Polymethyl Derivatives of Furo[3,4-c]pyran-4-one, Furo[3,4-c]pyridin-4-one and Pyrrolo[3,4-c]pyran-4-one (1)

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The title compounds were prepared from Michael adducts, obtained from acetoacetic esters and *trans*-3-hexene-2,5-dione, and from the corresponding dehydration products, by direct cyclization to oxygen rings or by reaction with ammonia (or methylamine) to give nitrogen rings.

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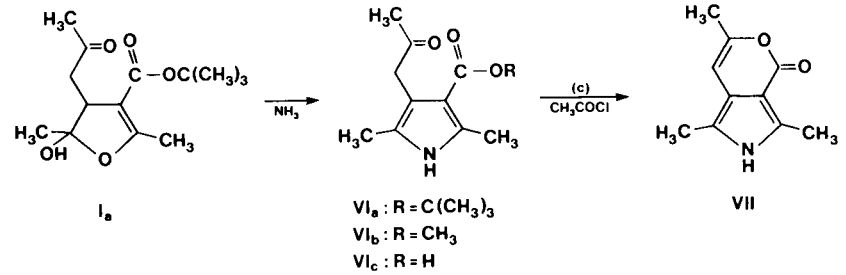
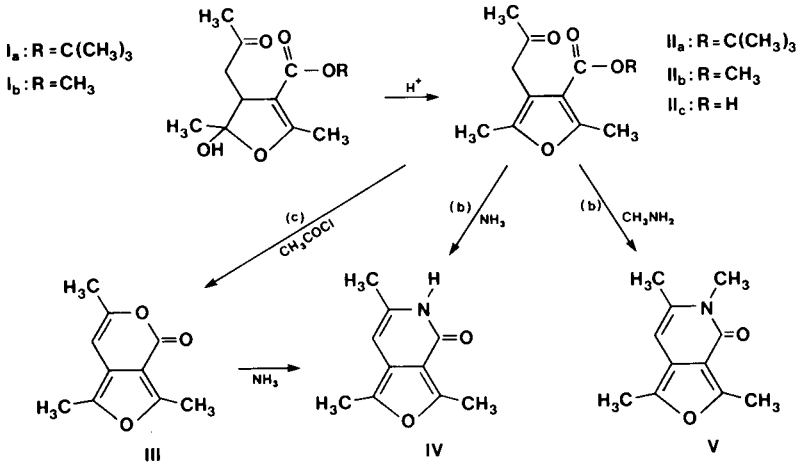
As we have shown in a previous paper (2), Michael addition of acetoacetic esters to *trans*-3-hexene-2,5-dione gave adducts with a cyclohemiacetal structure (I), which easily dehydrated to furan derivatives (II) by mild treatment with acid. We now wish to report on the utilization of these compounds as intermediates for the preparation of some bicyclic structures.

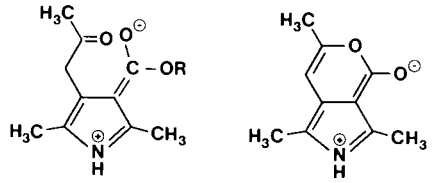
Treatment of the furan carboxylic acid (IIc) with an acyl chloride resulted in cyclization to the enol-lactone (III) (1,3,6-trimethyl-4*H*-furo[3,4-c]pyran-4-one); aqueous ammonia reacted with both the methyl ester (IIb) and the lactone (III) yielding the same bicyclic compound (IV) (1,3,6-trimethyl-4,5-dihydrofuro[3,4-c]pyridin-4-one). Similarly, methylamine reacted with IIb affording 1,3,5,6-tetramethyl-4,5-dihydrofuro[3,4-c]pyridin-4-one (V). Treatment with aqueous ammonia was tried directly on the dihydrofuran structures (I); whereas a very complex reaction mixture was formed from the methyl ester (Ib), a single reaction product was obtained from the *t*-butyl ester (Ia). This proved to be a pyrrole derivative (VIa) in which ammonia had displaced the ring oxygen of Ia with subsequent dehydration and aromatization.

Trifluoroacetic acid cleavage of the pyrrolic *t*-butyl ester (VIa) gave the free pyrrolecarboxylic acid (VIc), which was in turn dehydrated to the enol-lactone (VII) (1,3,6-trimethyl-4*H*-pyrrolo[3,4-c]pyran-4-one) by treatment with an acyl chloride. Diazomethane converted VIc to the methyl ester (VIb).

All efforts to convert the pyrrole derivatives (VI) and the pyrone (VII) to a pyrrolopyridone structure analogous to IV under a variety of conditions and using different reagents (ammonia, methylamine, sodium amide), were unsuccessful, possibly due to the poor electrophylic reactivity of the carboxylic carbonyl group caused by







VI VII

delocalization of the nitrogen electron pair.

This postulate is in agreement with the low carbonyl stretching frequencies in these structures (1640-1680 cm^{-1}). Activation of the carboxylic group was therefore attempted. Activation with dicyclohexyl carbodiimide in aqueous ammonia again resulted in no reaction, whereas activation through the *p*-nitrophenyl ester led to the enol-lactone (VII) directly.

To our knowledge, the four bicyclic compounds reported herein (III, IV, V, VII) are the first known examples of a [3,4-*c*] junction between a furan or pyrrole ring and a pyrone or pyridone ring (3). It is interesting to note their structural relationship to purine and xanthine bases, which might engender significant biological activity in these new structures.

EXPERIMENTAL

Elemental analyses were carried out with a Hewlett-Packard Model 185 C, H, N analyser. The melting points, determined with a Tottoli apparatus, were not corrected. Ir and nmr spectra were recorded with a Perkin-Elmer Model 257 and a Jeol C60-HL spectrometer. Unless otherwise indicated, nmr spectra were run in deuteriochloroform and ir spectra in a nujol mull. Chemical shifts were expressed in τ (s = singlet) and ir frequencies in cm^{-1}.

1,3,6-Trimethyl-4*H*-furo[3,4-*c*]pyran-4-one (III).

Compound IIc (1 g., 5.1 mmoles) was added to acetyl chloride (30 ml.), and the mixture was refluxed for 45 minutes. The excess chloride was distilled and the residue washed with petroleum ether, giving III, m.p. 97-100° (aqueous ethanol) (0.27 g., 30% yield); ir: 1760 (C=O), 1195 (C-O); nmr: 4.17 (s, signs of non-resolved allylic splitting, 1H, 7-H), 7.39 (s, 3H, 3-CH_3), 7.68 (s, 3H, 6-CH_3), 7.90 (s, 3H, 1-CH_3).

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.40; H, 5.66. Found: C, 66.99; H, 6.14.

1,3,6-Trimethyl-4*H*-pyrrolo[3,4-*c*]pyran-4-one (VII).

The same reaction as above converted VIc into VII, m.p. 203-206° (ethyl acetate) (38.5% yield); ir: 3150 (N-H), 1680 (C=O), 1175 (C-O); nmr (DMSO-d_6): -1.75 (broad, 1H, NH), 3.80 (s, signs of non-resolved allylic splitting, 1H, 7-H), 7.47 (s, 3H, 3-CH_3), 7.74 (s, 3H, 6-CH_3), 7.87 (s, 3H, 1-CH_3).

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.28; H, 6.40; N, 7.85.

1,3,6-Trimethyl-4,5-dihydrofuro[3,4-*c*]pyridin-4-one (IV).

A solution of IIb (0.8 g., 3.8 mmoles) in methanol (5 ml.) was added to aqueous ammonia (70 ml., 32%), and the mixture was left at 0° for 25 days. A crystalline product separated (IV), m.p. 185-188° (aqueous methanol) (0.4 g., 60% yield).

The same product was obtained by treating III with aqueous ammonia under the same experimental conditions (57% yield); ir: 3180 (N-H), 1665-1680 (C=O); nmr: 0.7 (broad, 1H, NH), 4.33 (s, signs of non-resolved allylic splitting 1H, 7-H), 7.35 (s, 3H, 3-CH_3), 7.67 (s, 3H, 6-CH_3), 7.89 (s, 3H, 1-CH_3).

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 68.05; H, 5.94; N, 7.89.

1,3,5,6-Tetramethyl-4,5-dihydrofuro[3,4-*c*]pyridin-4-one (V).

The same reaction as above using 35% aqueous methylamine instead of ammonia converted IIb into V, m.p. 156-158° (methanol) (43.5% yield); ir (potassium bromide disk): 1640 (C=O); nmr (hexadeuterioacetone): 4.08 (s, signs of non-resolved allylic splitting), 6.67 (s, 3H, 5-CH_3), 7.40 (s, 3H, 3-CH_3), 7.67 (s, 3H, 6-CH_3), 7.76 (s, 3H, 1-CH_3).

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.89; H, 6.89; N, 7.38.

2,5-Dimethyl-4-acetonylpyrrole-3-carboxylic Acid *t*-Butyl Ester (VIa).

A solution of Ia (3.5 g., 13 mmoles) in methanol (20 ml.) was added to aqueous ammonia (300 ml., 32%). The mixture was left at 0° for 20 days and then evaporated to dryness. The oily residue was crystallized from ethyl ether-petroleum ether giving VIa, m.p. 82-84° (petroleum ether) (2.1 g., 64.5% yield); ir: 3340 (N-H), 1705 (C=O ketone), 1675 (C=O ester), 1140 (C-O); nmr: 1.5 (broad, 1H, NH), 6.37 (s, 2H, CH_2), 7.70 (s, 3H, 2-CH_3), 7.92 (s, 3H, CH_3-CO), 8.03 (s, 3H, 5-CH_3), 8.52 (s, 9H, -$C(CH_3)_3$).

Anal. Calcd. for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57. Found: C, 67.02; H, 8.40; N, 5.75.

2,5-Dimethyl-4-acetonylpyrrole-3-carboxylic Acid (VIc).

Compound VIa (3 g., 12 mmoles) was dissolved in trifluoroacetic acid (12 ml.) and left at room temperature under nitrogen for 20 minutes. The *p*H was adjusted to 5 with an aqueous solution of sodium acetate (50%). A brown-yellow crystalline product, m.p. 178-182° (1.75 g., 75% yield) was obtained. Purification by crystallization was unsuccessful, and the analytical data refer to the crude product; ir: 3310 (N-H), 2550-2750 (COOH), 1710 (C=O ketone), 1670 (C=O carboxylic group); nmr (hexadeuterioacetone): -0.3 (broad, 1H, NH), 6.44 (s, 2H, CH_2), 7.65 (s, 3H, 2-CH_3), 8.00 (s, 6H, CH_3CO and 5-CH_3); the signal of the carboxylic proton is not visible.

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.08; H, 6.46; N, 6.88.

Since the product did not deliver carbon dioxide from sodium bicarbonate solution (4), its structure (VIc) was confirmed by a mass spectrum: m/e: 195(M^+), 152(M^+-$COCH_3$), 150(M^+-COOH), 134(M^+-CH_2COCH_3).

2,5-Dimethyl-4-acetonylpyrrole-3-carboxylic Acid Methyl Ester (VIb).

Reaction of VIc in methanol with ethereal diazomethane gave VIb, m.p. 92-94° (benzene-petroleum ether) (65% yield); ir: 3310 (N-H), 1710 (C=O, ketone), 1670 (C=O, ester), 1130 (C-O), nmr: 1.6 (broad, 1H, NH), 6.33 (s, 3H, OCH_3), 6.36 (s, 2H, CH_2), 7.65 (s, 3H, 2-CH_3), 7.86 (s, 3H, CH_3-CO), 7.98 (s, 3H, 5-CH_3).

Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.44; H, 7.60; N, 7.18.

Oxime of VIb.

The oxime derivative of VIb had m.p. 156-160° (ethyl ether); ir: 3280 (N-H and O-H), 1660 (C=O, ester), 1125 (C-O); nmr (hexadeuterioacetone): 0.1 (broad, 1H, NH), 0.7 (s, 1H, OH), 6.30 (s, 3H, OCH_3), 6.44 (s, 2H, CH_2), 7.60 (s, 3H, 2-CH_3), 7.92 (s, 3H, 5-CH_3), 8.28 (s, 3H, CH_3-C=N).

Anal. Calcd. for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 59.31; H, 6.77; N, 12.66.

Attempted Preparations of 1,3,6-Trimethyl-4,5-Dihydropyrrolo-[3,4-c]pyridin-4-one and its 5-Methyl Derivative.

Treatment of Ib with aqueous ammonia at 0° gave an inseparable mixture of products.

Treatment of VIb or VII with ammonia or methylamine solutions at 0° or at room temperature gave no reaction, the starting material being always recovered in high yields. More vigorous reaction conditions (sealed tube, 100-160°) led to inseparable mixtures, in which the starting material was still present.

Negative results were also obtained using sodium amide in benzene. Dicyclohexylcarbodiimide and VIc (molecular ratio 1:1) in methanolic solution were added to excess methanolic ammonia. The reaction mixture was left at 0° for 1 hour and then stirred at room temperature for 14 hours. A small amount of dicyclohexylurea was filtered off and the solution was evaporated giving the starting material (50% yield after crystallization). One mole of VIc was added to a solution of one mole of bis-(*p*-nitrophenyl)sulfite (5) in excess pyridine. The reaction mixture was left at 60° for 6 hours and then dry ammonia or methylamine was introduced; a yellow precipitate (*p*-nitrophenol) was filtered off. The solution was diluted with chloroform and washed with hydrochloric acid and sodium carbonate. The brown residue left after evaporation of the solvent was purified by crystallization with ethyl acetate and was found identical to VII (50% yield).

REFERENCES AND NOTES

(1) This work was carried out with the support of the Consiglio Nazionale delle Ricerche.

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