[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Reactions of Hydrogen with Derivatives of Pyrrole

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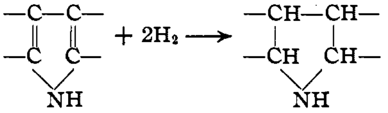
Catalytic hydrogenation has been but little used in the reduction of derivatives of pyrrole and in general the results hitherto reported have not been such as to stimulate the use of this method. Several N-alkylpyrroles have been more or less satisfactorily converted to the corresponding pyrrolidines, using platinum as a catalyst. The quantities hydrogenated were in general from 2 to 10 g. and the yields of pyrrolidines, when reported, were 13 to 100%.[2,3,4] The hydrogenations of 2-methylpyrrole, 2,4- and 2,5-dimethylpyrroles, 2-ethylpyrrole and 2-phenyl- and 2,5-diphenylpyrroles have been reported but the yields of pyrrolidines were not given.[3] Pyrrole-1-carboxylic acid and pyrrole-1-methylamine (1 g. each) have been hydrogenated with considerable difficulty over platinum to give yields of 23 and 55%, respectively, of the corresponding pyrrolidines.[5] Pyrrole itself has been hydrogenated over platinum[2,5] and nickel.[6,7] Palladium has also been used for 1-methylpyrrole in the vapor phase.[8] Vinyl- and aldehydopyrroles have been hydrogenated to the corresponding ethyl- and hydroxymethylpyrroles.[9]

An inquiry in the fall of 1932 by Dr. James B. Conant in regard to the feasibility of converting acyl- into alkylpyrroles by catalytic hydrogenation led to a study in this Laboratory of the reactions of pyrroles with hydrogen. The possibilities and the extent to which selective hydrogenation has been accomplished are perhaps best presented by considering the successes and failures of several types of transformations involving pyrroles and hydrogen.

I. The Hydrogenation of the Pyrrole Ring in Compounds not Having a Substituent on the Nitrogen.—

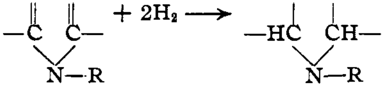


Two of the compounds of this type submitted to test (Table I) were relatively resistant to hydrogenation as compared with benzenoid or especially with furanoid compounds. Cramer[6] and later Winans[7] obtained about 50% yields of pyrrolidine from pyrrole over nickel kieselguhr catalysts at 200°. The reaction over Raney nickel takes place at a somewhat lower temperature (180°) but it has not been possible to obtain larger yields of pyrrolidine. The reaction proceeded rapidly (one hour) during the absorption of about 0.75 mole of hydrogen per mole of pyrrole and then became much slower. When the reaction mixture was worked up at this stage about half the pyrrole was recovered along with an equal amount of pyrrolidine. When the reaction was pressed to completion the yield of pyrrolidine was again about 50% but higher boiling products, and not pyrrole, were recovered. The 2,4-diethyl-3,5-dimethylpyrrole behaved similarly over Raney nickel except that the hydrogenation went 80% to completion at 180° at a good rate. A second treatment with nickel was necessary and a 70% yield of the diethyldimethylpyrrolidine was obtained, without the formation of high boiling condensation products.

Copper–chromium oxide is also active for the hydrogenation of the pyrrole ring, but temperatures of 200 to 250° are required and the catalyst is probably inferior to nickel for this transformation.

In none of the acyl or carbethoxy pyrroles unsubstituted on the nitrogen was it found possible to hydrogenate the ring without subjecting the compound to conditions under which the acyl or carbalkoxy groups would also react with hydrogen.

II. The Hydrogenation of the Pyrrole Ring in Compounds Having a Substituent upon the Nitrogen.—



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[1] The Wisconsin Alumni Research Foundation allotted funds for the research assistantship held by F. K. S. in the period Sept., 1933 to Sept., 1935.

[2] Craig and Hixon, THIS JOURNAL, **52**, 804 (1930); **53**, 188 (1931).

[3] De Jong and Wibaut, *Rec. trav. chim.*, **49**, 237 (1930).

[4] Ochiai and Tsuda, *Ber.*, **67**, 1011 (1934).

[5] N. Putokhin, *J. Russ. Phys.-Chem. Soc.*, **62**, 2216 (1930); *C. A.*, **25**, 3995 (1931).

[6] Cramer and Adkins, THIS JOURNAL, **52**, 4349 (1930).

[7] Winans, Ph.D. Thesis, Univ. of Wisconsin, 1933.

[8] Zelinsky and Jurjew, *Ber.*, **62**, 2589 (1929).

[9] Fischer and Orth, "Die Chemie des Pyrrols," Akademische Verlagsgesellschaft m. b. H., Leipzig, 1934, pp. 151 and 219.

TABLE I

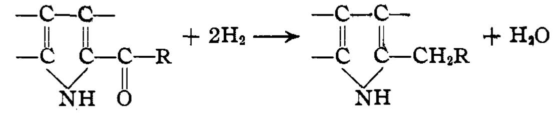
HYDROGENATION OF PYRROLE NUCLEUS

	Compound	Moles	Temp., °C.	Catalyst, g.	Time, hours	Products	Yield, %
1	Pyrrole	0.75	180	10Ni	1.0	Pyrrolidine	47
						Pyrrole	48
2	1-Phenylpyrrole	.07	135	2Ni	1.0	1-Phenylpyrrolidine	63
						1-Cyclohexylpyrrolidine	30
3	1-Phenylpyrrole	.10	240	5Cu	2.5	1-Cyclohexylpyrrolidine	62
						Cyclohexanol	25
4	1-Phenylpyrrole	.07	180	2Ni	0.8	1-Cyclohexylpyrrolidine	84
5	1-Carbethoxypyrrole	.10	160	3Ni	0.5	1-Carbethoxypyrrolidine	77
6	2,4-Diethyl-3,5-dimethylpyrrole	.07	180	5Ni	20.0	2,4-Diethyl-3,5-dimethylpyrrolidine	70
7	2,4-Diethyl-3,5-dimethylpyrrole	.07	250	6Cu	2.0	2,4-Diethyl-3,5-dimethylpyrrolidine	50
8	1,2-Dicarbethoxypyrrole	.18	50	5Ni	0.8	1,2-Dicarbethoxypyrrolidine	98
9	1,2-Dicarbethoxypyrrole	.20	85	5Ni	0.2	1,2-Dicarbethoxypyrrolidine	97

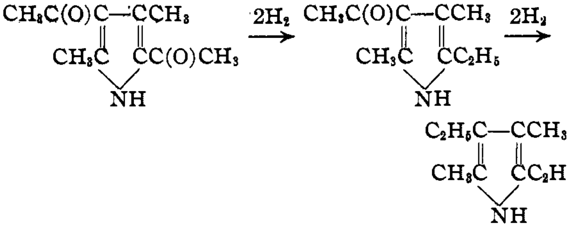
In contrast to the pyrroles of Class I above, the N-substituted pyrroles reacted readily with hydrogen over Raney nickel at temperatures from room temperature on up to 160° as shown in Table I. Three pyrroles of this type have been hydrogenated, *i. e.*, 1-phenylpyrrole, 1-carbethoxypyrrole, and 1,2-dicarbethoxypyrrole. The effect of the substituent upon the nitrogen in facilitating hydrogenation is particularly striking in the case of 1,2-dicarbethoxypyrrole which absorbed hydrogen at room temperature and was completely converted to the pyrrolidine at 50°. This ease of hydrogenation of the N-substituted compound is to be compared with the fact that 2-carbethoxypyrrole could not be hydrogenated to the corresponding carbethoxypyrrolidine at any temperature. The practical significance of these experiments is illustrated by a synthesis of proline which will be described in a later paper.

The effect of N-substitution in facilitating the hydrogenation of a pyrrole is also shown by the behavior of 1-phenylpyrrole, which was at 135° converted to the 1-phenylpyrrolidine, despite the fact that, as noted above, the pyrroloid ring in general appears to be much more resistant to hydrogenation than is the benzenoid ring. When the hydrogenation of 1-phenylpyrrole was allowed to proceed to completion, especially at temperatures of about 180°, 1-cyclohexylpyrrolidine was obtained in good yield (Table I).

III. The Conversions of Acyl- to Alkylpyrroles.[10]—



Since in acylpyrroles the carbon to oxygen linkage is in the 2-(or 3-) position with respect to a carbon to carbon double bond, it is not surprising that a carbonyl may be converted to methylene over either nickel or copper–chromium oxide. The reaction proceeded smoothly and almost quantitatively over either catalyst at 130 to 170° (Table II). The reaction proceeded equally well irrespective of whether the acyl group was acetyl or benzoyl or was in the 2-, or 3-(4- or 5-) positions and whether methyl, ethyl, or carbethoxy groups were also present in the molecule. However, there is a difference in the readiness of hydrogenation of an acyl group in the 2-(or 5-) position as contrasted with one in the 3-(or 4-) position. For example, 2,4-diacetyl-3,5-dimethylpyrrole was converted into 3-acetyl-5-ethyl-2,4-dimethylpyrrole in a 65% yield as well as to 2,4-diethyl-3,5-dimethylpyrrole in a 94% yield. The monoacetylpyrrole was obtained by interrupting the reaction after the absorption of two moles of hydrogen by one mole of the diacetylpyrrole. In none of the hydrogenations of acylpyrroles was there any evidence that hydrogen reacted with the ring at temperatures below 180°.



Attempts to stop the hydrogenation of acylpyrroles at the carbinol stage were entirely unsuccessful. In comparison it may be noted that no difficulty is encountered in stopping the hydrogenation of a furylaldehyde or ketone at the car-

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(10) This reaction was first carried out in this Laboratory by Charles F. Winans, in 1932.

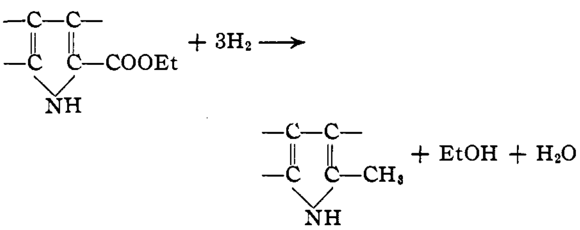
TABLE II

CONVERSION OF ACYL TO ALKYL PYRROLES

Compound	Moles	Temp., °C.	Catalyst, g.	Time, hours	Products	Yield, %
2-Carbethoxy-4-acetyl-3,5-dimethylpyrrole	0.14	170	5Ni	1.5	2-Carbethoxy-4-ethyl-3,5-dimethylpyrrole	95
3-Carbethoxy-5-acetyl-2,4-dimethylpyrrole	.15	160	5Cu	1.0	3-Carbethoxy-5-ethyl-2,4-dimethylpyrrole	93
3-Carbo-*t*-butoxy-5-acetyl-2,4-dimethylpyrrole	.10	170	3Cu	0.3	3-Carbo-*t*-butoxy-5-ethyl-2,4-dimethylpyrrole	80
3-Carbethoxy-5-benzoyl-2,4-dimethylpyrrole	.03	160	3Cu	.3	3-Carbethoxy-5-benzyl-2,4-dimethylpyrrole	92
2,4-Diacetyl-3,5-dimethylpyrrole	.06	160	3Cu	.3	2,4-Diethyl-3,5-dimethylpyrrole	94
2,4-Diacetyl-3,5-dimethylpyrrole	.05	175	2Cu	6.0	3-Acetyl-5-ethyl-2,4-dimethylpyrrole	65
3-Acetyl-5-ethyl-2,4-dimethylpyrrole	.02	135	1Cu	0.5	2,4-Diethyl-3,5-dimethylpyrrole	83

binol stage, and that this objective may be achieved with the aryl aldehydes and ketones if care is taken to interrupt the reaction after the reaction of the proper amount of hydrogen. Thus it would appear that the pyrrole ring upon the basis of this test is "superaromatic" while the furan ring is "subaromatic." The same conclusion would be drawn from the relative ease of hydrogenation of the furanoid, benzenoid and pyrroloid nuclei.

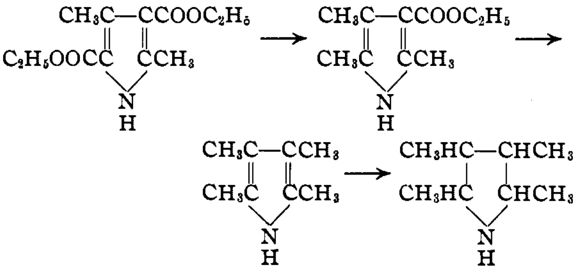
IV. The Conversion of Carbethoxy- to Methylpyrroles.—



The conversion of a carbethoxy group on a pyrrole ring to a methyl group requires a higher temperature than does the conversion of an acyl to an alkyl group described just above. In fact the temperature required for the formation of the methylpyrrole is within the range required for the hydrogenation of the pyrrole ring. Therefore the reaction must be interrupted at a certain stage in order to obtain the maximum yield of the pyrrole.

As a result of several experiments it was found that the best yields of the methylpyrroles were obtained from the corresponding monocarbethoxypyrroles when the reaction was interrupted after 3.5 moles of hydrogen per mole of pyrrole had been absorbed. However, the products so obtained (see Table III) consisted of a mixture of the original carbethoxypyrrole, the methylpyrrole and the methylpyrrolidine. The proportion of the methylpyrrole so obtained varied with the position of the carbethoxy group in the pyrrole. As with the acylpyrroles, there was found to be a difference in the ease of hydrogenolysis of the carbethoxypyrroles depending upon whether the carbethoxy group was in the 2- or the 3-position, the former undergoing hydrogenolysis the more readily. This is shown by the fact that a much larger proportion of the methylpyrrole was obtained by the interrupted hydrogenolysis of a 2-carbethoxypyrrole than a 3-carbethoxypyrrole. The yields of 2-methylpyrroles from two 2-carbethoxypyrroles were 30 and 53% while the yields of 3-methylpyrroles from two 3-carbethoxypyrroles were 0 and 10%. That is to say, hydrogen reacts more readily with a 2-carbethoxy group than with a pyrrole nucleus, but more readily with a pyrrole nucleus than with a carbethoxy group in the 3-position.

The 2,4-dicarbethoxy-3,5-dimethylpyrrole upon hydrogenation gave results which are in agreement with the above generalization and which are somewhat analogous to the results obtained with 2,4-diacetyl-3,5-dimethylpyrrole discussed in the previous section. The reaction proceeds as follows



The best yield of 3-carbethoxy-2,4,5-trimethylpyrrole was obtained when the reaction was stopped after 4.5 moles of hydrogen per mole of pyrrole had been absorbed. When the reaction was allowed to proceed until 5.2 moles of hydrogen was taken up the yield of monocarbethoxy compound was the same as before but none of the dicarbethoxy compound was recovered, instead more of the tetramethylpyrrolidine was produced. The maximum yield of the tetramethylpyrrole was obtained when the reaction was allowed to proceed until 6.6 moles of hydrogen per mole of pyrrole was absorbed. At the same time

TABLE III

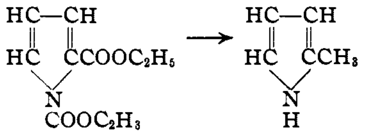
CONVERSION OF CARBETHOXY TO METHYL PYRROLES

Compound	Moles	Temp., °C.	Catalyst, g.	Time, hours	Moles H_2 absorbed	Products	Yield, %
2-Carbethoxy-4-ethyl-3,5-dimethylpyrrole	0.05	210	5Cu	0.3	0.175	3-Ethyl-2,4,5-trimethylpyrrole	30
						3-Ethyl-2,4,5-trimethylpyrrolidine	15
						Unchanged pyrrole	30
2,4-Dicarbethoxy-3,5-dimethylpyrrole	.05	220	5Cu	.3	.225	3-Carbethoxy-2,4,5-trimethylpyrrole	53
						2,3,4,5-Tetramethylpyrrole	Trace
						2,3,4,5-Tetramethylpyrrolidine	5
						Unchanged pyrrole	21
2,4-Dicarbethoxy-3,5-dimethylpyrrole	.07	220	6Cu	.3	.364	3-Carbethoxy-2,4,5-trimethylpyrrole	55
						2,3,4,5-Tetramethylpyrrole	8
						2,3,4,5-Tetramethylpyrrolidine	25
2,4-Dicarbethoxy-3,5-dimethylpyrrole	.05	225	5Cu	.5	.330	3-Carbethoxy-2,4,5-trimethylpyrrole	33
						2,3,4,5-Tetramethylpyrrole	13
						2,3,4,5-Tetramethylpyrrolidine	16
3-Carbethoxy-2,4,5-trimethylpyrrole	.06	230	4Cu	.8	.192	2,3,4,5-Tetramethylpyrrole	2
						2,3,4,5-Tetramethylpyrrolidine	33
						Unchanged pyrrole	45
3-Carbethoxy-5-ethyl-2,4-dimethylpyrrole	.05	225	4Cu	.5	.165	2-Ethyl-3,4,5-trimethylpyrrolidine	30
						Unchanged pyrrole	53
2-Carbethoxy-4-acetyl-3,5-dimethylpyrrole	.05	210	4Cu	.8	.265	2-Carbethoxy-4-ethyl-3,5-dimethylpyrrole	36
						3-Ethyl-2,4,5-trimethylpyrrole	23
						3-Ethyl-2,4,5-trimethylpyrrolidine	29
1,2-Dicarbethoxypyrrole	.10	200	4Cu	1.0	.400	2-Methylpyrrole	42

there was formed relatively more of the 3-carbethoxytrimethylpyrrole and some of the tetramethylpyrrolidine. An interrupted hydrogenation of 3-carbethoxy-2,4,5-trimethylpyrrole gave a small amount of the tetramethylpyrrole.

The hydrogenolysis of an acyl group and of a 2-carbethoxy group were combined in one operation to yield an alkylpyrrole. The 2-carbethoxy-4-acetyl-3,5-dimethylpyrrole was hydrogenated to give a 23% yield of 2-ethyl-3,4,5-trimethylpyrrole and a 36% yield of 2-carbethoxy-4-ethyl-3,5-dimethylpyrrole. The reaction was stopped when 5.3 moles of hydrogen per mole of pyrrole had been absorbed.

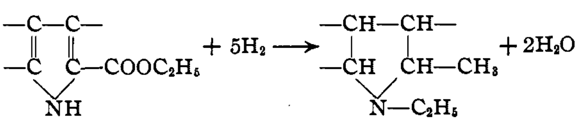
The 1,2-dicarbethoxypyrrole was hydrogenated using copper–chromium oxide catalyst at 200° and the reaction interrupted when 4 moles of hydrogen per mole of pyrrole had been taken up. A 42% yield of 2-methylpyrrole was obtained along with other products. In this reaction the carbethoxy group attached to the nitrogen atom was replaced by hydrogen



Although the interrupted hydrogenation of 2-carbethoxypyrrole using copper–chromium oxide catalyst was not tried, one would suppose by analogy that this and other 2-carbethoxypyrroles in addition to those actually investigated could be converted into 2-methylpyrroles by this method.

In spite of the relatively low yields of methylpyrroles obtained by this procedure, it offers an improved method of obtaining these compounds. A comparison of this with other methods for preparing these compounds is given in Table VI.

V. The Conversion of Carbethoxypyrroles to Methyl N-ethylpyrrolidines.—



Three types of reactions occur if hydrogen is allowed to react with a carbethoxypyrrole over copper–chromium oxide at 200 to 250°. The carbethoxy group is converted to a methyl group and ethyl alcohol, the ring is hydrogenated and the pyrrolidine and alcohol so formed react to give an N-ethylpyrrolidine. These reactions also occur over Raney nickel but a temperature of 250° is required and in methylcyclohexane solution partial

TABLE IV

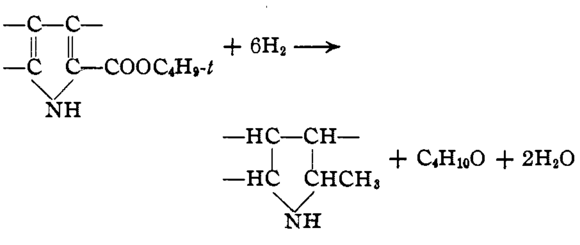
CONVERSION OF CARBALKOXY AND ACYL PYRROLES TO ALKYL PYRROLIDINES

	Compound[a]	Moles	Temp., °C.	Catalyst, g.	Time, hours	Products	Yield, %
1	2-Carbethoxypyrrole	0.10	250	2Ni	0.8	1-Ethylpyrrolidine	10
						Unchanged pyrrole	46
2	2-Carbethoxypyrrole	.07	250	4Cu	1.0	1-Ethyl-2-methylpyrrolidine	90
3	3-Carbethoxy-5-ethyl-2,4-dimethylpyrrole	.05	250	3Cu	4.0	2-Ethyl-3,4,5-trimethylpyrrolidine	35
						1,2-Diethyl-3,4,5-trimethylpyrrolidine	35
4	2-Carbethoxy-4-ethyl-3,5-dimethylpyrrole	.05	250	4Cu	1.2	3-Ethyl-2,4,5-trimethylpyrrolidine	8
						1,3-Diethyl-2,4,5-trimethylpyrrolidine	78
5	2-Carbethoxy-4-ethyl-3,5-dimethylpyrrole	.06	250	3Cu	5.0	1,3-Diethyl-2,4,5-trimethylpyrrolidine	80
6	3-Carbethoxy-5-ethyl-2,4-dimethylpyrrole	.05	250	3Cu	2.0	1,2-Diethyl-3,4,5-trimethylpyrrolidine	88
7	2,4-Dicarbethoxy-3,5-dimethylpyrrole	.06	250	4Cu	6.0	1-Ethyl-2,3,4,5-tetramethylpyrrolidine	70
8	3-Carbethoxy-5-benzyl-2,4-dimethylpyrrole	.04	250	4Cu	1.0	1-Ethyl-2-benzyl-3,4,5-trimethylpyrrolidine	52
						1-Ethyl-3,4,5-trimethylpyrrolidine	17
9	3-Carbo-*t*-butoxy-5-ethyl-2,4-dimethylpyrrole	.04	250	3Cu	3.0	2-Ethyl-3,4,5-trimethylpyrrolidine	80
10	2-Carbethoxy-4-ethyl-3,5-dimethylpyrrole	.05	250	2Ni	4.0	1,3-Diethyl-2,4,5-trimethylpyrrolidine	37
						1,3-Diethyl-4,5-dimethylpyrrolidine	37
11	1-Carbethoxypyrrole	.10	230	4Cu	2.0	1-Methylpyrrolidine	27
						1-Ethylpyrrolidine	37
12	2,4-Diacetyl-3,5-dimethylpyrrole	.06	200	4Ni	15.0	1,2,4-Triethyl-3,5-dimethylpyrrolidine	50

[a] Expts. 2, 5, 6, 7, 8 and 12 were carried out in ethanol as a solvent in order to obtain complete ethylation of the nitrogen. Dioxane was used in 9 in order to have an inactive solvent. Methylcyclohexane is not satisfactory for this purpose with carbethoxypyrroles at 250° as shown by the decarboxylation which took place in 1 and 10 with this solvent. Partial alkylation occurred in 3 and 4 due to the reaction of ethanol produced by the hydrogenation of the carbethoxy group.

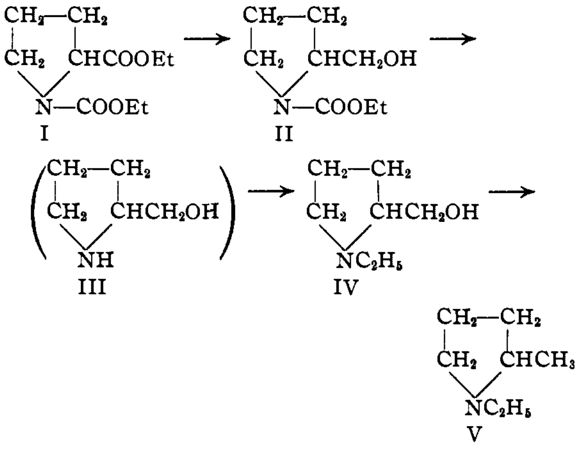
decarboxylation occurred. In either case the product so formed contained small amounts of the pyrrolidine not having a substituent upon the nitrogen. It is therefore better to carry out the reaction in an ethanol solution and thus complete the ethylation since it is difficult to separate the N-alkyl from the non-alkylated pyrrolidine. Several illustrations of the application of this type of reaction are given in Table IV. Partial hydrogenolysis of the benzyl group occurred in the reaction of hydrogen with a dimethylbenzylcarbethoxypyrrole.

VI. The Conversion of a Carbo-*t*-butoxypyrrole to a Methylpyrrolidine.—



The alkylation of the pyrrolidine nitrogen during hydrogenation of carbethoxypyrroles, referred to in the last section, may be avoided by using a *t*-butyl ester which upon hydrogenation gives a methyl group, *i*-butane and water (Table IV). It is probable that the same objective, *i. e.*, the preparation of a pyrrolidine not bearing a substituent upon the nitrogen, could also be attained by the use of an *i*-propyl ester.

VII. The Hydrogenation of 1,2-Dicarbethoxypyrrolidine.—



The 1,2-dicarbethoxypyrrolidine (I) upon complete hydrogenation gives 1-ethyl-2-methylpyrrolidine (V) just as would 1,2-dicarbethoxypyrrole. However, when the reaction was interrupted, two alcohols (II and IV) were obtained as shown in Table V. A third alcohol (III) is presumably formed as an intermediate product but none of it has been isolated from the reaction products.

TABLE V

HYDROGENATION OF CARBETHOXY PYRROLIDINES

Compound[a]	Moles	Temp., °C.	Catalyst, g.	Time, hours	Moles H_2 absorbed	Products	Yield, %
1,2-Dicarbethoxypyrrolidine	0.08	200	5Cu	1.5	0.240	1-Carbethoxy-2-oxymethylpyrrolidine	54
						1-Ethyl-2-oxymethylpyrrolidine	34
						1-Ethyl-2-methylpyrrolidine	2
1,2-Dicarbethoxypyrrolidine	.08	250	5Cu	0.5	.312	1-Carbethoxy-2-oxymethylpyrrolidine	62
						1-Ethyl-2-oxymethylpyrrolidine	23
						1-Ethyl-2-methylpyrrolidine	5
1,2-Dicarbethoxypyrrolidine	.08	250	5Cu	3.0	.498	1-Ethyl-2-oxymethylpyrrolidine	33
						1-Ethyl-2-methylpyrrolidine	27
1-Carbethoxy-2-oxymethylpyrrolidine	.07	200	5Cu	2.0	.168	1-Ethyl-2-oxymethylpyrrolidine	32
						1-Ethyl-2-methylpyrrolidine	7
						Unchanged pyrrolidine	41

[a] In ethanol as a solvent.

TABLE VI

PHYSICAL CONSTANTS AND COMPARISON OF METHODS OF PREPARATION OF PYRROLES

Pyrrole	M. p., °C.	B. p., °C.	At. press., mm.	Yield By hydrogenolysis	Yield By other[a] methods	Starting material
2-Carbethoxy-4-ethyl-3,5-dimethyl-	89–90	150	28	95	33–48	2-Carbethoxy-4-acetyl-3,5-dimethylpyrrole
3-Carbethoxy-5-ethyl-2,4-dimethyl-	107–108			70	Not stated	
3-Carbo-*t*-butoxy-5-ethyl-2,4-dimethyl-	128–129			80	Not prev. prepared	3-Carbo-*t*-butoxy-5-acetyl-2,4-dimethylpyrrole
3-Carbo-*t*-butoxy-5-acetyl-2.4-dimethyl-	154–155			37	Not prev. prepared	
3-Carbethoxy-5-benzyl-2,4-dimethyl-	119–121			52	"Small"	
3-Carbethoxy-2,4,5-trimethyl-	100–101	137	1	37–45	30	
2-Methyl-		146–147	740	27	22	Pyrrole
2,3,4,5-Tetramethyl-	108–110	130	7	13	24–32	2,4-Dicarbethoxy-3,5-dimethylpyrrole
3-Ethyl-2,4,5-trimethyl-(phyllopyrrole)	65–67	110–112	35	28–39	11	2-Carbethoxy-4-acetyl-3,5-dimetbylpyrrole
2,4-Diethyl-3,5-dimethyl-		89	7	53	9 as picrate	
3-Acetyl-5-ethyl-2,4-dimethyl-	157–158			65	Not prev. prepared	2,4-Diacetyl-3,5-dimethylpyrrole
2,4-Diacetyl-3,5-dimethyl-	129–131			55	28–34	
3-Carbethoxy-2,4-dimethyl-	77–78	153–155	8	38	52 (by decarboxylation)	2,4-Dicarbethoxy-3,5-dimethylpyrrole

[a] For the purpose of the comparisons the "best methods" of preparing the pyrrole as indicated by Fischer and Orth[9] is used.[11] When the synthesis by both "hydrogenolysis" and the "best method" started from the same compound, the latter is indicated in the last column of the table. When there was no common starting point the figures given are the over-all yields starting from the oximino compound in the Knorr synthesis.

Experimental Part

Pyrrole was prepared as described in "Organic Syntheses," and some was obtained as a gift from Drs. F. F. Blicke and Powers of the University of Michigan.[12] 1-Phenylpyrrole was prepared as by Craig and Hixon. 1-, 2- and 1,2-carbethoxypyrroles were obtained from pyrrole through the use of a Grignard reagent and chlorocarbonic ester as described in a later paper from this Laboratory on the synthesis of proline.

The 2-carbethoxy-4-acetyl-3,5-dimethylpyrrole, 3-carbethoxy-5-acetyl-2,4-dimethylpyrrole, 3-carbethoxy-5-benzoyl-2,4-dimethylpyrrole, 2,4-dicarbethoxy-3,5-dimethylpyrrole, 3-carbo-*t*-butoxy-5-acetyl-2,4-dimethylpyrrole and 2,4-diacetyl-3,5-dimethylpyrrole were prepared by the method previously described.[13] The two compounds last mentioned had not previously been prepared by this method. The 2,4-diacetyl-3,5-dimethylpyrrole was prepared as follows: oximino-diacetylmethane and diacetylmethane in equal molecular quantities (0.2 mole) were allowed to react with hydrogen (100 atm.) over Raney nickel (4 g.) in ethanol at 80°. After one hour a little over 0.4 mole of hydrogen had been absorbed. The solution was then filtered from the catalyst and evaporated in the steam-bath. The gummy residue was washed first with dilute alkali and then with water. The yield of this crude material, m. p. 129–131°, was 55% of the calculated. The material actually used in most of the experiments summarized in the tables was prepared by Knorr's method in 25 to 30% yield for material having a m. p. of 136°, recrystallized from alcohol.[14] If the product of either of these processes is not sufficiently pure for rapid hydrogenation after recrystallization from alcohol it may be treated in ethanol with hydrogen and Raney nickel at 75° for an hour or two.

The 3-carbo-*t*-butoxy-5-acetyl-2,4-dimethylpyrrole was

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[11] The 3-carbethoxy-5-benzyl-2,4-dimethylpyrrole is not referred to by Fischer and Orth but was reported by Bondetti and Lions, *C. A.*, **27**, 3212 (1933).

[12] Blicke and Powers, *Ind. Eng. Chem.*, **19**, 1334 (1927); McElvain and Bolliger, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, New York, 1932, p. 461.

[13] Winans and Adkins, THIS JOURNAL, **55**, 467 (1933).

[14] Ref. 9, p. 206, and Fischer and Neber, *Ann.*, **496**, 25 (1932).

TABLE VII

PHYSICAL CONSTANTS AND ANALYTICAL DATA FOR VARIOUS COMPOUNDS

				Analyses			
				Found		Calculated	
Compound	B. p., °C.	d^{25}	$n^{25}{}_D$	C	H	C	H
Pyrrolidine	88–89						
1-Phenyl-pyrrolidine	110–116 at 9 mm.	1.0260	1.5803				
1-Cyclohexyl-pyrrolidine	211–214	0.9099	1.4792				
1-Ethyl-2-methyl-pyrrolidine	119–120			(N_2)	12.38	(N_2)	12.40
1-Ethyl-3,4,5-trimethyl-pyrrolidine	52–55 at 23 mm.						
1-Ethyl-2,3,4,5-tetramethyl-pyrrolidine	163–165	.8064	1.4343	77.4	13.62	77.3	13.64
1-Ethyl-2-benzyl-3,4,5-trimethyl-pyrrolidine	139–141 at 12 mm.	.9123	1.4983	83.2	11.22	83.1	10.90
1,2-Diethyl-3,4,5-trimethyl-pyrrolidine	183–184	.8166	1.4388	77.7	13.43	78.0	13.69
1,3-Diethyl-2,4,5-trimethyl-pyrrolidine	184–185	.8151	1.4390	77.8	13.55	78.0	13.69
1,2,4-Triethyl-3,5-dimethyl-pyrrolidine	200–201	.8232	1.4430	78.2	13.46	78.6	13.75
2-Ethyl-3,4,5-trimethyl-pyrrolidine	147–151	.8035	1.4312	76.2	13.65	76.5	13.57
2,4-Diethyl-3,5-dimethyl-pyrrolidine	186–188	.8302	1.4428	77.3	13.72	77.3	13.63
1-Carbethoxy-pyrrolidine	98–99 at 20 mm.	1.0215	1.4498	58.6	9.07	58.7	9.15
1,2-Dicarbethoxy-pyrrolidine	133–134 at 7.5 mm.	1.0960	1.4530	56.2	8.02	55.8	7.97
1-Ethyl-2-oxymethyl-pyrrolidine	82–84 at 24 mm.	0.9577	1.4662	64.8	11.73	65.1	11.71
1-Carbethoxy-2-oxymethyl-pyrrolidine	134–135 at 8 mm.		1.462				
3-Carbo-*t*-butoxy-5-ethyl-2,4-dimethyl-pyrrole	M 128–129			69.8	9.41	69.9	9.48
3-Carbo-*t*-butoxy-5-acetyl-2,4-dimethyl-pyrrole	M 154–155			66.0	8.15	65.8	8.08
1,2-Dicarbethoxy-pyrrole	132–134 at 8 mm.			56.8	6.20	56.9	6.20
3-Acetyl-5-ethyl-2,4-dimethyl-pyrrole	M 157–158			72.7	9.17	72.7	9.17

prepared in 37% yield (m. p. 154–155° from 70% ethanol) by hydrogenating a mixture of oximinodiacetylmethane and *t*-butyl acetoacetate (0.2 mole each) over Raney nickel as in the preceding preparation. The catalyst was filtered from the hot solution, the latter evaporated to 150 ml., cooled and the crystalline product filtered off. A further crop of impure crystals may be obtained from the mother liquor. The *t*-butyl acetoacetate used in this preparation was obtained from Dr. S. M. McElvain.

The 3-carbethoxy-2,4-dimethylpyrrole was obtained by heating in a bomb under hydrogen 2,4-dicarbethoxy-3,5-dimethylpyrrole with piperidine at 250° for three to five hours. The yield of 38% so obtained can without doubt be improved by a study of the optimum conditions for decarboxylation.

The other compounds submitted to the action of hydrogen were prepared by hydrogenation as indicated in Tables I to V. The physical constants and analytical data for various compounds are given in Tables VI and VII.

The reactions of hydrogen and pyrroles described herewith were usually carried out in the "B" bomb with the valve and gage assembly described elsewhere.[15] In several cases a bomb of the same type but somewhat larger was used. The hydrogen pressures varied from 70 to 350 atmospheres, the greater number being at 200 to 300 atmospheres. Raney nickel[16] and copper–chromium oxide[17] were the catalysts used. Ethanol, dioxane and methylcyclohexane were variously used as the reaction media. In general the weight of solvent was two to three times the weight of the hydrogen acceptor. Dioxane free of ethanol is the most useful solvent but it may not be used with Raney nickel above 225°. Ethanol is a very satisfactory solvent but it may not be used above 150 or 170° if a pyrrolidine is formed, as alkylation of the nitrogen may occur. Methylcyclohexane is not a satisfactory medium for hydrogenations in which water is produced since immiscible layers may be formed. Therefore if a solvent is to be used dioxane or methylcyclohexane should be taken for the compounds of Table I, ethanol or dioxane for the compounds of Tables II, III and IV. Dioxane should be used for the compounds of Tables III, IV and V in which alkylation of pyrrolidines is to be avoided. There is of course no necessity for the use of solvents for liquid compounds although it is in general more convenient to use them.

The products listed in Table I, were obtained by fractional distillation of the reaction mixture in a Widmer column. The fractionations were made at 1 to 10 mm. except in the case of pyrrolidine, which was separated at atmospheric pressure. The products in Table II were obtained by crystallization directly from the reaction mixture and were recrystallized from 70% ethanol (excepting the 2,4-dimethyl-3,5-dimethylpyrrole which was obtained from the reaction mixture by distillation at 8 mm.).

The products in Table III were obtained from the reaction mixtures by fractional distillation. The solvent and pyrrolidine were taken off at 740 mm., the remaining products at reduced pressure (the alkylpyrroles at 7 to 70 mm. and the 3-carbethoxy-2,4,5-trimethylpyrrole at 1 mm.). The unchanged pyrroles were obtained as the distillation residue. All solid pyrroles were recrystallized from ethanol (70–95%). The 2,3,4,5-tetramethylpyrrole and the 3-ethyl-2,4,5-trimethylpyrrole were recrystallized in an atmosphere of nitrogen.

The products of nos. 1, 2, 9, 11, Table IV, were isolated by treating the solution (after filtering off the catalyst and in the case of no. 1, after removing the unchanged pyrrole by fractional distillation) with hydrochloric acid and evaporating off the solvent and water. The amine hydrochloride was recrystallized from ethanol and ether mixture, treated with concentrated potassium hydroxide

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[15] Adkins, THIS JOURNAL, **55**, 4272 (1933).

[16] Adkins and Covert, *ibid.*, **54**, 4116 (1932).

[17] Connor, Folkers and Adkins, *ibid.*, **54**, 1138 (1932).

solution and the amine was extracted with ether, dried over potassium carbonate and distilled. In the case of no. 2, the two amines were separated at this point by fractional distillation at atmospheric pressure.

The products of no. 8, Table IV, were obtained by fractional distillation at reduced pressure.

The remaining products in Table IV were obtained by fractional distillation at atmospheric pressure. The pairs of products of nos. 3, 4 and 10 were not separated from each other. The relative amounts of each were calculated from the neutralization equivalents of the mixtures.

In separating the products listed in Table V, the solvent and ethylmethylpyrrolidine were removed by distillation at atmospheric pressure. The amine was separated from the solvent by treatment with hydrochloric acid and evaporation. It was identified by means of its picrate prepared from the hydrochloride. The other products were separated by fractional distillation at reduced pressure.

Since 1-carbethoxy-2-oxymethylpyrrolidine boils at the same temperature as the 1,2-dicarbethoxypyrrolidine from which it is prepared it cannot be separated from it by fractional distillation. Furthermore, since the 1-carbethoxy-2-oxymethylpyrrolidine is itself hydrogenated to other products about as rapidly as is the 1,2-dicarbethoxypyrrolidine, it is difficult to destroy completely all of this latter compound and still obtain the oxymethyl derivative. The carbinol has a higher refractive index than the dicarbethoxypyrrolidine and reacts with acetyl chloride. It can be further hydrogenated to 1-ethyl-2-oxymethylpyrrolidine and 1-ethyl-2-methylpyrrolidine. Carbon and hydrogen analyses show the product obtained to be slightly contaminated with the 1,2-dicarbethoxypyrrolidine.

Among the solid derivatives prepared for the identification of various compounds may be noted the following: the picrate of 1-phenylpyrrolidine, m. p. 115–116°; of 1-cyclohexylpyrrolidine, m. p. 163–164°; of 1-ethylpyrrolidine, m. p. 183–184°; of 1-methylpyrrolidine, m. p. 215–216°; of 2,4-diethyl-3,5-dimethylpyrrole, m. p. 93–94°; of 1-ethyl-2-methylpyrrolidine, m. p. 193–194° (anal. of base, N_2 found 12.40, calcd. 12.38). The hydrochloride of 1-ethyl-3,4,5-trimethylpyrrolidine, anal. found 19.9 chlorine, calcd. 20.0.

Conclusions and Summary

Pyrroles are more resistant to hydrogenation than are any of the other unsaturated ring systems encountered in this Laboratory. The 2,3,4- and (or) 5-alkyl pyrroles react with hydrogen over nickel or copper–chromium oxide at 200 to 250°, but the ring in carbethoxypyrroles (except 1-carbethoxypyrroles) is not hydrogenated under conditions less drastic than those which bring about a hydrogenolysis of the carbethoxy group. In contrast to these compounds the ring in pyrroles with a carbethoxy or aryl group on the nitrogen atom is readily hydrogenated over Raney nickel from room temperatures upward. This fact has made it possible to prepare a number of new pyrrolidines as well as to obtain several others in much better yields than was formerly possible.

Because of the resistance of the nucleus toward hydrogenation it has proven feasible to convert acylpyrroles in excellent yields over copper–chromium oxide to the corresponding alkylpyrroles. Because of the difference in the ease of hydrogenolysis of an acyl group in the 2-(or 5-) position as compared with one in the 4-(or 3-) position it is feasible to preferentially hydrogenate a 2,-4-diacyl pyrrole to a 4-monoacyl pyrrole.

Similarly it has proven feasible to convert carbethoxy- to methylpyrroles although the higher temperature required for this reaction necessitates a careful control of the extent of reaction of hydrogen so as to avoid the excessive formation of pyrrolidines. A carbethoxy group in the 2-(or 5-) position may be selectively hydrogenated in the presence of a carbethoxy group in the 4-(or 3-) position.

The advantages of hydrogenolysis as a tool for the preparation of certain pyrroles may be seen by a comparison of the yields reported in Table VI. In almost every case the better yields were obtained by the methods described in this paper.

Acyl and carbethoxy pyrroles may be converted in excellent yields to the corresponding alkyl pyrrolidines over copper–chromium oxide at temperatures from 200 to 250°. When carbethoxy pyrroles are subjected to these conditions the nitrogen of the pyrrolidine is ethylated, but this reaction may be avoided through the use of *t*-butyl esters.

The hydrogenolysis of carbethoxypyrrolidines may be interrupted so that pyrrolidino-carbinols are obtained.

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