Reaction of Sulfene and Dichloroketene with Open-Chain *N,N*-Disubstituted α-Aminomethyleneketones. Synthesis of 4-Dialkylamino-3,4-dihydro-6-methyl-5-phenyl-1,2-oxathiin 2,2-Dioxides and of *N,N*-Disubstituted 4-Amino-3-chloro-(6-methyl-5-phenyl)(6-benzyl)-2*H*-pyran-2-ones

*Alberto Bargagna, Filippo Evangelisti and Pietro Schenone**

Istituto di Scienze Farmaceutiche dell'Università, Viale Benedetto XV-3, 16132 Genova, Italy

Received July 21, 1980

Cycloaddition of sulfene to *N,N*-disubstituted 4-amino-3-phenyl-3-buten-2-ones (III) occurred in good yield only in the case of aliphatic *N*-substitution to give 4-dialkylamino-3,4-dihydro-6-methyl-5-phenyl-1,2-oxathiin 2,2-dioxides, whereas *N,N*-disubstituted 4-amino-1-phenyl-3-buten-2-ones (IV) did not react at all. Polar 1,4-cycloaddition of dichloroketene to III and IV occurred partly in the case of aromatic *N*-substitution, with the exception of the morpholino derivative IVd, giving in low yield *N,N*-disubstituted 4-amino-3,3-dichloro-3,4-dihydro-(6-methyl-5-phenyl)(6-benzyl)-2*H*-pyran-2-ones, which were dehydrochlorinated with DBN to the corresponding 4-amino-3-chloro-(6-methyl-5-phenyl)(6-benzyl)-2*H*-pyran-2-ones (VII) in good yield. In some cases of aliphatic *N,N*-disubstitution of III and IV, cycloaddition led directly to *N,N*-dialkyl derivatives VII in low yield.

J. Heterocyclic Chem., **18**, 111 (1981).

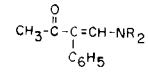
Our previous work on cycloaddition of sulfene to open-chain α-aminomethyleneketones (1-3) showed that this reaction occurred only with enaminones bearing an alkyl or aryl substituent R′ on C-2 of the appropriate rotamer *EZ*; when R′ = H, the cycloaddition did not occur.

We have now extended the cycloaddition of sulfene to other open-chain enaminones such as III bearing a phenyl substitution on C-2 in order to obtain the new cycloadducts V, where an exchange of substituents between C-5 and C-6 of the 1,2-oxathiin ring has taken place in comparison with previously described adducts (3).

For the preparation of enaminones III, we needed 4-hydroxy-3-phenyl-3-buten-2-one I, the synthesis of which has been described by von Auwers (4) in very low yield from 1-phenyl-2-propanone, ethyl formate and sodium. In reinvestigating the preparation of I we found that the solid obtained in the reaction was actually I, confirmed from the nmr spectrum (see Experimental), whereas the liquid residue, namely the main component, was a mixture of I and the hitherto unknown 4-hydroxy-1-phenyl-3-buten-2-one II in the approximate ratio of 32/68, as determined by nmr. The latter could be obtained 95% pure (still con-

Table I

N,N-Disubstituted 4-Amino-3-phenyl-3-buten-2-ones (IIIa-e) (a)



Compound No.	NR_2	Yield %	B.p./mm or M.p., °C	Molecular Formula	Analyses % Calcd./Found C	H	N
IIIa	$N(C_2H_5)_2$	96	145/0.1	$C_{14}H_{19}NO$	77.38	8.81	6.45
					77.35	9.04	6.63
IIIb	piperidino	87	68 (b)	$C_{15}H_{19}NO$	78.56	8.35	6.11
					78.61	8.22	6.06
IIIc	morpholino	60	73 (b)	$C_{14}H_{17}NO_2$	72.70	7.41	6.06
					72.74	7.42	6.06
IIId	$N(CH_3)C_6H_5$	62	82 (b)	$C_{17}H_{17}NO$	81.24	6.82	5.57
					81.22	6.80	5.44
IIIe	$N(C_6H_5)_2$	66	126 (b)	$C_{22}H_{19}NO$	84.31	6.11	4.47
					84.20	6.21	4.55

(a) Compounds IIIa-c were prepared according to the literature (5). Compounds IIId-e were also prepared according to the literature (6). 4-Dimethylamino-3-phenyl-3-buten-2-one could not be prepared from I and dimethylamine in benzene at room temperature, nor at 70° for 12 hours in a closed vessel, with or without molecular sieves. In all cases the sole product isolated from the reaction mixture by distillation *in vacuo* was 1-phenyl-2-propanone. (b) From anhydrous diethyl ether-petroleum ether (b.p. 40-60°) (5:1).

0022-152X/81/010111-06$02.25

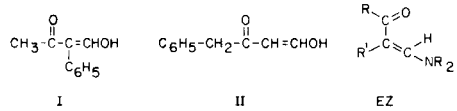
taining 5% of I) by repeated distillations *in vacuo* and coolings.

We therefore had the opportunity of preparing in high yield not only *N,N*-disubstituted 4-amino-3-phenyl-3-buten-2-ones IIIa-e (Table I) by reaction of α-hydroxymethyleneketone I with secondary amines [*cf.* (5,6)], but also *N,N*-disubstituted 4-amino-1-phenyl-3-buten-2-ones IVa-f (Table III) in the same way starting from impure α-hydroxymethyleneketone II, and to test both III and IV in the cycloadditions with sulfene and dichloroketene.

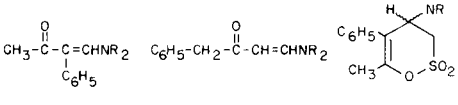
Both enaminones III and IV were *EZ* rotamers, as deduced from their ir and nmr spectra [*cf.* (1) and Tables II, IV]. As expected, only enaminones III reacted with sulfene (prepared *in situ* from methanesulfonyl chloride and triethylamine) to give in good yield *N,N*-disubstituted 4-amino-3,4-dihydro-6-methyl-5-phenyl-1,2-oxathiin 2,2-dioxides Va-c (Table V), provided that an aliphatic *N*-substituent was present [*cf.* (2)]. Enaminones IV did not react and were recovered unchanged from the reaction mixture.

Thus, these findings confirmed the features necessary for the open-chain enaminones in order to react with sulfene. The reaction with dichloroketene (prepared *in situ* from dichloroacetyl chloride and triethylamine) occurred in the case of enaminones III and IV bearing both aliphatic and aromatic *N*-substituents.

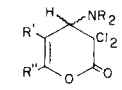
More exactly, the primary adducts VIa,b,d, in which a full or partial aromatic *N*-substitution was present, were



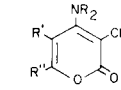
I II EZ



IIIa-e IVa-f Va-c



VIa: R' = C_6H_5, R'' = CH_3, NR_2 = $N(CH_3)C_6H_5$
VIb: R' = C_6H_5, R'' = CH_3, NR_2 = $N(C_6H_5)_2$
VIc: R' = H, R'' = $CH_2C_6H_5$, NR_2 = morpholino
VId: R' = H, R'' = $CH_2C_6H_5$, NR_2 = $N(C_6H_5)_2$



VIIa-c: R' = C_6H_5, R'' = CH_3
VIId-g: R' = H, R'' = $CH_2C_6H_5$

isolated in low yield. Also, enaminone IVe [NR_2 = $N(CH_3)C_6H_5$] gave an unstable cycloadduct, which was used crude in the dehydrochlorination next step. An exception, compared with our previous findings (3,7), was the isolation of the morpholino adduct VIc (Table VI).

Cycloadducts VIa-d could be dehydrochlorinated by refluxing with DBN in benzene (8) to give in good yield *N,N*-disubstituted 4-amino-3-chloro-(6-methyl-5-phenyl)-(6-benzyl)-2*H*-pyran-2-ones VIIb,c,e,g (Tables VII and VIII). In the case of a fully aliphatic *N*-substitution, the cycloaddition of dichloroketene to enaminones III led directly in low yield to the dehydrochlorinated product VIIa only in the case of IIIa, whereas for enaminones IV the sole isolated dehydrochlorination product was VIId from IVa (Tables VII and VIII). In all other cases (IIIb,c and IVb,c) we were unable to isolate any dehydrochlorination product even after treatment of the reaction mixture with DBN, although ir absorptions at 1780-1800 cm^{-1} seemed to indicate the presence of primary adducts.

Thus, the cycloaddition of dichloroketene to enaminones III and IV basically confirmed the general trends already found in the case of other open-chain enaminones (3,7).

EXPERIMENTAL

Uv spectra were measured in 95% ethanol with a Hitachi-Perkin-Elmer Model EPS-3T spectrophotometer. Ir spectra were taken on a Perkin-Elmer Model 257 spectrometer, and nmr spectra were recorded on a Perkin-Elmer Model R12 instrument (60 MHz, TMS as internal standard, J in Hz).

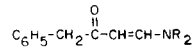
Table II

Uv, Ir and Nmr Spectral Data of Compounds IIIa-e

Compound No.	Uv λ max Nm (log ε)	Ir, Cm^{-1} (Tetrachloromethane) C=O	C=C	Nmr, δ (Tetrachloromethane)
IIIa	318 (4.25)	1660	1553	0.96 (t, J = 7.2, 2C*H*$_3$CH$_2$), 1.77 (s, CH_3CO), 3.00 (q, J = 7.2, 2C*H*$_2$CH$_3$), 7.24 (near s, C_6H_5), 7.48 (s, =CHN)
IIIb	318 (4.27)	1655	1550	1.50 (mc, 3CH_2 pip.) 1.75 (s, CH_3CO), 3.00 (mc, 2 NCH_2), 7.27 (near s, C_6H_5), 7.38 (s, =CHN)
IIIc	312 (4.01)	1663	1565	1.82 (s, CH_3CO), 3.01 (mc, 2NCH_2), 3.50 (mc, 2 OCH_2), 7.18 (mc, C_6H_5), 7.30 (s, =CHN)
IIId	237 (3.87) 331 (4.34)	1665	1545	1.93 (s, CH_3CO), 2.84 (s, NCH_3), 7.25 (mc, 2C_6H_5), 7.81 (s, =CHN)
IIIe	285 (3.94) 341 (4.22)	1670	1553	2.01 (s, CH_3CO), 6.87 (mc, 3C_6H_5), 7.82 (near s, =CHN)

Table III

N,N-Disubstituted 4-Amino-1-phenyl-3-buten-2-ones (IVa-f) (a)



Compound No.	NR_2	Yield %	B.p./mm or M.p., °C	Molecular Formula	Analyses % Calcd./Found C	H	N
IVa	$N(CH_3)_2$	92	160/0.1	$C_{12}H_{15}NO$	76.15	7.99	7.40
					75.97	8.06	7.19
IVb	$N(C_2H_5)_2$	82	185/0.1	$C_{14}H_{19}NO$	77.38	8.81	6.45
					77.47	8.83	6.28
IVc	piperidino	62	62 (b)	$C_{15}H_{19}NO$	78.56	8.35	6.11
					78.79	8.05	6.01
IVd	morpholino	66	80 (b)	$C_{14}H_{17}NO_2$	72.70	7.41	6.06
					72.89	7.56	6.15
IVe	$N(CH_3)C_6H_5$	73	215/0.1	$C_{17}H_{17}NO$	81.24	6.82	5.57
					81.60	6.89	5.39
IVf	$N(C_6H_5)_2$	63	106 (b)	$C_{22}H_{19}NO$	84.31	6.11	4.47
					84.05	6.10	4.48

(a) Compounds IVa-d were prepared according to the literature (5). Compounds IVe-f were also prepared according to the literature (6). (b) From anhydrous diethyl ether-petroleum ether 5:1.

Table IV

Uv, Ir and Nmr Spectral Data of Compounds IVa-f

Compound No.	Uv λ max Nm (log ε)	Ir, Cm^{-1} (Tetrachloromethane) C=O	C=C	Nmr, δ (Tetrachloromethane)
IVa	310 (4.31)	1657	1565	2.73 (s, 2, NCH_3), 3.47 (s, CH_2), 4.84 (d, J = 12.6, =CHCO), 7.16 (near s, C_6H_5), 7.34 (d, J = 12.6, =CHN)
IVb	313.5 (4.34)	1660	1565	1.06 (t, J = 7.2, $2CH_3CH_2$), 3.11 (q, J = 7.2, $2CH_2CH_3$), 3.49 (s, CH_2), 4.94 (d, J = 13.2, =CHCO), 7.21 (mc, C_6H_5), 7.40 (d, J = 13.2, =CHN)
IVc	314 (4.13)	1655	1565	1.52 (mc, $3CH_2$ pip.), 3.11 (mc, $2NCH_2$), 3.45 (s, CH_2), 4.94 (d, J = 13.2, =CHCO), 7.20 (near s, C_6H_5), 7.33 (d, J = 13.2, =CHN)
IVd	310 (4.11)	1662	1570	3.07 (mc, $2NCH_2$), 3.43 (s, CH_2), 3.51 (mc, $2OCH_2$), 4.92 (d, J = 12.6, =CHCO), 7.31 (near s, C_6H_5), 7.46 (d, J = 12.6, =CHN)
IVe	229 sh (3.86) 328 (4.36)	1663	1550	3.05 (s, NCH_3), 3.57 (s, CH_2), 5.25 (d, J = 13.2, =CHCO), 7.20 (mc, $2C_6H_5$), 7.81 (d, J = 13.2, =CHN)
IVf	226 sh (4.03) 275 (3.77) 336 (4.36)	1665	1555	3.48 (s, CH_2), 5.19 (d, J = 13.2, =CHCO), 7.12 (mc, $3C_6H_5$), 7.96 (d, J = 13.2, =CHN)

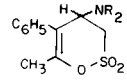
4-Hydroxy-3-phenyl-3-buten-2-one (I) and 4-Hydroxy-1-phenyl-3-buten-2-one (II).

To a solution of 1-phenyl-2-propanone (26.8 g., 0.2 mole) in anhydrous diethyl ether (50 ml.) containing sodium cut in small pieces (4.6 g., 0.2 mole), ethyl formate (22.2 g., 0.3 mole) was added slowly with stirring and ice-cooling. After standing overnight at room temperature, water (50 ml.) was added and the ether layer was washed with little water. The combined aqueous extracts were washed with ether, acidified with 6*M* hydrochloric acid and extracted thoroughly with ether. The ether extracts were washed with water, dried (sodium sulfate) and evaporated to give a near colorless liquid, b.p. 105°/0.1 mm, yield 18-19 g. (54-58%).

The liquid consisted of I and II in a mean ratio of 32/68, as revealed from the nmr spectrum. By cooling at 0° for 12 hours, pure I could be obtained as white crystals, m.p. 74° [lit. (4) 73-74°], yield 5.4 g. (~ 30%); ir (tetrachloromethane): ν max 1635, 1595, 1495 cm^{-1}; nmr (tetrachloromethane): δ 2.01 (s, CH_3CO), 7.21 (mc, C_6H_5), 8.09 (s, =CH-O), 15.5 (mc, OH, disappears with deuterium oxide).

Table V

4-Dialkylamino-3,4-dihydro-6-methyl-5-phenyl-1,2-oxathiin 2,2-Dioxides (Va-c) (a)



Compound No.	NR_2	Yield %	M.p., °C	Molecular Formula	Analyses % Calcd./Found C	H	N
Va	$N(C_2H_5)_2$	64	114 (b)	$C_{15}H_{21}NO_3S$	60.99	7.17	4.74
					60.95	7.20	4.74
Vb	piperidino	83	178 (b)	$C_{16}H_{21}NO_3S$	62.52	6.89	4.56
					62.46	6.93	4.44
Vc	morpholino	83	173 (b)	$C_{15}H_{19}NO_4S$	58.23	6.19	4.53
					58.41	6.22	4.31

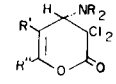
Ir and Nmr Spectral Data

Compound No.	Ir, Cm^{-1} (Chloroform) C=C		O=S=O	Nmr, δ (Deuteriochloroform)
Va	1667	1372	1148	0.79 (t, J = 7.2 $2CH_3CH_2$), 1.86 (d, J = 2.4, CH_3-6), 2.33 (q, J = 7.2, $2CH_2CH_3$), 3.20-3.55 (m, CH_2-3), 4.15-4.65 (m, CH-4), 7.25 (mc, C_6H_5)
Vb	1668	1375	1145	1.26 (mc, $3CH_2$ pip.), 1.88 (d, J = 2.4, CH_3-6), 2.38 (mc, $2NCH_2$), 3.3-3.6 (m, CH_2-3), 4.0-4.4 (m, CH-4), 7.37 (mc, C_6H_5)
Vc	1670	1375	1152	1.89 (d, J = 2.4, CH_3-6), 2.52 (mc, $2NCH_2$), 3.25-3.70 (m, $2OCH_2$ + CH_3-3), 4.05-4.45 (m, CH-4), 7.33 (m, C_6H_5)

(a) All compounds were prepared according to the literature (5), using anhydrous benzene as the solvent. (b) From anhydrous diethyl ether.

Table VI

N,N-Disubstituted 4-Amino-3,3-dichloro-3,4-dihydro-(6-methyl-5-phenyl)(6-benzyl)-2*H*-pyran-2-ones (VIa-d) (a)



Compound No.	R′	R″	NR_2	Yield %	M.p., °C (b)	Molecular Formula	Analyses % Calcd./Found C	H	N
VIa	C_6H_5	CH_3	$N(CH_3)C_6H_5$	25	86	$C_{19}H_{17}Cl_2NO_2$	63.00	4.73	3.87
							62.87	4.81	3.80
VIb	C_6H_5	CH_3	$N(C_6H_5)_2$	31	134	$C_{24}H_{19}Cl_2NO_2$	67.93	4.51	3.30
							68.12	4.66	3.23
VIc	H	$CH_2C_6H_5$	morpholino	10	94	$C_{16}H_{17}Cl_2NO_3$	56.16	5.01	4.09
							56.34	5.11	4.06
VId	H	$CH_2C_6H_5$	$N(C_6H_5)_2$	30	154	$C_{24}H_{19}Cl_2NO_2$	67.93	4.51	3.30
							67.73	4.62	3.25

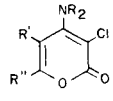
Ir and Nmr Spectral Data

Compound No.	Ir, Cm^{-1} (Chloroform) C=O	C=C	Nmr, δ (Deuteriochloroform)
VIa	1780	1688	2.01 (s, CH_3-6), 2.83 (s, NCH_3), 5.07 (near s, CH-4), 6.70-7.65 (m, $2C_6H_5$)
VIb	1775	1675	1.79 (s, CH_3-6), 5.60 (near s, CH-4), 6.8-7.5 (m, $3C_6H_5$)
VIc	1785	1695	2.60 (mc, $2NCH_2$), 3.45-3.80 (m, $2OCH_2$ + CH_2 + CH-4), 5.05 (d, J = 5.4, CH-5), 7.43 (near s, C_6H_5)
VId	1780	1695	3.28 (s, CH_2), 5.07 and 5.27 (2d, J = 6.6, CH=CH), 6.7-7.5 (m, $3C_6H_5$)

(a) All compounds were prepared according to the literature (9). (b) All compounds were recrystallized from anhydrous diethyl ether-acetone 10:1.

Table VII

N,N-Disubstituted 4-Amino-3-chloro-(6-methyl-5-phenyl)(6-benzyl)-2*H*-pyran-2-ones (VIIa-g) (a)



Compound No.	R′	R″	NR_2	Yield %	M.p., °C (b)	Molecular Formula	Analyses % Calcd./Found C	H	N
VIIa	C_6H_5	CH_3	$N(C_2H_5)_2$	21	123	$C_{16}H_{18}ClNO_2$	65.86	6.22	4.80
							65.97	6.27	4.53
VIIb	C_6H_5	CH_3	$N(CH_3)C_6H_5$	75	148	$C_{19}H_{16}ClNO_2$	70.04	4.95	4.30
							70.09	5.02	4.30
VIIc	C_6H_5	CH_3	$N(C_6H_5)_2$	72	198	$C_{24}H_{18}ClNO_2$	74.32	4.68	3.61
							74.20	4.74	3.72
VIId	H	$CH_2C_6H_5$	$N(CH_3)_2$	20	93	$C_{14}H_{14}ClNO_2$	63.76	5.35	5.31
							63.97	5.58	5.32
VIIe	H	$CH_2C_6H_5$	morpholino	75	109	$C_{16}H_{16}ClNO_3$	62.85	5.27	4.58
							62.94	5.27	4.48
VIIf	H	$CH_2C_6H_5$	$N(CH_3)C_6H_5$	20	92	$C_{19}H_{16}ClNO_2$	70.04	4.95	4.30
							69.98	5.13	4.10
VIIg	H	$CH_2C_6H_5$	$N(C_6H_5)_2$	70	176	$C_{24}H_{18}ClNO_2$	74.32	4.68	3.61
							74.05	4.69	3.55

(a) Compounds VIIb,c,e,g were prepared from VIa,b,c,d, respectively, by dehydrochlorination with DBN according to the literature (8). Compounds VIIa,d were obtained directly from IIIa and IVa, respectively, by reaction with dichloroacetyl chloride and triethylamine according to the literature (9), whereas VIIf was obtained by treatment with DBN, also according to the literature (8), of the crude, unstable adduct prepared as above from IVe. (b) All compounds were recrystallized from anhydrous diethyl ether-acetone 5:1.

Table VIII

Uv, Ir and Nmr Spectral Data of Compounds VIIa-g

Compound No.	Uv λ max Nm (log ε)	Ir, Cm^{-1} (Chloroform) C=O	C=C		Nmr, δ (Deuteriochloroform)
VIIa	301.5 (3.59) 332 (3.61)	1692	1627	1508	0.96 (t, J = 7.2, $2CH_3CH_2$), 2.04 (s, CH_3-6), 2.97 (q, J = 7.2, $2CH_2CH_3$), 7.37 (mc, C_6H_5)
VIIb	241 (4.18) 316 (3.84)	1705	1625	1510	2.13 (s, CH_3-6), 3.00 (s, NCH_3), 6.4-7.4 (m, $2C_6H_5$)
VIIc	232 sh (4.12) 282 (4.10) 316 sh (3.76)	1707	1630	1515	2.07 (s, CH_3-6), 6.7-7.3 (m, $3C_6H_5$)
VIId	238 (4.33) 271 (3.85) 321 (4.01)	1697	1655	1538	3.09 (s, $2NCH_3$), 3.72 (s, CH_2), 5.80 (near s, CH-5), 7.29 (near s, C_6H_5)
VIIe	239 (4.25) 276.5 (3.93) 323 (4.01)	1695	1648	1513	3.45 (mc, $2NCH_2$), 3.80 (mc, $2OCH_2$ + CH_2), 5.85 (s, CH-5), 7.33 (near s, C_6H_5)
VIIf	241 (4.06) 250 (4.07) 280 (3.87) 329 (3.94)	1695	1650	1525	3.46 (s, NCH_3), 3.68 (s, CH_2), 5.66 (near s, CH-5), 6.90-7.55 (m, $2C_6H_5$)
VIIg	252.5 (4.06) 272 (4.03) 349 (3.99)	1695	1645	1518	3.63 (s, CH_2), 5.61 (near s, CH-5), 6.85-7.35 (m, $3C_6H_5$)

By subsequent distillations *in vacuo* and coolings of the mother liquor, impure II (still containing 5% of I by nmr) was obtained as a liquid, yield 12.6 g. (~ 70%); nmr (tetrachloromethane): δ 3.54 (s, CH_2), 5.34 (d, J = 4.8, =CHCO), 7.34 (near s, C_6H_5), 7.88 (d, J = 4.8, =CH-O), 14.2 (mc, OH, disappears with deuterium oxide). These data were obtained by extrapolating the signals due to I.

Acknowledgement.

The authors wish to thank Dr. E. Sottofattori for the microanalyses and Dr. S. Morasso and Mr. F. Fasce for the uv, ir and nmr spectra. Financial support from CNR, Rome, is gratefully acknowledged.

REFERENCES AND NOTES

(1) F. Evangelisti, P. Schenone and A. Bargagna, *J. Heterocyclic Chem.*, **16**, 217 (1979).

(2) A. Bargagna, P. Schenone, F. Bondavalli and M. Longobardi, *ibid.*, **17**, 33 (1980).

(3) A. Bargagna, P. Schenone, F. Bondavalli and M. Longobardi, *ibid.*, **17**, 1201 (1980).

(4) K. von Auwers and H. Ludewig, *Ann. Chem.*, **526**, 130 (1936).

(5) P. Schenone, G. Bignardi and S. Morasso, *J. Heterocyclic Chem.*, **9**, 1341 (1972).

(6) G. Bignardi, P. Schenone and F. Evangelisti, *Ann. Chim. (Rome)*, **61**, 326 (1971).

(7) A. Bargagna, S. Cafaggi and P. Schenone, *J. Heterocyclic Chem.*, **17**, 507 (1980).

(8) F. Evangelisti, G. Bignardi, A. Bargagna and P. Schenone, *ibid.*, **15**, 511 (1978).

(9) G. Dignardi, F. Evangelisti, P. Schenone and A. Bargagna, *ibid.*, **9**, 1071 (1972).