A_N-ADDITIONS TO 2,5-DIMETHOXY-2,5-DIHYDROFURANS, CONTAINING ELECTRON-ACCEPTING SUBSTITUENTS IN POSITION 3

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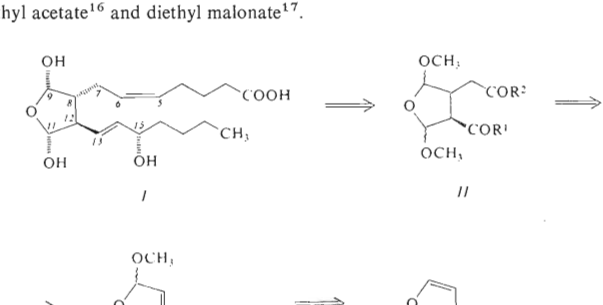
3-Acetyl-2,5-dimethoxy-2,5-dihydrofuran (*V*) was alkylated in position 4 with lithium dimethylcuprate and lithium dibutylcuprate. The reaction, proceeding with loss of methanol, afforded 4-acetyl-3-methyl-2-methoxy-2,3-dihydrofuran (*X*) and 4-acetyl-3-n-butyl-2-methoxy-2,3-dihydrofuran (*XI*), respectively. Addition of sodium salt of diethyl malonate gave 3-acetyl-4-bis(ethoxycarbonyl)methyl-2,5-dimethoxytetrahydrofuran (*XVII*) in 69% yield. Addition of methanol, n-butanol and tert-butyl alcohol to methyl 2,5-dimethoxy-2,5-dihydro-3-furoate (*VI*) in the presence of the corresponding alkoxides afforded the 4-alkoxy derivatives in 95%, 62% and 56% yield, respectively. Reaction of the compound *VI* with ethyl lithioacetate led to 3-ethoxycarbonylmethyl-4-methoxycarbonyl-2-methoxy-2,3-dihydrofuran (*XVI*) arising from the addition product by loss of methanol.

Synthetic analogues of prostaglandins[1-3] comprise *inter alia* compounds in which the cyclopentane ring is replaced by a heterocycle. One such possible structure is 10-oxaprostaglandin $F_{2\alpha}$ (*I*). Compounds of this type have not been hitherto studied; moreover, in the system mentioned the hydroxy groups at $C_{(9)}$ and $C_{(11)}$ are of the hemiacetal character. In application of these compounds at least partial equilibrium between the non-cyclic and cyclic hemiacetal forms should exist so that in the first approximation the configuration at these carbon atoms needs not to be considered.

The utilization of furan derivatives in the synthesis of compound *I* is shown in Scheme 1. The first retro-synthetic step corresponds in the synthetic direction to the acetal→hemiacetal conversion which for this type of compounds has already been described[4], and a strandard attachment of the side chains. The second step corresponding to nucleophilic addition of a two-carbon moiety to the α,β-unsaturated carbonyl compound *III*, is the subject of this communication. In the last step the furan derivatives *IV* are methoxylated; this problem has been already successfully solved[5]. Many addition reactions to five-membered unsaturated acetals of the 2,5-dialkoxy-2,5-dihydrofuran type have been described[6,7]; however, a C—C bond was created only in a preparatively interesting photochemical addition of acetaldehyde[8,9].

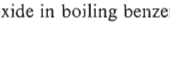
Already during synthesis of the model compounds, 3-acetyl-2,5-dimethoxy-

-2,5-dihydrofuran (*V*) and methyl 2,5-dimethoxy-2,5-dihydro-3-furoate (*VI*), we observed that these systems tend to add nucleophilic reagents such as sodium methoxide in methanol[5]. In this communication we discuss the results of attempted addition of alkoxides, organocuprates[10], ethyl diazo acetates[11–14], ethyl chloro acetate[15], ethyl acetate[16] and diethyl malonate[17].

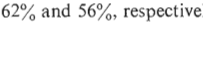


SCHEME 1

It was found[5] that the ester *VI* adds quantitatively methanol by mere standing of its methanolic solution at pH > 8 for 12 h (the product *VII* was isolated in 95% yield). Under identical conditions only 5% of ethanol were added and no reaction was observed with 2-propanol, *n*-butanol and tert-butyl alcohol. The reaction took place only with fivefold excess of sodium *n*-butoxide or two equivalents of potassium tert-butoxide in boiling benzene (yields 62% and 56%, respectively).



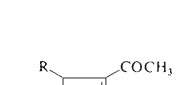
V, R = CH_3
VI, R = OCH_3



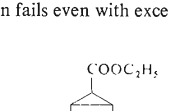
VII, R = CH_3 95 %
VIII, R = n-C_4H_9 62 %
IX, R = t-C_4H_9 56 %

In order to investigate 1,4-additions of alkyls the reaction of lithium dimethylcuprate[18–22] and lithium dibutylcuprate[23] with the ketone *V* was studied. The usual procedure[18,23] afforded the 4-acetyl-3-alkyl-2-methoxy-2,5-dihydrofurans *X* and *XI*.

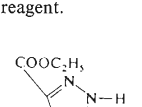
We assume that the reaction is a 1,4-addition of the organocuprate to the unsaturated conjugated system with subsequent stabilization by loss of methanol. This was proved by decomposition of the reaction mixture with perdeuteriomethanol which afforded the same products. This fact has been described and utilized for a double alkylation[24-26]. It was found empirically[27] that lithium dimethylcuprate adds only to α,β-unsaturated ketones with reduction potentials higher than −2·35 V. The value of −2·2 V, calculated for the enone *V*, is higher than the critical value and the compound therefore reacts; on the other hand, the value of −2·4 V for the enone *X* explains why the cuprate addition fails even with excess of the reagent.



X. R = CH_3 30 %.
XI. R = C_4H_9 24 %



XIII

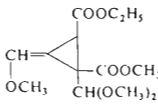


XIV

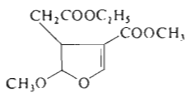
Because the yields were not satisfactory, we studied the reaction with complex cuprates. We tried magnesium ethyl-1-pentinylcuprate[28,29] and lithium butyl-1-pentinylcuprate[29], but we did not succeed in detection of the desired products.

Additions of ethyl diazo acetates, leading to formation of cyclopropane derivatives, are usually catalyzed with pure copper, copper alloys or copper complexes. Diazo acetate[30-32] was added to 2,5-dimethoxy-2,5-dihydrofuran (*XII*), synthesized by brominative methoxylation of furan[6]. The reaction was carried out under an inert gas with electrolytic copper powder, copper bronze or manganese acetylacetonate as catalysts, in boiling benzene, toluene or xylene, or without solvent. The reaction was followed by volumetric measurement of the liberated nitrogen or chromatographically. The aim of all these experiments was to reduce the amount of high-molecular compounds which were the main reaction products. Using a gas chromatograph – mass spectrometer we detected the expected product *XIII* but we did not succeed in its isolation. We isolated a product whose structure was in all probability *XIV*. The yield, related to the starting compound *XII*, was lower than 5%. Another route to three-membered ring system consists in Michael condensation of the ester *VI* with ethyl chloroacetate in the presence of sodium hydride and 18-crown-6 (ref.[15]). This reaction afforded in satisfactory yield the cyclopropyl derivative *XV*; we explain its formation by opening of the acetal ring which is stabilized by transformation into the exocyclic enol ether.

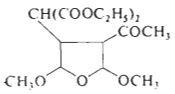
From the point of the planned synthesis, the addition of dialkyl cuprates, diazo acetate, or the Michael condensation gave no encouraging results, however, they lead to utilization of Michael addition of C-anions. We studied first the addition



XV



XVI



XVII

of the anion, formed *in situ* from ethyl acetate and lithium diisopropylamide in tetrahydrofuran at −78°C. The reaction product was isolated by distillation (74%) and identified as the dihydrofuran derivative *XVI*. This compound is again a product, stabilized by loss of methanol. It represents a suitable intermediate because it is an enol ether which on addition of water affords the desired derivative and, moreover, the activity of both the ester groups is differentiated: this fact is important for the stepwise introduction of both side chains. Another alternative is the addition of malonate ion, formed *in situ* from diethyl malonate and sodium hydride in tetrahydrofuran. Distillation afforded the product *XVII* which was obtained from the compound *V* in 69% yield.

EXPERIMENTAL

Melting and boiling points are uncorrected. Analytical samples were dried at 40 Pa for 12 h. The ^{1}H NMR spectra were taken on a Varian XL 100 (100 MHz) instrument in deuteriochloroform with tetramethylsilane as internal standard. The IR spectra were measured in tetrachloromethane on a Perkin–Elmer 325 spectrometer, mass spectra on a LKB Gas-chromatograph — mass spectrometer 9000. Tetrahydrofuran was dried by distillation from sodium and lithium aluminium hydride and stored above the same mixture with an indicator. Prior to use, the solvent was freshly distilled under dry argon or nitrogen. The commercial cuprous iodide was purified according to the described procedure[28,29] and dried at 100°C/50 Pa for 24 h. An ethereal solution of methyl lithium was prepared[26] and titrated[27] as described in the literature. Lithium dimethylcuprate[27] and lithium dibutylcuprate[30] were prepared according to the described procedures.

Methyl 2,4,5-Trimethoxytetrahydro-3-furoate (*VII*)

A solution of the ester *VI* (188 mg; 1 mmol) in methanol (10 ml) was adjusted to pH 8 with 1M sodium methoxide in methanol. After standing for 12 h, gaseous carbon dioxide was introduced into the mixture, which was then taken down *in vacuo* and distilled to give 210 mg (95%) of the ester *VII*, b.p. 135°C/1·5 kPa; reported[11] 130–145°C/1·6 kPa.

Methyl 4-n-Butoxy-2,5-dimethoxytetrahydro-3-furoate (*VIII*)

Sodium (115 mg) was added to a solution of the ester *VI* (188 mg; 1 mmol) in 1-butanol (20 ml) in an inert atmosphere. The mixture was kept at 100°C (steam bath) for 12 h, the volatile parts were evaporated *in vacuo* and the residue partitioned between water and ether (100 ml + 100 ml).

The ethereal layer was dried over anhydrous magnesium sulfate and taken down *in vacuo*, yielding 163 mg of chromatographically homogeneous product. For $C_{12}H_{22}O_6$ (262·3) calculated: 54·94% C, 8·45% H; found: 54·82% C, 8·56% H.

Methyl Tert-butoxy-2,5-dimethoxytetrahydro-3-furoate (*IX*)

A solution of the ester *VI* (188 mg; 1 mmol) and potassium tert-butoxide (224 mg; 2 mmol) in benzene (20 ml) was refluxed for 12 h. The mixture was diluted with benzene, washed with water (2 × 20 ml), dried over magnesium sulfate, taken down and the product isolated by gas–liquid chromatography (5% poly(butandiol succinate); Inerton, 180°C), yield 147 mg (56%). For $C_{12}H_{22}O_6$ (262·3) calculated: 54·94% C, 8·45% H; found: 54·92% C, 8·66% H.

4-Acetyl-3-methyl-2-methoxy-2,3-dihydrofuran (*X*)

A solution of methyl lithium in ether (1·4M; 20 ml) was added dropwise at −30°C under dry nitrogen to a suspension of cuprous iodide (1·9 g; 10 mmol) in ether (40 ml). After dissolution, the ketone *V* (1·74 g; 10 mmol) was added at −78°C, the mixture stirred for 15 min, decomposed with saturated solution of ammonium chloride (100 ml) and the aqueous layer extracted with ether (3 × 50 ml). The combined ethereal extracts were washed with saturated solution of sodium hydrogen carbonate, dried over sodium sulfate, taken down and the residue distilled, affording 0·5 g (30%) of the product *X*, b.p. 80–90°C/1·8 kPa. For $C_8H_{12}O_3$ (156·2) calculated: 61·52% C, 7·75% H; found: 61·66% C, 7·86% H. ^{1}H NMR spectrum: 1·15 (d, 3 H, CH_3); 2·15 (s, 3 H, CH_3CO); 2·92 (m, 1 H, H-3); 3·05–3·25 (m, 3 H, OCH_3); 4·97 (d, 1 H, H-2); 7·08 (s, 1 H, H-5). Mass spectrum *m/z* (%): 169 (16); 156 (55); 125 (31); 113 (35); 96 (58); 95 (25); 83 (24); 81 (41), 69 (16), 67 (44); 55 (28); 53 (7); 45 (20); 43 (100); 41 (45); 39 (55).

4-Acetyl-3-butyl-2-methoxy-2,3-dihydrofuran (*XI*)

A solution of butyl lithium in hexane (1·6M; 6·5 ml; 10 mmol) was added dropwise at −78°C under an inert gas to a slurry of cuprous iodide (0·9 g; 5 mmol) in tetrahydrofuran (24 ml). After stirring at −30°C for 1 h the mixture was cooled to −78°C and a solution of the ketone *V* (0·87 g; 5 mmol) in tetrahydrofuran (10 ml) was added dropwise. The mixture warmed spontaneously to 0°C and was worked up as described for the preparation of *X*. Distillation afforded 0·32 g (24%) of the product *XI*, b.p. 100°C/1·6 kPa. For $C_{11}H_{18}O_3$ (198·3) calculated: 66·62% C, 9·14% H; found: 66·53% C, 9·05% H. ^{1}H NMR spectrum: 1·75 (s, 3 H, CH_3); 2·24 (bs, 6 H, 3 × CH_2); 2·15 (s, 3 H, $COCH_3$); 2·86 (s, 1 H, H-3); 3·37 (s, 3 H, CH_3O); 5·05 (d, 1 H, H-2); 7·08 (2 × s, 1 H, H-5). IR spectrum (cm^{-1}): 613 m, 850 m, 952 w, 979 w, 1 220 w, 1 267 w, 1 380 m, 1 447 w, 1 458 w, 1 617 s, 1 663 s, 1 715 w, 1 865 m, 2 920 s, 2 970 s. Mass spectrum: 142 (77); 138 (29); 137 (40); 125 (40); 125 (46); 113 (27); 112 (46); 109 (43); 100 (36); 99 (34); 96 (20); 95 (74); 85 (29); 82 (26); 81 (71); 71 (46); 69 (26); 67 (34); 55 (54); 53 (16); 45 (57); 43 (83); 41 (100); 39 (89); 30 (94); 29 (34).

3-Ethoxycarbonyl-6-methoxy-5a,6-dihydro-4,5-diazacyclopentano[*c*]furan (*XII'*)

A mixture of 2,5-dimethoxy-2,5-dihydrofuran (1·8 g; 14 mmol), toluene (25 ml), ethyl diazoacetate (0·6 g; 5 mmol) and a trace of copper bronze was refluxed until the total amount of the liberated nitrogen was 110 ml. The mixture was filtered, taken down and subjected to preparative gas–liquid chromatography which afforded 53 mg (5%) of the product.

For $C_9H_{12}N_2O_4$ (212·2) calculated: 50·94% C, 5·70% H, 13·20% N; found: 51·02% C, 5·58% H, 13·12% N. ^{1}H NMR spectrum: 1·30 (t, 3 H, CH_3); 3·44 (s, 3 H, OCH_3); 4·28 (q, 2 H, CH_2—O); 6·42 (m, 2 H, H-5, H-6); 7·43 (s, 1 H, H-2); one exchangeable proton. Mass spectrum: 184 (9); 111 (100); 96 (8;95 (13); 55 (17); 53 (7); 52 (7); 51 (7); 53 (7); 41 (8); 39 (19).

2-Ethoxycarbonyl-1-methoxycarbonyl-1-dimethoxymethyl-3-methoxymethylenecyclopropane (*XV*)

A mixture of ethyl chloroacetate (1 g; 8 mmol), the ester *VI* (1·9 g; 10 mmol), sodium hydride (0·3 g of 80% dispersion in oil, 10 mmol), 18-crown-6 (0·2 g; 0·8 mmol) and tetrahydrofuran (10 ml) was stirred for 10 h, decomposed with methanol (1 ml) and taken down *in vacuo*. The residue was partitioned between water (100 ml) and 1,2-dichloroethane (100 ml). The aqueous layer was extracted with dichloroethane, the combined organic phases were washed with saturated sodium chloride solution and dried over magnesium sulfate. Evaporation and distillation gave 1·1 g (72%) of the product *XV*. For $C_{13}H_{20}O_7$ (288·3) calculated: 54·16% C, 6·99% H; found: 53·92% C, 7·04% H. ^{1}H NMR spectrum: 1·26 (t, 3 H, CH_3); 2·72 (m, 1 H, H-2); 3·3—3·8 (m, 12 H, OCH_3); 4·15 (q, 2 H, CH_2O); 4·9—5·11 (m, 1 H, $(OCH_3)_2$); 5·36—5·76 (m, 1 H, =CH—O).

3-Ethoxycarbonylmethyl-4-methoxycarbonyl-2-methoxy-2,3-dihydrofuran (*XVI*)

A solution of butyl lithium in hexane (1·6M, 12 ml; 19·2 mmol) was added dropwise at −78°C to a solution of diisopropylamine (1·94 g; 19·2 mmol) in tetrahydrofuran (20 ml) and after 30 min ethyl acetate (1·69 g; 1·88 ml; 19·2 mmol) in tetrahydrofuran (10 ml) was added under the same conditions. After 1 h a solution of the ester *VI* (2·82 g; 15 mmol) in tetrahydrofuran (10 ml) was slowly added dropwise. After 5 h the mixture was decomposed with an excess of saturated ammonium chloride solution (200 ml), extracted with chloroform (3 × 50 ml), dried over magnesium sulfate and taken down, yielding 2·68 g (74%) of the product *XVI*, b.p. 123°C/80 Pa. For $C_{11}H_{14}O_6$ (242·2) calculated: 54·54% C, 5·82% H; found: 54·76% C, 5·80% H. ^{1}H NMR spectrum: 1·25 (t, 3 H, CH_3); 2·22, 2·36, 2·74, 2·88 (AB system 2 H, CH_2CO); 3·23 (m, 1 H, H-3); 3·46 (s, 3 H, OCH_3); 3·70 (s, 3 H, $COOCH_3$); 4·12 (q, 2 H, CH_2—O); 5·35 (2 × s, 1 H, H-2); 7·23 (s, 1 H, H-5). IR spectrum: 850 m, 1 080 m, 1 097 s, 1 134 m, 1 176 m, 1 232 m, 1 252 m, 1 345 m, 1 370 m, 1 430 m, 1 628 s, 1 717 s, 1 739 s, 2 845 w, 2 910 w, 2 935 m, 2 950 m, 2 985.

3-Acetyl-4-bis(ethoxycarbonyl)methyl-2,5-dimethoxytetrahydrofuran (*XVII*)

A solution of diethyl malonate (5·16 g; 38 mmol) in tetrahydrofuran (15 ml) was added to a suspension of sodium hydride (1·03 g of 85% dispersion in mineral oil; 35 mmol) in tetrahydrofuran (35 ml). After addition, the ketone *V* (5 g; 29 mmol) was added under the same conditions. The mixture was stirred for 2 h, set aside overnight at room temperature, diluted with saturated sodium chloride solution (300 ml) and extracted with chloroform (3 × 100 ml). The combined organic extracts were dried over magnesium sulfate and taken down. Distillation of the residue afforded 6·7 g (69%) of the product *XVII*, b.p. 145°C/100 Pa. For $C_{15}H_{24}O_8$ (332·4) calculated: 54·21% C, 7·27% H; found: 54·17% C, 7·15% H. ^{1}H NMR spectrum: 1·27 (t, 3 H, CH_3); 2·26 (s, 3 H, CH_3CO); 3·05 (m, 1 H, H-4); 3·15 (m, 1 H, H-3); 3·21 (s, 3 H, OCH_3); 3·41 (s, 3 H, OCH_3); 4·19 (q, 2 H, CH_2—O); 4·93 (d, J_{45} = 2 Hz, 1 H, H-5); 5·20 (d, J_{23} = 3 Hz, 1 H, H-2). IR spectrum: 728 s, 910 s, 1 027 s, 1 097 s, 1 156 s, 1 177 m, 1 247 m, 1 303 m, 1 372 m; 1 447 m; 1 467 m, 1 615 w, 1 737 s, 1 754 s, 2 935 m, 2 935 m, 2 960 m, 2 990 m.

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