order with respect to ozone in both water and carbon tetrachloride media, (2) the rates of decomposition are different in the two media and much faster than that found in the gas phase, (3) an essentially constant concentration of reducible intermediates is found to exist in the water solutions investigated.

The observed data are consistent with the mechanism

$$O_3 + H_2O \xrightarrow{k_1} HO_3^+ + OH^- \quad (1)$$

$$HO_3^+ + OH^- \underset{k_2'}{\overset{k_2}{\rightleftharpoons}} 2HO_2 \quad (2)$$

$$O_3 + HO_2 \xrightarrow{k_3} HO + 2O_2 \quad (3)$$

$$HO + HO_2 \xrightarrow{k_4} H_2O + O_2 \quad (4)$$

The assumptions made in solving for the rate of disappearance of the ozone are (1) that reactions 1 and 3 are responsible for the ozone disappearance and are presumably relatively slow and rate determining, (2) that reaction 2 represents an equilibrium which is maintained as long as there is any ozone in the system, and (3) that reaction 4 is the chain breaking step.

The rate of ozone disappearance is given by

$$d[O_3]/dt = -k_1[O_3][H_2O] - k_3[O_3][HO_2] \quad (5)$$

and the steady state condition can be described by

$$d[HO]/dt = 0 \quad d[HO_2]/dt = 0 \quad d[HO_3^+]/dt = 0 \quad (6)$$

Application of equations 6 to 1–2–3–4 results in the expression for the ozone disappearance

$$d[O_3]/dt = -3k_3[HO_2][O_3] \quad (7)$$

From the equilibrium assumption of 2 where K is the equilibrium constant, equation 7 becomes

$$d[O_3]/dt = -3k_3K^{1/2}[HO_3^+]^{1/2}[OH^-]^{1/2}[O_3] \quad (8)$$

and integration gives

$$-\ln([O_3]/[O_3]_0) = 3k_3K^{1/2}[HO_3^+]^{1/2}[OH^-]^{1/2}t$$

Therefore a plot of $\ln([O_3]/[O_3]_0)$ *versus* t should be a straight line of slope $= -3k_3K^{1/2}[HO_3^+]^{1/2}[OH^-]^{1/2} = k_0$. Since $K^{1/2}$ and $[HO_3^+]^{1/2}$ are indeterminate, the rate determining step is reported as

$$k' = k_0/[OH^-]^{1/2} = 3k_3K^{1/2}[HO_3^+]^{1/2}$$

The heat of activation, $\Delta H^{\ddagger}$, can be obtained by plotting $\ln k'h/kT$ *versus* $1/T$ and determining the slope of the line. For $k' = 5.17 \times 10^{14}$ min.$^{-1}$ mole$^{-1/2}$ at 300° A. and $k' = 0.905 \times 10^{14}$ min.$^{-1}$ mole$^{-1/2}$ at 273° A., $\Delta H^{\ddagger}$ is found to be 9,900 cal./mole. The indeterminancy of values for $K^{1/2}$ and $[HO_3^+]^{1/2}$ precludes the possibility of deriving values for $\Delta S^{\ddagger}$ and $\Delta F^{\ddagger}$.

The difference in the magnitudes of the specific rate constants ás measured iodometrically and spectrophotometrically gives a good indication as to the validity of the postulated chain reaction mechanism. From Fig. 2 it is apparent that an increase of hydroxyl ion increases the rate of ozone disappearance but has little effect on the rate of change of the total oxidizing capacity of the solution. This can be interpreted as implying the existence of a relatively small ozone concentration as compared with the ($[O_3] + [HO] + [HO_2] + [HO_3^+]$) steady state concentration where ($[HO] + [HO_2] + [HO_3^+]$) is assumed to remain constant until near the end of each run.

Summary

Over a sixty-fold variation of hydroxyl ion concentration the rate constant for the decomposition of ozone in aqueous solutions has been shown to be of first order with respect to ozone concentration. The first order dependence occurs at 0° and 27°.

The observed reaction rates are shown to be dependent upon the one-half power of the hydroxyl ion concentration. A chain type mechanism is proposed and is shown to predict the observed dependencies upon ozone and hydroxyl ion concentrations.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF KANSAS]

The Effect of Fluorine Substitution on Medicinal Agents. II.[1] Synthesis of Some Fluorine-Containing α- and α,γ-Substituted Glycerol Ethers

BY ALBERT F. LINDENSTRUTH,[2] J. H. FELLMAN AND CALVIN A. VANDERWERF

Because of the increasing interest in the behavior of fluorine-containing medicinals and in compounds possessing central depressant action, we have undertaken the preparation and a study of the pharmacological properties of various fluorine-containing α- and α,γ-substituted glycerol ethers. The present work deals with a study of compounds in which the *meta* directing trifluoromethyl group and the *ortho–para* directing fluorine atom, substituted at the various positions in the phenyl group, replace the methyl group in the central depressant 3-(2-methylphenoxy)-propan-1,2-diol (Myanesin).[3,4,5,6] The following compounds were prepared and tested for central depressant activity: 3-(2-fluorophenoxy)-propan-

(1) For the first paper in this series, see Bradlow and VanderWerf, THIS JOURNAL, **70**, 654 (1948). The authors are indebted to the Office of Naval Research for a grant which made this and continuing investigations possible.

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(3) Gilbert and Descomps, *Compt. rend. soc. biol.*, **69**, 145 (1910).

(4) Berger and Bradley, *Brit. J. Pharmacol.*, **1**, 265 (1946).

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TABLE I

α- AND α,γ-SUBSTITUTED GLYCEROL ETHERS, $R^1—O—CH_2CHOHCH_2—O—R^2$

R^1	R^2	Yield, %	B. p. °C.	Mm.	M. p.,[a] °C.	Formula	Carbon, % Calcd.	Carbon, % Obs.	Hydrogen, % Calcd.	Hydrogen, % Obs.	P. D.[b] mM./kg.
2-Fluorophenyl	H	77	154–156	4	42–43	$C_9H_{11}O_3F$	58.1	58.3	6.0	5.9	1.9 ± 0.2[c]
3-Fluorophenyl	H	61	162–163	4	47–48	$C_9H_{11}O_3F$	58.1	57.8	6.0	5.9	8.0 ± 0.4[c]
4-Fluorophenyl	H	80	163–164	4	53–54	$C_9H_{11}O_3F$	58.1	58.5	6.0	6.2	2.8 ± .2[c]
2-Trifluoromethylphenyl	H	30	150–151	4	63–64	$C_{10}H_{11}O_3F_3$	50.9	50.8	4.7	4.8	2.0 ± .2[c]
3-Trifluoromethylphenyl	H	66	153–155	4	52–53	$C_{10}H_{11}O_3F_3$	50.9	51.1	4.7	5.0	1.5 ± .2[c]
2-Fluorophenyl	2-Fluorophenyl	81	180–182	3	53–54	$C_{15}H_{14}O_3F_2$	64.3	64.7	5.0	5.4	10.0 ± .5[d]
3-Fluorophenyl	3-Fluorophenyl	86	189–190	4	61–62	$C_{15}H_{14}O_3F_2$	64.3	64.5	5.0	4.7	.....
4-Fluorophenyl	4-Fluorophenyl	72	192–193	3	81–82	$C_{15}H_{14}O_3F_2$	64.3	64.5	5.0	5.0	.....
3-Trifluoromethylphenyl	3-Trifluoromethylphenyl	68	165–166	0.5	58–59	$C_{17}H_{14}O_3F_6$	53.7	53.9	3.7	3.9	.....

[a] Small traces of impurities lower the melting points very considerably and repeated recrystallization from anhydrous ether is necessary for isolation of pure products. [b] The loss of the righting reflex in white mice for at least one minute was considered as criterion for paralyzing action. In all cases a 10% propylene glycol solution was employed as the vehicle for injection. The volume injected was never more than 0.5 ml. [c] By subcutaneous administration. [d] Intraperitoneal injection.

1,2-diol, 3-(3-fluorophenoxy)-propan-1,2-diol, 3-(4-fluorophenoxy)-propan-1,2-diol, 3-(2-trifluoromethylphenoxy)-propan-1,2-diol, 3-(3-trifluoromethylphenoxy)-propan-1,2-diol, 1,3-di-(2-fluorophenoxy)-2-propanol, 1,3-di-(3-fluorophenoxy)-2-propanol, 1,3-di-(4-fluorophenoxy)-2-propanol and 1,3-di-(3-trifluoromethylphenoxy)-2-propanol.

Pharmacological Behavior.—Preliminary data on pharmacological behavior and paralyzing dose of these compounds were obtained according to the method of Berger[6] (see Table I). The fluorine substituted α-glycerol ethers appeared comparable in paralyzing action to the corresponding chlorine and bromine analogs, but slightly less effective than Myanesin. The *o*-fluoro analog was the most effective of this group. The strong *meta* directing trifluoromethyl analogs were extremely effective, especially when the trifluoromethyl group was in the *meta* position. The α,γ-disubstituted glycerol ethers possessed insignificant paralyzing action.

Preliminary experiments on the toxicity of fluorine-substituted 3-phenoxypropan-1,2-diols were conducted. At paralyzing dose levels there was no evidence of gross pathological changes at the end of two hours. The manifestation of hemorrhagic kidney and marked liver discoloration was noted at the end of twenty-four hours. Hemoglobinuria was induced with large doses of the trifluoromethyl derivatives. In general, fluorine substitution did not increase the toxicity of the substituted 3-phenoxypropan-1,2-diols above that of the corresponding chloro- or bromo-derivatives.

Experimental

Preparation of Fluoro- and Trifluoromethylphenols.—The *o*- and *p*-fluorophenols were prepared in over-all yields of 48 and 34% by the Schiemann reaction,[7,8] modified by use of the corresponding phenetidines followed by cleavage of the fluoroethers with aluminum bromide. *m*-Fluorophenol was prepared in 40% yields by the direct diazotization of *m*-aminophenol in anhydrous hydrogen fluoride.[9]

o-Trifluoromethylphenol was prepared by the method of Jones,[10] and its *m*-isomer was obtained in 58% yields by decomposition of the diazonium salt of *m*-aminobenzotrifluoride with water.[11]

Preparation of α-Substituted Glycerol Ethers.[12]—The appropriate fluorophenol (11.2 g., 0.10 mole) or trifluoromethylphenol (17.8 g., 0.11 mole) was added to a solution of 250 ml. of absolute alcohol and 2.3 g. (0.10 mole) of sodium. To the resulting clear solutions, 12.1 g. (0.11 mole) of glycerol-α-monochlorohydrin was added and the mixtures were then refluxed overnight. The salt was removed by filtration, the alcohol by distillation under atmospheric conditions, and the resulting oils were dissolved in ether. The ethereal solutions were washed with dilute sodium hydroxide solution, then with dilute hydrochloric acid, and finally with water, dried, and the oils fractionated. The resulting high boiling oils solidified upon cooling and were recrystallized from either a benzene–Skellysolve mixture or from ether.

Preparation of α,γ-Disubstituted Glycerol Ethers.—The α,γ-disubstituted glycerol ethers were prepared as described in the preceding section by treatment of 0.10 mole of the appropriate sodium fluoro- or trifluoromethylphenoxides with 6.5 g. (0.05 mole) of glycerol-α,γ-dichlorohydrin.

Summary

The preparation of nine new α- and α,γ-substituted fluorophenyl and trifluoromethylphenyl glycerol ethers and their effectiveness as central depressant agents are reported.

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