acid produces the corresponding amino esters in 45, 60 and 52% yields, respectively.

Treatment of ethyl *o*-aminocinnamate with quantities of bromine which correspond to eight and to two atoms for one molecule of ester yields a compound containing four atoms of bromine, two of which are apparently in the side chain.

Upon reaction with an amount of bromine sufficient to saturate the double bond and to replace all sensitive hydrogen atoms in the ring, ethyl *m*-aminocinnamate is transformed into a compound in which five atoms of bromine are present; reactions of this derivative indicate that two atoms of bromine are in the side chain and three in the aromatic nucleus. The use of one molecule of halogen for one of ester yields a tribromo derivative, in which all three halogen atoms are aromatic. Apparently, substitution of bromine in the ring precedes addition to the double bond.

If the ethyl ester of *p*-aminocinnamic acid is treated with an excess of bromine a compound containing three atoms of halogen is secured; only one of the bromine atoms is in the side chain. A plausible explanation of this result may be found by assuming that bromine first enters the ring and that the hydrogen bromide thus formed adds to the aliphatic unsaturated linkage. If two atoms of bromine for one molecule of ester are employed a tarry mixture is secured; no pure compound was obtained from this material.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

SOME ETHER-SUBSTITUTED DERIVATIVES OF DIETHYL MALONATE AND BARBITURIC ACID

BY ARTHUR J. HILL AND DEWITT T. KEACH[1]

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Since the preparation of 5,5-diethylbarbituric acid (Veronal or Barbital) by Fischer and von Mering, and the subsequent discovery of its hypnotic properties, a large amount of research has been carried out with a view to securing hypnotics superior to this substance.

In general these attempts have centered on substitution in Position 5, in which the effect of a very large number of organic radicals has been investigated. Among these, ether groups[2] of the types represented by —OC_6H_5 and —$CH_2CH_2.OR$ have been introduced, and their physiological effects studied. In connection with these, it is interesting to note that the

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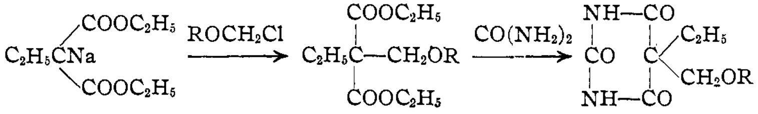
[1] From a part of the dissertation presented by DeW. T. Keach to the Faculty of the Graduate School of Yale University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Dox and Yoder, THIS JOURNAL, **44,** 1578 (1922). Ger. pat. 285,636 (1915); 295,492 (1917). U. S. pat. 1,217,446; 1,217,447 (1917).

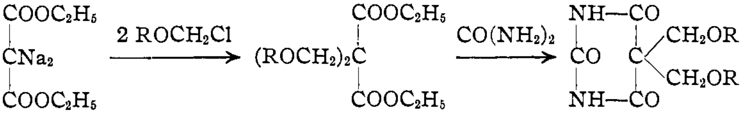
following 5,5-disubstituted barbituric acids have been reported to possess satisfactory sedative properties, associated with low toxicity: *bis*(ethoxyethyl), *bis*(phenoxyethyl), ethyl-phenoxyethyl, and benzyl-phenoxyethyl.

So far as the writers are aware, no systematic investigation has yet been made of the ether-substituted types represented by Formulas I and II, in which the hydrogen atoms of the 5 position have been replaced by alkoxy-methyl and ethyl, and by two alkoxy-methyl groups, respectively.

These new substances have now been synthesized by alkylation, in ether solution, of the sodium salt of malonic ester, or its mono-ethyl derivative, with chloro-ethers of the type $R.OCH_2Cl$, followed by condensation of the ether-substituted malonic esters, thus prepared, with urea, that is,



(I)



(II)

In the compounds represented by I, the ethyl group is common to the series, while R is methyl, ethyl, propyl, *n*-butyl, *iso*butyl or benzyl. Only three representatives of Type II have been prepared: in these R is methyl, ethyl or propyl.

The requisite chloro-ethers, two of which are new, were prepared by the method of Henry[3] and Favre,[4] according to which the alcohol furnishing the alkyl radical of the desired chloro-ether is mixed with aqueous formaldehyde, and treated with hydrogen chloride; that is, $CH_2O + C_2H_5OH + HCl = ClCH_2O.C_2H_5 + H_2O$.

Favre[4] reports *iso*butyl-chloromethyl ether as having a boiling point of 131°. Both the normal (b. p., 134°) and *iso*butyl (b. p., 120–121°) ethers have been prepared with great care during the course of this investigation, and, from the boiling points observed, it is certain either that Favre was dealing with the normal butyl compound, or that the boiling point given in the original paper is a typographical error. One of these chloro-ethers is therefore new, as well as the rather interesting benzyl-chloromethyl ether, $C_6H_5CH_2O.CH_2Cl$.

On account of their susceptibility to decomposition by heat, water and alcohol, the chloro-ethers of this type have not found extensive application as alkylating agents, yet the ease with which these new reactions have been carried out suggests the possibility of more general usage in this

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[3] Henry, *Bull. soc. chim. Belg.*, [3] **26**, 629 (1893).

[4] Favre, *Bull. soc. chim.*, [3] **11**, 1095, 879 (1894).

sense. The yields of the ether-substituted malonic esters, except in the cases when two ether groups were introduced, were above 50%, and in one case 74%. This is surprisingly good, considering the insolubility of the sodium malonates in ether, together with their tendency to become coated with sodium chloride during the reaction.

The condensations with urea were productive of yields ranging from 33 to 63%. Excepting 5,5-*bis*(methoxymethyl)barbituric acid, the new ureides possess a distinct water solubility, a property exceedingly valuable for therapeutic purposes. Pharmacological tests of these new "Barbital" analogs are now in progress.

Experimental Part

Preparation of the Chloro-ethers.—In all cases, except that of the benzyl-chloromethyl ether, the appropriate alcohol was mixed with one molecular proportion of 40% aqueous formaldehyde, and hydrogen chloride passed into the ice-cooled solution to saturation. The reaction mixture separated into two layers and there was an increase in volume. The upper layer was separated, dried over anhydrous calcium chloride and distilled. This procedure was unsuccessful in the case of benzyl-chloromethyl ether; in fact it was found impossible to secure this compound unless the benzyl alcohol was entirely free from benzyl chloride, and unless the reaction was carried out under such conditions as to prevent the formation of this halide as a by-product. The presence of benzyl chloride causes the complete decomposition of the chloro-ether upon distillation. Benzyl alcohol, containing benzyl chloride, was freed from the latter by conversion into the calcium chloride addition product, which was washed thoroughly with benzene and then decomposed with water. To prevent the formation of benzyl chloride in the reaction, a large excess (3 molecular proportions) of the formaldehyde solution was used. Under these conditions the reaction proceeded smoothly and in excellent yield. Physical and analytical data in connection with these new chloro-ethers are given in Table I.

TABLE I

CHLORO-ETHERS

Chloromethyl ether	B. p., °C.	Pressure, mm.	Yield, %	Analysis, Cl% Calcd.	Analysis, Cl% Found	
n-Butyl	134	760	37	28.88	27.95	27.93
*iso*Butyl	120–121	760	35	28.88	28.97	29.03
Benzyl	125	40	77	22.59	22.04	21.95

Methyl-chloromethyl ether, b. p. 59.5°; ethyl-chloromethyl ether, b. p. 80.0°; propyl-chloromethyl ether, b. p. 112.5°. (Ethers previously prepared.)

Preparation of the Ether-substituted Malonic Esters.—The esters $(ROCH_2)_2.C(COOC_2H_5)_2$ and $ROCH_2.C.(C_2H_5)(COOC_2H_5)_2$ were made by the same general procedure. The calculated amount of sodium, pressed into wire and cut into small pieces, was suspended in dry ether, and ethyl

ethyl-malonate, or ethyl malonate (a convenient amount is 60 g.) added slowly during constant stirring. When the reaction was complete, usually after about two hours, the flask was immersed in a freezing mixture, and slightly more than one molecular proportion of the chloro-ether was added slowly, the stirring being continued. Sodium chloride separated at once and after several hours' stirring the mixture was allowed to stand overnight. After filtration from the sodium chloride and unchanged sodium salt, the ether solution was dried with anhydrous sodium sulfate. The ether was then removed at 70°, and the ester distilled under diminished pressure. A summary of the experimental data is given in Table III.

Certain difficulties were met in the attempt to prepare diethyl *bis*(methoxymethyl)malonate, $(CH_3O.CH_2)_2.C.(COOC_2H_5)_2$. Kleber,[5] the first to attempt alkylation of the disodium salt of diethyl malonate with methyl-chloromethyl ether, isolated a product, which upon treatment with alkali gave an acid corresponding, upon analysis, to *bis*-methoxymethyl-malonic acid. Simonsen,[6] who attempted to repeat Kleber's observation, claims that the product of alkylation is diethyl *bis*(methoxymethyl)malonate. In this investigation, two major fractions were repeatedly obtained on distillation, but the condensation of these fractions with urea or guanidine justifies the conclusion that both the mono- and dialkylated products are produced by the reaction, the former in preponderance, and that they are not separated completely on distillation due to the small difference between their boiling points.

The analyses of the products produced by reaction with either guanidine or urea gave values between those calculated for the mono- and dialkylated pyrimidines. Further, it was found possible to alkylate some of the lower-boiling fraction with methyl-chloromethyl ether and raise its boiling point to approximately that of the dialkylated product. In every attempt to prepare a dialkylated malonic ester of this type, a lower-boiling fraction was obtained. Indeed, in the case of the *bis*-propoxymethyl derivative, this was definitely shown to be the mono-alkylated product by condensing it with urea and analyzing the product. (See Tables III and IV.)

A summary is given in Table II of the data relating to the constitution

TABLE II

THE ACTION OF METHYL-CHLOROMETHYL ETHER ON DISODIO DIETHYL MALONATE

Extent of alkylation with $ClCH_2.O.CH_3$	B. p. of malonic ester, °C.	Analyses of esters				Cond. prod. of ester			
		C, %		H, %		With urea N, %		With guanidine N, %	
		Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
Mono-methoxy methyl	95–100 (8 mm.)	...	...	..	..	16.19	16.98	24.60	...
bis-Methoxy methyl	120–130 (8 mm.)	53.22	53.13	8.12	8.03	12.98	14.81	19.57	20.83

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[5] Kleber, *Ann.*, **246,** 97 (1888).

[6] Simonsen, *J. Chem. Soc.*, **93,** 1780 (1908).

of the esters resulting from the action of methyl-chloromethyl ether on disodio diethyl malonate. The properties of the ureides are not recorded because these substances were not obtained in a state of analytical purity.

TABLE III

ETHER-SUBSTITUTED DERIVATIVES OF DIETHYL MALONATE

	Ester (substituted diethyl malonate)	B. p., °C.	Pressure, mm.	Yield, %	Analyses, % C, calcd.	Found	H, calcd.	Found
1.	Ethyl, methoxymethyl-	125–126	18	69	56.85	56.87	8.68	8.70
2.	Ethyl, ethoxymethyl-	120–121	13	74	58.53	57.67	9.01	8.89
3.	Ethyl, propoxymethyl-	135–140	15	50	59.97	59.55	9.29	9.28
4.	Ethyl, *n*-butoxymethyl-	133	5–6	50	61.27	61.09	9.56	9.65
5.	Ethyl, *iso*-butoxymethyl-	135	9–10	56	61.27	60.60	9.56	9.49
6.	Ethyl, benzyloxymethyl-	190–192	10–11	56	66.20	66.79	7.85	7.70
7.	Propoxymethyl-	107–108	2–3	21	...	...	..	..
8.	*bis*-Ethoxymethyl-	123–125	7–8	25	56.50	55.46	8.76	8.83
9.	*bis*-Propoxymethyl-	124–125	2–3	21	59.19	58.37	9.27	9.46

Condensation of the Esters with Urea.—The barbituric acids were prepared by the interaction of the ether derivatives of the malonic esters and urea, with alcoholic sodium ethylate as a condensing agent. One molecular equivalent of the ester, usually 25 g., was treated with 1.5 equivalents of urea in a solution of two equivalents of sodium in absolute alcohol. The success of these condensations was found to be greatly dependent upon the use of pure reagents. The mixture was heated on the water-bath for a period of ten hours. The alcohol was then evaporated; the sodium salt dissolved in the least possible amount of cold water, and acidified with concd. hydrochloric acid in order to precipitate the ureide. All crystallizations were carried out by heating on the steam-bath and not over a free flame. The experimental data are summarized in Table IV.

TABLE IV

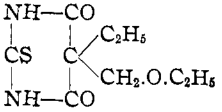
ETHER-SUBSTITUTED DERIVATIVES OF BARBITURIC ACID

	Barbituric acid derivative[a]	M. p., °C.	Analyses, N, % Calcd.	Found		Yield, %	Crystal form	Solubilities
1.	5,5-ethyl-methoxymethyl	184	14.03	13.82	13.99	35	Rosets	Sol. hot water, alc.;[b] insol. bz.
2.	5,5-ethyl-ethoxymethyl	166	13.11	12.98	13.10	37	Plates	Sol. alc., bz.[b] and water
3.	5,5-ethyl-propoxymethyl	174	12.28	12.17	12.06	48	Plates	Sol. alc., bz.[b] and water
4.	5,5-ethyl-*n*-butoxymethyl	135	11.57	11.50	11.50	45	Plates	Sol. alc., bz.[b] and water; 15% alc.[b]
5.	5,5-ethyl-*iso*butoxymethyl	177	11.57	11.30	11.26	56	Plates	Sol. alc., water, 15% alc.[b]
6.	5,5-ethyl-benzyloxymethyl	139–140	10.15	9.69	9.75	33	Plates	Sol. bz.,[b] water
7.	5,5-*bis*(ethoxymethyl)	201–203	11.48	11.58	11.55	63	Needles	Insol. abs. alc., bz.; sol. water, 80% alc.[b]
8.	5,5-*bis*(propoxymethyl)	187	10.29	10.21	10.49	44	Needles	Sol. water, alc., bz., 80% alc.
9.	5-propoxymethyl	163–165	13.97	14.19	14.16	44	Needles	Sol. aq. alc.[b]
10.	5,5-ethyl-ethoxymethyl-2-thio-	147	12.17	12.40	12.20	88	Scales	Sol. aq. alc.[b]

[a] The ureides were colorless with the exception of No. 10, which was cream-colored.

[b] Solvent used in crystallization.

As a different method of approach to these barbituric acid derivatives, 5,5-ethyl-ethoxymethyl-2-thiobarbituric acid, III (No. 10, Table IV), was prepared by condensing ethyl ethyl-ethoxymethyl malonate with thio-urea, in manner similar to that of the urea condensations. The yield was excellent. Attempts, however, to desulfurize this compound by digesting it in aqueous solution with 1.5 to 2 molecular proportions of chloroacetic acid resulted in failure. The thiobarbituric acid was either recovered unchanged by mild treatment, or decomposed by more drastic treatment with this reagent.



III

Summary

1. Ether-substituted derivatives of diethyl malonate, or of its mono-alkylated products, may be prepared by interaction of the sodium salts of these substances and chloro-ethers of the general formula $ROCH_2Cl$. Nine of these esters have been synthesized.

2. These ether-substituted malonic esters condense normally with urea, in sodium ethylate solution, giving analogs of "Barbital" (di-ethyl barbituric acid), in which the 5 position of barbituric acid is occupied by one or two alkoxy-methyl groups.

3. Chloromethyl-benzyl ether and chloromethyl-*iso*butyl ether have been prepared.

New Haven, Connecticut

[Contribution from the Polarimetry Section, Bureau of Standards, United States Department of Commerce][1]

STUDIES ON SALICIN. I. EXCEPTIONAL ROTATIONS OF THE HALOGENO-TETRA-ACETYL DERIVATIVES OF SALICIN. A NEW SYNTHESIS OF SALICIN[2]

By Alfons Kunz

Received September 30, 1925 Published January 8, 1926

Salicin, the well known glucoside of the willow, is doubtless a beta derivative, since it yields β-glucose by enzymotic hydrolysis.[3] According to the results of Irvine and Rose,[4] it possesses the butylene oxide ring of methyl glucoside and has the structure I.

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[1] Published by permission of the Director of the Bureau of Standards, U. S. Department of Commerce.

[2] Compare Michael, *Compt. rend.*, **89**, 355 (1879); *Ber.*, **12**, 2260 (1879).

[3] Hudson and Paine, This Journal, **31**, 1242 (1909).

[4] Irvine and Rose, *Proc. Chem. Soc.*, **22**, 113 (1906); *J. Chem. Soc.*, **89**, 814 (1906).