in 20 cc. of ethanol, and poured into a mixture of 10 cc. of concd. hydrochloric acid and 150 cc. of water. The aqueous layer was extracted with four 40- cc. portions of tetrachloromethane and two 15-cc. portions of benzene. The combined extracts were used to dissolve the organic layer. The solution was washed with eight 50-cc. portions of water. It was then dried over sodium sulfate and filtered through cotton. Removal of the solvent gave a brown oily residue. A part of this was dissolved in 70% ethanol, mixed with phenylhydrazine, and boiled for 2–3 min. On allowing to stand it overnight in a refrigerator, red needles melting at 179–180° separated.

Anal. Calcd. for $C_{13}H_{17}O_3N_3$: N, 14.04; mol. wt. 299.3. Found: N, 14.30.

Another part of the residual oil was washed with water again and extracted with petroleum ether. On concentrating the extract yellowish oily crystals separated. They were collected and recrystallized from ethanol to give a solid melting at 63.5–64°.

Anal. Calcd. for $C_{10}H_{11}O_4N$: N, 6.73; mol. wt. 209.2. Found: N, 6.81.

The method of oxidation of 4-nitro-2-hydroxybutyrophenone to 4-nitro-2-hydroxybenzoic acid was the same (potassium permanganate in potassium hydroxide solution) as used for the oxidation of 4-nitro-2-hydroxypropiophenone.[6]

Acknowledgment.—We wish to thank the Hungarian Academy of Sciences for a grant and the Microanalytical Laboratory of the Institute of Organic Chemistry of the University of Szeged (Mrs. K. L. Láng and Mrs. G. B. Bózóki) for the microanalyses.

Mannich Bases Derived from Acetylated Hydantoins

J. N. COKER AND M. FIELDS

Electrochemical Dept., Research Division, E. I. du Pont de Nemours & Co., Inc., Wilmington, Del.

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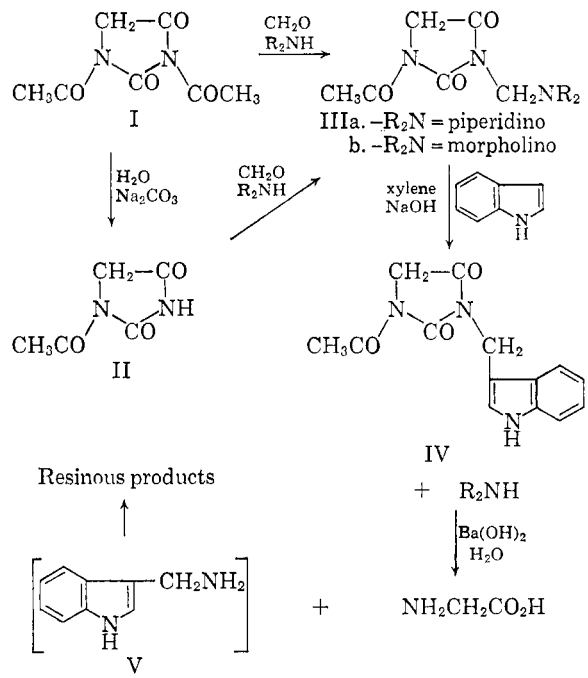
1,3-Diacetylhydantoin (I), prepared by the reaction of hydantoin with acetic anhydride in the presence of fused sodium acetate,[1] has been investigated as a precursor of the tryptophan side chain. Treatment of this compound with aqueous formaldehyde and either piperidine or morpholine was found to yield crystalline Mannich bases in excellent yield. Elemental analysis of these derivatives indicated that one of the acetyl groups had been replaced by an aminomethyl group.

Mannich base formation has also been observed with 1-acetylhydantoin (II), a compound readily prepared by the partial hydrolysis of 1,3-diacetylhydantoin.[1] Treatment of this material with aqueous formaldehyde and either piperidine or morpholine yielded the same Mannich bases obtained with 1,3-diacetylhydantoin.

Reaction of either Mannich base with indole under conditions similar to those described by Butenandt and Hellmann[2] gave a single condensation product in 20–32% yield. The latter compound had an elemental analysis which indicated the dialkylamino group had been replaced by an indolyl group. Upon alkaline hydrolysis[3] the compound yielded glycine along with an insoluble resinous product but no tryptophan.

On the basis of these results the Mannich bases have been identified as 1-acetyl-3-*N*-piperidinomethylhydantoin (IIIa) and 1-acetyl-3-*N*-morpholinomethylhydantoin (IIIb), respectively. The condensation product is indicated as being 1-acetyl-3-(3′-indolylmethyl)hydantoin (IV) since this compound on hydrolysis should be converted into glycine and 3-indolylmethylamine (V). The latter compound, which is relatively unstable, might be expected to form the resin isolated in its place under the conditions used to accomplish the hydrolysis.



The exact course of the reaction forming the Mannich bases from 1,3-diacetylhydantoin has not been determined. A possible intermediate is 1-acetylhydantoin, since this material could be produced by the alkaline conditions employed in the aminomethylation reaction.

Efforts to prepare Mannich bases by the reaction of either piperidine or morpholine and formaldehyde with various other glycine derivatives were unsuccessful. Compounds of the latter type examined include hydantoin, 3-methylhydantoin, aceturic acid, hippuric acid, acetaminoacetonitrile, *N*-phthaliminoacetonitrile, and 2-phenyl-5-oxazolone.

(1) L. Siemonsen, *Ann.*, **333**, 101 (1904).

(2) A. Butenandt and H. Hellmann, *Z. physiol. Chem.*, **284**, 168 (1949).

(3) W. K. Anslow and H. King, *J. Chem. Soc.*, 2463 (1929).

Experimental[4]

1-Acetyl-3-*N*-piperidinomethylhydantoin (IIIa).—1,3-Diacetylhydantoin (5.0 g., 0.027 mole) was dissolved in piperidine (10.0 g., 0.12 mole). To the resulting solution aqueous formaldehyde (5 ml. 36.2% solution equivalent to 1.85 g. or 0.062 mole) was added in one portion. The product precipitated immediately as a white crystalline mass. After cooling to 10–15°, this product was collected by filtration and washed with petroleum ether (four 15-ml. portions). After air drying, the product (6.7 g., 0.026 mole, 98%) melted at 150–152°. A single recrystallization from ethyl acetate raised this melting point to 160–161°.

Anal. Calcd. for $C_{11}H_{17}O_3N_3$: C, 55.25; H, 7.13; N, 17.59. Found: C, 55.48; H, 7.12; N, 17.78.

1-Acetyl-3-*N*-morpholinomethylhydantoin (IIIb).—1,3-Diacetylhydantoin (5.0 g., 0.027 mole) was dissolved in morpholine (10.0 g., 0.12 mole). To this solution aqueous formaldehyde (5 ml. 36.2% solution equivalent to 1.85 g. or 0.062 mole) was added in one portion. The solution which resulted was cooled to 15–20° and stirred to induce crystallization. The product deposited as a mass of white crystals. It was collected by filtration and washed with dry ether (two 5-ml. portions). After air drying it amounted to 6.2 g. (0.025 mole, 91%) and melted at 139–141°. A single recrystallization from ethyl acetate yielded the compound in pure form, m.p. 154–155°.

Anal. Calcd. for $C_{10}H_{15}O_4N_3$: C, 49.87; H, 6.23; N, 17.42. Found: C, 50.17; H, 6.41; N, 17.08.

1-Acetyl-3-(3′-indolylmethyl)hydantoin (IV).—1-Acetyl-3-piperidinomethylhydantoin (7.6 g., 0.030 mole), indole (3.6 g., 0.031 mole), and sodium hydroxide (0.2 g., 0.005 mole) were placed in dry xylene (60 ml.) and heated at 135–145° for 24 hr. under nitrogen. Upon cooling a brown amorphous precipitate deposited and was collected by filtration. After washing with a small amount of petroleum ether, the product was air dried. It weighed 3.6 g. Extraction of this material with ethyl acetate in a Soxhlet apparatus yielded 2.5 g. (0.0097 mole, 32%) of a product which melted at 197–198°.

Anal. Calcd. for $C_{14}H_{13}O_3N_3$: C, 62.00; H, 4.80. Found: C, 61.61; H, 4.96.

The same derivative was obtained in somewhat lower yield by condensing 1-acetyl-3-morpholinomethylhydantoin with indole under the conditions described above.

The hydrolysis of 1-acetyl-3-(3′-indolylmethyl)hydantoin was accomplished by heating the compound with aqueous barium hydroxide. This hydrolysis yielded an appreciable quantity of glycine, identified by paper chromatography, and an insoluble resinous product, which was not characterized. The absence of tryptophan in the hydrolyzate was also established by paper chromatography.

(4) All melting points are uncorrected.

SN2 Reactions of Chloroacetals

WALTER E. CONRAD, LEONARD A. LEVASSEUR, RAYMOND F. MURPHY, NANCY L. HARE, AND HELEN M. CONRAD

Chemistry Department, Bradford Durfee College of Technology, Fall River, Mass.

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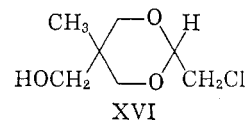
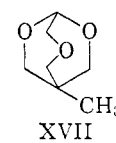
Nucleophilic substitutions of the chlorine atoms of bischloroethylidenepentaerythritol[1] (I) offer promise of producing several interesting difunctional compounds of possible interest in the synthesis of polymers and of fluids of high viscosity and low volatility. Because of the difficulty reported in effecting these reactions with sodium cyanide,[2] a study has been made of the nucleophilic substitution of the following cyclic acetals of chloroacetaldehyde: I; monochloroethylidenepentaerythritol (II); the acetal (III) of chloroacetaldehyde and 2-methyl-2-hydroxymethylpropanediol-1,3; two homologs of the latter (IV and V in Table I); and the chloroacetal of 2,2-dimethylpropanediol-1,3 (VI)[1] (see Table I).

The nucleophilic reagents chosen for study were ammonia and the anions of phenol and cyclohexanol. No difficulty was experienced in effecting S_N2 reactions with these reagents. In the reaction of ammonia with VI, the secondary amine was isolated, probably because the reaction was conducted in a two phase system. The product of the reaction of ammonia with I was a basic material, indicating that the reaction had taken place, but it was an intractable gum from which no pure product could be isolated.

Compounds III, IV, V, and their derivatives, are capable of existing in *cis* and *trans* forms. Distillation of III through a short packed fractionating column failed to effect a separation. If at least a part of III, IV, or V were present as the isomer in which the hydroxymethyl group is *cis* to the chloromethyl group (XVI for III),[3] it should be possible to effect cyclization to a bicyclic triether structure like XVII. However, treatment of III and IV



XVI



XVII

with sodium cyclohexyloxide gave the cyclohexyl ethers, but no product of cyclization. The same results were obtained with II, even though in this case the chloromethyl group would necessarily be *cis* to a hydroxymethyl group. Also, an attempt to cyclize V by refluxing with a solution of sodium hydroxide in diethylene glycol produced no evidence of formation of a cyclic product.

Experimental[4]

Preparation of 2-*n*-Propyl-2-hydroxymethylpropanediol-1,3.[5]—To a stirred mixture of 86.1 g. (1 mole) of *n*-valeralde-

(1) Correct systematic names for compounds I through VI are: I: 3,9-Bischloromethyl-2,4,8,10-tetraoxaspiro[5.5]undecane. II: 2-Chloromethyl-5,5-bishydroxymethyl-1,3-dioxane. III: 2-Chloromethyl-5-ethyl-5-hydroxymethyl-1,3-dioxane. V: 2-Chloromethyl-5-hydroxymethyl-5-propyl-1,3-dioxane. VI: 2-Chloromethyl-5,5-dimethyl-1,3-dioxane.

(2) J. B. Clements and L. M. Rice, *J. Org. Chem.*, **24**, 1958 (1959).

(3) The question whether this ring structure takes the chair, boat, or skew conformation is as yet unresolved.

(4) Microanalyses were performed by Weiler and Strauss Laboratories, Oxford, England; melting points and boiling points were uncorrected.

(5) An adaptation from the preparation of pentaerythritol. H. B. J. Schurink, *Org. Syntheses*, Coll. Vol. I, 425 (1941).