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REACTION OF DIMETHYLAMINOMETHYLENEMALONALDEHYDE BIS-N,O-ACETAL WITH KETONES. A NOVEL ROUTE TO N-METHYLPYRROLES

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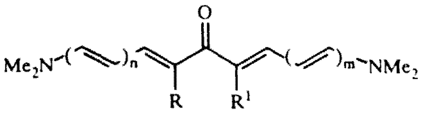
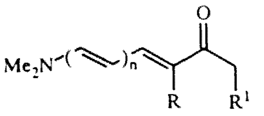
Condensation of the bis-N,O-acetal of dimethylaminomethylenemalonaldehyde with ketones, β-dimethylaminovinylketones, and δ-dimethylaminodienones is accompanied by an unusual intramolecular cyclization to give cross conjugated cyclic or acylic ketones containing an N-methyl-pyrrole ring in the β- or β- and β'-positions. This is a novel route to substituted pyrroles. Treatment of the bis-N,O-acetal of dimethylaminomethylenemalonaldehyde with 2-(3'-dimethylaminopropen-2'-ylidene)cyclopentanone gave a polyenyl tris-dimethylaminodiketone.

We have previously studied the condensation of conjugated ω-dimethylaminoaldehyde animals with cyclic and acyclic ketones [1-4]. The varied α,α'-bis(ω-dimethylaminopolyenyl)-ketones (BDAK) obtained have two chromophores which interact through the carbonyl group. As a result, they have a readily activated π-electronic optical system leading to a number of specific properties. These include a clearly observed solvatochromism [4], powerful thermochromism [5], fluorescence and generation of high efficiency laser radiation [6], and very ready alkylation and protonation at the carbonyl function with a marked change in color [7, 8]. In their monochromophoric mono-(ω-dimethylaminopolyenyl)ketones (MDAK), these properties are seen much more weakly or are altogether absent.

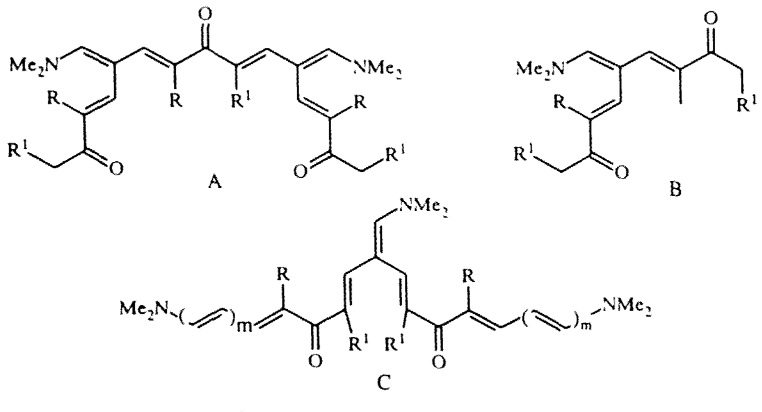


BDAK



MDAK

In this connection it was of interest to look at the properties of mono-, bis-, and tris-aminocarbonyl polyenes containing 2, 3, or more polyenyl chromophores in a single molecule. To synthesize compounds of this type we have studied the reaction of the β-dimethylaminomethylenemalonaldehyde bis-N,O-acetal (I) recently obtained by us [9] with ketones, β-dimethylaminovinylketones, and δ-dimethylaminodienones. Depending on the structure of the ketone and the ratio of reagents, the formation of polyenyl ketones of types A, B, or C might be expected:



$R = R^1 = H$; $R + R^1 = (CH_2)_n$; $n = 2, 3$; $m = 0, 1$

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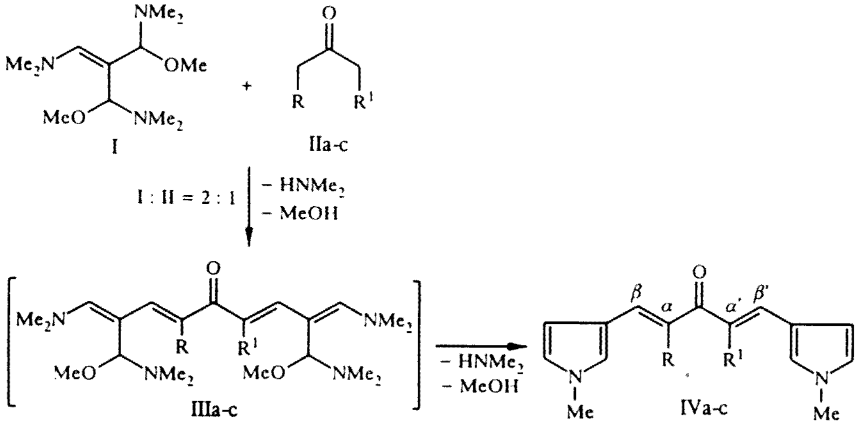
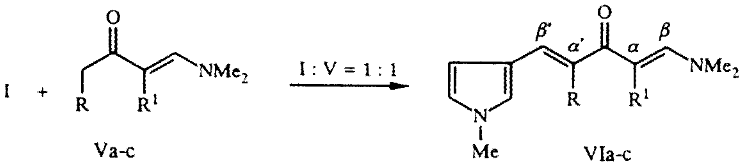
In order to prepare polyenyl type A bisdimethylaminoketones, we attempted condensation of bis-N,O-acetal I with acetone (IIa), cyclopentanone (IIb), and cyclohexanone (IIc) in the ratio I:II of 2:3. However, this ratio of reagents at 75-85°C gave only a complex mixture of products from which single compounds could not be separated. It was expected that a ratio of I:II of 2:1 would yield BDAK (IIIa-c) containing bis-N,O-acetal groups in the γ,γ'-positions. Use of IIIa-c as bis-N,O-acetals in reactions with ketones might then allow synthesis of BDAK of type A. However, it was not possible to prepare BDAK IIIa-c since an unexpected intramolecular cyclization reaction occurred to give the previously unknown β,β'-bis(N-methylpyrrol-3-yl)-divinylketones IVa-c in moderate yields. Their structures were shown by PMR, UV, and mass spectra (Tables 1, 2). Assignment of the proton signals in the N-methylpyrrole ring was based on literature data for N-methylpyrroles [10].



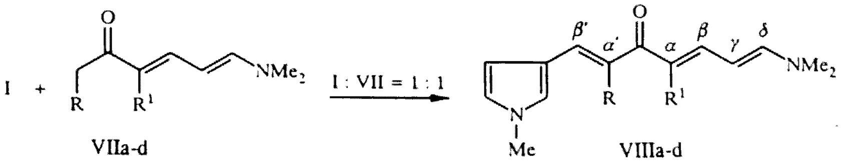
II–IV a R = R^1 = H, b R + R^1 = $(CH_2)_2$, c R + R^1 = $(CH_2)_3$

Treatment of bis-N,O-acetal I with β-dimethylaminovinylketones (Va-c, equimolar ratio of reagents) also occurred with this intramolecular cyclization to give the non-symmetrical β-dimethylamino-β'-(N-methylpyrrolyl)-α,α'-divinylketones (VIa-c) for the first time (35-56% yields).

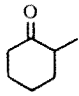


V, VI a R = R^1 = H, b R + R^1 = $(CH_2)_2$, c R + R^1 = $(CH_2)_3$

Reaction of I with δ-dimethylaminodienones (VIIa-d) in equimolar amounts occurs similarly to give the previously unknown α-(δ-dimethylaminopropen-γ-ylidene)-α'-(N-methylpyrrol-3-yl)methyleneketones (VIIIa-d) in 20-44% yields.



VII, VIII a R = R^1 = H, b R + R^1 = $(CH_2)_2$, c R + R^1 = $(CH_2)_3$,

d R = , R^1 = H

In the example of condensation of I with dienone VIIc, it was possible to separate the intermediate crystalline product (X) and the structure was confirmed by PMR spectroscopy (Table 2). Ketone IX, which contained by CH(OMe)NMe$_2$ group

TABLE 1. Conditions for Condensation of Ketones IIa-c, Va-c, VIIa-d with Bis-N,O-acetal I and Parameters for Synthesized Compounds

Starting ketone	Reaction conditions				Reaction product						
	molar ratio I:ketone	T, °C	reaction time, h	work up method	com-pound	Empirical formula*	mp, °C	UV spectrum, λ_{max}, nm (log ε)		mass spectrum, m/z	yield, %
								EtOH	toluene (heptane)		
IIa	2 : 1	90...100	1,3	D	IVa	$C_{15}H_{16}N_2O$	158...165 (decomp.)	393 (4,60)	371	–	10†
IIb	2 : 1	80...100	2,0	C	IVb	$C_{17}H_{18}N_2O$	239...243 (decomp.)	420 (4,75), 405 sh (4,67)	380, 398, 360 sh	266	13†
IIc	2 : 1	100...120	0,8	C	IVc	$C_{18}H_{20}N_2O$	168...170	400 (4,72)	375, 380 sh	–	10†
Va	1 : 1	100...120	1,3	B	VIa	$C_{12}H_{16}N_2O$	97...101 (decomp.)	380 (4,50)	359 [348]	204	38
Vb	1 : 1	100...110	0,5	B	VIb‡	$C_{14}H_{18}N_2O$	213...215 (decomp.)	405 (4,73), 416 sh (4,66)	386	230	40
Vc	1 : 1	100...120	1,0	D	VIc	$C_{15}H_{20}N_2O$	109...112	400 (4,55)	371 [358]	244	56
VIIa	1 : 1	78...83	0,75	D	VIIIa	$C_{14}H_{18}N_2O$	140...146 (decomp.)	448 (4,67)	418	230	30
VIIb	1 : 1	75...85	0,5	D	VIIIb	$C_{16}H_{20}N_2O$	>210 (decomp.)	474 (5,07)	421, 442	256	44
VIIc	1 : 1	85...95	0,5	D	VIIIc	$C_{17}H_{22}N_2O$	167...172	460 (4,99)	420	270	20
VIIc	1 : 1	85...95	0,5	B	IX	$C_{20}H_{33}N_3O_2$	158...163				40
VIId	1 : 1	70...80	0,3	D	VIIId	$C_{19}H_{24}N_2O_2$	>135 (decomp.)	506 (4,97)	480, 460 sh [460, 442 sh]	–	14
VIIb	1 : 2	95...100	0,75	A	X	$C_{26}H_{35}N_2O_2$	>210	480 (4,76)	450	–	65

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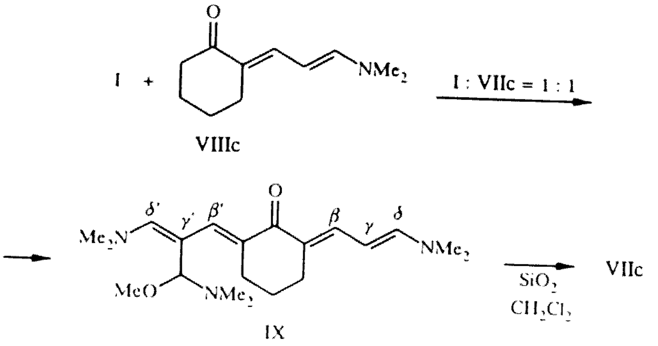
*Most compounds were difficult to analyze, hence, elemental analytical data are given here only for VIb and VIIIb. VIb) Found, %: C 72.28; H 8.01; N 11.95. Calculated, %: C 73.00; H 7.88; N 12.16. VIIIb) Found, %: N 10.43. Calculated, %: N 10.93.

†Reaction accompanied by strong tarring.

‡Compound VIb was also obtained using a I:Vb ratio of 1:2 in 49% yield.

in the γ'-position, gave the conjugated polyenyl ketone VIIIc in 50% yield when treated with silica gel in CH_2Cl_2 solution. The mass spectrum of IX showed only an m/z 270 ion which is apparently M^+ for VIIIc, formed in the mass spectrometer as a result of intramolecular cyclization.

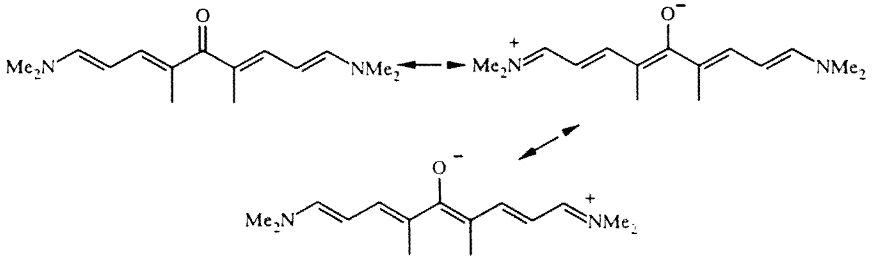


For separation of the conjugated polyenyl ketones IVa-c, VIc, and VIIIa-d the reaction mass, after heating had finished, was diluted with CH_2Cl_2 and held for 24 h in the presence of silica gel (see Experimental section).

Separation of the intermediate ketone IX indicates that cyclization to the N-methylpyrrolyl fragment during the synthesis of IV, VI, and VIII apparently occurs not in the starting bis-N,O-acetal I but in the initially formed products of its condensation with ketones. We have shown that heating I for 0.5 h at 80-120°C does not give the corresponding N-methylpyrrole.

Hence the condensation of I with ketones is a novel route to substituted pyrroles and is based on the reaction of the N,O-acetal function with one of the methyls of the dimethylamino group to form the pyrrole ring C_2-C_3 bond. This reaction evidently occurs very readily since, even in the presence in the reaction mixture of an excess of starting aminoketone, the N,O-acetal group in the intermediate BDAK does not react with a second molecule of ketone but takes part in pyrrole ring formation. It should be remembered that we had previously [10] reported N-methyl-3-phenylpyrrole as a by-product formed in an analogous intramolecular cyclization from the N,O-acetal of α-phenyl-β-dimethylaminoacrolein.

Cleavage of two protons from a methyl radical in the NMe_2 group in the intermediate BDAK (e.g., in III, IX) occurring with N-methylpyrrole ring formation is unusual and can be envisaged in BDAK through the existence of ionoid form contributions to their electronic structure [5, 11].



In this work, there was also found a single example where the reaction of the bis-N,O-acetal I with ketone VIIb (ratio of I:VIIb = 1:2) gave the previously unknown 1,15-dimethylamino-5,11-dioxo-4,6-dimethylene-10,12-dimethylene-8-dimethylaminomethylene-pentadeca-1,3,6,9,12,14-hexadiene (X) in 65% yield. Its structure was confirmed by PMR and UV data.

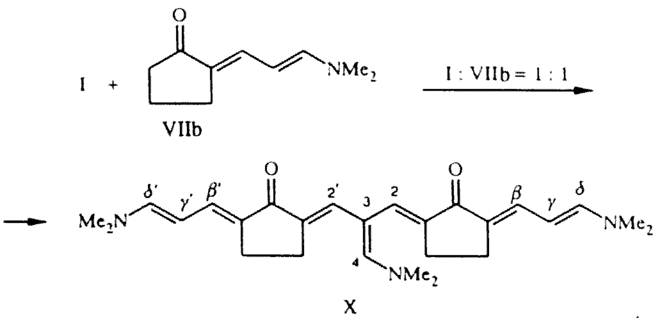


TABLE 2. PMR Spectra for Synthesized Compounds in CD_2Cl_2* with Chemical Shifts (δ, ppm)

Compound	Methine protons				NMe_2, s	Pyrrole ring protons				Remaining protons	Spin–spin coupling (J, Hz)
	$H\alpha$, d; $H\alpha'$, d	$H\beta$; $H\beta'$	$H\gamma$, t; $H\gamma'$, t	$H\delta$, d; $H\delta'$, d		2-H	4-H	5-H	NMe, s		
1	2	3	4	5	6	7	8	9	10	11	12
IVa	6,71 (2H)	7,64 (2H, d)	–	–	–	6,90 (2H, t)	6,45 (2H, t)	6,61 (2H, t)	3,68 (6H)	–	$J\alpha\beta = 16{,}0$, $J_{2,5} = J_{4,5} = 2{,}0$
IVb	–	7,39 (2H, br s)	–	–	–	6,96 (2H, br s)	6,40 (2H, br s)	6,69 (2H, br s)	3,70 (6H)	2,90 (4H, s, CH_2)	–
IVc	–	7,58 (2H, br s)	–	–	–	6,92 (2H, t)	6,39 (2H, t)	6,65 (2H, t)	3,69 (6H)	1,86 (2H, m, CH_2), 2,81 (4H, m, CH_2)	$J_{2,5} = J_{4,5} = 2{,}5$
VIa	5,19 (1H), 6,43 (1H)	7,61 (1H, d), 7,40 (1H, d)	–	–	3,00 (6H, br s)	6,83 (1H, t)	6,36 (1H, t)	6,59 (1H, t)	3,64 (3H)	–	$J\alpha\beta = 14{,}0$, $J\alpha'\beta' = 16{,}0$, $J_{2,5} = J_{4,5} = 2{,}5$
VIb	–	6,84 (1H, t), 7,26 (1H, t)	–	–	3,10 (6H)	7,12 (1H, t)	6,32 (1H, t)	6,62 (1H, t)	3,66 (3H)	2,62 (2H, m, CH_2), 2,99 (2H, m CH_2)	$J\beta,CH_2 = J\beta',CH_2 = 1{,}7$, $J_{2,5} = J_{4,5} = 2{,}5$
VIc	–	6,84 (1H, t), 7,57 (1H, t)	–	–	3,07 (6H)	7,44 (1H, t)	6,32 (1H, t)	6,61 (1H, t)	3,66 (3H)	1,73 (2H, m, CH_2), 2,69 (4H, m, CH_2)	$J\beta,CH_2 = J\beta',CH_2 = 1{,}5$, $J_{2,5} = J_{4,5} = 2{,}5$
VIIIa	6,78 (1H), 6,03 (1H)	7,41 (1H, t), 7,43 (1H, d)	5,23 (1H), –	6,55 (1H), –	2,90 (6H)	6,85 (1H, br s)	6,39 (1H, br s)	6,59 (1H, br s)	3,62 (3H)	–	$J\alpha\beta = J\beta,\gamma = J\gamma,\delta = 12{,}5$, $J\alpha'\beta' = 15{,}0$
VIIIb	–	7,14 (1H, d), 6,90 (1H, t)	5,03 (1H), –	6,30 (1H), –	2,91 (6H)	7,20 (1H, t)	6,34 (1H, t)	6,63 (1H, t)	3,68 (3H)	2,68 (2H, m, CH_2), 2,79 (2H, m, CH_2)	$J\beta,\gamma = J\gamma,\delta = 12{,}5$, $J\beta',CH_2 = 2{,}5$, $J_{2,5} = J_{4,5} = 2{,}5$

TABLE 2. (continued)

1	2	3	4	5	6	7	8	9	10	11	12
VIIIc	–	7,41 (1H, d), 6,88 (1H, t)	5,10 (1H), –	6,80 (1H), –	2,92 (6H)	7,51 (1H, t)	6,35 (1H, t)	6,62 (1H, t)	3,68 (3H)	1,80 (2H, m, CH_2), 2,51 (2H, m, CH_2), 2,72 (2H, m, CH_2)	$J\beta,\gamma$ – $J\gamma,\delta$ – –12,5, $J\beta,CH_2$ – 2,5, $J_{2,5}$ – $J_{4,5}$ – 2,5
VIIId[†]	6,10 (1H), –	7,49 (1H, dd), 6,88 (1H, t)	–	6,81 (1H), –	2,91 (6H)	7,39 (1H, t)	6,32 (1H, t)	6,62 (1H, t)	3,66 (3H)	1,74 (2H, m, CH_2), 2,47 (2H, m, CH_2), 2,62 (2H, m, CH_2), 17,79 (1H, s, H...O)	$J\alpha\beta$ – $J\beta\gamma$ – –14,0, $J\gamma,\delta$ – –12,5, $J\beta',CH_2$ – –2,0, $J_{2,5}$ – –$J_{4,5}$ – 2,0
IX	–	7,31 (1H, d), 7,23 (1H, br s)	5,09 (1H), –	6,74 (1H), 6,60 (1H)	2,82 and 2,89 (12H)	–	–	–	–	1,74 (2H, m, CH_2), 2,48 (4H, m, CH_2), 2,17 (6H, s, N<u>Me</u>$_2$), 3,40 (3H, s, OMe), 4,16 (1H, s, CH)	$J\alpha\beta$ – –$J\alpha'\beta'$ –12,5
X[‡]	–	7,15 (1H, d), 7,04 (1H, d)	4,97 (1H), 5,04 (1H)	6,81 (1H), 6,72 (1H)	2,88, 2,92 and 2,94 (18H)	–	–	–	–	2,22 (4H, m, CH_2), 2,53 (4H, m, CH_2), 6,79 (1H, s, 4-H), 7,00 (1H, br s 2-H), 7,35 (1H, br s, 2′-H)	$J\beta,\gamma$ – $J\gamma,\delta$ – –$J\beta',\gamma'$ – –$J\gamma',\delta'$ – 12,0

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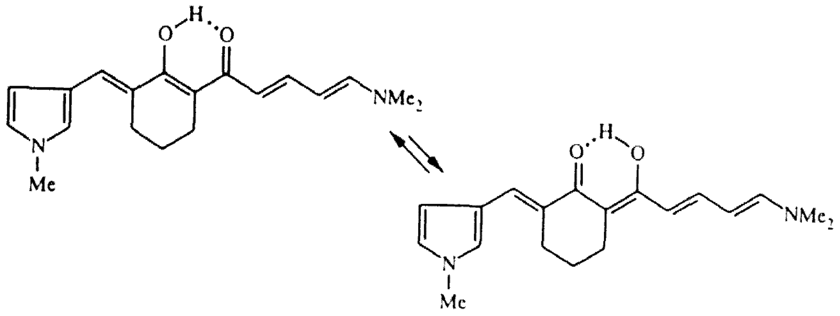
[*] Spectrum of IVa recorded in $CDCl_3$.

[†] Hγ signal obscured by residual CH_2Cl_2.

[‡] Chemical shifts of Hβ, Hγ, Hδ, 2-H and Hβ′, Hγ′, Hδ′, 2′-H interchangeable.

From the PMR spectral data given (Table 2), it appears that all of the synthesized ketones have a trans-configuration of the methine protons (^3J = 12-16 Hz) and that VIIIa-d and X exist in an S-trans conformation ($^3J\beta,\gamma = {}^3J\beta' = 12.5$ Hz).

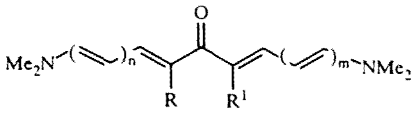
Both diketone VIIId and starting diketone VIId [12] exist as a chelate with an intramolecular hydrogen bond, as confirmed by PMR spectroscopy (Table 2).



VIIId

From a comparison of the electronic absorption data in various solvents (see Table 1) it is apparent that all of the synthesized polyenyl ketones show a positive solvatochromism and that, in going from toluene to ethanol, λ_{max} undergoes a bathochromic shift of 21 to 40 nm.

Change of the N-methylpyrrole ring in the synthesized ketones to a dimethylaminovinyl fragment causes a significant bathochromic shift of λ_{max}. This is apparent when comparing the electronic absorption spectra of ketones IVa,c, VIa,c with the absorption spectra of compounds synthesized before [1, 2] which contain the dimethylaminovinyl group in place of heterocyclic substituents. The most pronounced shift of λ_{max} (90 and 77 nm) to the short wavelength region occurs in the symmetrical ketones IVa,c which contain two N-methylpyrrole rings.



XIa-d

		λ_{max}, nm
a	$R + R^1 = (CH_2)_3$, n = m = 1	490
b	$R = R^1 = H$, n = m = 1	470
c	$R + R^1 = (CH_2)_3$, n = m = 0	440
d	$R = R^1 = H$, n = m = 0	430

The results of a study of the protonation, alkylation and spectroluminescence of the polyenyl ketones synthesized will be given in a subsequent publication.

EXPERIMENTAL

UV spectra were recorded on a Specord UV-VIS instrument. PMR spectra were obtained on a Bruker WM-250 (^1H 250 MHz) with chemical shifts relative to TMS.

The starting ketones were synthesized by known methods: Va [13], Vb [14], Vc [15], VIIa-c [1], and VIIId [12].

Reaction conditions and compound parameters for IVa-c, VIa-c, VIIIa-d, IX and X are given in Table 1.

Condensation of Ketones IIa-c, Va-c and VIIa-d with bis-N,O-acetal I (general method). A mixture of I and ketone II, V, or VII (with the relevant reagent ratio, temperature, and reaction time) was held as shown in Table 1. Different methods were used for work up of the reaction product once it had been cooled to room temperature (methods A-D below).

A. Dry acetone was added to the reaction mixture containing the crystalline product and the precipitate was separated and washed with dry acetone to give VIb and X.

B. The reaction product was triturated with absolute ether and the crystalline product (VIa, IX) filtered and washed with absolute ether.

C. The product was dissolved in CH_2Cl_2 and L40/100 μ SiO_2 was added (2.5 g SiO_2 and 35 ml CH_2Cl_2 to every gram of product). After 24 h the silica was filtered off, washed with CH_2Cl_2, and the filtrate evaporated. Dry acetone was added to this residue and the precipitate was separated and washed with dry acetone to give IVb, c.

D. To the silica gel treated reaction product (method C) after evaporation of CH_2Cl_2 there was added absolute ether and the precipitate was separated and washed with absolute ether to give IVa, VIb, c, and VIIIa-d. Product VIIIc can also be prepared by work up of IX according to method C.

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