b. p. 56–60° (20 mm.) was 75%.[9] The bromide was also prepared by the direct addition of bromine at 5° to trimethylethylene prepared by dehydrating tertiary amyl alcohol with 15% sulfuric acid. The use of a solution of bromine in aqueous sodium bromide solution was also tried. Neither of these methods had any advantage over the direct treatment of tertiary amyl alcohol with pure bromine. The dibromide (1740 g.) was hydrolyzed with stirring, first refluxing and later distilling off the methyl isopropyl ketone. The product on redistillation through a 90 × 1.5 cm. packed column weighed 477 g., b. p. 90–93.4° (734 mm.), n_D^{20} 1.3880, yield 55% based on the tertiary amyl alcohol used. A small amount of high boiling material, b. p. 69–82° (29 mm.), n_D^{20} 1.4630. 42.6% bromine, with strong lachrymatory power was obtained.

The results with the other twelve dibromides are summarized in Table I.

Summary

1. The hydrolysis and rearrangement of isobutylene dibromide and trimethylethylene dibromide are practical methods of converting tertiary butyl and tertiary amyl alcohols to isobutyraldehyde and methyl isopropyl ketone in good yields.

2. The hydrolysis of thirteen other dibromides prepared from aliphatic tertiary alcohols has been studied. With seven of these the rearranged aldehyde or ketone has been obtained in poor yield. With the others, polymerizations occur apparently due to the formation of substituted butadienes and other unsaturated products.

(9) Full details of the preparation of the dibromide and of its hydrolysis to methyl isopropyl ketone will appear in "Organic Syntheses," Vol. XIII, 1933.

STATE COLLEGE, PENNSYLVANIA RECEIVED AUGUST 27, 1932
PUBLISHED MARCH 7, 1933

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

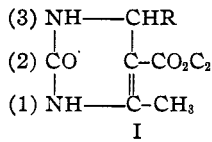
Researches on Pyrimidines. CXXXI. The Reduction of 1,2,3,4-Tetrahydropyrimidines

BY KARL FOLKERS[1] AND TREAT B. JOHNSON

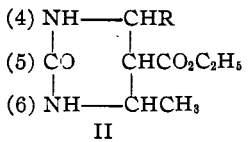
Several new members of a hitherto little studied class of tetrahydropyrimidines were described in a recent publication from this Laboratory.[2] These were represented by the general formula, I, in which R designates an alkyl, aryl or arylalkyl group. Inasmuch as the investigation of these compounds was primarily to ascertain whether they were of pharmacological interest, it was desirable to hydrogenate a few of them to the hexahydropyrimidine derivative, II, if possible, and then to determine the effect on the physiological activity. Furthermore, these hexahydropyrimidines possessing an ureide structure could probably be hydrolyzed to substituted β,β-diamino-isobutyric acids, III, which in themselves would be interesting substances and otherwise difficult to obtain.

(1) Squibb and Sons Research Fellow in Organic Chemistry.

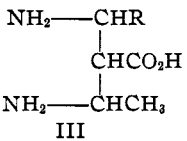
(2) Folkers, Harwood and Johnson, THIS JOURNAL, **54**, 3751 (1932).



I



II



III

In contrast to the large amount of published work on keto-pyrimidines, there is relatively little literature on the more reduced pyrimidine structures. Over colloidal palladium or platinum, the 5,6 double bond of uracil was quite resistant to reduction at 20–25°, but at 75° it was reduced to dihydrouracil.[3] The reduction of the 5,6 double bond of N-1-methyl-6-phenyluracil-N-3-acetic acid or its methyl ester could not be accomplished at 20–25° with a colloidal palladium catalyst. Hydrogen iodide was also ineffective.[4] Hilbert[5] found that the 5,6 double bond of uracil-4-ethyl acetate and 3-methyl-uracil could be hydrogenated with Adams platinum catalyst at 20–25°, but the rate was very slow.

The only reduction experiment on a pyrimidine of type I was made by Biginelli,[6] the discoverer of the reaction leading to the formation of these compounds. He reported that 2-keto-4-phenyl-5-carbethoxy-6-methyl-1,2,3,4-tetrahydropyrimidine, IV, when treated with sodium amalgam, yielded, in addition to unaltered material, a compound of m. p. 229–230° which he believed to be the hexahydropyrimidine derivative, and another solid melting at 59–60°. Biginelli's analysis of the higher melting compound indicated the adsorption of one mole of hydrogen, whereas the hydrogen content of the lower melting one was high for an additional mole of hydrogen.

Although his directions for the sodium amalgam reduction were incomplete, attempts were made to duplicate them, but they were without satisfactory results. The use of 2.5% sodium amalgam in glacial acetic acid was also without success, for 94.1% of the compound was recovered unaltered. Neither did hydrogen iodide effect reduction. Two grams of the pyrimidine dissolved in 200 ml. of ethanol was unaffected in the presence of 0.15 g. of platinum catalyst after four hours. However, by using a large amount of catalyst and glacial acetic acid as solvent, hydrogenation was effected. The drop in pressure indicated the absorption of 3 moles and the product, which melted at 237.5–238.5°, was shown by analysis to contain six more atoms of hydrogen. Since these experimental conditions do not give reduction of the carbamido- or carbethoxy groups, and excluding cleavage, the benzenoid nucleus must have been reduced while the double bond of the pyrimidine ring remained intact. This product, 2-keto-4-cyclohexyl-5-carbethoxy-6-methyl-1,2,3,4-tetrahydropyrimidine, dissolved

(3) Johnson and Brown, *Proc. Nat. Acad. Sci.*, **7**, 75 (1920); Brown and Johnson, THIS JOURNAL, **45**, 2702 (1923).

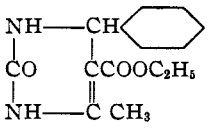
(4) Evans and Johnson, *ibid.*, **52**, 5000 (1930).

(5) Hilbert, *ibid.*, **54**, 2078 (1932).

(6) Biginelli, *Gazz. chim. ital.*, **23**, [1] 360 (1893).

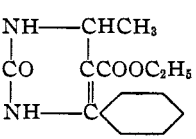
in glacial acetic acid would not absorb more hydrogen in the presence of a large amount of fresh catalyst and over a long period of time at 20–25°. Since a temperature of 75° facilitated reduction in ethanol solvent of the uracil series, this pyrimidine was tested under these conditions. However, there was not the slightest reduction of 2 g. of the 4-cyclohexyl derivative dissolved in 200 ml. of ethanol after forty-two hours at 60–75° in the presence of 0.57 g. of platinum catalyst.

It seemed probable then that the compound of m. p. 229–230° obtained by Biginelli was one containing a partially hydrogenated benzenoid nucleus. Such reduction has been quite widely accomplished by the use of sodium.[7] It is to be noted in the above-mentioned papers on uracil derivatives that reduction of the 5,6-double bond caused a marked drop in the melting point, whereas Biginelli's reduction raised the melting point. In reference to Biginelli's product of m. p. 59–60°, he stated that it was probably a mixture of two isomeric hexahydropyrimidines, the one of m. p. 229–230° and another which had not been obtained pure. This seemed unlikely since his hydrogen analysis was 0.27–0.31% high and the fact that he stated the substance, on long contact with water, decomposed to emanate an odor of benzaldehyde, an observation which indicates the tetrahydro rather than the hexahydropyrimidine structure.



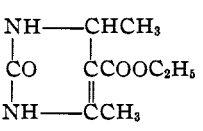
M. p. 206–208°

IV



M. p. 165–166.5°

V



M. p. 192.5–193.5°

VI

Possibly the normal resistance to reduction of the 5,6-double bond of pyrimidine IV was enhanced by the nature and number of the groups present on this portion of the pyrimidine nucleus, for usually highly substituted structures are more difficult to hydrogenate than the unsubstituted ones. For a single example, 1-alkyl-4-piperidones have been hydrogenated in five to eight hours by the Adams platinum catalyst, but the sole substitution of a carbethoxy group in the 3 position of the piperidine nucleus decreased the rate of hydrogenation to fifty hours.[8] Undoubtedly, the resistance to reduction would also be partially dependent on the actual position of the groups. So it was of interest to hydrogenate the isomer of pyrimidine IV in which the methyl and phenyl groups are interchanged, or 2-keto-4-methyl-5-carbethoxy-6-phenyl-1,2,3,4-tetrahydropyrimidine, V.[9]

(7) Houben, "Die Methoden der organischen Chemie," Georg Thieme, Leipzig, 1925, Vol. II, p. 326.

(8) Bolyard and McElvain, THIS JOURNAL, **51**, 923 (1929).

(9) The preparation of this pyrimidine from urea, acetaldehyde and benzoylacetic ester is described in the experimental part of this paper, and demonstrates further applicability of this type of condensation. Furthermore, since no conversion of the isomers IV and V has been noticed, the 5,6 double bond of this structure must be somewhat stable.

The product of this reduction showed that both the 5,6 double bond and the benzenoid nucleus were reduced, and demonstrated the dependence of double bond reduction on position in the cycle. Besides the analysis of the product, the presence of the hexahydropyrimidine ring was further indicated by saponification to the carboxylic acid derivative. Treatment of these tetrahydropyrimidines IV with alcoholic alkali results in rupture of the pyrimidine ring, but reduction of the 5,6-double bond stabilizes the ring so that the corresponding pyrimidine-5-carboxylic acids are obtainable on hydrolysis.

An attempt to hydrogenate 2-keto-4,6-dimethyl-5-carbethoxy-1,2,3,4-tetrahydropyrimidine, VI, was made to determine if replacing the phenyl group by an alkyl group would alter the resistance of the 5,6-double bond to reduction. This substance, in common with the other pyrimidines of this series, was too insoluble in ethanol at 20–25° to allow the use of this solvent. In 150 ml. of glacial acetic acid there was no reduction of 9.9 g. of this pyrimidine during nine hours in the presence of 0.62 g. of platinum catalyst. Even after standing thirty-eight hours, it was demonstrated that the catalyst still possessed some degree of activity for, after releasing the pressure and decanting the solution, it effected complete reduction of 0.1 mole of maleic acid in 200 ml. of glacial acetic acid in forty-five minutes.

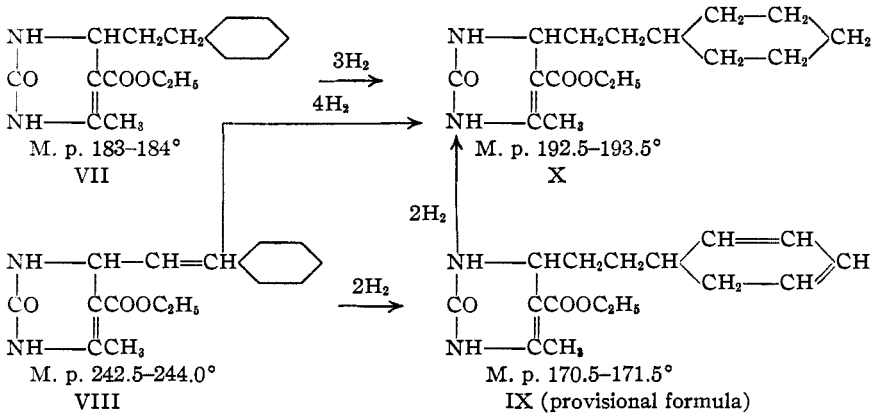
The selective reduction of the benzenoid nucleus over the 5,6-pyrimidine double bond in compound IV made it of interest to hydrogenate a compound in which the two rings were separated by one or two carbon atoms. For this purpose, 2-keto-4-phenylethyl-5-carbethoxy-6-methyl-1,2,3,4-tetrahydropyrimidine, VII, was selected.

Thayer and McElvain[10] have reported the reduction over the Adams platinum catalyst of certain 1-R-4-piperidones in which R was the phenyl, benzyl or phenylethyl group. This catalyst at 20–25° effected the reduction of both the aromatic nucleus and keto group when R was phenyl, and when R was benzyl the net result was apparently the same, but with a retarded rate of nuclear hydrogenation. When the two nuclei were separated by two carbon atoms, as when R was phenylethyl, only the keto group underwent reduction.

The 4-phenylethylpyrimidine, VII, on the absorption of three moles of hydrogen gave a product which melted sharply at 192.5–193.5°, and, as shown below, must be the result of aromatic nucleus reduction. The 4-styrylpyrimidine derivative, VIII, on hydrogenation to completion absorbed four moles and gave a product of m. p. 192.5–193.5° which by analysis was shown to contain eight additional atoms of hydrogen, or only enough to reduce completely the styryl group. The mixed melting point of the complete reduction products of the 4-phenylethyl and 4-styryl derivatives was 192.5–193.5°, so they both must be the 4-β-cyclohexylethyl-

(10) Thayer and McElvain, THIS JOURNAL, **49**, 2862 (1927).

tetrahydropyrimidine derivative, X. Therefore, this separation of benzenoid and pyrimidinoid nuclei did not alter their selective reduction.



The rate of hydrogenation of the 4-styryl derivative was unusually interesting. Two moles of hydrogen were quickly absorbed in ten minutes, whereas the last two were absorbed over a period of three hours. The experiment was repeated and stopped at the perceptible break in the absorption rate. It was found that this used catalyst was still active enough to carry the reduction of another sample to the same point, thus demonstrating the ease of the absorption of the first two moles. The intermediate product obtained in all cases melted sharply at 170.5–171.5°, and was shown by analysis to contain four additional hydrogen atoms. The sharpness of its melting point and its lack of change on recrystallization indicate it to be a pure substance. Hydrogenation of other phenylpyrimidines interrupted after adsorption of integral moles of hydrogen gave products, evidently mixtures, which melted over a 5 to 8° range and changed on recrystallization. On further reduction this intermediate product absorbed two more moles of hydrogen to give the product first obtained which melted at 192.5–193.5°. Since all the hydrogen absorbed by this 4-styrylpyrimidine derivative was used only in saturating the four double bonds of the styryl group, it seemed most probable that the ethylenic double bond and the adjacent double bond in the benzenoid nucleus absorb the first two moles of hydrogen as a conjugated system, or through a simultaneous catalytic reaction. The two following considerations also indicate that the two double bonds are not independent of one another in their reduction or that in any case the particular activation which precedes the formation of this intermediate is derived from the chemical and physical characteristics of this 4-styryl derivative.

First, by interrupting the hydrogenation of the 4-phenylethyl derivative at the absorption of one mole, a product was obtained which melted at 171.5–180° and apparently was a mixture. Therefore, this molecule which

contained one of the double bonds already saturated could not attain the necessary state of activation. Indeed, one does not expect direct catalytic hydrogenation of simple benzene nuclei to produce easily pure di- or tetrahydro derivatives, although such hydrogenation of condensed benzene nuclei is common.

Second, the rapid and continuous absorption of the first two moles of hydrogen, together with the conception of the possible mechanisms leading to the intermediate, would not lead one to expect to isolate a pure compound if the process were interrupted after the absorption of one mole. This was found to be true, for a mixture melting at 191–200° resulted from allowing the 4-styryl derivative to absorb one mole of hydrogen. In this experiment the amount of catalyst was decreased in order that the primary process or processes would be more distinct.

Further data on these pyrimidines will be made available through their absorption spectra measurements which are being carried out at Mount Holyoke College under the direction of Professor Emma P. Carr.

Experimental Part

The reductions discussed in this paper were carried out under 3 atmospheres' pressure in the usual hydrogenation apparatus, and with the Adams platinum catalyst.[11]

The 2-keto-4-R-5-carbethoxy-6-methyl-1,2,3,4-tetrahydropyrimidines in which R was the phenyl, methyl, phenylethyl or styryl groups have already been described.[12]

Table I contains a summary of the data on the various hydrogenations. After filtration of the catalyst, the products were precipitated by pouring the filtrates into 500–1000 ml. of water. After washing, the products were recrystallized from dilute alcohol or by dissolving in an excess of alcohol and distilling to incipient crystallization. The yields express the pure products, the loss being that of one to three recrystallizations. The actual amount hydrogenated in each case was chosen so that the total absorption would be an integral number (3–7) of gage scale divisions in order that the pressure drop could be more accurately interpreted. All melting points were taken with a standardized thermometer. The catalyst did not seem to accumulate poisons from these reductions so that it could be reworked and used again successfully. The carbon and hydrogen analyses were micro determinations carried out in the laboratory of Dr.-Ing. A. Schoeller, Berlin-Schmargendorf, Tölzerstrasse 19, Germany. The nitrogen analyses were macro Kjeldahl determinations.

2-Keto-4-methyl-5-carbethoxy-6-phenyl-1,2,3,4-tetrahydropyrimidine, V.—Three grams of urea, 3.3 g. of acetaldehyde, and 12 g. of ethyl benzoylacetate were added to 25 ml. of glacial acetic acid (10°) and then heated on a steam-bath for twenty hours, after which four drops of concentrated hydrochloric acid from a 5-ml. pipet were added, and the heating continued for another twenty-four hours. After cooling, the solution was poured into 200 ml. of water. After several days the oil was removed by long suction from the solid which slowly formed. The cake was washed with 50% alcohol; crude yield, 6.2 g. After several recrystallizations from dilute alcohol, crystals were obtained of the constant m. p. 165–166.5°.

Anal. (micro) Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.58; H, 6.20; N, 10.77. Found: C, 64.53; H, 6.26; N (micro), 10.97, 10.85.

(11) "Organic Syntheses," John Wiley and Sons, New York, 1932, Coll. Vol. I, pp. 55, 452.

(12) Folkers, Harwood and Johnson, THIS JOURNAL, **54**, 3751 (1932).

TABLE I

HYDROGENATION OF 2-KETO-4-R-5-CARBETHOXY-6-METHYL-1,2,3,4-TETRAHYDROPYRIMIDINES

	R =	Amt., mole	Catalyst, g.	Glacial acetic acid, ml.	Hydrogen, mole	Time, hrs.
1	Phenyl-	0.05	0.70	125	0.15	6.5
2	Phenyl-	.05	.32	150	.05	4.0
3	Phenyl-	.05	.40	150	.15	24.0
4	Cyclohexyl-	.05	.70	150		8.0
5	Phenylethyl-	.025	.40	200	.025	2.0
6	Phenylethyl-		.70	100	.050	1.0
7	Styryl-	.025	.70	150	.10	3.2
8	Styryl-	.025	.20	150	.050	0.33
9	Styryl-	.025	.10	150		0.13
10	2-Dihydrophenylethyl-	.025	.70	130	.050	0.66

	Product R =	M. p., °C.	Yield, %		Analysis, % C	H	N	
1	Cyclohexyl	237.5–238.5	64.7	Calcd.	63.11	8.33	10.52	
				Found	63.30	8.34	10.37	10.38
2	Mixture	192.5–193.5						
3	Cyclohexyl	237.5–238.5						
4	Cyclohexyl	237.5–238.5						
5	Mixture	171.5–180						
6	2-Cyclohexylethyl	192.5–193.5	65.3	Calcd.	65.25	8.90	9.52	
				Found	65.41	9.00	9.50	9.41
7	2-Cyclohexylethyl	192.5–193.5	84.4					
8	2-Dihydrophenylethyl	170.5–171.5	94.5	Calcd.	66.16	7.60	9.65	
				Found	66.36	7.73	9.46	9.41
9	Mixture	191–200						
10	2-Cyclohexylethyl	192.5–193.5						

2-Keto-4-methyl-5-carbethoxy-6-cyclohexylhexahydropyrimidine.—Six and one-half grams of pyrimidine V was dissolved in 100 ml. of glacial acetic acid and shaken with 0.7 g. of catalyst under three atmospheres for twenty-four hours. After catalyst filtration, practically all the acetic acid was distilled under diminished pressure below 50°, and the residue was poured into 175 ml. of cold water to precipitate the product. After recrystallization from alcohol and water, a melting point of 110–172° showed that reduction was not complete. Hydrogenation was repeated using 0.5 g. of fresh catalyst. After drying to constant weight at 60° and 23 mm., the product now melted at 179–181° and was not changed after four recrystallizations. It was 2-keto-4-methyl-5-carbethoxy-6-cyclohexylhexahydropyrimidine.

Anal. (micro) Calcd. for $C_{14}H_{24}N_2O_3$: C, 62.63; H, 9.01; N, 10.44. Calcd. for $C_{14}H_{22}N_2O_3$: C, 63.11; H, 8.33; N, 10.52. Found: C, 62.94, 62.76; H, 8.90, 9.01; N (micro), 10.31; N (macro), 10.23, 10.05.

2-Keto-4-methyl-5-carboxylic acid-6-cyclohexyl-hexahydropyrimidine.—Thirteen-hundredths gram of the above ester was refluxed for forty minutes with 25 ml. of 0.15 *N* alcoholic alkali. The solution, after dilution and acidification with hydrochloric acid, was distilled until all ethanol had been removed. On cooling the residue, the acid crystallized, m. p. 290–291° with decomposition. The melting point did not change after recrystallization from dilute alcohol.

Anal. Calcd. for $C_{12}H_{20}N_2O_3$: C, 59.96; H, 8.39; N, 11.66. Found: C, 59.71; H, 8.36; N, 11.00.

Summary

1. The behavior of some 2-keto-4-alkyl-5-carbethoxy-6-methyl-1,2,3,4-tetrahydropyrimidines on catalytic reduction has been investigated.

2. It has been shown that the 5,6-double bond in such pyrimidine combinations is very resistant to change.

3. In all cases examined the 4-aryl groups were attacked by hydrogen in the presence of the catalyst and reduced to the corresponding hexahydro or saturated structure.

4. In only one case examined, namely, 2-keto-4-methyl-5-carbethoxy-6-phenyl-1,2,3,4-pyrimidine, where phenyl is substituted on carbon adjacent to the 5,6-double bond, did we succeed in reducing the 5,6-double bond in the pyrimidine ring.

5. The pharmacological behavior of these highly reduced structures is now under investigation.

NEW HAVEN, CONNECTICUT RECEIVED SEPTEMBER 1, 1932
PUBLISHED MARCH 7, 1933

[CONTRIBUTION FROM THE INSECTICIDE DIVISION, BUREAU OF CHEMISTRY AND SOILS]

A Study of the Toxicity of Rotenone Hydrochloride, Acetylrotenone and Rotenolone Using the Goldfish as the Test Animal[1]

BY W. A. GERSDORFF

The toxicological examination of derivatives of rotenone and related compounds with the use of the goldfish as the test animal has been continued in this Laboratory with the threefold hope of discovering a material more toxic and more stable than rotenone, and at the same time securing data by which a correlation may be made between the toxicity and chemical structure. The method used by the author has been described in a previous paper[2] and studies by that method of some of the compounds have also been published.[3,4] This paper presents the results of a similar examination of rotenone hydrochloride, acetylrotenone and rotenolone prepared in the Insecticide Division of the Bureau of Chemistry and Soils.

Rotenone hydrochloride (m. p. 193°) was prepared from rotenone by H. L. Haller according to the method of S. Takei.[5] The compound is formed by the addition of hydrochloric acid at the double bond of the

(1) Presented before the Division of Agricultural and Food Chemistry at the Meeting of the American Chemical Society, Denver, Colo., August 22–26, 1932.

(2) Gersdorff, THIS JOURNAL, **52**, 3440–3445 (1930).

(3) Gersdorff, *ibid.*, **52**, 5051–5056 (1930).

(4) Gersdorff, *ibid.*, **53**, 1897–1901 (1931).

(5) Takei, *Ber.*, **61B**, 1003–1007 (1928).