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STUDIES ON STRUCTURALLY SIMPLE BUTENOLIDES. V. REACTIONS OF PROTOANEMONIN WITH PIPERIDINE AND C-NUCLEOPHILES. A GENERAL APPROACH TO ITS BEHAVIOUR AS ELECTROPHILIC ACCEPTOR

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Abstract.- Reaction of protoanemonin, 1, with piperidine, dimethyl malonate anion, and lithium dimethyl- and dibutylcuprates are reported. Thus, while in the first case almost no regioselectivity is observed, in the other cases the obtained products are the result of nucleophilic attack to the exocyclic C-C double bond of 1 exclusively, giving the 1,6-adduct in the first step of the reaction. These adducts can evolve, with participation of unreacted protoanemonin in the reaction conditions, to polycyclic compounds, through 1,6-addition, alkylation and intramolecular Michael addition processes. Constitution of the compounds obtained have been assigned on the basis of spectral characteristics and mechanistic approaches. The behaviour of 1 in front of nucleophiles has been rationalized and generalized by means of experimental results and theoretical calculations.

INTRODUCTION

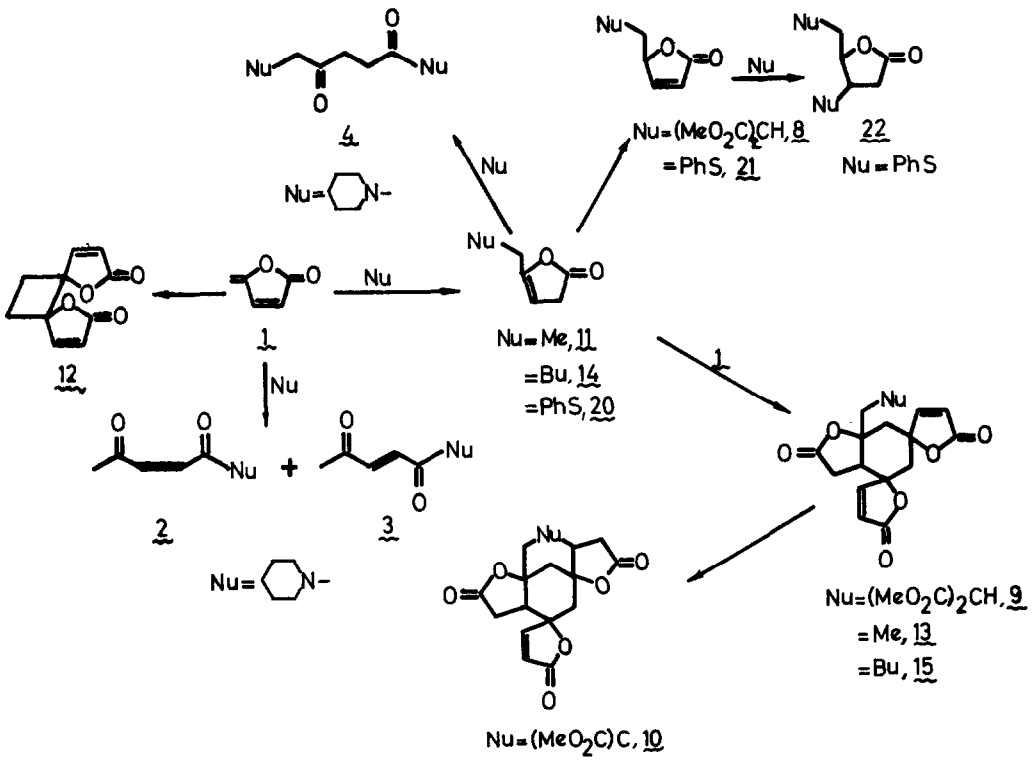
Protoanemonin, 5-methylene-5H-furan-2-one, 1, is a well known antibacterial principle released by maceration of the plant tissue of *Anemona pulsatilla L.* and several other *Ranunculaceae*[1]. However, aside from its tendency to give a hard polymer from which a dimer, anemonin, can be isolated, very little is known about its reactivity. Yet protoanemonin shows an interesting ambident electrophile behaviour that has been explored by us in front of S- and O-nucleophiles and reported in recent papers[2]. We now present the addition reactions of N- and C-nucleophiles to 1. The results of these experiments altogether, obtained over a wide range of nucleophiles, allow us to generalize and rationalize the behaviour of protoanemonin in these processes on the basis of experimental data and theoretical calculations using Klopman's equation in a quantitative sense.

RESULTS

Reaction of protoanemonin, 1, with piperidine. Piperidine was chosen as a model of N-nucleophiles, because of its acceptable nucleophilicity, its weak basicity and its nature of secondary amine, important to avoid further evolution of the adducts formed.

Reaction of 1 with piperidine was carried out under the conditions detailed in Table 1, leading in all cases to a mixture of the following compounds: the piperidine amides of *cis*-acetylacrylic and *trans*-acetylacrylic acids, 2 and 3 respectively, and the piperidine amide of 5-(N-piperidyl)-4-oxopentanoic acid, 4 (Scheme 1). Obviously, the first two products are the result of the direct amine addition to the protoanemonin carbonyl, with subsequent ring opening, while the amide 4 comes from an initial 1,6-conjugate addition followed by attack of a second mole of amine to the carbonyl. Total yields are between 51 and 61%. The 1,6-addition was favoured at higher temperatures,

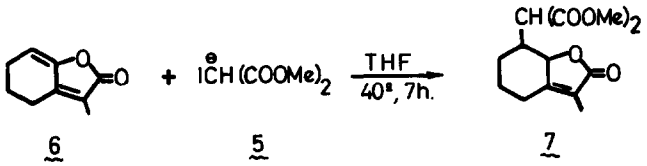
as it can be deduced from Table 1, comparing the molar percentage for the adduct 4: 77% at room temperature and 53-59% at 0°C. Thus, the regioselectivity increases with the temperature.



Scheme 1

Reactions of protoanemonin, 1, with C-nucleophiles. Up to date, there is only one reported example on the reactivity of protoanemin, 1, with carbanions. Inubushi and coworkers[3] have made 1 to react with 2-methyl-1,3-cyclopentanedione anion, obtaining the 1,6-adduct in 14% yield. We tried for our studies the dimethyl malonate anion and dialkylcuprates, as representative models of two different kinds of soft C-nucleophiles. The cyanide anion, also tried as a particular type of ambident nucleophile, gave no definite products.

i) Reaction with dimethyl malonate sodium salt, 5. Reactions were carried out under the conditions shown on Table 1. R. Scheffold[4] had reported the reaction of the unsaturated lactone 6 with 5, giving the 1,6-adduct 7 in 42% yield (Scheme 2). Nevertheless, reaction of protoanemonin, 1, with 5 under the same conditions (entry 4) afforded a very complex mixture in which only one definite product, later identified as 10, was detected.



Scheme 2

The total yields in isolated and identified products were very low when sodium methoxide was used to generate the malonate anion 5 (Table 1, entries 4 and 5). Since the ability of the pair MeO^-/MeOH to add to protoanemonin had been demonstrated[2b], we associated its presence in the reaction medium with the poor yields obtained. Then, in order to avoid undesirable reactions, we used sodium hydride as a base. Working with 1 eq of malonate and 1 eq of NaH, the cycloadducts 9 and 10 were obtained in higher yield (entry 6), in about the same molar ratios. On the other hand, when

two equivalents of malonate were used for 1 eq of NaH (entry 7), the total yield increased twofold, giving a mixture of 9 and 10, in which 9 (m.p. 169-170°), was the major component. Longer reaction times favoured the formation of 10, m.p. 244-245° in the same conditions (entry 8).

Finally, when the reaction was performed using 1 eq of NaH and 20 eq of malonate, the total yield decreased, 10 was only detected as a trace and the 1,6-adduct 8 was obtained for the first time, although only in 1% yield (entry 9).

Identification of compounds 8, 9 and 10 was made on the basis of mechanistic considerations, spectral characteristics and by analogy to the structure of adduct 13 elucidated through X-ray diffraction analysis[5], since 9 and 10 gave, under repeated recrystallizations, crystals unsuitable for X-ray studies.

ii) Reaction with lithium dialkylcuprates. Reaction of protoanemonin, 1, with 1 eq of Me_2CuLi at 0°C afforded 4-oxohexanoic acid in 21% yield as the only isolated product (Table 1, entry 10). Evidently, this acid results from the very rapid saponification of the 1,6-adduct 5-ethyl-3H-furan-2-one, 11, during the basic working-up. The enol lactone 11 could be isolated in 27% yield when

Table 1. Reactions of protoanemonin with piperidine, dimethyl malonate anion and lithium dialkylcuprates.

Entry[a]	Reactant	Equiv.	Time[c]	Temp. (°C)	Product	Yield (%)[e]	% Molar
(1)	Piperidine	1	15	0	2	4	11
					3	10	30
					4	37	59
(2)[b]	Piperidine	1	20	20	2	1	4
					3	6	19
					4	46	77
(3)	Piperidine	1	20	0	2	6	16
					3	13	31
					4	42	53
(4)	$MeONa/CH_2(COOMe)_2$	1:1	7 h	40	10	traces	--
(5)	$MeONa/CH_2(COOMe)_2$	1:1	13	20	9	1	25
					10	3	75
(6)[b]	$NaH/CH_2(COOMe)_2$	1:1	15	0	9	8	47
					10	9	53
(7)[b]	$NaH/CH_2(COOMe)_2$	1:2	15	0	9	22	69
					10	10	31
(8)[b]	$NaH/CH_2(COOMe)_2$	1:2	30	0	9	22	56
					10	17	44
(9)[b]	$NaH/CH_2(COOMe)_2$	1:20	15	0	9	15	99
					10	traces	--
					8[d]	1	1
(10)	Me_2CuLi	1	22	0	11	21	100
(11)	Me_2CuLi	1	12	-30	11	27	100
(12)	Me_2CuLi	1	12	-78	1	33	85
					12	2	2
					13	15	13
(13)	Bu_2CuLi	1	12	-30	12	traces	--
					14	9	89
					15	3	11
(14)	Bu_2CuLi	1	12	-15	14	17	100

[a] All the experiments were carried out using DME as a solvent, except in entry 4 (THF), under argon atmosphere.
[b] Addition of the reactant to the protoanemonin solution. All other experiments were performed with inverse addition.
[c] In minutes, except in entry 4.
[d] Isolated as the open-chain compound 4-oxohexanoic acid.
[e] Calculated on isolated products.

performing the experiment at -30°C, provided that care is taken to neutralize quickly the hydrolyzing reaction mixture (entry 11).

When decreasing the temperature to -78° (entry 12), protoanemonin was recovered in 33% yield, along with its dimer anemonin, 12, (2%) and the cycloadduct 13, m.p. 129-130° (15%). In this case, the 1,6-adduct 11 was not detected.

With 1 eq of lithium dibutylcuprate at -30° (optimal conditions with Me_2CuLi), 5-pentyl-3H-fu-

ran-2-one, 14, was obtained in 9% yield (entry 13). A solid, m.p. 239-240°, isolated in 3% yield, was identified as 15 by comparison with 13. At -15°, the yield of 14 increased twofold, but it could not be improved by working at higher temperatures because Bu_2CuLi decomposes above -10°.

From these results we can deduce that protoanemonin is able to react with lithium dialkylcuprates and its reactivity increases with the temperature, the thermal stability of cuprates being an important limiting factor. Me_2CuLi has been shown to be more reactive than Bu_2CuLi in similar conditions.

DISCUSSION

I. Elucidation of product constitution.

Compound 4 has been previously described[6]. Its undescribed IR spectrum shows considerable enamine chararacter (OH absorption at 3600-2600 cm^{-1}), which accounts for its unstability.

Stereoisomeric piperidides 2 and 3 were readily assigned to configurations Z and E, respectively, by ^1H NMR (olefinic coupling constants of 12.0 and 16.3 Hz, respectively), while their constitution was easily deduced from their MS, IR and ^{13}C NMR spectra.

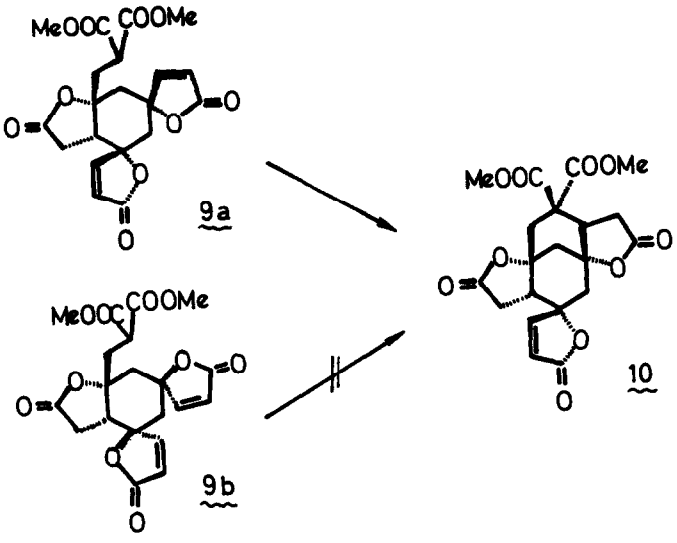
The 1:1 adduct 8 between 1 and dimethyl malonate was identified by its IR, ^1H NMR and MS spectra. The 80 MHz ^1H NMR of 8 was fully analyzed (LAOCOON)[5]. The related adducts 11 and 14 have been previously reported[7,8].

The constitution of tetracyclic 3:1 adduct 9 was fully characterized by IR, ^1H NMR, ^{13}C NMR, MS and elemental analysis. Its mass spectrum showed a very small molecular ion at m/z 420, and peaks at high m/z for M-MeO (389), $M-(OMe)_2$ (358), $M-CH_2(CO_2Me)_2$ (288) and the base peak at $M-CH_2CH(CO_2Me)_2$ (275), which showed that the malonate moiety was linked to a CH_2 group, as required by the initial 1,6-addition discussed below (Scheme 4). The ^1H NMR spectrum showed four olefinic protons as doublets (J = 5.5 Hz for all of them) at δ 7.59, 7.44, 6.25 and 6.13 ppm. Those are typical shifts for β (7.8) and α (6.25) protons of α,β-butenolides[6,9]. However, the absence of allylic coupling, so common in these compounds ($|J_{\alpha\gamma}| \approx |J_{\beta\gamma}| \approx 2.0$ Hz) pointed to γ-disubstituted α,β-butenolide rings. Other protons in 9 absorbed undifferentiated at δ 2.1-3.0 ppm (integral ~ 8H), at 3.57 δ ($(MeOOC)_2\underline{CH}$) as a double doublet (J = 7.4 Hz, J' = 4.9 Hz) and at 3.77 and 3.78 δ, as two sharp singlets (two $\underline{CH_3}O$). The ^{13}C NMR spectrum, in acetone-d_6, showed almost as many signals as carbons required for the 3:1 adduct, showing lack of symmetry in the molecule (only the methoxycarbonyl groups appeared isochronous). In the ester carbonyl region, the signal at 173.8 δ should be assigned to a saturated γ-lactone ring[10], the more intense signal at 171.3 δ to both malonate moiety carbonyls and the two signals at 170.0 and 170.1 δ at both α,β-butenolide carbonyls[3,6]. Two β-olefinic carbons at 160.8 and 159.4 δ and two α-olefinic carbons at 122.8 and 120.9 δ were shown to bear one proton each by spin echo multiplicity sorting, SEFT[11]. Three signals at 87.9, 85.6 and 84.9 ppm, corresponding to quaternary carbons (SEFT), were assigned to the oxygen-bearing sp^3 carbons of the lactone rings[10]. The two methoxy carbons appeared together at 53.0 δ, and two methine carbons (SEFT) absorbed at 47.6 and 44.0 δ. The remaining four signals were shown to correspond to methylene groups (SEFT), and appeared at 40.4, 39.7, 39.5 and 30.3 δ. Although a complete assignment of all signals is rather difficult and will not be tried on such a meager evidence, the number and position of all signals is clearly in agreement with the structure assigned to 9. Although this evidence does not exclude other alternative structures, the constitution proposed for 9 is both mechanistically sound (Scheme 4) and analogous to that of 13, which has been determined by X-ray analysis[5].

The 3:1 pentacyclic adduct 10 was shown to be an isomer of 9: besides being formed in the same reaction, it displayed a prominent molecular ion at m/z 420 in its mass spectrum. Furthermore, the 80 MHz ^1H NMR spectrum of 10 was quite similar to that of 9 but the number of olefinic protons was only two, at 7.03 and 6.17 δ (both doublets, J = 5.5 Hz), corresponding to one single spiranic butenolide ring. The ^{13}C NMR spectrum of 10 showed five carbonyl signals, two protonated olefinic carbons, three γ-carbons of α,β-butenolide and γ-butyrolactone rings and ten more signals in the aliphatic sp^3 region, thus showing 20 signals for its 20 carbon atoms.

We tried a correlation experiment between 9 and 10. Thus, treatment of 9 with 1 eq of NaH in

DME at 0°C for 30 minutes, conditions similar to those employed in the reaction between 1 and 5 which gave rise to both 9 and 10, did not isomerize 9 to 10. We think that this experiment is to be taken as indirect evidence of a different stereochemistry for 9 and 10 at the spiranic butenolide rings. Obviously, if 9a had the configuration of the tetracyclic adduct, the reaction conditions employed should have resulted in almost quantitative isomerization to 10 via highly favoured intramolecular Michael addition (Scheme 3). Instead, unmodified 9 was recovered in over 80% yield.



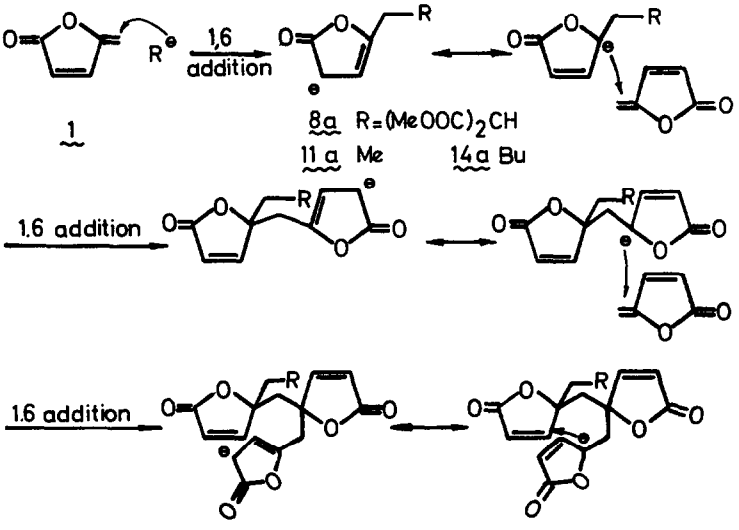
Scheme 3

Relative configuration of all asymmetric centers in 10 has been assigned through its 300 MHz 2-D COSY NMR spectrum[5]. The very thin silky needles of crystalline 10 were not suitable for X-ray analysis.

The spectral properties of 13 closely resemble those of 9, discussed above. However, in this case a suitable crystal could be submitted to X-ray analysis to confirm the proposed structure[5].

II. Mechanistic approaches.

The formation of the compounds obtained in the reaction of protoanemonin with piperidine is easily understood and it can be accounted for as the result of the kinetic competition between two processes, involving: i) direct addition to carbonyl, giving the acrylamides 2 and 3, and ii) 1,6-conjugate addition, that leads to 4 after further addition to carbonyl of a second mole of amine.



Scheme 4

Of a greater interest appear to be the mechanistic pathways followed by protoanemonin in the reaction with malonate anion 5, to give the polycyclic compounds 9 and 10. The proposed mechanism for the formation of 9 is shown in Scheme 4, and it seems also to be operative when nucleophiles are dialkylcuprates, giving compounds 13 and 15.

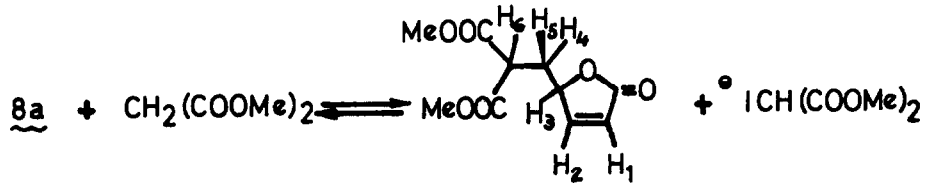
Obviously, the pentacycle 10 comes from 9a (Scheme 3) by intramolecular Michael addition.

Formation of cycloadducts requires the presence of the nucleophile as a promoter for the reaction. Thus, reaction of protoanemonin and NaH in the absence of nucleophile (malonic ester or cuprates) under otherwise identical conditions led, after 15 minutes, to 79% recovery of 1, in addition to its dimer, anemonin, (12%) and some polymeric material of unknown nature. No trimers of 1 were detected.

The mechanism shown in Scheme 4 is related to that proposed by Inubushi[3] to account for the cycloadduct formed in 7% yield, by reaction of protoanemonin with 2-methyl-1,3-cyclopentanedione, in the presence of potassium fluoride in dimethyl sulfoxide as a solvent. On the other hand, this mechanism is identical to that reported by Scheffold[4] to explain a similar cycloadduct obtained by reaction of 2-methylprotoanemonin with methyl acetoacetate anion. Stereochemical details about these adducts have not been given in any case.

Nevertheless, with the malonate anion 5 as nucleophile, yields of polycyclic compounds 9 and 10 are higher than in reactions involving dialkylcuprates, where the major product was always the single 1,6-adduct. Furthermore, in the first case, a tetracycle (9a) evolved to the pentacycle 10.

The mechanism proposed in Scheme 4 implies in its first step a conjugate 1,6-addition of nucleophile to 1, giving the anionic adduct (8a, 11a or 14a), followed by 1,6-addition of this species on a second molecule of 1. This second step is equivalent to an alkylation of the originally formed anionic intermediate. This is a minor reaction in the case of 11a or 14a, but gives rise to the major products for 8a. One might wonder why the malonate shows such a strong effect on the reactivity of the anionic intermediate. Our mechanism accounts for these facts on the basis of the relative acidity of malonic esters and the γ-proton of α,β-butenolides. When malonic esters are present in the reaction mixture, together with 8a, the equilibrium shown in Scheme 5 is possible.



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Scheme 5

This equilibrium will be shifted to the right when a great excess of malonate is present and indeed the 1,6-adduct 8 has only been obtained working with 20 eq of malonate (Table 1, experiment 9). Moreover, in this case the total yield of polycyclic adducts was 15%, much lower than working in the presence of 1 eq of malonate in similar conditions. In this last case, the equilibrium should be very shifted to the left, thus favouring the formation of 9 and 10 from anion 8a. Actually, the total yield for these compounds was now 32%.

Another important feature is the role of protoanemonin as a key intermediate in elimination--addition processes that take place when α,β-butenolides with good leaving-groups (halides or sulfonates) as substituents at δ-position, are treated with slightly basic nucleophiles, due to the great acidity of the allylic proton. We had already reported this fact in earlier works[2], wherein the nucleophiles used were benzenethiolate, resulting lactones 20, 21 and 22, and CN^-/MeOH, that lead to methyl 2-methoxy-5-oxopentanoate. We can now extend this behaviour of 1 to the reactions of butenolides with other nucleophiles, since the amide 4 was obtained by treatment of 5-bromomethyl--5H-furan-2-one with piperidine[6] and the enol lactone 11 was formed in the reaction of 5-p-toluenesulfonylmethyl-5H-furan-2-one with Me_2CuLi, among other products[10]. These results let us to relate starting butenolides and the products found with protoanemonin, as the common intermediate in

all those processes.

III. Theoretical calculations.

We have used Klopman's equation in order to rationalize the differential behaviour of protoanemonin in front of nucleophiles, whose nature must be closely related with the obtained results.

Data concerning to the HOMO of employed nucleophiles (except dialkylcuprates) are shown in Table 2, while those concerning to the LUMO of protoanemonin are represented in Fig. 1. Introduction

Table 2. HOMO and effective HOMO energy levels, atomic charges and coefficients of the reacting atoms for different nucleophiles.

Nucleophile	E HOMO (eV)	E* effective HOMO (eV)	Charge	c^2
Piperidine	-9.949	-9.949	-0.34	0.68
Pirrolidine	-9.985	-9.985	-0.33	0.67
Azide anion	-2.229	-8.275	-0.63	0.41
MeO^-	-2.416	-7.385	-0.75	0.61
n-BuO^-	-2.641	-7.329	-0.75	0.42
n-PrS^-	-2.574	-6.254	-0.88	0.54
$(MeO_2C)_2CH^-$	-3.468	-3.468	-0.48[a]	0.69
CN^-	-3.270	-3.270	-0.44[a]	0.67
PhS^-	-3.047	-3.693	-0.67	0.94
$PhCH_2S^-$	-2.898	-2.911	-0.85	0.93

[a] Charge on reacting carbon atom. (Supposed to react at the carbon atom).

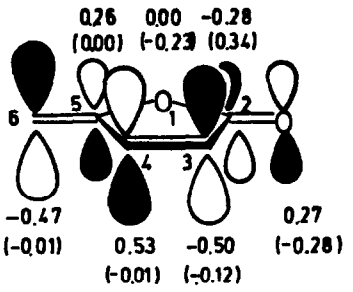

Fig. 1.- Atomic coefficients (and charges) for the MNDO calculated LUMO (-0.924 eV) of protoanemonin 1.

of these values in the equation (see experimental part) allowed us to made the plot of Fig. 2, from which we can classify the studied nucleophiles in three groups:

a) Amines, alkoxide and propanethiolate anions, that will attack mainly to the carbonyl carbon atom. (Left-hand of the plot).

b) Cyanide and malonate anions that might show no regioselectivity in the reaction with 1.

c) Benzenethiolate and phenylmethanethiolate anions that will react with the olefinic carbon atoms (C-4 or C-6). (Right-hand of the plot).

The slightly bigger contribution of the atomic orbitals of C-4 than those of C-6 to the LUMO of 1 (Fig. 1) leads to an expected preference for the C-4 over C-6 nucleophilic attack. Experimentally, an almost complete lack of C-4 attack is observed, probably due to steric effects making kinetically more favoured the reaction with the terminal exocyclic C=C bond.

Predictions from Fig. 2 are in good agreement with experimental results in almost all cases, and generally, reaction rates are in direct ratio with the ΔE involved in each process.

The case of piperidine is borderline since the ratio carbonylic/olefinic attack is nearly one. Thus, experimental results can be justified considering that many approximations have been done to evaluate quantitatively ΔE and therefore these values are not completely reliable when so small regioselectivity is shown. A similar reason can be invoked to explain the apparent disagreement between the theoretical prediction and the results obtained in the reaction of 1 with the malonate anion 5 as nucleophile. Moreover, in this case the reaction evolves towards the formation of polycyclic products with the participation of unreacted protoanemonin, following different mechanisms that imply acid-base equilibria. Thus, the results are not comparable to the expected ones from theoretical calculations.

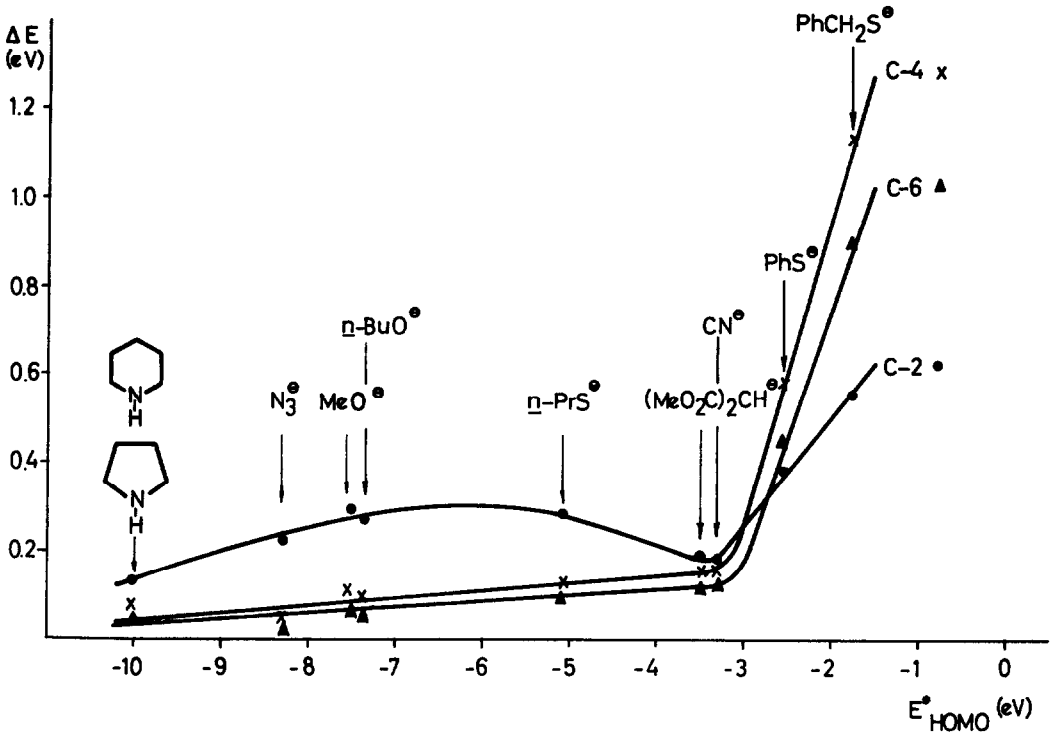

Fig. 2.- Plot of ΔE versus E^*_{HOMO} at different reaction sites. MO energy levels of molecules containing sulfur have been already corrected.

CONCLUSION

We can conclude that protoanemonin is very reactive in front of nucleophiles, leading to products that result from an initial attack to the carbonylic carbon or the olefinic atom C-6, the regioselectivity depending mainly on the nature of the nucleophile used.

The obtained results have been rationalized using the frontier orbitals approach and we are able now to predict the behaviour of protoanemonin in front of other nucleophiles not used up to present (i.e. pyrrolidine, azide).

Furthermore, we have confirmed from our study the role of 1 as intermediate in elimination--addition processes, that take place when slightly basic nucleophiles react with α,β-butenolides, having a good leaving-group as substituent at δ-position.

Moreover, we think that our work, jointly with the recent paper of Inubushi et al.[3], would stimulate the use of the well known, but meagerly employed, molecule of protoanemonin as synthon in organic synthesis.

EXPERIMENTAL SECTION

Melting points have been determined on a Kofler hot stage and are uncorrected. Distillation of small amounts of substance were effected on a rotational distillation Büchi, Model KRV 65/30 (only external or oven temperature is given). IR spectra were recorded on a Perkin-Elmer 1310 Spectrophotometer. 80 MHz ^1H and 20 MHz ^{13}C NMR spectra were recorded on a Bruker WP 80 SY Spectrometer. Che-

mical shifts are given in ppm relative to internal TMS (δ scale). MS data were obtained at 70 eV on a Hewlett-Packard 5985B Spectrometer. Preparative high performance liquid chromatography (HPLC) was performed on a Perkin-Elmer Series 2 Chromatograph using a reverse phase (ODS) preparative column (10 μ). Elemental analyses were performed on a Perkin-Elmer 240B elemental analyzer. Calculations were carried out on a VAX-11/780 Computer in the Computer Center of this University.

Methods used in Theoretical Calculations. Electronic structures of the nucleophiles and protoanemonin were calculated by the SCF semiempirical molecular orbital method MNDO[12]. Measurements of ΔE from Klopman's aquation[13] were made taking the value 10 as "efective dielectric constant (ε)", similar to that of DME (ε = 7.2), used as solvent in the reactions. The resonance integrals, β_{C-X}, have been calculated as the geometric average of the individual β values ($\beta_{C-X} = \sqrt{\beta_C \beta_X}$)[18], and finally considering $\beta_C = 1$. Table 3 shows the β^2_{C-X} values calculated and the C-X interatomic distances used[14]. The first n-type molecular orbital is taken as efective HOMO[15] and their energy levels have been corrected for sulphur nucleophiles, since it has been established that the MNDO calculated first ionization potentials for them disagree with the experimental values[16].

Table 3. β^2_{C-X} values (related to β_{C-C}) and C-X distances.

X	β^2_{C-X}	C-X (Å)
N	$1.39\ \beta_C$	1.45
C	$\beta^2_{C-C} = \beta^2_C$	1.52
O	$1.76\beta_C$	1.40
S	$1.72\beta_C$	1.81

Reaction of 1 with piperidine. Piperidine amides of cis- and trans-acetylacrylic and 5-(N-piperidyl)-4-oxopentanoic acids 2, 3 and 4 respectively. A typical experiment was run as follows: To a stirred ice-cooled solution of protoanemonin[17] (250 mg, 2.6 mmol) in anhydrous DME (10 ml) a solution of piperidine (221 mg, 2.6 mmol) in anhydrous DME (17 ml) was added, under argon atmosphere, over 5 min. After 15 min, the solvent was evaporated at reduced pressure without heating, to afford 437 mg of a crude, that was chromatographed on silica gel begining with CH_2Cl_2-ethyl acetate (4:1) and ending with CH_3OH- ethyl acetate (1:1) as eluents.

The following compounds were obtained:

Protoanemonin (56 mg, 22% recovery).

Amide 2 (31 mg, 7% yield); ^{1}H NMR ($CDCl_3$) 1,59 (complex absorption, 6H), 2.28 (s, 3H), 3.63 (m, 2H), 6.22 (d, J = 12 Hz, 1H), 6.44 (d, J = 12 Hz, 1H): IR ($CHCl_3$) 3000, 2940, 2860, 1695, 1675, 1620, 1460, 1445, 1360, 1250, 1230, 1175, 1135, 1020, 850 cm^{-1}; MS, m/z 181 (M, 1), 166(8), 98(11), 97(16), 84(100), 56(9), 55(10), 43(12). The unstability of compound 2, as well as that of its isomer 3, avoided the preparation of analytical samples.

Amide 3 (60 mg, 13% yield); ^{1}H NMR ($CDCl_3$) 1.54 (m, 6H), 2.25 (s, 3H), 3.50 (m, 4H), 6.86 (d, J = 16.3 Hz, 1H), 7.16 (d, J = 16.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) 24.3, 25.5, 26.4, 28.6, 43.1, 47.1, 132.0, 136.6, 163.8, 197.3; IR ($CHCl_3$) 3000, 2940, 2860, 1695, 1675, 1640, 1610, 1440, 1360, 1280, 1250, 1165, 1020, 970, 850 cm^{-1}; MS m/z 181 (M, 1.7), 98(9), 97(8), 85(6), 84(100), 56(9), 55(9), 43(12).

Amide 4[6] (147 mg, 42% yield); ^{1}H NMR ($CDCl_3$) 1.59 (m, 12H), 2.59 (m, 8H), 3.28 (s, 2H), 3.53 (m, 4H); ^{13}C NMR ($CDCl_3$) 23.7, 24.4, 25.5 (2C), 26.0, 26.9, 28.6, 30.6, 35.2, 42.9, 46.4, 54.6, 68.0, 169.8, 207.9; IR ($CHCl_3$) 3000, 2940, 2860, 1720, 1625, 1440, 1390, 1360, 1250, 1130 cm^{-1}; IR (film) 3400 cm^{-1} (broad band); MS, m/z 266 (M, 2.4), 181(12), 99(7), 98(100), 84(9), 70(5), 69(7), 56(5), 55(9), 42(10), 41(11).

Reaction of 1 with dimethyl malonate sodium salt: 5-(2,2-dimethoxycarbonylethyl)-5H-furan-2-one (8), tris-γ-lactone of cyclohexane-1,3,5-trihydroxy-4-hydroxycarbonylmethyl-5-(2,2-dimethoxycarbonylethyl)-1,3-di-(Z)-acrylic acid (9) and tris-γ-lactone of bicyclo[3.3.1]-nonane-1,3,5-trihydroxy-4,8-dihydroxycarbonylmethyl-7,7-dimethoxycarbonyl-3-(Z)-acrylic acid (10). A typical experiment was run as follows: A mixture of NaH (62 mg, 2.6 mmol, from 113 mg of 55% oil dispersed NaH) and dimethyl malonate (688 mg, 5.2 mmol) in anydrous DME (9 ml) was stirred at 0°C. After 15 min the resulting solution was added to a stirred and ice-cooled solution of 1 (250 mg, 2.6 mmol) in anhydrous DME (10 ml) over 6 min, under argon atmosphere. After 30 min, 1% HCl (10 ml) was added and the mixture was extracted with CH_2Cl_2, dried over sodium sulfate and the solvents removed at reduced pressure. The residue (786 mg) was chromatographed on silica gel begining with CH_2Cl_2 and ending with 9:1 CH_2Cl_2-Et_2O as eluents, to afford, along with 48% recovered dimethyl malonate, the following products:

Tetracyclic compound 9, m.p. 169-170° (from methanol); ^{1}H NMR ($CDCl_3$) 2.06-3.00 (complex absorption, 8H), 3.57 (dd, J = 4.92, J' = 7.38 Hz, 1H), 3.77 (s, 3H), 3.78 (s, 3H), 6.13 (d, J = 5.5 Hz, 1H), 6.25 (d, J = 5.5 Hz, 1H) 7.44 (d, J = 5.5 Hz, 1H), 7.59 (d, J = 5.5 Hz, 1H); ^{13}C NMR (acetone-d_6)30.3, 39.5, 39.7, 40.4, 44.0, 47.6, 53.0 (2C), 84.9, 85.6, 87.9, 120.9, 122.8, 159.4, 160.8, 170.0, 170.1, 171.3 (2C), 173.8; IR (KBr) 3090, 2940, 2920, 1780-1725 (broad band), 1605, 1440, 1290, 1200, 1145, 1110, 1085, 1020, 930, 820 cm^{-1}; MS, m/z 421 (M, 1), 275(83), 247(21), 113(28), 109(43), 97(36), 82(54), 69(22), 68(21), 59(100), 55(80), 54(34). Anal. Calc. for $C_{20}H_{20}O_{10}$: C, 57.14; H, 4.80. Found: C, 57.01; H, 4.92.

Pentacyclic compound 10, m.p. 244-245° (from methanol); ^{1}H NMR ($CDCl_3$) 1.84-3.03 (complex absorption, 12H), 3.75 (s, 3H), 3.79 (s, 3H), 6.17 (d, J = 5.5 Hz, 1H), 7.03 (d, J = 5.5 Hz, 1H); ^{13}C NMR (DMSO-d_6) 26.9, 30.9, 35.3, 39.0, 39.7, 42.1, 43.0, 53.1, 53.7, 55.0, 81.8, 82.1, 87.8, 122.0,

158.1, 169.3, 170.7, 170.9, 173.1, 173.2; IR (KBr) 3080, 2940, 1780, 1730, 1605, 1435, 1270, 1230, 1200, 1160, 995, 930, 820 cm^{-1}; MS, m/z 420 (M, 2.4), 200(31), 172(47), 140(35), 113(47), 112(21), 109(30), 97(49), 91(23), 82(31), 81(32), 69(38), 59(100), 55(82), 54(41), 53(71). Anal. Calcd. for $C_{20}H_{20}O_{10}$: C, 57.14; H, 4.80. Found: C, 57.14; H, 4.95.

Operating as described above, but under the conditions shown in Table 1, entry 9, the adduct 8 was isolated by preparative HPLC (70% MeOH-H_2O as eluent, flux 1 ml/min, λ (detector) = 230 nm) in 1% yield (3 mg). The ^1H NMR spectrum ($CDCl_3$) was fully analyzed by iterative simulation (LAOCOON)[5] and yielded the following parameters (see Scheme 5 for numbering): 2.10 ($J_{4,5}$ = 14.6, $J_{4,6}$ = 5.5, $J_{4,3}$ = 8.8 Hz, H_4), 2.53 ($J_{4,5}$ = 14.6, $J_{5,6}$ = 8.8, $J_{5,3}$ = 3.8 Hz, H_5), 3.65 ($J_{4,6}$ = 5.5, $J_{5,6}$ = 8.8 Hz, H_6), 3.75 (s, 3H), 3.78 (s, 3H), 5.13 (m, H_3), 6.13 ($J_{1,2}$ = 5.7, $J_{1,3}$ = 2.0 Hz, H_1), 7.42 ($J_{1,2}$ = 5.7, $J_{2,3}$ = 1.7 Hz, H_2). Other spectral data for compound 8 were: IR (film) 3100, 2960, 2920, 2860, 1750 (broad), 1600, 1440, 1260, 1110, 830 cm^{-1}; MS m/z 228 (M, 32), 169 (M-$COOCH_3$, 72), 168 (M-$HCOOCH_3$, 100), 141(16), 137(53), 136(51), 132(16), 113(19), 109(61), 82(17), 59(18), 55(91), 43(30).

Reaction of 1 with Me_2CuLi: 5-ethyl-3H-furan-2-one (11) and tris-γ-lactone of cyclohexane-5-ethyl--1,3,5-trihydroxycarbonylmethyl-1,3-di-(Z)-acrylic acid 13. A typical experiment was run as follows: To a stirred solution of Me_2CuLi (prepared from CuI (496 mg, 2.6 mmol) and MeLi (3.3 ml of a 1.6 M ethereal solution, 5.3 mmol) in anhydrous Et_2O (13 ml), cooled at -30°, protoanemonin (250 mg, 2.6 mmol) dissolved in anhydrous DME (7 ml) was added dropwise over 6 min, under argon atmosphere. After 6 min of additional stirring, HCl (10 ml of a 0.7 M aq solution) was added. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate and the solvents removed at reduced pressure. Chromatography on silica gel of the residue afforded lactone 11[7] (80 mg, 27% yield) as the only defined product. ^1H NMR ($CDCl_3$) 1.15 (t, J = 6.6 Hz, 3H), 2.31 (m, 2H), 3.15 (m, 2H), 5.09 (m, 1H); ^{13}C NMR ($CDCl_3$) 10.0, 21.5, 33.7, 97.2, 158.6, 176.6; IR ($CHCl_3$) 3020, 2970, 2950, 2920, 2870, 1795, 1710, 1675, 1510, 1400, 1365, 1315, 1220, 1165, 1115, 1055, 990, 980, 965, 935, 915, 840 cm^{-1}; MS, m/z 112 (M, 37), 97(13), 83(23), 57(13), 56(10), 55(100), 53(7), 41(5).

Working as described above, but under the conditions shown in Table 1 entry 12, compound 13 was obtained in 15% yield, along with anemonin, 12 (2% yield) and 33% of recovered 1. Characteristics of 13: M.p. 129-130° (from methanol); ^1H NMR ($CDCl_3$) 0.97 (t, J = 6.8 Hz, 3H), 1.91 (q, J = 6.8 Hz, 2H), 1.91-2.69 (complex absorption, 7H), 6.03 (d, J = 5.5 Hz, 1H); IR (KBr), 3100, 2980, 2950, 1790-1760 (broad band), 1610, 1450, 1360, 1240, 1170, 1190, 1140, 1110, 930, 820 cm^{-1}; MS, m/z 275 (M-29, 100), 247(19), 179(18), 109(25), 97(15), 82(29), 55(25), 54(18). Anal. Calcd. for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 62.93; H, 5.12.

Reaction of 1 with Bu_2CuLi: 5-pentyl-3H-furan-2-one (14) and tris-γ-lactone of cyclohexane-1,3,5--trihydroxycarbonylmethyl-5-pentyl-1,3-di-(Z)-acrylic acid 15. A typical experiment was run as follows: To a stirred solution of Bu_2CuLi (prepared from CuI (496 mg, 2.6 mmol) and BuLi (3.3 ml of 1.6M solution in hexane, 5.3 mmol) in anydrous ether (13 ml), cooled at -30°, protoanemonin (250 mg, 2.6 mmol) dissolved in anydrous DME (7 ml) was added dropwise over 6 min, under argon atmosphere. After 6 min of additional stirring, HCl (10 ml of 0.7M aq solution) was added. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate and the solvents removed ar reduced pressure. The residue (323 mg) was chromatographed on silica gel, begining with CH_2Cl_2-hexane (4:1) and ending with CH_2Cl_2-ethyl acetate (4:1) as eluents, to afford the following compounds:

i) Lactone 14[8] (36 mg, 9% yield). ^1H NMR ($CDCl_3$) 1.83 (t, J = 4.9 Hz, 3H), 1.06-1.68 (complex absorption, 6H), 2.22 (m, 2H), 3.09 (m, 2H), 5.00 (m, 1H); ^{13}C NMR ($CDCl_3$) 13.8, 22.2, 25.4, 28.2, 31.1, 33.8, 98.0, 157.5, 176.7; IR ($CHCl_3$) 3020, 2950, 2930, 2860, 1795, 1710, 1675, 1465, 1400, 1365, 1265, 1120, 1090, 990, 935 cm^{-1}; MS, m/z 154 (M, 26), 125(12), 112(12), 111(82), 99(13), 98(100), 97(20), 83(32), 70(23), 56(16), 55(62), 41(19), 39(16). Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.72, H, 9.18.

ii) A product which constitution was assigned to 15 (10 mg, 3% yield), m.p. 239-240° (from methanol). ^1H NMR (acetone-d_6) 0.77 (m, 3H), 1.15 (m, 6H), 1.52-2.83 (complex absorption, 9H), 5.95 (d, J = 5.5 Hz, 1H), 6.09 (d, J = 5.5 Hz, 1H) 7.49 (d, J = 5.5 Hz, 1H), 7.59 (d, J = 5.5 Hz, 1H); MS, m/z 275 (M-C_5H_{11}, 7), 169(27), 139(40), 123(29), 115(29), 107(27), 95(24),79(87), 68(35), 55(84), 43(70), 41(100).

Reaction of protoanemonin with NaH. To a stirred and ice-cooled solution of protoanemonin (250 mg, 2.6 mmol) in anhydrous DME (10 ml), a suspension of NaH (62.4 mg, 2.6 mmol) in DME (10 ml) was added under argon atmosphere. After 15 min, HCl (10 ml of a 1% aq solution) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over sodium sulfate and the solvents were removed under reduced pressure. The residue (233 mg) was chromatographed on silica gel, begining with ethyl acetate-hexane (1:2) and ending with ethyl acetate-methanol (1:2) as eluents, to afford 176 mg of recovered protoanemonin, 12 mg of anemonin, 12, and 16 mg of unidentified polymeric material. The ^{13}C NMR and MS spectra of 12, reported herein for the first time, are the following: ^{13}C NMR (DMSO-d_6) 22.8, 89.9, 119.6, 155.7, 171.1; MS, m/z 192 (M, 3.7), 164(40), 136(23), 110(24), 97(12), 96(100), 82(52), 68(53), 54(37).

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