2. The reactivity of the chlorine atom in three series of compounds of the type $A(CH_2)_nCl$ has been measured and compared with the reactivity of the chlorine atom in *n*-butyl chloride.

3. The halogen atom is more reactive in the compounds ACH_2Cl than in ACl or ACH_2CH_2Cl in the three series studied in which A is benzoyl, phenyl and carbethoxy, respectively. The influence of the group on the chlorine atom in the compounds of the type ACH_2Cl is roughly proportional to the effect of the same group on the activity of the hydrogen atom in the compounds of the type ACH_3.

4. In the benzoyl series the compound ACH_2CH_2Cl is 80 times more reactive than a simple normal alkyl chloride; in the phenyl and carbethoxy series the activity of the corresponding compound is of the same order as that of the alkyl chlorides. The compounds $ACH_2CH_2CH_2Cl$ in the benzoyl and phenyl series are more reactive than the compounds ACH_2CH_2Cl, this increase being large in the benzoyl series; in the carbethoxy series no such increase is apparent. The chlorine atom in the next higher homolog in the phenyl and carbethoxy series is only as reactive as that in butyl chloride; no higher homologs were available in the benzoyl series. Phenylamyl, phenylhexyl and phenylheptyl chlorides do not differ significantly in their reactivity from one another or from *n*-butyl or *n*-amyl chlorides.

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ACETONYL-BARBITURIC ACID AND SOME OF ITS DERIVATIVES

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Monochloro-acetone, notwithstanding its cheapness, ease of preparation and reactivity, has seldom been used as an alkylating agent. The acetonyl group, CH_3COCH_2, has many properties in common with the simple alkyls, and its introduction into certain types of compounds, particularly those of pharmaceutical interest, where the ethyl or the allyl group is ordinarily employed, might be expected to yield derivatives similar in character though perhaps with somewhat modified physiological properties.

In the barbituric acid series, for example, some 60 or more alkyl substitutions have been made on the 5-carbon atom, and in addition to these, various alkoxyl, alkoxyalkyl, hydroxyalkyl and dialkylamino-alkyl substitution products have been described. Apparently, however, the preparation of keto-alkyl-barbituric acids has not been attempted. This is rather surprising in view of the fact that the ketones in general have hypnotic properties, at least two of them, diethylketone and acetophenone,

having found use as sleep-producing drugs. Unfortunately, with our present state of knowledge, the prediction of physiological properties is largely guess work. The carbonyl group, —CO—, is common to many hypnotics, three such groupings being present in all hypnotics of the veronal type. On this assumption, the introduction of a fourth carbonyl on the side chain might be expected to intensify hypnotic action. Thus, acetonyl-ethylbarbituric acid should be a stronger hypnotic than propyl-ethylbarbituric acid. As a matter of fact, the additional carbonyl group actually diminished the hypnotic action, but the explanation is to be sought in the physical properties of the substance rather than in its chemical constitution.

With acetonyl-barbituric acid as a starting point, several new barbituric acids were prepared by further substitution on the 5-carbon atom. Though disappointing from the standpoint of physiological action, these substances are worthy of description as new derivatives.

Experimental Part

Acetonyl-barbituric Acid.—Ordinarily both the mono- and dialkylated barbituric acids are prepared from the esters of the corresponding mono- and di-alkyl malonic acids. Our attempts to introduce the acetonyl group into ethyl malonate were not very encouraging. Chloro-acetone is very reactive toward sodium ethylate, and the alcoholic suspension of the sodium salt of ethyl malonate reacted precisely as did sodium ethylate itself. Even in the cold and with efficient stirring, the separation of sodium chloride began almost immediately, but the liquid rapidly took on an orange, then a deep red color. From 160 g. of ethyl malonate, 92.5 g. of chloro-acetone and 23 g. of sodium in 400 cc. of absolute alcohol, we recovered 117 g. of pure ethyl malonate and obtained 24 g. of a viscous yellow oil boiling in a vacuum over a considerable range of temperature and leaving a tarry residue. The separation of sodium chloride, however, was quantitative. On account of the very small yield, the purification and identification of the oil were not attempted. It is not unlikely that ethyl acetonyl-malonate could be prepared in better yield by suitable modifications in the technique of alkylation.[1] Such a method would at best be less satisfactory than the direct alkylation of barbituric acid which in this case gave excellent yields.

Fifty g. of crystalline barbituric acid was dissolved in 250 cc. of hot water, and to this solution was gradually added a solution of 41.5 g. of crystalline sodium acetate and 28.2 g. of chloro-acetone in 300 cc. of 80% alcohol. The aqueous solution of barbituric acid was kept boiling under a reflux condenser while the alcoholic solution was added

[1] Gault and Salomon [*Compt. Rend.*, **174**, 755 (1922)] have recently prepared ethyl acetonal-malonate in 65% yield by treating a suspension of sodio-ethyl malonate in absolute ether with bromo-acetone in the cold. Ethyl ethane-tetracarboxylate was obtained as a by-product.

from a dropping funnel during the course of one hour. A bright yellow color gradually developed and at the same time a yellow precipitate formed. After all of the reagent had been added the refluxing was continued for two hours longer. As the mixture cooled, an abundance of scaly, yellow crystals settled to the bottom; yield, 44.8 g., or 80%. The substance was purified by suspending it in 300 cc. of cold water, adding a 10% solution of sodium hydroxide to exact neutrality, and filtering from a small residue (1.4 g.) of white needles (diacetonyl-barbituric acid). The yellow filtrate when acidified with hydrochloric acid gave flat, yellow crystals.

Acetonyl-barbituric acid is a fairly strong acid, liberating acetic acid from its salts. It is difficultly soluble in cold water, more soluble in hot water and nearly insoluble in alcohol, but readily soluble in dil. alkalies. It melts at 238–240° with decomposition. The yellow color is in striking contrast to the color of the ordinary alkyl barbituric acids. All attempts to remove the color by treatment with charcoal failed. Further substitution, however, on the 5-carbon atom invariably gave colorless products.

Analyses. Subs., 0.1737: CO_2, 0.2870; H_2O, 0.0710. Calc. for $C_7H_8N_2O_4$: C, 45.65; H, 4.34. Found: C, 45.06; H, 4.54.

Subs., 0.2383, 0.2343: 25.84, 25.73 cc. of 0.1 *N* acid. Calc.: N, 15.22. Found: 15.19, 15.37.

Acetonyl-bromobarbituric Acid.—Like the mono-alkyl barbituric acids acetonyl-barbituric acid is easily halogenated. A suspension of 2.0 g. of the substance in 50 cc. of water was treated with slightly more than the calculated amount (2 equivalents) of bromine and the mixture stirred vigorously. As the bromine gradually disappeared, the yellow acid changed into a white, heavy, granular sediment. This was filtered off, washed with cold water and weighed. The increase in weight amounted to 1.0 g., representing a quantitative yield. Recrystallization from hot water gave long white needles which were practically tasteless. Heated in a capillary tube the substance begins to decompose at about 143° without melting.

Analysis. Subs., 0.2948: AgBr, 0.2062. Calc. for $C_7H_7N_2O_4Br$: Br, 30.41. Found: 29.77.

Acetonyl-chlorobarbituric Acid.—Two g. of acetonyl-barbituric acid was suspended in 50 cc. of water in a small Erlenmeyer flask and chlorine passed in until an increase in weight corresponding to 2 equivalents of chlorine was obtained, disregarding any slight loss by evaporation of water. Gentle warming facilitated the reaction. The yellow, scaly crystals changed into a white, granular sediment leaving a yellow mother liquor. The product, after it had been filtered and washed, weighed 2.4 g., representing a quantitative yield. Recrystallization from hot water gave long white needles which were practically tasteless. Both the bromo and chloro derivatives are fairly stable to hot water, but long continued boiling liberates halogen acid and the substance reverts to the yellow acetonyl-barbituric acid. The chloro derivative melts at about 245° with previous decomposition beginning at about 175°.

Analysis. Subs., 0.2892: AgCl, 0.1898. Calc. for $C_7H_7N_2O_4Cl$: Cl, 16.25. Found: 16.24.

Diacetonyl-barbituric Acid.—A second acetonyl group enters the barbituric acid ring much less readily than the first. When barbituric acid is treated with two molecular equivalents each of chloro-acetone and sodium acetate instead of one, the amount of diacetonyl derivative formed is only slightly greater, the main product being the mono derivative as before. In neutral solution, as, for example, with the sodium salt of acetonyl-barbituric acid, the yield of diacetonyl derivative is much greater.

Ten g. of acetonyl-barbituric acid was suspended in 30 cc. of water and 10% sodium hydroxide solution added until an exactly neutral solution was obtained; 5.1 g. of chloro-acetone was then added and the mixture refluxed for 4 hours. A gradual separation of crystals occurred. These were filtered off and found to consist of a mixture of yellow scales and white needles. Treatment with very dilute sodium hydroxide solution dissolved the yellow crystals leaving the white needles practically pure; yield, 4.0 g. The substance is almost insoluble in cold water and in alcohol, and soluble in alkali. In contrast to the sour-tasting mono-acetonyl derivative, it has a bitter and slightly sweetish taste; m. p., 264–266° (decomp.).

Analyses. Subs., 0.2146, 0.3831: 18.55, 32.60 cc. of 0.1 *N* acid. Calc. for $C_{10}H_{12}N_2O_5$: N, 11.67. Found: 11.92, 12.11.

Acetonyl-allylbarbituric Acid.—In our previous experience in the direct alkylation of barbituric acid and mono-alkylbarbituric acids allyl bromide was found to be the most reactive of the ordinary alkyl halides. This reacts readily also with acetonyl-barbituric acid.

Ten g. of acetonyl-barbituric acid was dissolved in 100 cc. of dil. sodium hydroxide solution, the solution made exactly neutral and refluxed with 6.6 g. of allyl bromide. A separation of crystals began in about 20 minutes, after which the refluxing was continued for one hour. From the cooled mixture 11.2 g. of prismatic crystals was obtained. Recrystallization from alcohol gave a pure white product in large crystals with a bitter taste; m. p., 216–217°.

Analysis. Subs., 0.2455: 22.09 cc. of 0.1 *N* acid. Calc. for $C_{10}H_{12}N_2O_4$: N, 12.50. Found: 12.59.

The same substance was also obtained by treatment of allylbarbituric acid with chloro-acetone and sodium acetate. The first method gave the better yield.

Acetonyl-benzylbarbituric Acid.—Five g. of acetonyl-barbituric acid neutralized to sodium hydroxide and made up to 25 cc. with water was refluxed 1 hour with 3.5 g. of benzyl chloride. No apparent reaction occurred. Sufficient alcohol was then added to give a homogeneous liquid. The solution was found to be acid to litmus owing to a partial hydrolysis of the benzyl chloride. It was again neutralized and a few drops more of benzyl chloride were added. After four hours' refluxing the yellow color had become much fainter, and on cooling the mixture 6.7 g. of crystals separated. Recrystallization from alcohol gave large, colorless, prismatic crystals with a bitter taste and a melting point of 224–225°. The substance is insoluble in water but readily soluble in alcohol.

Analysis. Subs., 0.2152, 0.2351: 15.68, 17.72 cc. of 0.1 *N* acid. Calc. for $C_{14}H_{14}N_2O_4$: N, 10.22. Found: 10.20, 10.54.

Acetonyl-ethylbarbituric Acid.—Ten g. of ethylbarbituric acid was dissolved in a mixture of 60 cc. of water and 30 cc. of alcohol by boiling under a reflux condenser. To the boiling solution a solution of 10 g. of chloro-acetone and 15 g. of sodium acetate in 75 cc. of alcohol and 30 cc. of water was gradually added and the refluxing continued for two hours. Evaporation of the solution gave 8 g. of white, flat crystals that had a bitter taste; m. p., 238–239°. The substance is difficultly soluble in water and somewhat more soluble in alcohol.

Analysis. Subs., 0.2126: 20.12 cc. of 0.1 *N* acid. Calc. for $C_9H_{12}N_2O_4$: N, 13.21. Found: 13.23.

It is thus apparent that further substitution in acetonylbarbituric acid may be effected with allyl, benzyl and acetonyl, the readiness of alkylation occurring in the order named. Other alkylating agents failed to react, at least to the extent necessary for the isolation of the product. With

methyl sulfate, butyl bromide and *iso*-amyl iodide we obtained only a recovery of the original acetonyl-barbituric acid. The comparative ease with which chloro-acetone reacted with ethylbarbituric acid suggests the possibility of preparing homologs by introducing the acetonyl group into homologous alkyl barbituric acids.

Four of the above derivatives, diacetonyl, -acetonyl-benzyl-, acetonyl-ethyl-, and acetonyl-allylbarbituric acids were subjected to physiological test. Intraperitoneal injection in white mice of solutions in dilute alkali in amounts representing the effective dose of veronal produced no noticeable effect. Three times this dosage in the case of acetonylethyl gave after one hour the characteristic symptoms of muscular incoördination which lasted about two hours, after which recovery began without any approach to the stage of unconsciousness. The hypnotic action is therefore less than one-third that of veronal.

Summary

The acetonyl group may be substituted directly on the 5-carbon atom of barbituric acid by means of chloro-acetone. Further substitution by halogen is readily effected, or by allyl, benzyl and acetonyl. The less reactive alkyl halides as butyl bromide, do not react readily with acetonyl-barbituric acid, but the acetonyl and alkyl groups may be introduced in the reverse order by treatment of the mono-alkyl barbituric acid with chloro-acetone. The acetonyl-alkyl barbituric acids are much less effective as hypnotics than the dialkyl barbituric acids with the same length of side chains.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

THE ALKYL TITANATES

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In studying the selective activation of titania[1] it was necessary to prepare various alkyl titanates (titanium alkoxides). Since the interest in these compounds is entirely apart from the work upon the causation of organic reactions by titania, their preparation and properties are presented in advance of the latter. The tetramethyl, -ethyl, -*iso*propyl, and *N*-butyl titanates have been prepared for the first time. Demarçay[2] believed that he obtained the tetra-ethyl ester but we have found that he was in error. His compound was a solid, crystallized from alcohol, while the true tetra-ethyl titanate is a colorless liquid that may be distilled at 145°

[1] Compare Adkins, THIS JOURNAL, 44, 2175 (1922).

[2] Demarçay, *Compt. rend.*, 80, 51 (1875).