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

# The Reactions of Hydrogen with Derivatives of Pyrrole.[1] II

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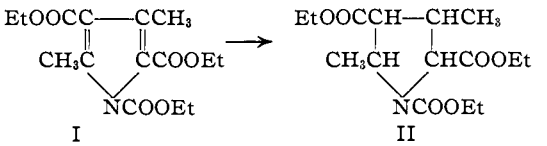
Signaigo found that the pyrrole rings in 1-carbethoxy and 1,2-dicarbethoxypyrrole were hydrogenated to pyrrolidine rings much more rapidly and under milder conditions than is pyrrole. The temperature required for the hydrogenation of the ring was reduced by almost 150° due to the presence of the carbethoxy group. This suggested the desirability of ascertaining the effect of substituents on the nitrogen in facilitating the hydrogenation of the very resistant pyrrole ring in various substituted pyrroles.

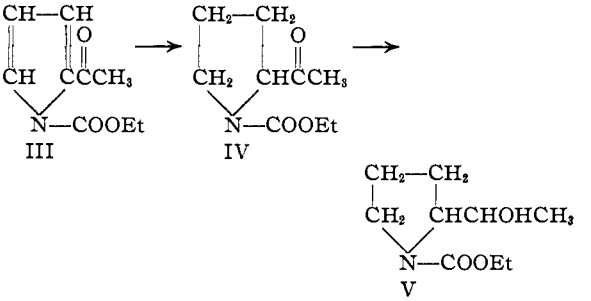
A carbethoxy group has been substituted on the nitrogen of nine different pyrroles and the compounds submitted to hydrogenation. The results are given as entries 1, 3, 4, 5, 6, 7, 12, 13, 14, 15, 16 in Table I for the type of reaction indicated in the conversion of I to II. In the case of five pyrroles which had carbethoxy and alkyl groups on the carbon atoms of the ring as well as a carbethoxy on the nitrogen, the ring was hydrogenated smoothly within less than an hour at 120 to 200°. The pyrrolidines, corresponding to the pyrroles, were isolated in yields of 60 to 95% (see entries 4, 5, 6, 7 and 14).



I II

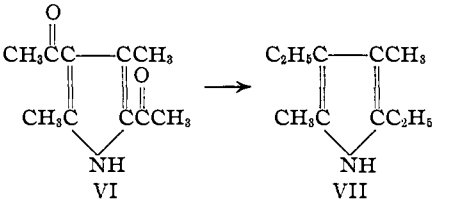
These results are to be contrasted with the fact that the parent carbethoxypyrroles cannot be hydrogenated to carbethoxypyrrolidines under any known conditions.

Even more striking illustrations of the efficacy of a carbethoxy group on the nitrogen in facilitating the hydrogenation of the ring are shown by the behavior of three acetylpyrroles. A carbonyl group is in general hydrogenated under as mild conditions as is a carbon to carbon double bond. Only in the case of unsaturated ketones such as mesityl oxide has it been possible to hydrogenate the alkene prior to the carbonyl linkage. It has not been possible to hydrogenate phenyl or furfural ketones to the corresponding cyclohexyl or tetrahydrofuryl ketones. Yet 1-carbethoxy-2-acetylpyrrole, III, was converted in 77% yield to the corresponding pyrrolidine, IV, within twenty minutes at 80°. Similar results were obtained with 1-carbethoxy-3-acetyl-2,4-dimethylpyrrole (entries 13 and 16).



III IV V

The hydrogenation of the ketone group to the carbinol will take place under similar conditions so that if the hydrogenation is not interrupted after the addition of two moles of hydrogen per mole of pyrrole, reaction continues and the pyrrolidine alcohols, *e. g.*, V, are obtained in yields of 71 to 94% (entries 12, 13 and 14). When hydrogenation of the carbonyl group of an acetylpyrrole proceeds more readily than hydrogenation of the ring, an ethylpyrrole is formed. This latter type of reaction, VI to VII, has been illustrated in the earlier paper and offers a useful transformation in the case of acetylpyrroles not having a carbethoxy group on the nitrogen.



VI VII

1-Benzoylpyrrole is converted to 1-benzoylpyrrolidine as readily as is the corresponding carbethoxypyrrole. However, in the case of two other N-benzoyldimethyl-carbethoxypyrroles, the benzoyl group proved ineffective in facilitating the saturation of the ring (entries 8, 9 and 10). Instead the benzoyl group was cleaved from the nitrogen and converted to benzyl alcohol or toluene. This reaction, VIII to IX, occurred rap-

(1) The first paper of this title is by Signaigo and Adkins, THIS JOURNAL, **58**, 709 (1936).

(2) Dr. Rainey held a research assistantship supported by the Wisconsin Alumni Research Foundation in 1935–1936 and was the Monsanto Company Fellow in 1936–1937 and 1937–1938.

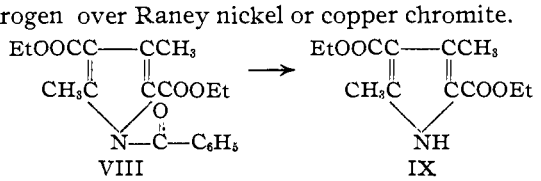
TABLE I

HYDROGENATIONS[a]

| No. | Compounds | Moles | Temp., °C. | Catalyst, g. | Time, hours | % yield of products |
|---|---|---|---|---|---|---|
| 1 | 1-Carbethoxypyrrole | 0.1 | 70 | 3 Ni | 0.3 | 93 1-Carbethoxypyrrolidine |
| 2 | 1-Benzoylpyrrole | .1 | 70 | 3 Ni | 1.0 | 93 1-Benzoylpyrrolidine |
| 3 | 1-Carbethoxy-2,4-diethyl-3,5-dimethylpyrrole | .06 | 180 | 6 Ni | 1.2 | 87 1-Carbethoxy-2,4-diethyl-3,5-dimethylpyrrolidine |
| 4 | 1,2,4-Tricarbethoxy-3,5-dimethylpyrrole | .3 | 180 | 6 Ni | 1.0 | 95 1,2,4-Tricarbethoxy-3,5-dimethylpyrrolidine |
| 5 | 1,2-Dicarbethoxy-3,5-dimethylpyrrole | .1 | 120 | 3 Ni | 1.0 | 90 1,2-Dicarbethoxy-3,5-dimethylpyrrolidine |
| 6 | 1,2-Dicarbethoxy-4-ethyl-3,5-dimethylpyrrole | .07 | 170 | 3 Ni | 1.0 | 90 1,2-Dicarbethoxy-4-ethyl-3,5-dimethylpyrrolidine |
| 7 | 1,3-Dicarbethoxy-2,4-dimethylpyrrole | .15 | 200 | 6 Ni | 6.0 | 60 1,3-Dicarbethoxy-2,4-dimethylpyrrolidine |
| 8 | 1-Benzoyl-2,4-dicarbethoxy-3,5-dimethylpyrrole | .06 (.13) | 125 | 3 Ni | 0.8 | 85 2,4-Dicarbethoxy-3,5-dimethylpyrrole<br>60 Benzyl alcohol |
| 9 | 1-Benzoyl-2,4-dicarbethoxy-3,5-dimethylpyrrole | .04 (.20) | 150 | 3 Ni | 4.0 | 85 2,4-Dicarbethoxy-3,5-dimethylpyrrole |
| 10 | 1-Benzoyl-3-carbethoxy-2,4-dimethylpyrrole | .06 (.15) | 150 | 3 Ni | 0.4 | 85 3-Carbethoxy-2,4-dimethylpyrrole<br>60 Benzyl alcohol |
| 11 | 1-Trimethylacetyl-2,4-dicarbethoxy-3,5-dimethylpyrrole | .09 (.32) | 270 | 3 Ni | 3.0 | Not identified |
| 12 | 1-Carbethoxy-2-acetylpyrrole | .13 | 140 | 3 Ni | 2.0 | 94 1-Carbethoxy-2-α-hydroxyethylpyrrolidine |
| 13 | 1-Carbethoxy-3-acetyl-2,4-dimethylpyrrole | .1 | 180 | 3 Ni | 2.0 | 80 1-Carbethoxy-2,4-dimethyl-3-α-hydroxyethylpyrrolidine |
| 14 | 1,2-Dicarbethoxy-4-acetyl-3,5-dimethylpyrrole | .05 | 180 | 3 Ni | 1.0 | 71 1,2-Dicarbethoxy-4-α-hydroxyethyl-3,5-dimethylpyrrolidine |
| 15 | 1-Carbethoxy-2-acetylpyrrole | .1 (.21) | 80 | 6 Ni | 0.3 | 77 1-Carbethoxy-2-acetylpyrrolidine<br>15 1-Carbethoxy-2-α-hydroxyethylpyrrolidine |
| 16 | 1-Carbethoxy-3-acetyl-2,4-dimethylpyrrole | .06 (.12) | 100 | 3 Ni | 1.0 | 73 1-Carbethoxy-3-acetyl-2,4-dimethylpyrrolidine |
| 17 | 1,3,5-Trimethyl-2,4-dicarbethoxypyrrole | .06 (.12) | 250 | 6 Ni | 5.0 | 57 1,3,5-Trimethyl-2,4-dicarbethoxypyrrole<br>29 1,2,3,4,5-Pentamethylpyrrolidine |
| 18 | 1,3,5-Trimethyl-2,4-dicarbethoxypyrrole | .08 | 250 | 6 $CuCr_2O_4$ | 4.0 | 80 1,2,3,4,5-Pentamethylpyrrolidine |
| 19 | 1,3,5-Trimethyl-2,4-dicarbethoxypyrrole | .13 (.5) | 220 | 6 $CuCr_2O_4$ | 1.0 | 27 1,3,5-Trimethyl-2,4-dicarbethoxypyrrole<br>23 1,2,3,4,5-Pentamethylpyrrolidine<br>36 1,2,3,5-Tetramethyl-4-carbethoxypyrrole |
| 20 | 1-Ethyl-2,4-dicarbethoxy-3,5-dimethylpyrrole | .1 (.2) | 250 | 3 Ni | 4.0 | 55 1-Ethyl-2,4-dicarbethoxy-3,5-dimethylpyrrole<br>19 1-Ethyl-2,3,4,5-tetramethylpyrrolidine |
| 21 | 3-Carbethoxy-2,4-dimethylpyrrole | .2 (.54) | 220 | 6 Ni | 2.4 | 6 3-Carbethoxy-2,4-dimethylpyrrole<br>10 1-Ethyl-2,3,4-trimethylpyrrolidine<br>50 1-Ethyl-3-carbethoxy-2,4-dimethylpyrrolidine<br>12 Pyrrolidones |
| 22 | 3-Carbethoxy-2,4-dimethylpyrrole | .1 | 220 | 3 Ni | 7.0 | 66 3-Carbethoxy-2,4-dimethylpyrrole<br>5 1-Ethyl-2,3,4-trimethylpyrrolidine<br>15 Carbethoxypyrrolidines |
| 23 | 1-Ethyl-3-carbethoxy-2,4-dimethylpyrrole | .07 (.17) | 220 | 3 Ni | 0.8 | 3 1-Ethyl-2,3,4-trimethylpyrrolidine<br>78 1-Ethyl-3-carbethoxy-2,4-dimethylpyrrolidine |
| 24 | 2-Carbethoxy-3,5-dimethylpyrrole | .1 (.21) | 220 | 3 Ni | 7.0 | 18 1-Ethyl-2,3,5-trimethylpyrrolidine<br>60 2-Carbethoxy-3,5-dimethylpyrrole |
| 25 | 2-Carbethoxypyrrole | .2 (.6) | 220 | 12 Ni | 2.5 | 35 1-Ethyl-2-methylpyrrolidine<br>34 2-Carbethoxypyrrole<br>14 1-Ethyl-2-hydroxymethylpyrrolidine |
| 26 | 1-Ethyl-3-carbethoxy-2,4-dimethylpyrrolidine | .11 (.22) | 190 | 5 $CuCr_2O_4$ | 1.0 | 3 1-Ethyl-2,3,4-trimethylpyrrolidine<br>83 1-Ethyl-3-hydroxymethyl-2,4-dimethylpyrrolidine |

[a] Dioxane was used as a solvent except in 11, 17 and 20, where methylcyclohexane, and 14, 18, 19, 21, 23, 24, 25 and 26, where ethanol were used. The figures in parentheses in the third column refer to the moles of hydrogen absorbed in certain hydrogenations that were interrupted before the absorption of hydrogen was complete.

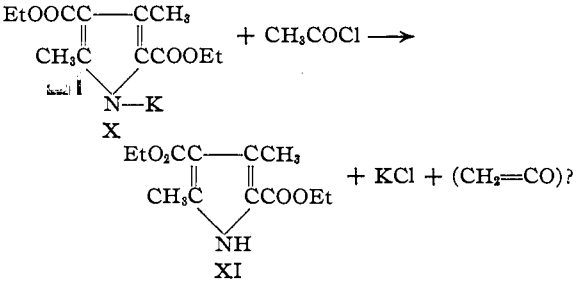
idly at 125°, a temperature 100° below that at which other amides show any reaction with hydrogen over Raney nickel or copper chromite.




VIII IX

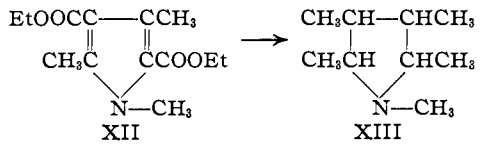
An acetyl group on the nitrogen presumably would not undergo this type of cleavage and so might be effective in facilitating the hydrogenation of the ring. Unfortunately all attempts to prepare such a compound as 1-acetyl-2,4-dicarbethoxy-3,5-dimethylpyrrole were unsuccessful. The 1-carbethoxy and 1-benzoylpyrroles were made by the reaction of the sodium or potassium pyrrole with chloroformic ester or benzoyl chloride. When acetyl chloride was used the

metal on the nitrogen was replaced by hydrogen instead of by acetyl, *i. e.*



Similar results were obtained when diphenylacetyl chloride or acetic anhydride was substituted for acetyl chloride. Attempts to isolate ketene or diphenyl ketene from the reaction products were unsuccessful; however, resinous products were obtained in addition to the pyrrole and sodium or potassium chloride. The acylation reaction went in orthodox fashion when trimethylacetyl chloride was used instead of acetyl chloride. This fact supports the suggestion that the abnormal reaction with the two acid chlorides was due to their enolization.

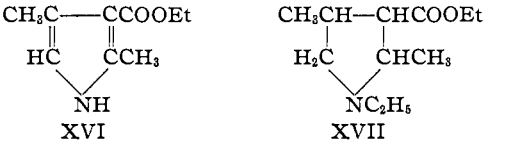
Methyl or ethyl groups on the nitrogen did not facilitate the hydrogenation of the pyrroloid ring in 2,4-dicarbethoxy-3,5-dimethylpyrrole (entries 17 and 20). If the conditions of hydrogenation were made sufficiently drastic, reaction proceeded as in the case of the dicarbethoxypyrrole having no substituent on the nitrogen, that is, pyrrolidines containing no oxygen were obtained, *e. g.*



This latter type of reaction proceeds much more readily over copper chromite than over Raney nickel as shown by a comparison of entries 18 and 19 with 17.

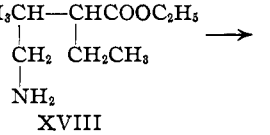
The fact that a carbethoxy group on the nitrogen facilitates the hydrogenation of the pyrroloid ring while an alkyl group does not, is understandable on the basis of the difference in the electromeric effect of the two types of groups. It is well known that the double bonds in pyrroles destroy the basic properties of the nitrogen, presumably because the pair of electrons, through which nitrogen forms salts, are drawn toward the unsaturated linkages. This suggests that the resistance of the double bonds to addition results from this electromeric shift. The presence of a carbethoxy group on the nitrogen would change the direction of electromeric shift, so that it would be from the nitrogen toward the oxygen of the carbonyl group. Thus the alkene linkages would be freed at least in part of the electromeric shift which in pyrrole or 1-methylpyrrole apparently hinders addition of hydrogen. These electromeric shifts are indicated in the conventional manner in formulas XIV and XV.

3-Carbethoxy-2,4-dimethylpyrrole, XVI, is a notable exception among the carbethoxypyrroles not having a substituent on the nitrogen, in that the ring could be hydrogenated without destroying the carbethoxy group. The hydrogenation did not go well in dioxane and only low yields of a mixture of carbethoxy pyrrolidines could be obtained (entry 22). But in ethanol the hydrogenation went quite well and 50% yields of 1-ethyl-3-carbethoxy-2,4-dimethylpyrrolidine, XVII, were regularly obtained (entry 21). The 1-ethyl derivative of XVI also gave a 78% yield of XVII (entry 23).

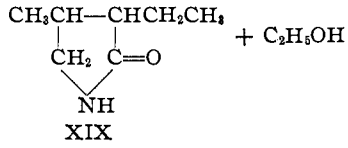


The ethylation of the nitrogen is inevitable when a pyrrolidine is formed at high temperatures by hydrogenation in the presence of ethanol.

There was also obtained a 12% yield of pyrrolidones, XIX and XX. This result was reminded of the results obtained by Folkers[3] in the hydrogenation of ethyl nicotinate, a compound which also has a carbethoxy group in the $\beta$-position with respect to a nitrogen. A nitrogen to carbon linkage in such a position is labile toward hydrogenolysis so that the formation of a cyclic amide as the result of ring cleavage followed by ring formation is understandable. The sequence of reactions would be from XVI to XVIII to XIX.

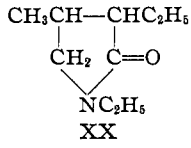


(3) Folkers and Adkins, THIS JOURNAL, **54**, 1145 (1932).



XIX

If the open chain amine were ethylated before ring closure then the pyrrolidone would have the structure, XX. Ethylation would not follow

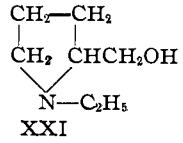


XX

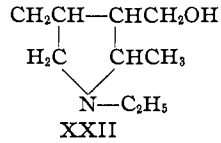
ring closure because amides are not alkylated under the conditions of the formation of the pyrrolidone. The presence of two pyrrolidones in the mixture was indicated by the experimental results.

The conversion of a carbethoxy group to a methyl group is the normal reaction when a carbethoxy group on a pyrrole nucleus reacts with hydrogen. Numerous illustrations of this type of reaction were reported by Signaigo and a few are given in Table I. The hydrogenation of the carbethoxy group presumably preceded the hydrogenation of the ring, since Signaigo was able to interrupt the reaction in several instances and obtain fair yields of the corresponding methylpyrroles. In fact it is feasible, as shown in the earlier paper and confirmed in entry 19, to hydrogenate a carbethoxy group in the 2-position to a methyl group without modifying the pyrrole ring or a carbethoxy group in the 4-position.

However, one case is now known where the hydrogenation of the ring apparently preceded the hydrogenation of the carbethoxy group, for a 14% yield of the alcohol XXI was obtained by the hydrogenation of 2-carbethoxypyrrole in ethanol. If the carbethoxy group had been hydrogenated before the ring, the alcohol first formed would have been converted immediately to methyl under the influence of the pyrroloid nucleus. If the ring is saturated as in the case of 1-ethyl-3-carbethoxy-2,4-dimethylpyrrolidine, XVII (entry 26), the corresponding alcohol, XXII, may be obtained in a yield of 83%.



XXI



XXII

**Preparation of Pyrroles.**—A number of the pyrroles were prepared by the procedure or method previously described for the compound or a similar one. Among these may be noted 2,4-diethyl-3,5-dimethylpyrrole,[1] 2,4-dicarbethoxy-3,5-dimethylpyrrole,[4] 2-carbethoxy-4-acetyl-3,5-dimethylpyrrole in 55% yield,[5] 2-acetylpyrrole in 50% yield,[6] 2,4-diacetyl-3,5-dimethylpyrrole in 30% yield from diacetylmethane,[7] 2-carbethoxy-4-ethyl-3,5-dimethylpyrrole in 90% yield,[1] 1,3,5-trimethyl-2,4-dicarbethoxypyrrole (b. p. 142–144 at 1 mm., m. p. 113–114°) in 87% yield,[4] and 2,4-diethyl-3,5-dimethylpyrrole in 85% yield from 2,4-diacetyl-3,5-dimethylpyrrole.[1]

1-Ethyl-2,4-dicarbethoxy-3,5-dimethylpyrrole was prepared by the reaction of diethyl sulfate with the sodium derivative of 2,4-dicarbethoxy-3,5-dimethylpyrrole.[4] After distilling the product (50 g.) at 144–147° (1 mm.), it was stirred with 150 ml. of petroleum ether (b. p. 60–68°) and the insoluble portion discarded. The product was again distilled and after crystallization from petroleum ether had a m. p. of 39–39.5°.

Four pyrroles were prepared by eliminating a carbethoxy group. One of these was by the acid hydrolysis method of Fischer and Walach[8] with decarboxylation at the β-carbon, while three were alkaline hydrolyses by the method of Knorr[9] with decarboxylations at the α-carbon.

2,4-Dicarbethoxy-3,5-dimethylpyrrole (200 g.) was treated with sulfuric acid at 50° for one hour. There was obtained 140 g. of 2-carbethoxy-4-carboxy-3,5-dimethylpyrrole and 20 g. of the starting material. The ester was decarboxylated in glycerol as described below, the product was distilled at 155–160° (29 mm.) and recrystallized from ethanol. The 2-carbethoxy-3,5-dimethylpyrrole, m. p. 124–125°, weighed 92 g.

2,4-Dicarbethoxy-3,5-dimethylpyrrole (120 g.) in 375 ml. of 95% alcohol with 33 g. of sodium hydroxide was heated under a reflux (two hours) until a sample poured into water was soluble. The whole solution was then poured into 500 ml. of cold water and the solution acidified to Congo red with 10% hydrochloric acid. The product was sucked dry on a filter, washed with 100 ml. of water and dried at 100° for about four days.

Dry glycerol (50 ml.) was placed in a 500-ml. distilling flask and swirled so that the inner surface of the flask was covered. The powdered acid was poured into the flask and 50 ml. of glycerol added. The flask was heated with a free flame until carbon dioxide was no longer evolved, and the product distilled at 145–155° (7 mm.). Petroleum ether (150 ml.) and water (25 ml.) were added to the distillate, the mixture heated and the hydrocarbon layer decanted. Upon cooling the solution in an ice-salt mixture 3-carbethoxy-2,4-dimethylpyrrole crystallized out in yields of 72–82%. After distillation at 152° (7 mm.) the compound melted at 75–76°.

3-Acetyl-5-carbethoxy-2,4-dimethylpyrrole (41 g.) was hydrolyzed and decarboxylated in the same way. The resultant crude ketone was distilled at 159–160° (10 mm.) and dissolved in 100 ml. of hot 70% alcohol. Upon cooling 20 g. of 3-acetyl-2,4-dimethylpyrrole, m. p. 136–137°, separated.

(4) Corwin and Quattlebaum, THIS JOURNAL, **58**, 1084 (1936).
(5) Fischer, Bauman and Rudl, *Ann.*, **475**, 238 (1929).
(6) Oddo, *Ber.*, **43**, 1012 (1911).
(7) Fischer and Neber, *Ann.*, **496**, 25 (1932).
(8) Fischer and Walach, *Ber.*, **58**, 2820 (1925).
(9) Knorr, *Ann.*, **236**, 325 (1886).

1-Ethyl-2,4-dicarbethoxy-3,5-dimethylpyrrole (53 g.) was also hydrolyzed and decarboxylated by the same method to give 23 g. of 1-ethyl-3-carbethoxy-2,4-dimethylpyrrole, b. p. 137–140° (7 mm.).

**1-Carbethoxypyrroles.**—Potassium (0.4 mole) was powdered under 100 ml. of dry toluene in a liter flask. Toluene (300 ml.) and the pyrrole (0.3 mole) were added to the cold mixture, and the mixture refluxed with stirring until hydrogen was no longer evolved (one to five hours). Ethyl chlorocarbonate (0.45 mole) was added dropwise during ten minutes to the cold solution which was frequently shaken. The reaction mixture was heated on the steam-bath for one to three hours until the white precipitate of potassium pyrrole was replaced by the dark, more finely divided potassium chloride. The salt was separated by filtering or centrifuging and the toluene distilled at 20–30 mm.

The ethyl chlorocarbonate (Eastman practical grade) had been purified by shaking with calcium chloride and fractionated through a Widmer column, the first third being rejected and the portion boiling 90–92° (740 mm.) sealed in glass containers which were opened just before use.

1-Carbethoxypyrrole (b. p. 175–180° at 740 mm.), 1-carbethoxy-2-acetylpyrrole (b. p. 145–150° at 24 mm.) and 1-carbethoxy-2,4-diethyl-3,5-dimethylpyrrole (b. p. 123–126° at 7 mm.) were separated by fractionation in the indicated temperature range.

1,2-Dicarbethoxy-4-acetyl-3,5-dimethylpyrrole was separated from 2-carbethoxy-4-acetyl-3,5-dimethylpyrrole by evaporating the toluene solution to 200 ml. seeding it with the latter compound and allowing it to stand overnight. After discarding the crystals, the toluene was evaporated at 20–30 mm. and the desired compound fractionated at 160–164° (1 mm.). The distillate solidified and was recrystallized from petroleum ether. The product melted at 74–75.5° and probably contained 2 to 3% of the starting material.

1-Carbethoxy-3-acetyl-2,4-dimethylpyrrole, 1,3-dicarbethoxy-2,4-dimethylpyrrole, 1,2-dicarbethoxy-3,5-dimethylpyrrole, 1,2-dicarbethoxy-4-ethyl-3,5-dimethylpyrrole and 1,2,4-tricarbethoxy-3,5-dimethylpyrrole were purified by evaporating the toluene at 20–30 mm. in a bath held below 150°, adding 150 ml. of petroleum ether and allowing the mixture to stand with stirring for two hours. The unreacted pyrrole not having a carbethoxy group on the nitrogen was insoluble in the petroleum ether and thus could be filtered out. The solvent was evaporated and the product fractionated. The first third of the distillate was seeded with a crystal of the starting material and allowed to stand for two hours. Any crystals were discarded and the product refractionated.

The 1-benzoylpyrroles and the 1-trimethylacetylpyrrole were prepared as were the 1-carbethoxypyrroles, using benzoyl chloride or trimethylacetyl chloride instead of ethyl chlorocarbonate. The petroleum ether procedure was used for purifying the 1-trimethylacetylpyrrole while fractionation alone was used for the 1-benzoylpyrroles.

The yields in twelve cases averaged 69%, the only significant deviations from the average being 1,2,4-tricarbethoxy-3,5-dimethylpyrrole (77%), 1,2-dicarbethoxy-3,5-dimethylpyrrole (38%), and 1,2-dicarbethoxy-3,5-dimethyl-4-ethylpyrrole (40%). The recovery of the starting material in the two latter cases was 22 to 30%, so that the yields even here were satisfactory.

**Hydrolysis of 1,2,4-Tricarbethoxy-3,5-dimethylpyrrolidine.**—The carbethoxy group on the nitrogen of the corresponding pyrrole may be removed with 3% alcoholic potassium hydroxide within fifteen minutes at room temperature or one minute at 78°. However, the carbethoxy group on the pyrrolidine resisted all the usual methods of hydrolysis so that very drastic conditions were necessary.

The pyrrolidine (80 g.) and 40% hydrochloric acid (100 ml.), held in a beaker within a steel bomb, were heated at 150° for two to three hours. The dark red product was poured into 150 ml. of water, the non-basic material extracted with ether, and the water layer evaporated at 7 mm. on a steam-bath and finally at 1 to 2 mm. The crude acid (52 g.) so obtained, according to titration, contained about 5% of an impurity. It was esterified by refluxing for three hours with dry ethanol containing hydrogen chloride. The mixture was again saturated with hydrogen chloride, refluxed for another hour, the alcohol and water evaporated. The residue was poured on a mixture of 50 g. of cracked ice in 100 ml. of water and 200 ml. of ether contained in a separatory funnel. An ice-cold 10% solution of sodium hydroxide was first added until the mixture was just alkaline to litmus, and then 30 g. of potassium carbonate added and the separatory funnel shaken vigorously. The ether layer was separated immediately and the water layer extracted with 100 ml. of ether. The ether extracts were dried over sodium sulfate and the product (24 g.) distilled at 140–142° (7 mm.). The water solution was evaporated and the residue submitted to the esterification process described above. A small additional amount (6 g.) of 2,4-dicarbethoxy-3,5-dimethylpyrrolidine was obtained. The pyrrolidine showed a neutral equivalent of 248 (calcd. 243) when titrated using the methyl red-methylene blue indicator.

**Hydrogenation and Separation of Products.**—The apparatus, procedures and preparation of the catalysts (except as noted below) were similar to those used in the earlier work[1] and recently described in detail.[10] In hydrogenating with Raney nickel in a methylcyclohexane solution it is necessary that the catalyst be entirely free of water, else it will not be well suspended in the reaction mixture. It is advisable, therefore, in this case to place a quantity of the catalyst, which has been kept under ethanol, in a distilling flask and add a quantity of methylcyclohexane. The mixture should then be distilled until no more water or alcohol comes over. The catalyst may then be kept under dry methylcyclohexane until it is to be used.

The products listed in Table I were in general separated by fractionation through a "modified Widmer column" having a glass helix 21 mm. long with 18 turns, the procedure being the one recently described.[11] Other columns having shorter helices or a sharper pitch, as well as a short Vigreux column with a receiver sealed to the side arm, were used for higher boiling compounds and for substances of high melting point. The products were characterized by boiling points, refractive indices, neutral equivalents,

(10) Adkins, "Reactions of Hydrogen," Univ. of Wisconsin Press, Madison, Wis., 1937.

(11) Martha E. Smith and Adkins, THIS JOURNAL, **60**, 662 (1938).

TABLE II[a]

PHYSICAL CONSTANTS AND ANALYTICAL DATA

| Compound | B. p., °C. | Mm. | $d^{25}_4$ | $n^{20}D$ | Analyses, % Calcd. | Found | | Calcd. | Found | |
|---|---|---|---|---|---|---|---|---|---|---|
| 1,2-Dicarbethoxy-3,5-dimethylpyrrolidine | 146–147 | 11 | 1.048 | 1.4497 | C, 59.2 | 59.2 | | H, 8.70 | 8.67 | |
| | 137–138 | 7 | | | | | | | | |
| 1,3-Dicarbethoxy-2,4-dimethylpyrrolidine | 146–147 | 7 | 1.055 | 1.4538 | C, 59.2 | 59.3 | 58.9 | H, 8.70 | 8.89 | 8.63 |
| 1,2-Dicarbethoxy-4-ethyl-3,5-dimethyl-pyrrolidine | 164–166 | 11 | 1.042 | 1.4626 | C, 62.0 | 61.5 | 61.7 | H, 9.29 | 9.12 | 9.17 |
| 1,2,4-Tricarbethoxy-3,5-dimethylpyrrolidine | 151 | 1.2 | 1.109 | 1.4620 | | | | N, 4.44 | 4.61 | 4.42 |
| | 132 | 0.3 | | | | | | | | |
| 2,4-Dicarbethoxy-3,5-dimethylpyrrolidine | 140–142 | 7 | 1.051 | 1.4498 | M, 243 | 248 | | N, 5.76 | 5.59 | 5.52 |
| 1-Ethyl-3-carbethoxy-2,4-dimethylpyrrolidine | 86–89 | 7 | 0.9305 | 1.4397 | C, 66.3 | 66.3 | | H, 10.62 | 10.65 | |
| | | | | | M, 199 | 199 | | | | |
| 1-Carbethoxy-2,4-diethyl-3,5-dimethyl-pyrrolidine | 119–121 | 7 | | 1.4610 | | | | N, 6.17 | 6.10 | 6.15 |
| 1-Benzoylpyrrolidine[12] | 169–170 | 8 | | 1.5621 | C, 75.4 | 75.2 | | H, 7.43 | 7.43 | |
| 1-Carbethoxy-2-acetylpyrrolidine | 138–140 | 11 | 1.084 | 1.4623 | C, 58.4 | 58.3 | 58.3 | H, 8.16 | 8.25 | 8.19 |
| | 125–127 | 7 | | | | | | | | |
| 1-Carbethoxy-3-acetyl-2,4-dimethylpyrrolidine | 151–156 | 8.5 | 1.052 | 1.4674 | C, 61.9 | 61.5 | 61.5 | H, 8.98 | 8.94 | 8.91 |
| 1-Carbethoxy-2-α-hydroxyethylpyrrolidine | 162–165 | 25 | 1.083 | 1.4686 | C, 57.7 | 57.5 | | H, 9.15 | 9.15 | |
| | 135–137 | 7 | | | Z, 1.00 | 0.92 | 1.05 | N, 7.49 | 7.57 | 7.41 |
| 1-Carbethoxy-3-α-hydroxyethyl-2,4-dimethylpyrrolidine | 166–171 | 8.5 | 1.048 | 1.4727 | C, 61.4 | 61.2 | 61.2 | H, 9.82 | 9.76 | 9.84 |
| | | | | | Z, 1.00 | 1.1 | 1.1 | | | |
| 1,2-Dicarbethoxy-4-α-hydroxyethyl-3,5-dimethylpyrrolidine | 165–170 | 1 | | 1.4722 | C, 58.5 | 58.3 | | H, 8.77 | 8.62 | {4.96 |
| | | | | | Z, 1.00 | 0.7 | 0.8 | N, 4.84 | 4.84 | {5.10 |
| 1-Ethyl-3-hydroxymethyl-2,4-dimethyl-pyrrolidine | 100–102 | 8 | 0.9303 | 1.4649 | C, 68.7 | 68.8 | 68.7 | H, 12.18 | 11.89 | 12.01 |
| | | | | | M, 157 | 161 | | N, 8.92 | 8.67 | 8.89 |
| 1,2,3,4,5-Pentamethylpyrrolidine | 146–149 | 742 | 0.8003 | 1.4345 | M, 141 | 142 | | N, 9.93 | 9.72 | 9.84 |
| 1-Ethyl-2,3,4-trimethylpyrrolidine | 147–150 | 740 | | 1.430 | M, 141 | 142 | | N, 9.93 | 10.05 | |
| 1-Ethyl-2,3,5-trimethylpyrrolidine | 139–142 | 740 | | 1.429 | M, 141 | 142 | | N, 9.93 | 10.12 | |
| 1,2,4-Tricarbethoxy-3,5-dimethylpyrrole | 158–160 | 1.2 | 1.139 | 1.4991 | | | | N, 4.50 | 4.28 | 4.35 |
| 1-Carbethoxy-2,4-diethyl-3,5-dimethylpyrrole | 123–126 | 7 | | 1.4859 | | | | N, 6.28 | 6.43 | 6.11 |
| 1,2-Dicarbethoxy-3,5-dimethylpyrrole | 156–158 | 11.5 | 1.096 | 1.4930 | | | | N, 5.85 | 5.73 | 5.65 |
| | 149–151 | 7 | | | | | | | | |
| 1,3-Dicarbethoxy-2,4-dimethylpyrrole | 159–162 | 9 | | 1.5009 | M. p. 35–38 | | | N, 5.85 | 5.68 | 5.70 |
| 1,2-Dicarbethoxy-4-ethyl-3,5-dimethylpyrrole | 126–129 | 1 | 0.997 | 1.4973 | | | | N, 5.24 | 5.14 | 5.23 |
| 1-Carbethoxy-2-acetylpyrrole | 148–149 | 24 | 1.134 | 1.5073 | | | | N, 7.73 | 7.86 | |
| | 119–121 | 7 | | | | | | | | |
| 1-Carbethoxy-3-acetyl-2,4-dimethylpyrrole | 166–167 | 10.5 | 1.116 | 1.5168 | | | | N, 6.70 | 6.83 | |
| | 162–164 | 8 | | | | | | | | |
| 1,2-Dicarbethoxy-4-acetyl-3,5-dimethylpyrrole | 161–165 | 1 | | | M. p. 74–76 | | | N, 4.08 | 4.78 | 4.96 |
| 1-Benzoyl-2,4-dicarbethoxy-3,5-dimethyl-pyrrole | 191–195 | 1 | | | M. p. 74–75 | | | N, 4.08 | 4.00 | 4.05 |
| 1-Benzoyl-3-carbethoxy-2,4-dimethylpyrrole | 144–148 | 1 | | 1.5671 | M. p. 65–66 | | | N, 5.16 | 5.07 | 5.27 |
| 1-Trimethylacetyl-2,4-dicarbethoxy-3,5-dimethylpyrrole | 148–149 | 1 | | | M. p. 56–58 | | | N, 4.33 | 4.53 | 4.33 |
| 1-Ethyl-2,4-dicarbethoxy-3,5-dimethylpyrrole | 145–148 | 1 | | 1.5124 | M. p. 39–39.5 | | | N, 5.24 | 5.15 | 5.15 |
| 1-Ethyl-3-carbethoxy-2,4-dimethylpyrrole | 138–141 | 7 | 1.021 | 1.5034 | | | | N, 7.18 | 6.95 | {7.20 |
| 1,2,4,5-Tetramethyl-3-carbethoxypyrrole | 121–125 | | | | M. p. 72–73 | | | N, 7.18 | 7.23 | {6.95 |
| 1-Ethyl-2-carboxy-4-carbethoxy-3,5-dimethyl-pyrrole | | | | | M. p. 137 | | | | | |
| 1-Benzoylpyrrole[14] | 169–170 | 8 | | 1.5889 | | | | N, 8.00 | 7.85 | |
| Picrate of 1,2,3,4,5-pentamethylpyrrolidine | | | | | M. p. 192–193 dec. | | | N, 15.14 | | 15.25 |
| Picrate of 1-ethyl-2,3,4-trimethylpyrrolidine | | | | | M. p. 105–108 | | | N, 15.14 | | 15.40 |
| Picrate of 1-ethyl-2,3,5-trimethylpyrrolidine[13] | | | | | M. p. 135–138 | | | N, 15.14 | | 15.32 |
| Dinitrophenylhydrazone of 1-carbethoxy-2-acetylpyrrolidine | | | | | M. p. 102–104 | | | N, 19.3 | 19.9 | 20.0 |
| Dinitrophenylhydrazone of 1-carbethoxy-3-acetyl-2,4-dimethylpyrrolidine | | | | | M. p. 108–110 | | | N, 17.8 | | 17.5 |
| Picrate of 1-ethyl-2,4-dimethyl-3-carbethoxypyrrolidine | | | | | M. p. 110–112 | | | N, 13.08 | 13.23 | 13.48 |
| Hydrochloride of 1-ethyl-2,4-dimethyl-3-carbethoxypyrrolidine | | | | | M. p. 96–99 | | | Cl, 15.04 | 15.11 | |
| Hydrochloride of 1-ethyl-3-hydroxymethyl-2,4-dimethylpyrrolidine | | | | | M. p. 90–95 | | | Cl, 18.31 | 18.27 | |

[a] M and Z refer to neutral equivalent and active hydrogen by the Zerewitinoff method, respectively. All boiling and melting points are corrected for stem exposure. In three cases the refractive indices, reported at 25° for solids melting at higher temperatures, were determined in supercooled liquids.

analysis and formation of solid derivatives when feasible. Many of these data are given in Table II. Pyrrolidines boiling below 150° are partially carried over with the solvent so that in these cases the amines were separated as hydrochlorides and in most cases reconverted to the amines and fractionated along with the other products. Special procedures (keyed to the numbers in the first column of Table I) are briefly described below.

9. The product was not distilled but was crystallized from 70% ethanol.

10. The product (b. p. 151–156° at 7 mm.) was identified by a mixed melting point (75–76°) with an authentic sample.

13. The hydrogenation slowed up after an hour so the catalyst was replaced and the hydrogenation repeated.

(12) Von Braun and Beschke, *Ber.*, **39**, 4122 (1906).

(13) Ochiai and Tsudo, *ibid.*, **67**, 1013 (1934).

(14) Pictet, *ibid.*, **37**, 2797 (1904).

15. The ratio of ketone to alcohol was estimated by means of the refractive indices and by the comparison of the weight of 2,4-dinitrophenylhydrazone obtained from a sample of the mixture and from a sample of the pure ketone. The ketone (13 g.) was obtained distilling 138.5–140° (11 mm.) while the alcohol came over at 144–145° (11 mm.).

21. The basic and neutral compounds were separated from each other before fractionation. 3-Carbethoxy-2,4-dimethylpyrrole, b. p. 150–155° (7 mm.), was identified by a mixed melting point, 75–76°. 1-Ethyl-2,3,4-trimethylpyrrolidine was characterized by its neutral equivalent and nitrogen analysis. 1-Ethyl-3-carbethoxy-2,4-dimethylpyrrolidine gave a neut. equiv. of 198 (calcd. 199). The pyrrolidone fraction showed an analysis for carbon, hydrogen and nitrogen intermediate between the two compounds of formulas **XIX** and **XX**. Upon hydrogenation over copper chromite at 260° two moles of hydrogen (per average molecular weight) were taken up and a 40% yield of a mixture of pyrrolidines (b. p. 150–155°) was obtained which showed a neutral equivalent intermediate between the two pyrrolidines which would be produced by the hydrogenation of pyrrolidones of the structures **XIX** and **XX**.

22. The "carbethoxypyrrolidine" fraction boiled at 81–89° (7 mm.).

23. In order to obtain pure 1-ethyl-3-carbethoxy-2,4-dimethylpyrrolidine it was necessary to separate a small amount of a non-basic component in the fraction b. p. 86–89° (7 mm.).

24. The unchanged pyrrole in the residue from fractionation was obtained by crystallization from 70% ethanol.

25. 1-Ethyl-2-hydroxymethylpyrrolidine (b. p. 75–81° at 11 mm.) showed a neut. equiv. of 130 (calcd. 129) and its boiling point and refractive index were approximately in agreement with the values given by Signaigo.[1]


## Summary

It has been demonstrated in nine instances that the substitution of a carbethoxy group on the nitrogen of a pyrrole lowers the temperature required for the hydrogenation of the nucleus, thus making it possible to hydrogenate the pyrrole ring in preference to a carbonyl or carbethoxy group. This fact has made it possible to prepare five carbethoxy, two acetyl and three α-hydroxyethylpyrrolidines from acetyl or carbethoxy pyrroles. Methyl and ethyl groups on the nitrogen were relatively ineffective in lowering the temperature of hydrogenation of the ring. A benzoyl group on the nitrogen was in two of three cases so readily removed by hydrogenolysis that it was ineffective in facilitating the hydrogenation of the pyrrole nucleus.

In only one instance has it been possible to prepare a carbethoxypyrrolidine by the direct hydrogenation of a carbethoxypyrrole having a hydrogen on the nitrogen. In only one instance has it been possible to prepare a hydroxymethylpyrrolidine by the hydrogenation of a carbethoxypyrrole, the normal reaction being the reduction of the carbethoxy to a methyl group. The hydrogenation of a carbethoxy to a hydroxymethyl group in a pyrrolidine was carried out successfully.

Directions have been given for the preparation of a number of pyrroles, particularly those having a substituent on the nitrogen, and for the hydrolysis of N-carbethoxypyrrolidines.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[CONTRIBUTION FROM THE INSTITUTO DE FISIOLOGIA, FACULTAD DE MEDICINA, BUENOS AIRES]

# Acetylated Amides of Aldonic Acids

BY V. DEULOFEU AND E. RESTELLI DE LABRIOLA

Acetylated amides of aldonic acids were first prepared by Zemplén and Kiss,[1] who employed two different methods: (a) acetylation of the amide, (b) hydrolysis of the acetylated nitriles.

With the exception of the work of Miksic[2] in 1926 no other papers were published on those substances to this year, when almost simultaneously Hurd and Sowden,[3] Zemplén, Balassa and Gardonyi,[4] and Robbins and Upson[5] published their work on the preparation of the acetylated amides of aldonic acids. The first two groups of workers employed hydrolysis of the nitriles as a method of preparation; Robbins and Upson the acetylation of the amide with acetic anhydride and zinc chloride.

We were also engaged from the end of 1937 with the preparation of those substances by the acetylation of the amides with pyridine–acetic anhydride, a method that we have found very suitable for this work, as can be seen from our data in the experimental part, and in agreement with the findings of Robbins and Upson. Of course our work overlaps

(1) Zemplén and Kiss, *Ber.*, **60**, 165 (1925).

(2) Miksic, *Vestn. Kral. Ces. Spol. Nauk. Cl.*, II, 18 (1926); from *C. A.*, **23**, 2941 (1929).

(3) Hurd and Sowden, THIS JOURNAL, **60**, 235 (1938).

(4) Zemplén, Balassa and Gardonyi, *Ber.*, **71**, 768 (1938).

(5) Robbins and Upson, THIS JOURNAL, **60**, 1788 (1938).