Compound	Color
5-Methyltetronic acid[15]	Deep purple
5,5-Dimethyltetronic acid[44]	Deep purple
5-Benzyltetronic acid	Deep purple
6-Phenyl-4-hydroxy-5,6-dihydro-2-pyrone (α- and β-forms)	Pale pink on standing

(44) Reid, Fortenbaugh and Patterson, *J. Org. Chem.*, **15**, 572 (1950).

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

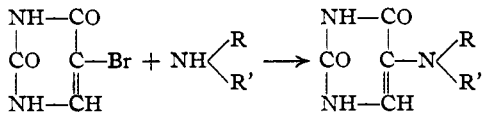
Some 5-Substituted Aminouracils

BY ARTHUR P. PHILLIPS

Investigation of the reaction of 5-bromouracil with a variety of amines showed that short refluxing in two or more molecular proportions of primary and some secondary amines rapidly gave excellent yields of 5-substituted aminouracils.

In connection with attempts to discover new chemotherapeutic agents among possible antimetabolites of nucleic acid derivatives[1,2] it became desirable to obtain a variety of 5-substituted aminouracils.

The route explored was the reaction of 5-bromouracil with the appropriate amines

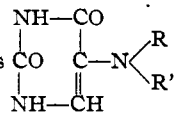


Although the high reactivity for replacement reactions of pyrimidines bearing a 2,4- or 6-chloro group is well known, little has been done with halogen in the 5-position. Previously 5-bromouracil has been treated only with ammonia[3] and dimethylamine,[4a,4b] both reactions having been carried out in a sealed tube at 150–180°. Moreover, Lythgoe[5] and Johnson[6] both state that replacing chlorine or bromine in the 5-position by ammonia is a difficult or impractical procedure.

In the present work it has been found that 5-bromouracil reacts rapidly to give excellent yields of the substituted aminouracils when refluxed for brief intervals with two to five molecular proportions of the amines. The amines used included a variety of aliphatic primary and secondary types, cyclohexylamine, piperidine and morpholine. Yields in general ranged between 70 and 100%. So far numerous attempts to obtain 5-anilinouracils by this method have failed. This apparent failure of aniline to react may possibly be related to its lesser basicity and other ways of overcoming this lack are being considered.

As an alternative route in the preparation of 5-methylamino- or ethylaminouracils, to avoid the necessity of long reaction times at elevated temperatures and in closed systems required for the volatile reactants involved, benzylmethyl- and benzylethyl-amines have been employed. When 5-bromouracil is boiled for about 5 minutes with two equivalents of benzylmethylamine at least 80% of 5-benzylmethylaminouracil (VII) is obtained. The hydrochloride of VII when submitted to catalytic hydrogenation over palladized charcoal according to the

TABLE I

5-SUBSTITUTED AMINOURACILS 

Cmpd. no.	R	R'	Yield, %	M.p., °C.	Crystn.[a] solvent	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
I[b]	CH_3	H	100	243–244[c] foams chars >280	M.E	33.8	33.7	4.6	4.4
II	C_2H_5	H	72	243–245[c]	M	37.6	37.5	5.3	5.4
III	n-C_3H_7	H	90	264–265[c] sinters	A	40.9	41.3	5.9	5.6
IV	n-C_4H_9	H	100	250–253[c] sinters	A	43.7	44.0	6.4	6.3
V	Cyclohexyl	H	100	>305	Neutr.	57.4	57.1	7.2	7.4
VI	$HOCH_2CH_2$	H	85	267–268	M	42.1	42.2	5.3	5.3
VII	CH_3	$C_6H_5CH_2$	90	267–269	Aq. HOAc	62.3	62.3	5.7	6.0
				242–243[c]	M	53.8	53.6	5.3	5.3
VIII	C_2H_5	$C_6H_5CH_2$	50	201–202[c]	A.E	Cl, 12.6	12.5		
IX	Piperidino		78	285–290[c]	M.E	46.6	46.7	6.1	6.0
X	Morpholino		75	>310	Aq.	48.7	49.0	5.6	5.6
XI[d]	C_6H_5NH	H	40	250–255	HOAc				

[a] A, ethanol; Aq., water; E, ether; HOAc, acetic acid; M, methanol; Neutr., dissolved in aqueous alkali, then reprecipitated with dilute acid. [b] Compound I was prepared by catalytic debenzylation of compound VII. [c] Melting point and analysis are of the hydrochloride. [d] Known compound; P. A. Levene, *J. Biol. Chem.*, **63**, 653 (1925).

(1) G. H. Hitchings, *et al.*, *J. Biol. Chem.*, **183**, 1 (1950).
(2) G. H. Hitchings, *et al.*, *Ann. N. Y. Acad. Sci.*, **52**, 1318 (1950).
(3) H. L. Wheeler and T. B. Johnson, *Am. Chem. J.*, **31**, 603 (1904).
(4) (a) H. L. Wheeler and H. F. Merriam, *ibid.*, **32**, 355 (1904); (b) T. B. Johnson and I. Matsuo, THIS JOURNAL, **41**, 788 (1919).
(5) B. Lythgoe, *Quart. Reviews*, **3**, 181 (1949).
(6) T. B. Johnson in Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1938, 1st edition, Vol. II, p. 965.

method exploited by Baltzly and Buck[7] gives by the debenzylation process 5-methylaminouracil (I) in quantitative yield.

Experimental

The method of preparation and isolation of the substituted 5-aminouracils is illustrated by a few examples. Other experimental details for all the products are summarized in Table I.

5-Butylaminouracil (IV).—A mixture of 5 g. (0.026 *M*) of 5-bromouracil and 7 g. (0.1 *M*) of *n*-butylamine was refluxed for 2 hours on a steam-bath. The bromouracil gradually dissolved and a white flocculent precipitate slowly formed. After cooling 50 cc. of water was added to the reaction mixture and the *p*H was adjusted to 6–7 by addition of hydrochloric acid. The white insoluble product was collected by filtration, washed with much cold water, and after drying weighed 5 g. (100%). When recrystallized from methanol it melted at 286–288° (dec.). For analysis it was best purified by recrystallization from methanol–ether mixtures as its hydrochloride (see Table I).

5-(N-Morpholino)-uracil (X).—After refluxing in a metal-bath at 140–150° for 1 hour a mixture of 9.5 g. (0.05 *M*) of 5-bromouracil and 20 g. (0.23 *M*) of morpholine gave on cooling and diluting with cold water 10 g. (100%) of X. Recrystallized from hot water this yielded 7.5 g. (75%) of fluffy white needles; m.p. > 310°.

5-Benzylmethylaminouracil (VII).—A mixture of 10 g. (0.052 *M*) of 5-bromouracil and 24 g. (0.2 *M*) of benzylmethylamine was heated for 5 minutes at 180–190° in a metal-bath. A violent reaction set in as the boiling point of the amine was approached. After cooling the solid cake was broken up and washed out with 6 *N* hydrochloric acid. Next morning the white insoluble product was collected by filtration, washed with 6 *N* hydrochloric acid, then with ethanol and ether. The yield of VII was 12.5 g. (90%) and when recrystallized from methanol it melted at 242–243°.

5-Methylaminouracil (I) from VII.—A suspension of 2.7 g. (0.01 *M*) of VII in 70 cc. of methanol was shaken with palladized charcoal and hydrogen in the usual way.[7] The hydrogen uptake was rapid and 0.01 *M* had been absorbed within about 6 minutes. After removal of the catalyst and concentration of the methanol filtrate the addition of ether precipitated 1.8 g. (100%) of I; m.p. 242–243°.

Acknowledgment.—The author is grateful to Mr. Samuel W. Blackman for the microanalytical results included.

TUCKAHOE 7, NEW YORK RECEIVED SEPTEMBER 15, 1950

(7) R. Baltzly and J. S. Buck, THIS JOURNAL, **65**, 1984 (1943).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF GENERAL MILLS, INC.]

1,4-Addition Reactions. V. The Synthesis of Substituted Cyclohexenes and Cyclohexanes[1]

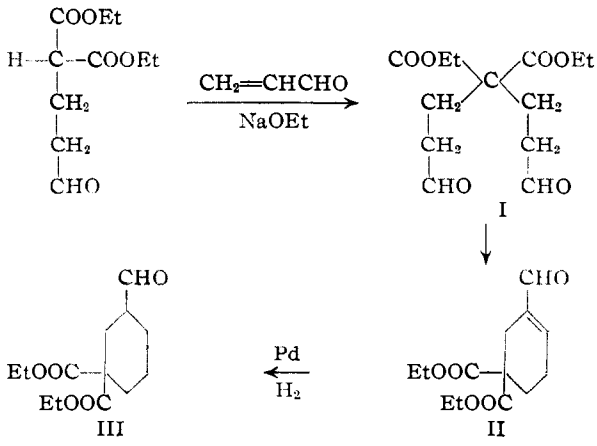
BY OWEN A. MOE, DONALD T. WARNER AND MARJORIE IWEN BUCKLEY

The stepwise 1,4-addition of ethyl malonate and ethyl cyanoacetate to 2 moles of α,β-unsaturated aldehydes has been studied. The reaction between γ,γ-dicarbethoxybutyraldehyde yielded small quantities of the dialdehydo compound (γ,γ-dicarbethoxypimelic dialdehyde); however, the principal product was 1-formyl-5,5-dicarbethoxy-1-cyclohexene. Similarly, the reaction between γ-carbethoxy-γ-cyanobutyraldehyde and acrolein and the reaction between γ,γ-dicarbethoxy-α-methylbutyraldehyde and methacrolein yielded cyclic type products. These reactions constitute convenient preparations of several cyclohexene and cyclohexane aldehydes.

The 1,4-addition of malonate systems and cyclic imides to aliphatic α,β-unsaturated aldehydes has been well established,[2,3,4,5] and the utility of the resulting aldehydo compounds in the synthesis of amino acids has been demonstrated.[4,6,7]

In connection with some earlier work involving the addition of ethyl malonate to acrolein,[3] it was observed that a considerable quantity of a viscous residue remained when the aldehydo compound, namely, γ,γ-dicarbethoxybutyraldehyde, was separated from the crude reaction mixture by distillation under reduced pressure. At that time it was considered plausible that this residue consisted primarily of the di-addition product. However, an extensive investigation[8] of this residue has demonstrated the absence of aldehydo groups. The present paper reports the results of a study concerned with the synthesis of some di-addition products.

The 1,4-addition of γ,γ-dicarbethoxybutyraldehyde to acrolein proceeded to yield the dialdehydo compound I which was characterized as the bis-2,4-dinitrophenylhydrazone. In subsequent experiments, the principal product was compound II which was characterized as the 2,4-dinitrophenylhydrazone. It should be noted that the compounds containing the structural features represented by I possess all the prerequisites demanded for a successful aldol type reaction. Hence, cyclic products such as the cyclohexene type represented by II must be considered most probable.



The reaction between γ,γ-dicarbethoxy-α-methylbutyraldehyde and methacrolein appeared attractive for experimental investigation since the in-

(1) Paper No. 108, Journal Series, General Mills, Inc., Research Dept.

(2) O. A. Moe and D. T. Warner, THIS JOURNAL, **70**, 2763 (1948).

(3) D. T. Warner and O. A. Moe, *ibid.*, **70**, 3470 (1948).

(4) O. A. Moe and D. T. Warner, *ibid.*, **71**, 1251 (1949).

(5) D. T. Warner and O. A. Moe, *ibid.*, **71**, 2586 (1949).

(6) D. T. Warner and O. A. Moe, *ibid.*, **70**, 2765 (1948).

(7) D. T. Warner and O. A. Moe, *ibid.*, **70**, 3918 (1948).

(8) The results of this investigation will be described in a later paper.