 ml.) and water (2.5 ml.), potassium borohydride (150 mg.) was added, and the mixture was refluxed overnight. Cooling and acidification to *p*H 5.5 with acetic acid, followed by heating on the steam bath for 0.5 hr., then dilution with water, filtration, washing with water, and drying, gave 57 mg. of crude bissemicarbazone of 7β-methylhydrocortisone. Extraction of the filtrate with methylene chloride and ethyl acetate, after addition of saturated sodium chloride solution, yielded a further 22 mg. (total yield 79 mg.). The infrared spectrum of this material (Nujol) indicated substantially complete reduction of the 11-ketone group.

Cleavage of the 3,20-bissemicarbazone was now carried out by adding the steroid (79 mg.) to 14 ml. of a 3:2 chloroform-tetrahydrofuran mixture and 7.4 ml. of 1.25 *N*-hydrochloric acid. The two-phase system was stirred vigorously at room temperature for 1.5 hr. The organic phase was then separated, and the aqueous phase was extracted four times with chloroform. The chloroform extracts and the original chloroform phase were combined, washed with water, and evaporated *in vacuo* to give a solid. Acetylation overnight at room temperature with pyridine–acetic anhydride, followed by chromatography of the acetylated product furnished 7β-methylhydrocortisone acetate (V, 11 mg.), needles (from acetone-hexane) m.p. 185–190°, $[\alpha]_D$ +131°, λ_{max}^{MeOH} 243 mμ. (ε 15,000); λ_{max}^{Nujol} 3.0, 5.74, 5.82, 6.15, 8.15 μ.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.38; H, 7.94.

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Quaternary 2-Oxomorpholinium Salts[1]

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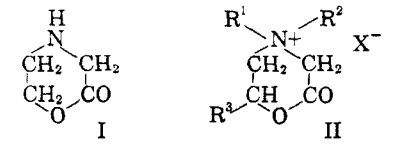
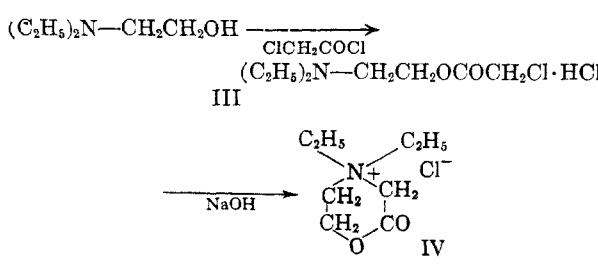
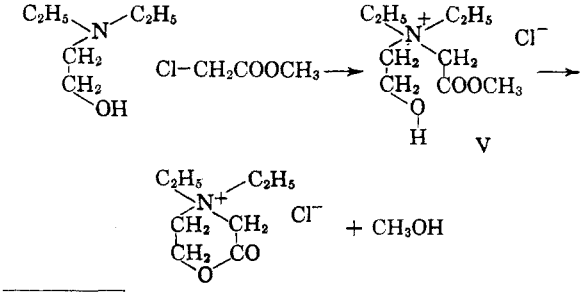
Quaternary 2-oxomorpholinium salts are based on the ring system of 2-oxomorpholine (I) which also might be called morpholactone to emphasize its lactone nature. The quaternary diethyl derivative of II ($R^1 = R^2 = C_2H_5$; $R^3 = H$; X = Cl) has been synthesized by Blicke and Faust[2] the following way.





The hydrochloride III gave 4,4-diethyl-2-oxomorpholinium chloride (IV) in a yield of 26%, m.p. 198–199.° Before the paper of Blicke and Faust appeared we had already synthesized IV and several related compounds by a condensation of β-dialkylamino alcohols and haloacetic esters. Presumably this reaction proceeds in two steps. The first step is the formation of the quaternary



(1) The larger part of these experiments has been performed at the B. F. Goodrich Research Center, Brecksville, Ohio.

(2) F. F. Blicke and J. A. Faust, *J. Am. Chem. Soc.*, **76**, 3158 (1954).

TABLE I

2-OXOMORPHOLINIUM SALTS (II)

R_1, R_2	R_3	X	Yield, %	M.P., °C.	Analysis
C_2H_5,C_2H_5	H	Cl	95	204.5–205	Calcd. for $C_8H_{16}ClNO_2$: C, 49.74; H, 8.29; N, 7.25; Cl, 18.31. Found: C, 49.53; H, 8.37; N, 7.23; Cl, 18.70
C_2H_5, C_2H_5	H	Br	94	226–227 dec.	Calcd. for $C_8H_{16}BrNO_2$: Br, 33.60. Found: Br, 33.92
CH_3, CH_3	CH_3	Cl	80	242 dec.	Calcd. for $C_7H_{14}ClNO_2$: C, 46.92; H, 7.82; N, 7.82; Cl, 19.55. Found: C, 46.99; H, 7.85; N, 7.76; Cl, 19.93
CH_3, CH_3	CH_3	Br	95	240 dec.	Calcd. for $C_7H_{14}BrNO_2$: Br, 35.71. Found: Br, 35.92
CH_3, CH_2CH_2OH	H	Cl	89	185–186	Calcd. for $C_7H_{14}ClNO_3$: C, 43.07; H, 7.17; N, 7.17; Cl, 17.94. Found: C, 42.93; H, 6.93; N, 7.20; Cl, 18.13
$CH_2CH_2OCH_2CH_2$	H	Cl	85	260–262 dec.	Calcd. for $C_8H_{14}ClNO_3$: C, 46.30; H, 6.76; N, 6.76; Cl, 16.90. Found: C, 46.12; H, 6.74; N, 6.76; Cl, 16.87
$CH_2CH_2OCH_2CH_2$	H	Br	95	247–248	Calcd. for $C_8H_{14}BrNO_3$: Br, 31.74. Found: Br, 31.60
$(CH_2)_4$	H	Br	94	227	Calcd. for $C_8H_{14}BrNO_2$: Br, 33.89. Found: Br, 33.68
$(CH_2)_5$	H	Cl	86–87	256–258	Calcd. for $C_9H_{16}ClNO_2$: N, 6.85. Found: N, 6.55

salt (V) and the second is a ring closure in which alcohol is eliminated.

Spiro-2-oxomorpholinium salts are obtained in a similar manner when cyclic aminoalcohols such as β-(*N*-pyrrolidyl)ethanol and β-(*N*-piperidyl)-ethanol are used.

The reaction is performed by heating the dialkylaminoalcohol and the haloacetic ester in a solvent such as toluene, xylene, or benzene. Only small amounts of the quaternary salts can be prepared without using a solvent because of the strongly exothermic reaction. The alcohol formed is distilled off and the precipitated quaternary salt filtered and washed with acetone. The product is then recrystallized from absolute ethanol, methanol, or isopropyl alcohol.

The alcohols (ethanol, methanol) formed during the reaction have been characterized as their 3,5-dinitrobenzoyl derivatives.

The aqueous solutions of the quaternary 2-oxomorpholinium salts have a *p*H of 3 to 4. Some of them show biologic activity and influence phagocytosis.[3]

When β-(*N*-phenyl-*N*-ethylamino)ethanol and ethyl chloroacetate were allowed to react, only quaternization was observed and no ring closure occurred. Since this behavior might be attributed to a steric hindrance of the aromatic ring we plan to extend this preliminary experiment in order to study the influence of substituents on the ring closure.

The quaternary 2-oxomorpholinium salts prepared are listed in Table I.

EXPERIMENTAL

In order to obtain good yields the starting materials, particularly the aminoalcohols, have to be freshly distilled.

4,4-Diethyl-2-oxomorpholinium chloride. Methyl chloroacetate (108 g., 1 mole), 117 g. (1 mole) of β-(*N*,*N*-diethylamino)ethanol, and 300 ml. of dry xylene were heated and stirred for 3 hr. at 120 to 130°. The methanol which formed during the reaction was continuously removed and identified as the 3,5-dinitrobenzoyl derivative (m.p. 111–112°). The precipitated quaternary salt (184 g.) was filtered, washed with acetone, and recrystallized twice from absolute ethanol.

The salt is difficultly soluble in absolute ethanol but readily soluble in 95 to 98% ethanol.

About the same yield was obtained when ethyl chloroacetate was used instead of methyl chloroacetate.

2-Oxo-3-oxa-6-azoniaspiro[4.5]decane bromide. *N*-(β-Hydroxyethyl)pyrrolidine (11.5 g., 0.1 mole) and 15.3 g. (0.1 mole) of methyl bromoacetate were heated in 40 ml. of benzene for 1 hr. at 75 to 80°. The white precipitate, 22.2 g., was recrystallized from a mixture (1:1) of absolute ethanol and methanol.

Acknowledgment. The authors wish to express their gratitude to the Analytical Department of the B. F. Goodrich Research Center for the analytical work performed.

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Melibiose Monohydrate[1]

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Melibiose was originally prepared from raffinose by controlled acid hydrolysis[2] and later by the action of baker's yeast,[3,4] and was isolated, not without difficulty,[3–5] as the dihydrate, m.p. 83°; this dihydrate was the β anomer since it showed in water $[\alpha]_D^{23}$ +111.7° changing to +129.5°.[3–7]

Whereas studies reported[5,7,8] in the literature appear to have been carried out with the β form of

(1) Paper No. 3973 of the Scientific Journal Series, Minnesota Agricultural Experiment Station.

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