Carbohydrate Research, 134 (1984) 75–82
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

REACTIONS OF SUGAR NITRO-ALKENES WITH ACETOACETIC ESTERS*

ANTONIO GOMEZ SANCHEZ, MANUEL MANCERA**, FRANCISCO ROSADO,
Department of Organic Chemistry, Faculty of Pharmacy, University of Seville, and Institute of Fat and its Derivatives, C.S.I.C., Seville (Spain)

AND MANUEL RICO
Institute of Optics and State of Matter, C.S.I.C., Madrid (Spain)

(Received April 30th, 1984; accepted for publication, May 29th, 1984)

ABSTRACT

3,4,5,6,7-Penta-*O*-acetyl-1,2-dideoxy-1-nitro-D-*gluco*-hept-1-enitol reacts with methyl acetoacetate in an unusual Michael reaction, giving the normal adduct (**6**), and a bicyclic derivative (**9**) that arises from quasi-dimerization of the former when a high concentration of the base is used. Acetylation of compound **9** gives the hydroxylamine *O*-acetate (**10**).

From the reactions of 3,4,5,6,7-penta-*O*-acetyl-1,2-dideoxy-1-nitro-D-*galacto*-hept-1-enitol with ethyl and *tert*-butyl acetoacetate, the normal adducts (**7** and **8**) were isolated. The structures of compounds **6** to **10** were established on the basis of their spectral properties (u.v., i.r., mass, and ^{1}H- and ^{13}C-n.m.r.)

INTRODUCTION

The addition of a nucleophilic substituent to an α,β-unsaturated acyclic 1-nitroald-1-enitol can provide a way of introducing suitable functional groups into the β position of the nitroalkene. The compounds so obtained could be good starting-materials in the synthesis of heterocyclic glycosides and *N*- or *C*-glycosyl, or acyclic *C*-glycosyl, compounds.

The addition reactions of sugar nitro-alkenes with 3-aminocrotonic esters have proved to follow a complex pattern[2,3] in which pyrrole derivatives are formed, along with the normal, Michael adducts. A complex pathway was also observed[4] when studying the reaction of 1,3-dicarbonyl compounds with a model nitro-alkene (β-nitrostyrene). An abnormal product possessing a dimeric, 2,3-dihydro-2-

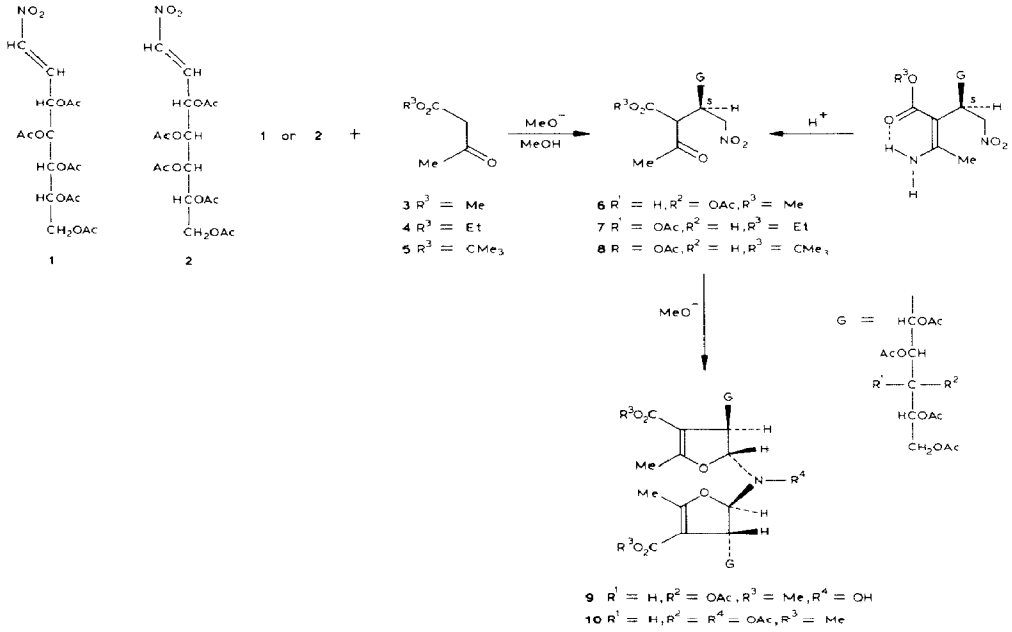
*Studies on Sugar Nitro-olefins, Part V. For Part IV, see ref. 1.
**To whom correspondence should be addressed, at Department of Organic Chemistry, Faculty of Pharmacy, Seville, Spain.

0008-6215/84/$ 03.00

(hydroxyamino)furan structure was isolated; this was readily transformed into a pyrrole derivative.

The addition reactions of some acetoacetic esters (**3, 4,** and **5**) with acyclic 1-nitrohept-**1**-enitols having the D-*gluco* and D-*galacto* configuration are now discussed. The formation of normal Michael adducts (**6, 7,** and **8**) and of "abnormal" compounds (**9** and **10**) is described, and their structure determined on the basis of their spectral properties (u.v., i.r., mass, and ^{1}H- and ^{13}C-n.m.r.).

The normal adducts (**6–8**) were identified as the compounds obtained by mild hydrolysis of the 3-aminocrotonate adducts previously described[1].



RESULTS AND DISCUSSION

3,4,5,6,7-Penta-*O*-acetyl-1,2-dideoxy-1-nitro-D-*gluco*-hept-1-enitol (**1**) reacted with an equimolecular proportion of the acetoacetic ester **3** in methanol containing sodium alkoxide, at room temperature, yielding the normal Michael adduct (**6**) and the abnormal, bicyclic derivative (**9**). Monitoring of the reaction by t.l.c. showed that the former was the main product when catalytic amounts of sodium alkoxide were used; it was isolated by column chromatography. When using an equimolar proportion of base, the reaction gave the abnormal derivative (**9**) as the major, crystalline compound, accompanied by formation of nitrite ion (positive Griess–Illosvay test[5]). Compound **9** was also formed when the isolated adduct (**6**) was treated with sodium methoxide in methanol. Acetylation of **9** with acetic anhydride–pyridine gave the acetate of the hydroxylamine **10**.

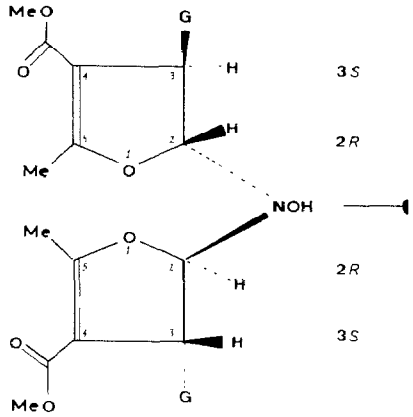
On the other hand, when 3,4,5,6,7-penta-*O*-acetyl-1,2-dideoxy-1-nitro-D-*galacto*-hept-1-enitol (**2**) was allowed to react with the β-keto esters **4** and **5** under the same conditions, only the normal adducts (**7** and **8**) could be isolated, regardless of the proportion of alkoxide used. A progressive increase in the proportion of base did, in fact, transform the adducts **7** and **8** into new compounds, but these could not be isolated, either by crystallization or chromatography.

Compounds **6, 7,** and **8** gave a positive reaction with $FeCl_3$, which is characteristic of α-substituted, β-keto esters[6]. Their structures were assigned on the basis of their elemental analyses and spectral data (u.v., i.r., and ^{1}H-n.m.r.). The u.v. spectra showed strong maxima at the same wavelengths as those observed for the starting β-keto esters[7] (λ_{max} ~255 nm). The i.r. spectra revealed a small proportion of the enol form; there were weak bands at 1640 and 1605 cm^{-1}, attributed to ν(C=O) of the chelated ester and ν(C=C), respectively. The ν(C=O) of the keto group appeared at 1715–1720 cm^{-1}, and that of the ester portion of the β-keto esters at 1745 cm^{-1}, overlapping the bands of the acetoxyl groups. In the ^{1}H-n.m.r. spectra, the ester group gave a singlet at δ 1.60; the CH_2NO_2 group, a two-proton multiplet (two double-doublets) at δ ~4.50–4.65; and the Me-C=O and OAc groups, a series of singlets at δ ~1.95–2.25. These compounds have a new chiral center at C-3 and therefore, four diastereoisomers are possible. However, these compounds can also be obtained by mild, acid hydrolysis of the adducts derived from 3-aminocrotonic esters and the nitro-alkenes **1** and **2**, and it was proved[1] that these adducts have the (*S*) chirality for C-3. As the chirality of this center should not be affected by the hydrolysis reaction, the same (*S*) chirality was assumed for this carbon atom in compounds **6–8**.

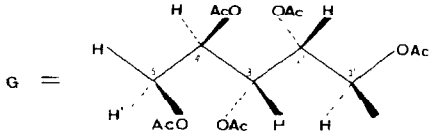
The molecular formulas of compounds **9** and **10** were deduced from the results of elemental analyses and mass spectrometry. Their structures followed from their spectral and chemical properties. The compounds maintained the β-alkoxy-substituted, α,β-unsaturated ester arrangement, as indicated by the u.v. and i.r. spectra, which were analogous to those of the normal adducts. The ^{1}H- and ^{13}C-n.m.r. spectra provided evidence of two, equivalent O-C(Me)=C($COCH_3$)CHCH structures. The two methyl groups attached to the alkenic carbon bonds appeared as a doublet at δ 2.19–2.22 (J 1.0 Hz) in the ^{1}H-n.m.r. spectra, and a quartet at δ 14.00 in the ^{13}C-n.m.r. spectra, and the OMe groups at δ 3.62–3.64 and 51.03, respectively. The singlet at δ 164.90 can be attributed to C-5, and that at somewhat lower field, δ 101.86, to C-4. The H-2 and H-3 signals appeared as a doublet at δ 5.58 ($J_{2,3}$ 3.8 Hz) and a double quartet at δ 3.38–3.39 ($J_{2,3}$ 3.8, $J_{3,1'}$ 1.2, $J_{3,Me\text{-}5}$ 1.0 Hz). The small value of $J_{2,3}$ seems to indicate a *trans* disposition[8]. The presence of the N-OH group in compound **9** was suggested by the bands at 3565, 3460, and 3265 cm^{-1}, due to free, intramolecularly and intermolecularly bonded ν(OH). For compound **10**, these bands disappeared and, instead, a strong C=O absorption at high frequency was shown. In the ^{1}H-n.m.r. spectra, the N-OH was identified as a one-proton signal at δ 7.29 that disappeared on addition of D_2O to the samples. The 2,3-dihydro-2-(hydroxyamino)furan structures were indicated by the high δ values of C-2

(δ 91.75) and H-2 (δ 5.58, J 3.8), in accordance with an O-CHN moiety. In the i.r. spectra, certain bands in the region of 1000–900 cm^{-1} can be attributed to furan-ring vibrations.

The aforementioned results suggested the existence in the molecule of a symmetry element containing the NOH group. The possibility of a symmetry plane can be rejected, because the compounds are optically active, and because the two G groups have the D-*gluco* configuration, so that they cannot be mirror images. The molecules should possess C_2 symmetry, as indicated in formula **11**.



11



The conformation of the alditol chain was deduced on the basis of the first-order coupling-constants[9,10] of the protons. A sickle conformation was inferred, in which H-1′ and H-2′, and H-4′ and H-5′, are in *anti*-periplanar and *gauche* arrangements, respectively.

The final configuration of the molecule (2*R*,3*S*,2*R*,3*S*) was proposed after taking into account the assumptions that the quasi-dimerization process should not affect the chirality of C-3, and that H-2 and H-3 are *trans*-disposed.

EXPERIMENTAL

General methods. — Optical rotations wee measured with a Perkin–Elmer 141 polarimeter. Thin-layer chromatography (t.l.c.) was conducted on plates

coated with silica gel HF_{254} (Merck) with the solvent indicated for each compound, and detection was achieved with 1:1 sulfuric acid–water or iodine vapor. Column chromatography was performed on silica gel 60 (Merck, 70–230 mesh). Solutions were evaporated *in vacuo* at temperatures below 40°. U.v. spectra were recorded with a Beckman DBGT spectrophotometer, and i.r. spectra, with a Perkin–Elmer 457 spectrophotometer. ^{1}H-N.m.r. spectra were recorded at 60 or 90 MHz with a Perkin–Elmer R-12B or R-32 spectrometer, and ^{13}C-n.m.r. spectra at 25.2 MHz with a Varian XL-100-15 spectrometer operated in the pulsed, Fourier-transform mode. Mass spectra were recorded with a Hitachi–Perkin–Elmer RMU-6M instrument.

*Reaction of 3,4,5,6,7-penta-*O*-acetyl-1,2-dideoxy-1-nitro-*D-gluco- *and* D-galacto-*hept-1-enitol* (**1** *and* **2**) *with β-dicarbonyl compounds* **3**, **4**, *and* **5**. — *A. Formation of the adducts* **6**–**8**. Nitro-alkene **1** (2.16 g, 5 mmol) was added to a solution of methyl acetoacetate (0.58 g, 5 mmol) in methanol (5 mL). The mixture was treated with catalytic amounts of 0.7M sodium methoxide in methanol, and stirred at room temperature. T.l.c. with 10:1 diethyl ether–hexane indicated the formation of adduct **6** (R_F 0.36, major product) and a second product having R_F 0.22. The solution was treated with Amberlite IR-120 (H^+) resin, the suspension filtered, and the filtrate evaporated, to yield a residue which was chromatographed on silica gel using 7:1 diethyl ether–hexane as the eluant. Evaporation of fractions containing the component of R_F 0.36 gave pure compound **6** (18%); amorphous; $[\alpha]^{24}_{5461}$ +113.3° (*c* 0.6, $CHCl_3$); λ^{EtOH}_{max} 254 nm (log ε 3.73); ν^{KBr}_{max} 1750 (CO_2Me and OAc), 1715 (C=O), and 1555 cm^{-1} (NO_2); δ ($CDCl_3$) 1.90, 1.98, 2.01, 2.05, 2.07, 2.11 (6 s, total intensity 18 H, :C-Me and OAc), 3.10–3.42 (m, 2 H, H-3,4), 3.64 (s, 3 H, CO_2Me), 3.95 (dd, 1 H, H-5″), 4.05 (dd, 1 H, H-5′), 4.78 (dd, 1 H, CH_aNO_2), 4.82 (dd, 1 H, CH_bNO_2), and 5.10–5.60 (m, 4 H, H-1′,2′,3′,4′).

Anal. Calc. for $C_{22}H_{31}NO_{15}$: C, 48.08; H, 5.68; N, 2.54. Found: C, 48.35; H, 5.85; N, 2.18.

Addition compounds **7** and **8** arising from **2** were obtained in the same way. Adduct **7** was isolated as an amorphous solid that crystallized by treatment with diethyl ether–hexane; yield 68%; R_F 0.53 (7:1 diethyl ether–hexane); m.p. 86–88°; λ^{EtOH}_{max} 252 nm (log ε 3.35); ν^{KBr}_{max} 1740 (CO_2Et and OAc), 1714 (C=O), and 1560 cm^{-1} (NO_2); δ ($CDCl_3$) 1.23 (t, 3 H, CO_2Et), 1.96, 2.01, 2.03, 2.07, 2.09, 2.15 (6 s, total intensity 18 H, :C-Me and OAc), 3.16–3.20 (m, 2 H, H-3,4), 3.80 (dd, 1 H, H-5″), 3.90 (dd, 1 H, H-5′), 4.16 (q, 2 H, CO_2Et), 4,60 (dd, 1 H, CH_aNO_2), 4.75 (dd, 1 H, CH_bNO_2), and 5.20–5.40 (m, 4 H, H-1′,2′,3′,4′).

Anal. Calc. for $C_{23}H_{33}NO_{15}$: C, 49.02; H, 5.90; N, 2.49. Found: C, 48.68; H, 6.11; N, 2.83.

Adduct **8** crystallized on refrigeration of the reaction mixture (yield, 60%); R_F 0.69 (7:1 diethyl ether–hexane); m.p. 152–154° (from ethanol); $[\alpha]^{24}_{5461}$ +40° (*c* 0.5, $CHCl_3$); λ^{EtOH}_{max} 255 nm (log ε 3.24); ν^{KBr}_{max} 1745 (CO_2CMe_3 and OAc), 1725 (C=O), and 1560 cm^{-1} (NO_2); δ ($CDCl_3$) 1.57 (s, 9 H, CO_2CMe_3), 1.96, 2.00, 2.02, 2.04, 2.08, 2.10 (6 s, total intensity 18 H, :C-Me and OAc), 3.10–3.23 (m, 2 H,

TABLE I

^{1}H- AND ^{13}C-N M R -SPECTRAL DATA[a] FOR COMPOUNDS **9** AND **10**

^{1}H-N.m.r. spectra Compound	*H-1'*	*H-2'*	*H-3'*	*H-4'*	*H-5'*	*H-5''*	*H-2*	*H-3*	*OMe*	*OAc*	*:C-Me*	*N-OH (N-OAc)*
9	5.51dd	5.52d	5.33d	5.02d	4.20dd	3.91dd	5.58d	3.39dq	3.64s	2.17	2.19d	7.29s
	$J_{1',2'}$ 7.6	$J_{2',3'}$ 2.1	$J_{3',4'}$ 8.5	$J_{4',5'}$ 2.9	$J_{5',5''}$ 12.5		$J_{2,3}$ 3.8	$J_{1',3}$ 1.2		1.96 1.95 1.91 1.88	$J_{3\text{-Me}(5)}$ 1.0	
				$J_{4',5''}$ 5.4								
10	5.50dd	5.52d	5.30d	5 03d	4.22dd	3 88dd	5.57d	3.39dq	3.62s	2.18	2.22d	2.08s
	$J_{1',2'}$ 7.6	$J_{2',3'}$ 2.1	$J_{3',4'}$ 8.5	$J_{4',5'}$ 2.9	$J_{5',5'}$ 12.5		$J_{2,3}$ 3.8	$J_{1',3}$ 1.2		1.96 1.94 1.90 1.87	$J_{3\text{-Me}(5)}$ 1.0	
				$J_{4',5''}$ 5.4								

^{13}C-N.m.r. spectra	*C-1'*	*C-2'*	*C-3'*	*C-4'*	*C-5'*			
9	69.89d	69.32d	68.64d	68.30d	61.71t			
	—							
	OAc-1'	*OAc-2'*	*OAc-3'*	*OAc-4'*	*OAc-5'*			
	20.89q	20.59q	20.59q	20.59q	20.42q			
	170.70s	170.70s	170.01s	169.90s	169.56s			
	C-2	*C-3*	*C-4*	*C-5*	*C=O(4)*		*OMe(4)*	*Me(5)*
	91.75d	47.40d	101.86s	164.90s(168.48s)	168.48s(164.90s)		51.03q	14.00q

[a]Values of δ in p.p.m. from tetramethylsilane.

H-3,4), 3.71 (dd, 1 H, H-5″), 4.21 (dd, 1 H, H-5′), 4.41 (dd, 1 H, CH_aNO_2), 4.52 (dd, 1 H, CH_bNO_2), and 5.21–5.40 (m, 4 H, H-1′,2′,3′,4′).

Anal. Calc. for $C_{25}H_{37}NO_{15}$: C, 50.75; H, 6.30; N, 2.36. Found: C, 50.82; H, 6.20; N, 2.13.

B. Formation of the unusual Michael product (**9**). — Compound **1** (5 mmol) was added to a stirred solution of methyl acetoacetate (5 mmol) in methanol (5 mL) containing an equimolar amount of sodium methoxide (0.27 g). After 4 h, t.l.c. in 10:1 diethyl ether–hexane showed the presence of compounds **9** (R_F 0.20, major product) and **6**. The mixture was made neutral with Amberlite IR-120 (H^+) resin, and then evaporated under diminished pressure, to give a syrup which was partitioned by column chromatography with 7:1 diethyl ether–hexane. Evaporation of the fractions containing **9** yielded this product (54%); recrystallized from diethyl ether–hexane, it had m.p. 157–159°, $[\alpha]_{5461}^{24}$ +168.4° (*c* 0.95, $CHCl_3$); λ_{max}^{EtOH} 248 nm (log ε 4.02); ν_{max}^{KBr} 3460 (OH), 1750 (CO_2Me and OAc), 1712 (C=O), and 1650 cm^{-1} (C=C). For ^1H- and ^{13}C-n.m.r.-spectral data, see Table I.

Anal. Calc. for $C_{44}H_{59}NO_{27}$: C, 51.10; H, 5.76; N, 1.36. Found: C, 51.44; H, 5.83; N, 1.66.

Acetylation of compound **9**. — A sample of compound **9** (0.24 g, 0.25 mmol) in pyridine (2.5 mL) was treated with acetic anhydride (1.2 mL) for 24 h. The resulting solution was poured into ice–water (20 mL). Compound **10** afforded a gummy precipitate which was extracted with chloroform; the chloroform extract was successively washed with dilute sulfuric acid, 5% sodium hydrogencarbonate, and water, dried ($MgSO_4$), and evaporated, to yield a solid (85%); m.p. 88–90° (from methanol–water); R_F 0.30 (7:1 diethyl ether–hexane); λ_{max}^{EtOH} 245 nm (log ε 4.02); ν_{max}^{KBr} 1770–1755 (CO_2Me and OAc), 1709 (C=O), and 1646 cm^{-1} (C=C). For ^1H- and ^{13}C-n.m.r.-spectral data, see Table I.

Anal. Calc. for $C_{46}H_{61}NO_{28}$: C, 51.34; H, 5.72; N, 1.30. Found: C, 51.39; H, 5.74; N, 1.35.

Conversion of adduct **6** *into compound* **9**. — Sodium methoxide (0.7M) in methanol (2 mL) was gradually added to a stirred suspension of compound **6** (0.5 g) in dry methanol (5 mL), and stirring was continued until t.l.c. indicated no further transformation. Concentration of the mixture gave compound **9**, identical (m.p. and mixed m.p., R_F, and i.r. spectra) with the sample prepared as already described.

ACKNOWLEDGMENT

This work was supported by a grant from the C.A.I.C.T. of the Ministry of Education and Science of Spain.

REFERENCES

1 A. Gomez sanchez M. Mancera, F. Rosado, and J. Bellanato, *Carbohydr. Res.*, 134 (1984) 63–74.

2 A. Gomez Sanchez, M. Mancera, F. Rosado, and J. Bellanato, *J. Chem. Soc., Perkin Trans. 1*, (1980) 1199–1205.

3 A GOMEZ SANCHEZ, M MANCERA, F. J CABALLERO, AND J BELLANATO, *An Quím* , 79 (1983) 175–183
4 A. GOMEZ SANCHEZ, B M STIEFEL, R F FERNANDEZ, C. PASCUAL AND J. BELLANATO, *J. Chem. Soc , Perkin Trans. 1*, (1982) 441–447.
5 A. I. VOGEL, *Química Analítica Cualitativa*, 5th edn., Kapelusz S. A., Buenos Aires, 1974, p. 264
6 I. SMITH, in W. HEINEMANN (Ed.), *Chromatographic and Electrophoretic Techniques*, Vol. 1. Medical Books, London, 1969.
7 A. E. GILLAM AND E S STERN, *An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry*, 2nd edn., Arnold, London, 1957, p. 257
8 J. BADIN AND G DESCOTES, *Bull Soc Chim. Fr* , (1970) 1949–1951; C BOTTEGHI, G. CONSIGLIO, G CECCARELLI, AND A STEFANI, *J Org Chem.*, 37 (1972) 1835–1837.
9 M. BLANC-MUESSER, J. DEFAYE, AND D. HORTON, *Carbohydr. Res* , 87 (1980) 71–86.
10 F GARCIA GONZALEZ, M. GOMEZ GUILLEN, J. A. GALBIS PEREZ, P ARECES BRAVO, AND E. ROMAN GALAN, *An Quím* , 76 C (1980) 130–135