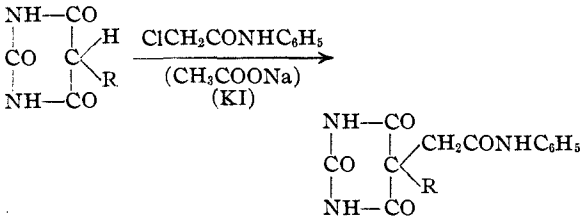
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Alkyl-acetanilido-barbituric Acids

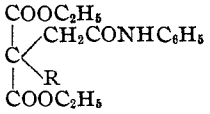
BY JOHN A. TIMM

Of the many derivatives of barbituric acid, which have been prepared and tested for their value as sedatives and hypnotics, the molecules of none, as far as the author is aware, contain the acetanilido group attached to the 5 carbon atom. The well-known use of acetanilide as an antipyretic suggested its use as a substituent in the barbituric acid ring. Accordingly various 5-alkyl-barbituric acids have been condensed with chloroacetanilide using a modification of the method of Dox and Houston[1] who used sodium acetate to condense chloroacetone and barbituric acid in alcohol-water solution. In our experiments it was found that sodium acetate alone would not effect condensation but that if potassium iodide were added also condensation proceeded with satisfactory yields as follows.



The following barbituric acids were prepared by this method: 5-ethyl-5-acetanilido-; 5-*n*-butyl-5-acetanilido-; 5-isobutyl-5-acetanilido-; 5-isoamyl-5-acetanilido-; and 5-allyl-5-acetanilido-. Their possible pharmacological activity will be tested and published elsewhere.

Attempts were made to condense chloroacetanilide with the sodium salts of various ethyl monoalkylmalonates in absolute alcohol solution to obtain malonic esters of the type



which might then have been condensed with urea to form the desired barbituric acids. These attempts failed as did the similar ones of Dox and Houston[1] in which they attempted to condense chloroacetone with alkylmalonic esters.

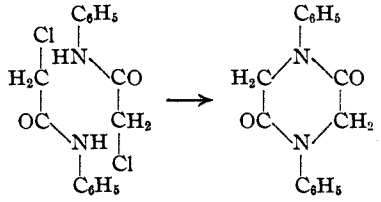
Experimental Part

Barbituric Acids Containing the Acetanilido Group.—One molecular proportion of the appropriate alkyl-barbituric acid was dissolved in 35% alcohol by gentle heating on a water-bath in a flask provided with a stirrer and a reflux condenser. An equimolecular proportion of chloroacetanilide,[2] a one and one-half molecular proportion of sodium acetate, and a quarter molecular proportion of potassium iodide were dissolved in warm 80% alcohol. The second solution was added slowly to the first and the mixture refluxed with stirring for seven hours. The desired product crystallized partially during the process of the reaction. The mixture was cooled in an ice-bath and the product filtered off. Partial evaporation of the filtrate yielded a second crop of crystals. The product in each case was recrystallized from 80% alcohol. All are colorless, crystalline solids which melt with decomposition. Physical and analytical data of these new compounds are summarized in Table I.

TABLE I

	Barbituric acid, 5-acetanilido-	Melting range, °C., with dec.	Yield, %	N Analyses, % Calcd.	Found	
1	5-Ethyl-	243–247	52	14.53	14.40	14.39
2	5-*n*-Butyl-	250–256	47	13.25	13.32	13.24
3	5-Isobutyl-	250–255	57	13.25	13.29	13.34
4	5-Isoamyl-	245–250	65	12.69	12.64	12.73
5	5-Allyl-	237–242	58	13.95	13.98	13.92

Attempt to Prepare Ethyl Acetanilidoethylmalonate.—When an equimolecular proportion of chloroacetanilide was warmed on a water-bath with the sodium salt of ethyl ethylmalonate until the absolute alcohol solution became neutral, condensation did not take place in the desired manner to form ethyl acetanilidoethylmalonate. A white solid separated which proved to be diphenyl-diketo-piperazine (m. p. 263°)[3] formed from the condensation of two molecules of chloroacetanilide:



The oily layer was extracted with ether; dried over sodium sulfate; the ether removed and the remaining oil distilled *in vacuo*. A colorless oil was obtained, b. p. 164° (9 mm.), which contained 7.24% of nitrogen. This could not have been ethyl acetanilidoethylmalonate whose nitrogen content is 4.36%. It might have been ethoxyacetanilide (N, 7.8%).

The author wishes to express his appreciation to Dr. Arthur J. Hill for his helpful suggestions during the progress of this work and to Mr. John B. Howard for his help in the analysis of these new compounds.

(1) Dox and Houston, THIS JOURNAL, 46, 252 (1924).

(2) Prepared by the method of Jacobs and Heidelberger, *J. Biol. Chem.*, 21, 104 (1915).

(3) Abenius, *Ber.*, 21, 1665 (1888).

Summary

The following 5,5-barbituric acid derivatives have been prepared: ethyl-acetanilido-, *n*-butyl-acetanilido-, isobutyl-acetanilido-, isoamyl-acetanilido- and allyl-acetanilido-.

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Studies in the Ketone Sugar Series. V. The Validity of Hudson's Rules of Isorotation in the Ketose Group. Preparation of the True α-Pentaacetylfructose<2,6>

BY EUGENE PACSU AND FRANCIS B. CRAMER

Twenty years ago Hudson and Brauns[1] prepared a positively rotating pentaacetylfructose by acetylation of β-tetraacetylfructose<2,6> in the presence of zinc chloride. Since this pentaacetate was different from the β-pentaacetylfructose-<2,6> obtained[2] from the same tetraacetate by using sulfuric acid with acetic anhydride for the acetylation, it was allocated to the α-series. Five years later Brauns[3] prepared from β-tetraacetylfructose<2,6> two chloroacetylfructoses, designating the one having specific rotation[4] −161 in chloroform as the α-, and the one having 45.3 in chloroform as the β-form. Subsequently, Brauns' allocations were reversed at the suggestion of Hudson,[5] the dextrorotatory compound becoming the α-, and the levorotatory the β-chloroacetylfructose. On the assumption that these two isomers constituted an α,β-pair with the same ring which is present in the parent β-tetraacetylfructose, Hudson[5] calculated the rotation of carbon 2 to be a_{Cl} = 37,800, and that of the acetylated basal chain common to them, comprising asymmetric carbon atoms 3,4 and 5, to be $b_{\text{fruct. ac.}}$ = −21,200. The fact that the constant a_{Cl} was found to be the same both in sign and magnitude as A_{Cl} = 37,900[6] for the aldoses was regarded as evidence that the substitution of —CH_2OAc for —H does not change the rotation of carbon atom 2. This conclusion seemed to be confirmed by the additional fact that the values of a_F and a_{Br} in the ketose group also have been found to be practically equal to the corresponding values of A_F and A_{Br} for the aldose group. It appeared therefore, safe to assume that a_{Ac} = A_{Ac} = 19,100, which is the average value for the aldoses. However, combining a_{Ac} = 19,100 with the constant $b_{\text{fruct. ac.}}$ = −21,200, the specific rotations for α-, and β-pentaacetylfructoses become −5 and −103°, respectively, in chloroform, whereas the two known pentaacetates of fructose show 34.7 and −121.0°, respectively. In view of this disagreement, Hudson concluded that "it seems very unlikely that the dextrorotatory pentaacetate can be the expected α-form." As to the other known pentaacetate, of specific rotation −121.0°, Hudson stated that "it may be the expected β-form, though the difference of 18° in specific rotation makes such a conclusion uncertain." However, it was recently proved[7] that neither "α-chloroacetylfructose" nor "α-pentaacetylfructose" possesses a ring structure in its molecule, but both of these "α"-isomers are derivatives of the open-chain fructose, the former being 1,3,4,5-tetraacetyl 6-chloro*keto*fructose, and the latter 1,3,4,5,6-pentaacetyl*keto*fructose. Consequently, all calculations and conclusions based on the assumption that either the two chloro acetates or the two pentaacetates of fructose constitute α,β-stereoisomeric pairs, are invalid. This discovery *ipso facto* invalidated the above inference that the values of the different A_x constants for the aldoses are equal to those of the corresponding a_x constants in the ketose group. It also reopened the problem of the validity of the principle of optical superposition in the ketose series for further investigation. In order to test this principle it is necessary to know the optical rotations of a true α,β-stereoisomeric pair of any ketose or ketose derivative. It is remarkable that in the ketose series, contrasting with the aldose, no such true, α,β-pair has hitherto been known with cer-

(1) Hudson and Brauns, THIS JOURNAL, **37**, 2736 (1915).

(2) Hudson and Brauns, *ibid.*, **37**, 1283 (1915).

(3) Brauns, *ibid.*, **42**, 1846 (1920).

(4) Unless otherwise stated the rotations given are all for sodium light and 20°.

(5) Hudson, THIS JOURNAL, **46**, 477 (1924).

(6) The revised mean value of this constant is A_{Cl} = 39,450. It is obtained by using A_{Cl} = 38,100 found by Hudson and Kunz [THIS JOURNAL, **47**, 2052 (1925)] for chloroacetyllactose instead of the old value of A_{Cl} = 30,300 [Hudson, *ibid.*, **46**, 462 (1924)].

(7) Pacsu and Rich, *ibid.*, **54**, 1697 (1932); **55**, 3018 (1933).