# PSEUDOESTERS AND DERIVATIVES. XXII [1]. SYNTHESIS OF 5-HYDROXY-3-PYRROLIN-2-ONES AND 5-HYDROXYPYRROLIDIN-2-ONES BY AMMONOLYSIS OF 5-METHOXYFURAN-2 (5H)-ONES AND DERIVATIVES

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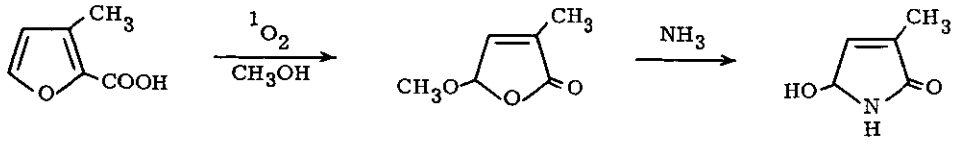
Abstract - The ammonolysis of 4-substituted 5-methoxyfuran-2(5H)-ones 4a-e under mild conditions affords the respective 5-hydroxy-3-pyrrolin-2-ones 5a-e. However, 4-dialkylamino derivatives 4f,g do not react with ammonia under the same conditions. Similar ammonolysis of furanone derivatives 7a,b, 10 and 13 yields the pyrrolidinones 8a,b and hexahydroisoindolones 11, and 14, respectively. The corresponding methoxylactams 6a-e, 9a-b and 12 are readily obtained by refluxing the hydroxylactams 5a-e, 8a,b and 11, respectively with acid-catalyzed methanol.

5-Alkoxyfuran-2(5H)-ones have proven to be versatile synthetic intermediates, suitable for the elaboration of other heterocyclic systems [2,3,4]. In a previous paper [5], we have reported the synthesis of 5-hydroxy-3-pyrrolin-2-one and some 3- and 5-substituted derivatives thereof by ammonolysis of the corresponding 5-methoxyfuran-2(5H)-one, readily available by sensitized photooxygenation of the appropriate furan derivative. Thus, the furanone 2, prepared in 90% yield by sensitized photooxygenation of 1, could be converted by ammonolysis into the 5-hydroxy-3-methyl-3-pyrrolin-2-one (3) in 65% yield. This was, as far as we know, the first synthesis of compound 3, which resulted to be identical to the (±)-jatropham, an antitumor alkaloid isolated

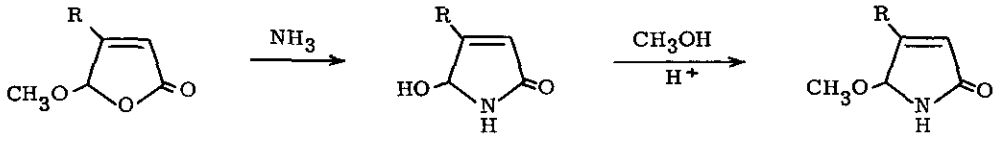



1 2 3

from Jatropha macrorhiza by Cole et al. [6], who proposed the structure 5a for the compound. However, Furukawa et al. in a recent work [7] revised this assignment and proposed for the structure of its isomer 3. Furthermore, Furukawa et al. [7] and Nagasaka et al. [8] have developed novel

alternative routes to 3 and 5a, which confirmed the revised structural assignment.

Because of the potential biological interest of pyrrolinones, it was the purpose of the present study to widen the scope of our ammonolysis reaction to other furanone derivatives, which could give rise to 4-substituted 5-hydroxy-3-pyrrolin-2-ones, 5-hydroxypyrrolidin-2-ones, and similar derivatives of hydrogenated isoindol-1-ones. In earlier parts of this series [3,9] we have reported the preparation of a number of 4-substituted 5-methoxyfuran-2(5H)-ones (4a-g). In the present work we have effected the ammonolysis on these substrates in order to prepare the corresponding pyrrolinones and to obtain information on the influence of electron-withdrawing and electron-releasing substituents in 4-position upon the reactivity of the substrates towards the ammonia.




| | a | b | c | d | e | f | g |
|---|---|---|---|---|---|---|---|
| R | $CH_3$ | Cl | Br | $OCH_3$ | $SCH_2Ph$ | $N(CH_2)_5$ | $N(CH_2)_4$ |

The ammonolysis of the 4-halogenated furanones 4b,c is effected by treatment with concentrated aqueous ammonia at 0°C using reaction periods not exceeding 30 min (Table I). Under these mild conditions, only the 4-halogenated pyrrolinones 5b,c can be isolated in moderate yields, but neither nucleophilic substitution of the halogen, nor addition to the double bond is observed.

Table I. Preparation and spectral data of 4-substituted 5-hydroxy-3-pyrrolin-2-ones

| Compd. No | Temp. °C | Time h. | Yield (%) | Mp °C | IR C=O | $^1$H-NMR NH[a] | H-3[b] | H-5 | OH[a] | Other signals |
|---|---|---|---|---|---|---|---|---|---|---|
| 5a | 22 | 1.0 | 72 | 157[c] | 1690 | 8.06 | 5.65 | 5.16 | d | 1.92 ($CH_3$) |
| 5b | 0 | 0.5 | 60 | 122[e] | 1680 | 8.66 | 6.28 | 5.44 | 5.60 | - |
| 5c | 0 | 0.5 | 62 | 135[e] | 1690<br>1670 | 8.66 | 6.42 | 5.46 | d | - |
| 5d | 22 | 3.5 | 68 | 163[f] | 1665 | 7.81 | 5.07 | 5.30 | 6.26[g] | 3.83 ($OCH_3$) |
| 5e | 22 | 5.0 | 70 | 164[e] | 1660<br>1630 | 8.35 | 5.89 | 5.49 | 6.48[h] | 4.28 ($CH_2$) 7.51 ($C_6H_5$) |

[a] Disappears in presence of $D_2O$. [b] Fine splitting by the NH proton which disappears in presence of $D_2O$. [c] Literature[4]: mp 154-157°C. [d] Not observed. [e] From ethyl acetate-light petroleum. [f] From ethyl acetate-methanol. [g] $J_{5,5'OH} = 8.5$. [h] $J_{1,5'OH} = 9.1$.

When the substituent R on the furanone is methyl, methoxy or benzylthio (4a, d, e), the ammonolysis proceeds readily at room temperature, and after 1-5 h affords the expected pyrrolinone 5a, d, e in good yield. However, the presence of a dialkylamino group in 4-position (4f, g) inhibits the ammonolysis, which does not take place at room temperature. Longer reaction periods (30 days), addition of methanol in order to enhance solubility, or heating to 50-60° C also failed to provide the desired products.

The presence of electron-releasing substituents conjugated with the enone system, diminishes the electrophilicity of the carbonyl, thus deactivating this carbon to nucleophiles; in fact, furanones 4d, e require longer reaction times and furanones 4f, g, which possess the strong electron-releasing 4-dialkylamino group, do not react at all [10].

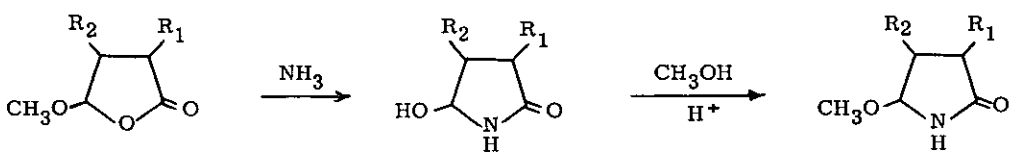
The above prepared hydroxypyrrolinones 5a-e, by refluxing with methanol and an acid catalyst, are readily converted into the corresponding 5-methoxy-3-pyrrolin-2-ones 6a-e (Table II). It is interesting to note that the halogenated pyrrolinones 6b, c react with oxygen, nitrogen and sulphur nucleophiles, thus facilitating the entry to other pyrrolinone derivatives [1].

Table II. Preparation and spectral data of 4-substituted 5-methoxy-3-pyrrolin-2-ones

| Compd. No | Yield (%) | Mp °C | IR | $^1$H-NMR | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | C=O | NH[a] | H-3[b] | H-5[b] | $OCH_3$ | Other signals |
| 6a | 70 | 83 | 1690 | 8.36 | 5.80 | 5.20 | 3.13 | 1.90 ($CH_3$) |
| 6b | 55 | 90[d] | 1730 | 8.77 | 6.40 | 5.48 | 3.24 | |
| 6c | 58 | 85[d] | 1700<br>1670 | 8.82 | 6.62 | 5.21 | 3.22 | |
| 6d | 65 | 107[c] | 1705<br>1678 | 7.90 | 5.10 | 5.25 | 3.15 | 3.78 ($OCH_3$) |
| 6e | 65 | 82[c] | 1685 | 8.38 | 5.94 | 5.36 | 3.12 | 4.22 ($CH_2$) 7.38 ($C_6H_5$) |

[a] Disappears in presence of $D_2O$. [b] Fine splitting by the NH proton which disappears in the presence of $D_2O$. [c] From ethyl acetate-light petroleum. [d] From light petroleum.

We have also examined the synthesis of pyrrolidinones by ammonolysis of the tetrahydrofuranones 7a, b, available by catalytic hydrogenation of the 5-methoxyfuran-2(5H)-ones [11]. The reaction also proceeds under mild conditions and the obtained hydroxypyrrolidinones 8a, b are converted into methoxypyrrolidinones 9a, b by refluxing with acid-catalyzed methanol.




7a, b 8a, b 9a, b

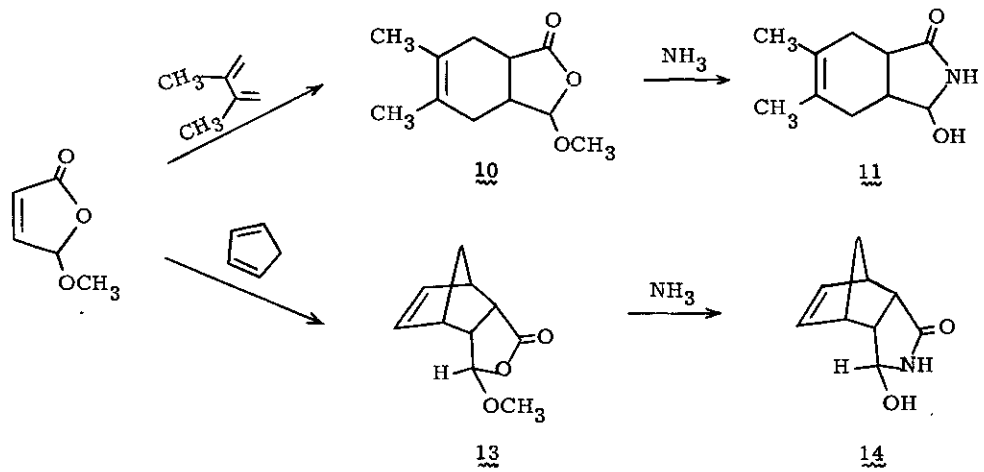
a: $R_1$ = H, $R_2$ = H; b: $R_1$ = $CH_3$, $R_2$ = H

Table III. Preparation and spectral data of 5-hydroxy- and 5-methoxypyrrolidin-2-ones

| Compd. No | Yield (%) | Mp °C | IR | $^1$H-NMR | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | C=O | NH[a] | H-3 | H-4 | H-5 | OH | $OCH_3$ | Other signals |
| 8a | 65 | 90[b] | 1660 | 8.15 | 2.40-1.50 | | 5.11[c] | 5.69[d] | | |
| 8b | 66 | liq[e] | 1680[f]<br>1660 | 8.17 | 2.40-1.60 | | 5.06[c] | 5.73 | | 1.04 ($CH_3$) |
| 9a | 60 | 52[g] | 1680 | 8.62 | 2.40-1.80 | | 5.0<br>4.8 | | 3.24 | |
| 9b | 60 | liq[e] | 1700[f] | 8.62 | 2.40-1.50 | | 4.9<br>4.7 | | 3.22<br>3.19 | 1.08 ($CH_3$) |

[a] Disappears in the presence of $D_2O$. [b] From acetone. [c] Fine splitting by NH proton which disappears in the presence of $D_2O$. [d] $J_{5,5'OH}$ = 6.7. [e] Mixture of diastereoisomers. [f] Film. [g] From ethyl acetate.

The ammonolysis also occurs in fused furanone systems of type 10 and 13, readily available by Diels-Alder reaction of simple dienes with 5-alkoxyfuran-2-(5H)-one [12,13,14]. The process may serve as an expedient entry to isoindole derivatives.




EXPERIMENTAL

Mps are uncorrected. All new compounds gave satisfactory microanalyses. IR spectra were recorded on a Perkin-Elmer model 257 grating spectrometer as nujol mulls, $\nu$ values in $cm^{-1}$. $^1$H-NMR spectra on a Varian EM-390 spectrometer, in DMSO-$d_6$ solutions (unless otherwise stated); signals are reported in $\delta$ units with TMS as internal standard. Silica gel Merck $F_{254}$ (layers 2 mm) and DC-Alufolien 60 $F_{254}$ were normally used for preparative and analytical t.l.c. Analytical g.l.c. was performed on a Perkin-Elmer F-11 model instrument (Reoplex 4% on Chromosorb G).

5-Hydroxy-3-pyrrolin-2-ones (5a-e) and 5-hydroxypyrrolidin-2-ones (8a,b):

General Procedure. - A mixture of the furanone 4 or 7 (10 mmol) and concentrated aqueous ammonia (25 ml) was stirred at room temperature until the starting material was consumed (disappearance of the furanone was monitored by g.l.c. or t.l.c.). Reaction times not longer than 30 min and cooling at 0° C are recommended for the ammonolysis of halogenated furanones 5b and 5c. The reaction mixture was concentrated under reduced pressure on a rotatory evaporator, the temperature not exceeding 40° C. Analytical samples were obtained by preparative t.l.c. or crystallization from the appropriate solvent.

5-Methoxy-3-pyrrolin-2-ones (6a-e) and 5-methoxypyrrolidin-2-ones (9a,b):

General Procedure. - A solution of the 5-hydroxy 3-pyrrolin-2-one (5) or 5-hydroxypyrrolidin--2-one (8) (2 mmol) in methanol (40 ml, containing 3-4 drops of concentrated hydrochloric acid) was heated under reflux for 15-20 min. The reaction mixture was neutralized with anhydrous sodium acetate. The methoxylactam was purified by crystallization or preparative t.l.c.

3-Methoxy-5,6-dimethyl 1,3,3a,4,7,7a-hexahydroisobenzofuran-1-one (10)

Prepared as described[12] for its 3-ethoxy analogue. A solution of 2,3-dimethyl-1,3-butadiene (20 mmol) and 5-methoxyfuran-2(5H)-one (10 mmol) in xylene (5 ml) was heated under reflux for 30 h. The solvent was removed and the residue distilled. Bp 136-140° C/4 mm; mp 30° C. IR: 1780, 1770 (C=O). $^1$H-NMR ($CDCl_3$): 1.66 (s, 6H, $CH_3$); 1.90-2.79 (m, 4H, C-4, C-7); 2.80-3.20 (m, 2H, C-3a, C-7a); 3.48 (s, 3H, $OCH_3$); 5.0 (s, 1H, C-3).

3-Hydroxy-5,6-dimethyl-1,3,3a,4,7,7a-hexahydroisoindol-1-one (11)

Ammonolysis of 10 following the general procedure (24 h at room temperature) afforded 11 in 65% yield. Recrystallized from ethyl acetate-light petroleum, mp 98° C. IR: 1680 (C=O). $^1$H-NMR: 1.58 (s, 6H, $CH_3$); 1.80-2.90 (m, 6H, C-3a, C-4, C-7, C-7a); 4.57 (s, fine splitting by coupling with NH proton which disappears in presence of $D_2O$, 1H, C-3); 6.28 (br s, 1H, OH); 8.12 (br s, 1H, NH).

3-Methoxy-5,6-dimethyl-1,3,3a,4,7,7a-hexahydroisoindol-1-one (12)

According to the general procedure hydroxylactam 11 was converted into 12 in 60% yield. Recrystallized from ethyl acetate-light petroleum mp 85° C. IR: 1720, 1685 (C=O). $^1$H-NMR: 1.57 (s, 6H, $CH_3$); 1.88-2.82 (m, 6H, C-3a, C-4, C-7, C-7a); 3.20 (s, 3H, $OCH_3$); 4.35 (s, fine splitting, 1H, C-3); 8.62 (br s, 1H, NH).

3-Methoxy-4,7-methano-1,3,3a,4,7,7a-hexahydroisobenzofuran-1-one (13)

Prepared as described[12] for its 3-ethoxy analogue. A mixture of freshly distilled cyclopentadiene (12 mmol) and 5-methoxyfuran-2(5H)-one (10 mmol) was kept 24 h at room temperature. The precipitate was recrystallized from light petroleum, mp 58-60° C. IR: 1760, 1750 (C=O). $^1$H-

NMR ($CCl_4$): 1.53 (m, 2H, $CH_2$); 2.53 - 3.30 (m, 4H, C-3a, C-4, C-7, C-7a); 3.38 (s, 3H, $OCH_3$); 4.71 (s, 1H, C-3); 6.21 (m, 2H, CH=CH).

3-Hydroxy-4,7-methano-1,3,3a,4,7,7a-hexahydroisoindol-1-one (14)

Ammonolysis of 13 following the general procedure (15 h at room temperature) afforded 14 in 70% yield[15]. Recrystallized from ethyl acetate, mp 173°C. IR: 1680, 1660 (C=O). $^1$H-NMR: 1.38 (m, 2H, $CH_2$); 2.8-3.2 (m, 4H, C-3a, C-4, C-7, C-7a); 4.42 (m, 1H, C-3); 5.67 (d, 1H, OH, J=7 Hz), 6.14 (m, 2H, CH=CH); 7.86 (br s, 1H, NH).

Analytical Data of New Compounds

| | | | | | | |
|---|---|---|---|---|---|---|
| 5b | Calc. for $C_4H_4O_2NCl$: | C, 36.0; | H, 3.0; | N, 10.5; | Cl, 26.5. | |
| | Found .....: | 35.7; | 3.0; | 10.4; | 26.2. | |
| 5c | Calc. for $C_4H_4O_2NBr$: | C, 27.0; | H, 2.2; | N, 7.9; | Br, 45.0. | |
| | Found .....: | 27.2; | 2.5; | 8.1; | 44.9. | |
| 5d | Calc. for $C_5H_7O_3N$ : | C, 46.5; | H, 5.5; | N, 10.8. | | |
| | Found ..... : | 46.4; | 5.4; | 10.7. | | |
| 5e | Calc. for $C_{11}H_{11}O_2NS$: | C, 59.7; | H, 5.0; | N, 6.3; | S, 14.5. | |
| | Found .....: | 59.5; | 4.9; | 6.5 | 14.7. | |
| 6a | Calc. for $C_6H_9O_2N$ : | C, 56.6; | H, 7.1; | N, 11.0. | | |
| | Found ..... : | 56.4 | 7.3 | 10.9. | | |
| 6b | Calc. for $C_5H_6O_2NCl$: | C, 40.7; | H, 4.2; | N, 9.5 | Cl, 24.0. | |
| | Found .....: | 40.8 | 4.2 | 9.5 | 24.2 | |
| 6c | Calc. for $C_5H_6O_2NBr$: | C, 31.2; | H, 3.1; | N, 7.3; | Br, 41.7. | |
| | Found .....: | 31.1 | 3.1 | 7.3 | 41.4. | |
| 6d | Calc. for $C_9H_9O_3N$ : | C, 50.3; | H, 6.3; | N, 9.8. | | |
| | Found .....: | 50.3 | 6.5 | 9.9. | | |
| 6e | Calc. for $C_{12}H_{13}O_2NS$: | C, 61.3; | H, 5.6; | N, 5.9; | S, 13.6. | |
| | Found .....: | 60.9 | 5.6 | 5.9 | 13.9. | |
| 8a | Calc. for $C_4H_7O_2N$ : | C, 47.5; | H, 7.0; | N, 13.9. | | |
| | Found .....: | 47.7 | 7.0 | 13.7. | | |
| 9a | Calc. for $C_5H_9O_2N$ : | C, 52.2; | H, 7.9; | N, 12.2. | | |
| | Found .....: | 52.0 | 8.1 | 12.0. | | |
| 10 | Calc. for $C_{10}H_{15}O_2N$: | C, 66.3; | H, 8.3; | N, 7.7. | | |
| | Found .....: | 66.1 | 8.2 | 8.0. | | |
| 12 | Calc. for $C_{11}H_{17}O_2N$: | C, 67.7; | H, 8.8; | N, 7.2. | | |
| | Found .....: | 67.6 | 8.8 | 7.1. | | |
| 13 | Calc. for $C_{10}H_{12}O_3$ : | C, 66.7; | H, 6.7. | | | |
| | Found .....: | 66.5 | 6.6. | | | |
| 14 | Calc. for $C_9H_{11}O_2N$ : | C, 65.5; | H, 6.7; | N, 8.5. | | |
| | Found .....: | 65.2 | 6.6 | 8.3. | | |

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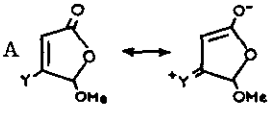
10. Consistent with this explanation is the observation that the UV spectra of dialkylaminofuranones 4f,g show a $\lambda_{max}$ ~ 277 nm ($\varepsilon$ = 25.000-29.000), indicating a greater contribution of ionic structure B (Y = $NR_2$) than in methoxyfuranone 4d [Y = OMe; $\lambda_{max}$ = 224 ($\varepsilon$ = 11.500)].

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14. The stereochemistry at C-3 of 10 was irrelevant in order to study the ammonolysys reaction and was not investigated. However, a detailed study of the $^1$H-NMR of 13 was consistent with the endo stereochemistry shown, with the MeO group placed on the convex face. The endo stereochemistry of 13 was additionally proven by hydrolysis and subsequent oxidation to afford the known endo-cis dicarboxylic acid (F. Fariña and T. Moore, unpublished results).
15. Compound 14 is also obtained by Diels-Alder cycloaddition of cyclopentadiene with 5-hydroxy-3-pyrrolin-2-one [11].

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