[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Researches on Pyrimidines. CXLII. The Acetylation of 2-Keto-tetra- and Hexahydropyrimidines

BY KARL FOLKERS[1] AND TREAT B. JOHNSON

Some reactions and derivatives of 2-keto-4-phenyl-5-carbethoxy-6-methyl-1,2,3,4-tetrahydropyrimidine were recently described.[2a] There were no facts, however, regarding the degree of basicity of these tetra- and hexahydropyrimidines, and knowledge of this characteristic was desirable.

The presence of the carbonyl group in urea, I, greatly weakens the basicity of the amino groups, and when urea is converted to a cyclic ureide[3] of type II, the substance is neutral or slightly acidic; but if converted to a ureide of type III, the substance is definitely acidic. It was then logical to expect that the linkage of an unsaturated hydrocarbon chain to urea, as in IV, would produce a substance of basicity which was between neutral and that of urea, and reduction of the unsaturation, V, would increase the basicity.

NH_2CONH_2 I

NHCONHCOC(—)=C— II

NHCONHCOC(=)CO III

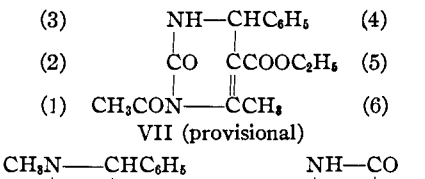
NHCONHCH(—)C(—)=C— IV

NHCONHCH(—)CH(—)CH— V

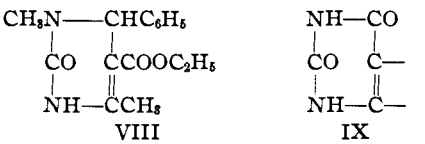
These expectations were borne out, and data of other theoretical interest were obtained, by studying the behavior of acetic anhydride toward these 2-keto-tetra- and hexahydropyrimidines. These facts are also of probable practical value for the characterization of certain pyrimidine hydrogenation products which are being studied in this Laboratory.

When an acetic anhydride solution of the 2-ketopyrimidine derivative, VI, was refluxed for a moderate time, the reaction was incomplete, but after many hours a pure mono-acetyl derivative separated on cooling. The acetyl group has been provisionally placed at position 1, as in structure VII, because of the following facts.

NHCONHCH(C_6H_5)C($CO_2C_2H_5$)=CCH_3 VI



VII (provisional)



VIII IX

Due to the symmetry of the keto and carbethoxy group positions with respect to the nitrogens, the predominating influence on the basicity of the imino groups would appear to be the relative effects of the phenyl group and the pyrimidine double bond. As already described,[2a] the 2-ketopyrimidine derivative, VI, on being converted to the 2-chloro derivative and reaction with sodium methoxide, yielded a N-methyl derivative which was assigned structure VIII primarily because of absorption spectrum measurements. In the uracil type, IX, the 3-imino group (or the 3,4-lactam-lactim grouping) is frequently the most reactive, and it is the least basic because of the adjoining carbonyls. Similarly, with regard to the conversion of pyrimidine VI to VIII, one might infer that the 3-imino group was the most reactive, and was the least basic because of its attached groups, —CONHCH(C_6H_5)—. Therefore, the most basic group (1-imino) might be expected to react first with acetic anhydride.

An attempt was made to synthesize the 1-acetylpyrimidine derivative, VII, by the condensation of acetylurea, benzaldehyde and ethyl acetoacetate.[2b,d] However, there was no pyrimidine condensation, for the acetylurea was entirely recovered.[4]

(1) Eli Lilly and Co. Post-doctorate Research Fellow, 1933–1934.

(2) (a) Folkers and Johnson, THIS JOURNAL, **55**, 2886 (1933). For related studies on 2-ketopyrimidines, see: (b) Folkers, Harwood and Johnson, *ibid.*, **54**, 3751 (1932); (c) Folkers and Johnson, *ibid.*, **55**, 1140 (1933); (d) *ibid.*, **55**, 3784 (1933); (e) *ibid.*, **56**, 1180 (1934); (f) *ibid.*, **55**, 3361 (1933).

(3) The older definition of a ureide was a mono- or di-acylurea. Typical cyclic ureides were parabanic acid, hydantoin, uracil, barbituric acid, etc. They contained a —CONHCONH— or —CONHCONHCO— grouping. The present usage of the term cyclic ureide frequently includes those compounds which contain simply the ureido group, —NHCONH— as an integral part of the ring; *i. e.*, 2-ketopyrimidines, 2-ketoglyoxalines, etc.

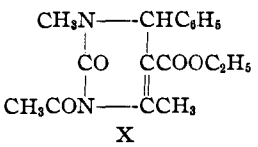
(4) The lack of condensation in this case with acetyl urea might be considered as supporting evidence that biuret in the Biginelli reaction with benzaldehyde and ethyl acetoacetate reacted to form an eight-membered ring

NHCONHCONHCH(C_6H_5)C($CO_2C_2H_5$)=CCH_3

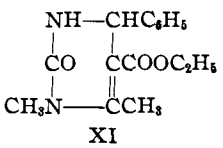
and not an N-carbamylpyrimidine. Biginelli, *Atti accad. Lincei*, [5] **3**, 195 (1894); *Chem. Centr.*, **65**, 823 (1894).

Other syntheses[5] for constitutional proof appeared so very unpromising, in view of other reactions of this type,[2a,d] that their attempt was not warranted now.

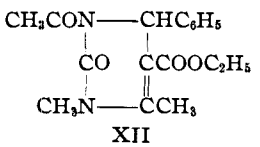
On this basis, the 3-methylpyrimidine derivative, VIII, should react also with acetic anhydride to give the 1-acetyl-3-methylpyrimidine derivative, X, and it was found to do so. The treatment of the 1-methylpyrimidine derivative, XI, with acetic anhydride should indicate whether the 3-imino group was sufficiently basic for reaction. An experiment proved that the 1-methyl-3-acetyl-pyrimidine, XII, was formed.



X



XI

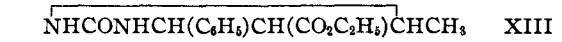


XII

It was now obvious that strong supporting evidence for the 1-acetylpyrimidine structure, VII, would be had if it could be converted to the 2-chloro derivative, and thence to a N-methyl-N-acetylpyrimidine derivative whose properties could be compared with those of structures X and XII. The sole product of these reactions was the 2-ketopyrimidine derivative, VI, which indicated that the acetyl group had been removed on the treatment with phosphorus oxychloride. The absence of methylation was readily explained by the unusual reactivity of the 2-chloro derivative.[2a] It was now found that the 1-acetylpyrimidine derivative, VII, was easily hydrolyzed to the original 2-keto derivative, VI, when its dilute alcoholic hydrochloric acid solution was refluxed.

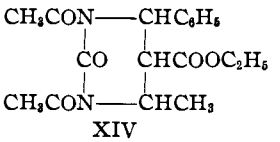
The 6-methyl group of the 1-acetylpyrimidine derivative, VII, was completely inert toward benzaldehyde in an acetic anhydride solution.[6]

From the above it was now clear that either of the imino groups of such 2-keto-tetrahydropyrimidines, separately, but not together, was capable of reaction with acetic anhydride. The expected increase in basicity due to reduction of the double bond, or conversion to the corresponding hexahydropyrimidine, was manifested[7] by the formation of a N-diacetyl derivative, XIV, from the 2-ketohexahydropyrimidine derivative, XIII.

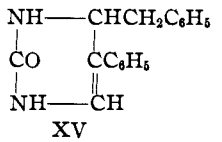


XIII

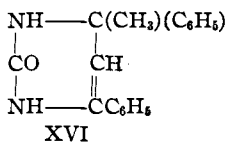
This diacetyl derivative, XIV, on treatment with alcoholic sodium hydroxide, was converted to the 2-keto-4-phenyl-5-carboxy-6-methyl-hexahydropyrimidine,[2e] by saponification of the acetyl and carbethoxy groups.



XIV

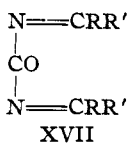


XV

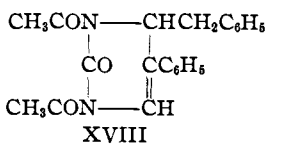


XVI

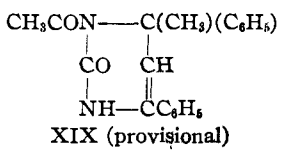
It has been shown that phenylacetaldehyde and acetophenone will react with urea to form condensation products.[2f] Evidence was presented with greatly favored pyrimidine structures XV and XVI for these products, as contrasted with an acyclic structure, XVII, proposed by Scholtz.[8]



XVII



XVIII



XIX (provisional)

From consideration of the above described acetyl derivatives, if the pyrimidine structure XV were correct, then it should be expected to form a monoacetyl derivative, or possibly a diacetyl derivative, since there was no substitution at the 6-position and the phenyl group was further removed from the 4-position. Actually, the diacetyl derivative was formed, as represented by structure XVIII. This diacetyl derivative had further significance in that it verified the position of the cyclic double bond in structure XV, which

(5) The reaction (?) of benzaldehyde on ethyl β-(1-acetylcarbamido)-crotonate (from reaction (?) of isocyanic acid on ethyl β-acetylaminocrotonate) for the 1-acetyl derivative. The reaction (?) of benzaldehyde on ethyl β-(3-acetylcarbamido)-crotonate (from reaction (?) of acetyl isocyanate on ethyl β-aminocrotonate) for the 3-acetyl derivative.

(6) Shaw and Wagstaff, *J. Chem. Soc.*, 97 (1933). It was interesting to note that the 6-methyl group of 2-keto-5-carbethoxy-6-methyl-2,3-dihydropyrimidine did react with benzaldehyde; Bergmann and Johnson, *Ber.*, **66**, 1492 (1933).

(7) This 2-ketohexahydropyrimidine also exhibited a slight solubility in dilute hydrochloric acid, whereas the corresponding tetrahydropyrimidine did not.

(8) Scholtz, *Arch. Pharm.*, **253**, 111 (1915).

was previously assigned the 5,6-position rather than the 1,6. Had the double bond been in the 1,6-position, and excluding rearrangement, only a monoacetyl derivative could have been formed.

Similarly, the acetophenone-urea condensation product gave a mono-acetyl derivative which was evidence favoring pyrimidine structure XVI rather than XVII. The acetyl group has been provisionally placed at the 3-position, as in XIX, on the basis of the above discussion.

Experimental

The significant data on the acetylpyrimidine derivatives and their properties are summarized in Table I and comments. Ethanol was used for recrystallizations unless otherwise indicated.

TABLE I

ACETYLATION OF PYRIMIDINES

No.	Reactants, g.	Ac_2O, ml.	Time, hrs.	Product derivatives	Yield
1	12 A	60	8[d]	1-Acetyl-A[b]	85.5[c]
2	1 B	5	4.5	1-Acetyl-B	0.9 g.[e]
3	1 C	5	4.5	3-Acetyl-C	.9 g.[f]
4	2 D	10	9	1,3-Diacetyl-D	..[g]
5	2 E	10	3	1,3-Diacetyl-E	1.9 g.[h]
6	4 F	20	4.5	3-Acetyl-F	..[i]

		Analyses, %			
		Calcd.		Found	
No.	M. p., °C.[a]	C	H	C	H
1	175.5–177	63.54	6.00	63.31	6.21
2	164.5–166	64.52	6.37	64.60	6.57
3	108 –109.5	64.52	6.37	64.39	6.54
				64.35	6.60
4	101.5–102.5	62.39	6.40	62.32	6.63
				62.18	6.51
5	104.5–105	72.37	5.79	72.42	6.00
6	182 –183	74.47	5.93	74.31	6.05

COMMENTS ON TABLE I

REACTANTS

A = 2-keto-4-phenyl-5-carbethoxy-6-methyl-1,2,3,4-tetrahydropyrimidine, VI.

B = 2-keto-3-methyl-4-phenyl-5-carbethoxy-6-methyl-1,2,3,4-tetrahydropyrimidine, VIII.

C = 1-methyl-2-keto-4-phenyl-5-carbethoxy-6-methyl-1,2,3,4-tetrahydropyrimidine, XI.

D = 2-keto-4-phenyl-5-carbethoxy-6-methyl-hexahydropyrimidine, XIII.

E = 2-keto-4-benzyl-5-phenyl-1,2,3,4-tetrahydropyrimidine, XV.

F = 2-keto-4-methyl-4,6-diphenyl-1,2,3,4-tetrahydropyrimidine, XVI.

NOTES

[a] Corrected.

[b] *Anal.* Calcd.: N, 9.27. Found: N, 9.00, 8.99.

[c] Expressed total yield of recrystallized product. Sixty-two per cent. was obtained by one recrystallization of the crystals which separated from the cooled acetic anhydride solution. A second crop was obtained by adding water to the filtrate to hydrolyze the anhydride. This second crop amounted to 23% when recrystallized from the mother liquor of the first crop.

Hydrolysis.—After refluxing 0.5 g. of the acetyl derivative for two hours with 15 ml. of ethanol and 5 ml. of concd. hydrochloric acid, cooling, filtering and washing, 0.4 g. of the original pyrimidine (A) was obtained, m. p. and mixed 206.5–208° (corr.).

Phosphorus Oxychloride Treatment.—Two and one-tenth grams of the acetyl derivative was heated on the steam-bath for forty-five minutes with 4 ml. of phosphorus oxychloride. The technique from here, including the addition of methanol-sodium methoxide, was essentially that already described.[2a] A yield of 1.1 g. of the original pyrimidine (A) was obtained, m. p. and mixed 205.5–207°. Second crop, *ca.* 0.1 g., m. p. 203–204°. Residue, m. p. 198–201° with a little yellow gum.

[d] When one gram of A was refluxed with 4 ml. of Ac_2O for one and one-half hours, the reaction was incomplete, as shown by the m. p. 155–157°.

[e] Crude yield after product precipitated by addition of water had been once recrystallized. Three more recrystallizations raised m. p. of 154–157° to 164.5–166° and three more did not alter it.

[f] Pure after one crystallization of water precipitated product.

[g] The higher melting isomer was used for acetylation, m. p. 230–233.5°.[2e] After hydrolysis of the anhydride, dilute sodium hydroxide was added to neutralize the acid. The viscous oil would not crystallize from ethanol. About 0.3 g. yield of crystals, m. p. 101–102°, were eventually obtained by evaporation at 25° of methanol–petroleum ether solution.

Hydrolysis.—The oily diacetyl derivative from 1 g. of pyrimidine derivative was refluxed for three hours with alcoholic sodium hydroxide, and after alcohol distillation, acidification, etc., 0.5 g. (m. p. and mixed, 253–255°; m. p. pure acid, 256.5–258°) of 2-keto-4-phenyl-5-carboxy-6-methyl-hexahydropyrimidine[2e] was obtained.

[h] Crude yield (m. p. 103–104.5°) after one crystallization of water precipitated product.

[i] The anhydride was hydrolyzed and the acid neutralized with alkali. The separated oil was taken up in ethanol–ethyl acetate and the solvents allowed to evaporate overnight. The crystals were filtered, washed with ethyl acetate, yield 0.3 g., m. p. 173.5–177°. Two recrystallizations from dilute ethanol yielded the pure derivative. The yield here was small. This and unreported results on the chemistry of this pyrimidine (XV) indicate much greater reactivity in side reactions of pyrimidine XV as contrasted with its empirical isomer, XIV.

Summary

From further study of 2-keto-4-phenyl-5-carbethoxy-6-methyl-1,2,3,4-tetrahydropyrimidine and its N-methyl derivatives, it was concluded that either of the imino groups separately, but not together, was capable of reaction with acetic anhydride. Reduction of the 5,6-pyrimidine double bond, or decreasing the effect of the substituents at the 4- and 6-positions, increased ba-

sicity, as manifested by solubility in dilute acid, and the reaction of both imino groups, together, with acetic anhydride.

The formation of acetyl derivatives from the condensation products of phenylacetaldehyde and acetophenone with urea furnished additional evidence in favor of the pyrimidine structures and the location of the cyclic double bond, previously assigned to these products.

NEW HAVEN, CONNECTICUT RECEIVED MARCH 5, 1934

[CONTRIBUTION FROM THE LAMBERT PHARMACAL COMPANY]

Alkylchlororesorcinols and Alkyl Ethers of Chlororesorcinol

BY R. R. READ, G. F. REDDISH AND E. M. BURLINGAME

Among the continually increasing number of phenolic substances interesting because of their germicidal properties are the chlorine substituted hydroxy alkylbenzenes. The relationship between germicidal activity, as measured in terms of phenol coefficient, and the nature of substituting groups has been reported upon frequently during the past decade. The work reported here deals with alkylchlororesorcinols and mono alkyl ethers of chlororesorcinol, the chlorine being attached to the nucleus in each case.

Experimental

The alkylchlororesorcinols were all prepared by the procedure shown schematically.

(1) Resorcinol ⟶ chlororesorcinol ⟶ chlororesorcinol ester ⟶ acylchlororesorcinol ⟶ alkylchlororesorcinol

and in a few cases by the procedure

(2) Acylresorcinol ⟶ acylchlororesorcinol ⟶ alkylchlororesorcinol

and in several other instances.

(3) Alkylresorcinol ⟶ alkylchlororesorcinol

The first method seems most satisfactory as not requiring any isolation of intermediates except the chlororesorcinol and in yielding few by-products.

A typical preparation follows: 27.0 g. of chlororesorcinol was melted in a three-necked flask equipped with stirrer, thermometer and reflux; 1.5 g. of anhydrous zinc chloride was added and while the melt was maintained just above the fusing point 32.4 g. of *n*-octanoyl chloride added over a period of twenty minutes. The melt was then maintained at steam-bath temperature one-half hour, after which the temperature was raised to 150° and there maintained one and one-half hours. Without isolating the ketone it was transferred to a larger flask, equipped with a heavy stirrer and reflux, which contained 100 g. of zinc, amalgamated with 2 g. of mercuric chloride, and 200 cc. of 17% hydrochloric acid. This mixture was heated to refluxing temperature while being violently stirred.

The vigor of the stirring and solubility of the ketone determined the reduction time. Alcohol in amounts up to 20% by volume was used when the reduction appeared to proceed too slowly.

After about eight hours the floating oil gave a negative test (olive-green) with alcoholic ferric chloride. The oil was taken up in two volumes of toluene, washed three times with hot water and dried by distilling off the toluene. The resultant oil distilled at 196–204° (6 mm.), the distillate being a white crystalline solid weighing 26 g. Redistillation gave 22 g. boiling at 195–197° (6 mm.). This was crystallized from ligroin and recrystallized from petroleum ether.

Since different bacteriologists vary considerably in their determination on identical products,[1] the phenol coefficient of a related substance is included in Table I for comparative purposes.

TABLE I

Chlororesorcinol derivative	Phenol coefficient[a]	B. p. °C.	B. p. Mm.	M. p., °C.	Chlorine, % Found	Chlorine, % Calcd.
Ethyl	6	140–142	8	solid	21.2	20.6
n-Butyl	45	153–158	5	70–72	17.7	17.7
n-Hexyl	240	172–175	6–7	43	15.4	15.5
n-Heptyl	625	185–187	7	48–49	14.3	14.6
n-Octyl	665	195–197	6	54–56	13.0	13.8
n-Hexyl resorcinol	60					

[a] Coefficients determined by the F. D. A. method using 0.5 cc. of *Staphylococcus aureus* at 20° with the following modification adopted due to low solubility of these substances. The chlorophenol was dissolved in 95% alcohol in such a concentration that the significant determinations were made in 5–8% alcohol solutions. Attempts to use only water as solvent can yield most variable results due to formation of emulsions instead of true solutions.

(1) Read and Miller, THIS JOURNAL, **54**, 1197 (1932), footnote 8; Blicke and Stockhaus, *J. A. Ph. A.*, **22**, 1092 (1933).