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Reactions of α-Azidovinyl Ketones with β-Keto Esters

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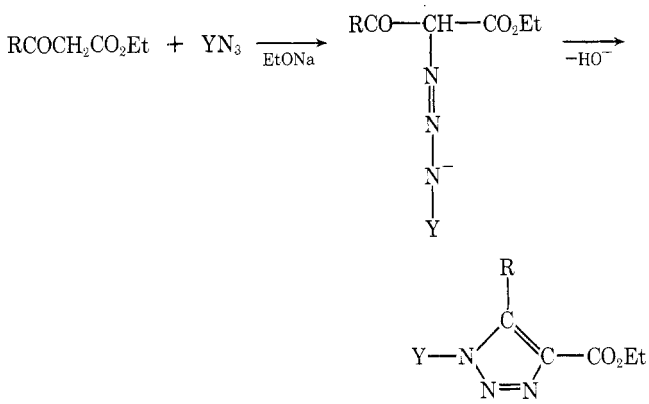
The base-catalyzed reactions of ethyl acetoacetate with α-azidochalcone, α-azido-(*m*-nitrobenzylidene)acetophenone, and α-azidobenzylideneacetone, as well as the reaction of ethyl benzoylacetate with α-azidobenzylideneacetone, were found to give substituted triazolycyclohexanones (**5a,b** and **8a,b**). Ethyl benzoylacetate also reacted with α-azidochalcone or its nitro-substituted derivative, but yielded the N-1-substituted triazoles **10a,b.** Structure assignment of all the products was essentially based upon ^1H and ^{13}C NMR analysis and further confirmed by analytical and other spectral data.

The reaction of aryl azides and alkyl azides with active methylene compounds under basic conditions to give *v*-triazoles (Scheme I) is called the Dimroth reaction after its discoverer.[1] The mechanism of this synthetically important reaction has been shown to involve a two-step cycloaddition process via a triazene intermediate.[2]

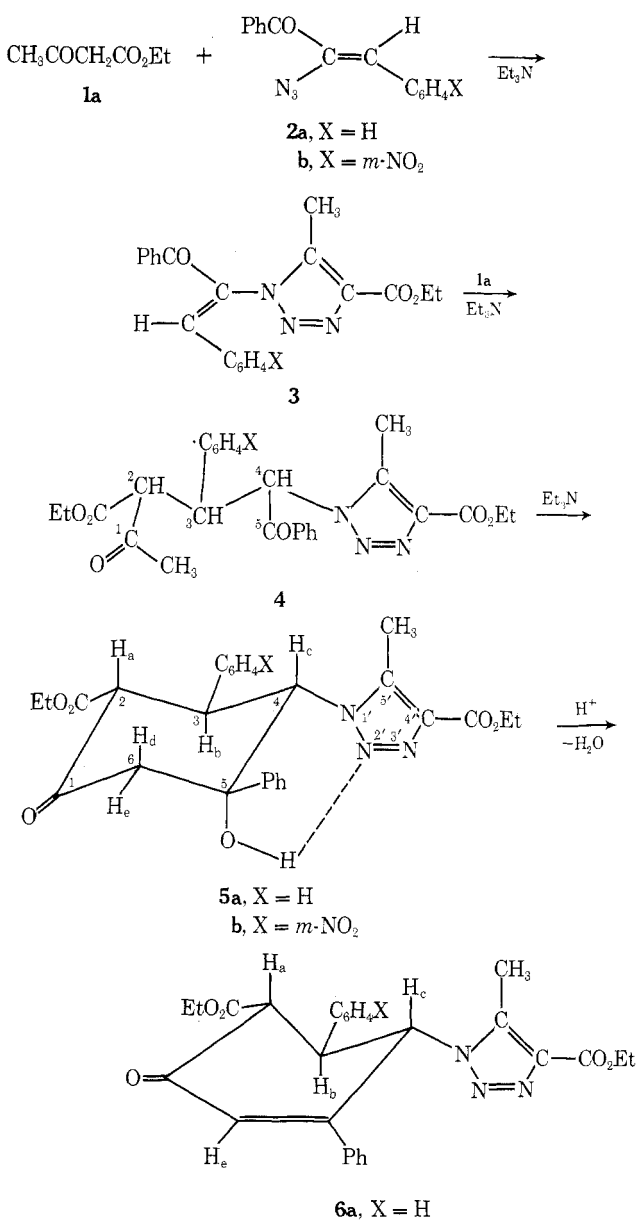
Scheme I
The Dimroth Reaction



Recently, the Dimroth reaction has been extended to simple vinyl azides[3] and β-azidovinyl ketones.[4] In both cases vinyl-substituted *v*-triazoles were obtained. In this paper, we describe our results of the reactions of α-azidovinyl ketones with β-keto esters where the initially formed vinyltriazoles underwent further reaction with the active methylene compounds.

Chemical Results. Treatment of ethyl acetoacetate (**1a**) with α-azidochalcone (**2a**) or its nitrosubstituted derivative **2b** in the presence of triethylamine furnished white, crystalline products to which structures **5a** and **5b** are assigned on the basis of analytical and spectral properties (see discussion NMR). From Scheme II it is apparent that the initially formed Dimroth product **3** has undergone a Michael-type addition with the active methylene compound **1a** in the presence of triethylamine to give **4.** This reaction is expected to occur readily, since the electron density of the olefinic double bond is decreased by the presence of two strong electron-withdrawing substituents. Under the basic reaction conditions, **4** then underwent an intramolecular aldolization, resulting in the formation of **5a,b.** Under acid-

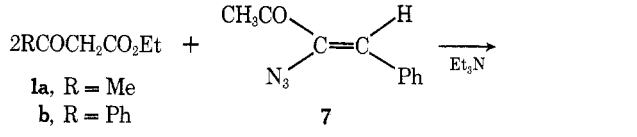
Scheme II



6a, X = H
b, X = *m*-NO_2

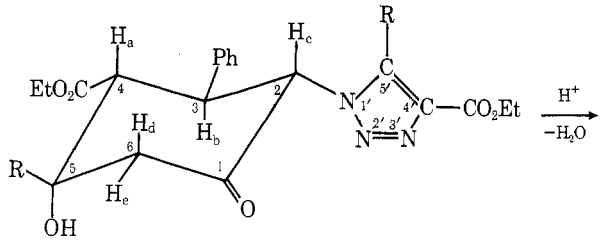
ic conditions, dehydration of **5a,b** occurred to give **6a,b** in high yields.

Ring closure of the Michael adduct **4** in Scheme II thus occurred between the methyl group attached to C_1 and the carbonyl in position 5. If the phenyl group in position 5 is replaced by a methyl group, cyclization proceeded in the other direction as found for the reactions of ethyl acetoacetate (**1a**) and ethyl benzoylacetate (**1b**) with α-azidobenzylideneacetone (**7**). Compounds **8a,b** then were obtained as the only reaction products. Acid-catalyzed dehydration of **8a,b** furnished **9a,b** in high yields.

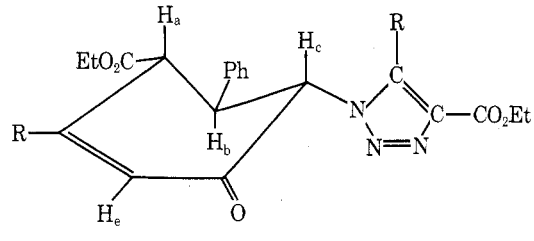


1a, R = Me
b, R = Ph

7

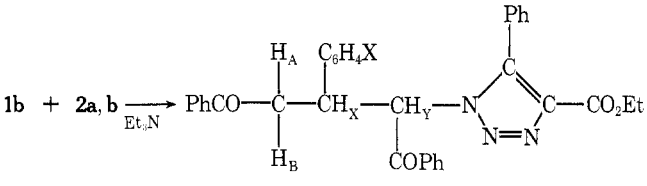


8a, R = CH_3
b, R = Ph



9a, R = CH_3
b, R = Ph

Cyclization to a cyclohexanone cannot occur when the methyl group attached to C_1 in **4** is replaced by a phenyl or substituted phenyl group. Thus, when ethyl benzoylacetate (**1b**) was treated with **2a** or **2b** in the presence of triethylamine, products **10a** and **10b** were obtained which resulted from base-induced decarbethoxylation of the Michael adducts.

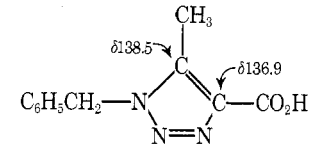


10a, X = H
b, X = *m*-NO_2

Discussion of the ^{1}H and ^{13}C NMR Spectra. The NMR data (Tables I and II) which have led to structure elucidation of the triazole derivatives will now be discussed briefly.

The ^{1}H NMR spectra of compounds **5a** and **5b** showed the presence of only one type of methyl group for both CH_3CH_2 functions. The protons H_a, H_b, and H_c occupy axial positions as evidenced by the large coupling constants J_{ab} and J_{bc} (ca. 12 Hz). Furthermore, the hydroxyl proton of **5a** in $CDCl_3$ was found as a doublet, coupled to the axial proton H_d which resonated as a doublet of doublets. The magnitude of this long-range coupling (J = 2.5 Hz) is indicative of a W arrangement and, hence, points to an axial position for the hydroxyl function.[5] We further suggest that the favorable W arrangement is aided by hydrogen bonding of the hydroxyl proton with the N-2′ atom of the neighboring triazole ring. Addition of D_2O in $CDCl_3$ caused a fast disappearance of the hydroxyl absorption, while at the same time the H_a proton (but not H_c) exchanged slowly for deuterium. In DMSO-d_6 solution at 90°, the H_d absorption (but not H_e) also disappeared completely.[6] All the evidences presented above thus indicate that the large substituents occupy the preferred equatorial positions in the cyclohexanone ring. For the sake of completeness, we also mention here that the ketones **5a** and **5b** equilibrate with their respective enols upon standing in DMSO-d_6 at room temperature. This was seen in the NMR spectrum by the presence of a second ethyl absorption and a low-lying OH singlet at δ 12 (hydrogen bonding with the ester group in position 2). The keto–enol equilibrium compositions are as follows: 90.5:9.5 for **5a** and 85.5:14.5 for **5b.**

Compound **5a** was also subjected to ^{13}C NMR analysis (see Table II). Assignment of the carbon atom absorptions of the triazole moiety was based on comparison with model compound **11,** prepared from benzyl azide and ethyl acetoacetate by the method of Dimroth.[1] Noteworthy from Table II is the higher field absorption of the ketone carbon atom (δ 202.6) compared with the value found for cyclohexanone (δ 208.8).[7] The difference in chemical shift (6 ppm) is the same as that found for the C=O carbon absorptions of acetone (δ 206.0) and ethyl acetoacetate (δ 200.5)[8] and, hence, is due to the presence of an ester function in β position to the ketone group.



11

Compounds **6a** and **6b,** obtained by acid dehydration of **5a** and **5b,** were also fully characterized by their NMR spectra (see Tables I and II). The observed coupling constants in the ^{1}HNMR spectra are consistent with literature data.[9] A comparison of the ^{13}C NMR data of compounds **5a** and **6a** in Table II shows the expected upfield shift of the C_1 atom absorption by introduction of a double bond in conjugation with the ketone function.[7] In DMSO-d_6 solution, **6a** and **6b** were converted completely into their respective enols upon standing at room temperature. The isomerization process was slow for **6a** (within 1 month) but fast for **6b** (within a few minutes). The ^{1}H NMR data given in Table I for **6b** are those of the enol form.

As mentioned in the previous section, **1a** reacted with **7** to give **8a** and not the analog of **4a** (with Me instead of Ph in position 5). This was apparent from the ^{1}H NMR spectra, where H_c and H_d (in addition to OH) exchanged for deuterium upon addition of D_2O in DMSO solution. Proton H_a in **8a** is no longer flanked by two electron-withdrawing groups and did not exchange.

The ^{1}H NMR spectra of **8a** in several solvents (see Table I) pointed to an equilibrium between two forms. Indeed, the absorption lines for H_a, H_b, H_c, and the triazole methyl groups were broadened (in $CDCl_3$ and acetone-d_6) or dedoubled (in DMSO-d_6). When a DMSO-d_6 solution was heated to ca. 100°, the dedoubling disappeared and only one form was seen, having coupling constants J_{ab} and J_{bc} of 12 Hz. On the contrary, when an acetone-d_6 solution of **8a** was cooled to −20°, the H_c and triazole CH_3 signals were dedoubled and the two forms were clearly distinguished. Both forms showed large values for J_{ab} and J_{bc} (12 Hz), consistent with axial positions for the H_a, H_b, and H_c

Table I
100-MHz ^{1}H NMR Data

Compd	Solvent	Chemical shifts, ppm						Coupling constants, Hz			
		H_a	H_b	H_c	H_d and H_e	OH	CH_3 in $C_{5'}$	J_{ab}	J_{bc}	J_{de}	Other J values
5a	$CDCl_3$	4.39 (d)	4.70 (dd)	5.24 (d)	3.49 (dd) and 2.98 (d)	5.50 (d)	1.78 (s)	12	11	14	$J_{d,OH} = 2.5$
	DMSO-d_6	4.42 (d)	4.68 (dd)	5.64 (d)	4.08 (d) and 2.70 (d)	5.95 (s)	1.61 (s)	12	11	14	
5b	DMSO-d_6	4.51 (d)	4.94 (dd)	5.85 (d)	3.99 (d) and 2.77 (d)	6.17 (s)	1.62 (s)	12	11	14	
6a	$CDCl_3$	4.28 (d)	4.46 (dd)	5.96 (br, d)	6.54 (d)		2.03 (s)	13	9.5		$J_{ce} = 2.2$
	DMSO-d_6	4.64 (d)	4.10 (br, m)	6.75 (br, d)	6.56 (d)		2.00 (br, s)	13	10		$J_{ce} = 2$
6b (enol)	$CDCl_3$		4.33 (d)	5.70 (d)	6.96 (s)	12.2	2.63 (s)		1.2		
						CH_3 in C_5					
8a	$CDCl_3$	3.40 (d)	4.40 (br)	5.64 (br)	2.84 (s)	1.44 (s)	2.40 (br)	12			
	Acetone-d_6	3.74 (d)	4.60 (br)	5.90 (br)	3.20 (d) and 2.72 (d)	1.46 (s)	2.34 (br)	12		14	
	DMSO-d_6	3.62 (br, d)	4.59 (br, dd)	5.85 and 6.30 (br)	3.24 (d) and 2.62 (d)	1.40 (s)	2.15 and 2.56 (br)			14	
8b	DMSO-d_6	4.08 (d)	4.75 (dd)	5.42 (d)	3.72 (d) and 2.56 (d)			12	12	14	
9a	$CDCl_3$	4.09 (m)	4.57 (dd)	5.30 (d)	6.19 (m)	2.07 (d)	2.22 (s)	11	13		$J_{a,e} = 2$; $J_{CH_3,H_e} = 0.5$
	DMSO-d_6	4.28 (m)	4.28 (m)	6.18 (m)	6.35 (s)	2.05 (s)	2.30 (s)				
9b	DMSO-d_6	4.92 (dd)	4.39 (dd)	5.72 (d)	6.50 (d)			11	13		$J_{ae} = 2.0$

Table II
^{13}C NMR Chemical Shifts[a] with Respect to Me_4Si (DMSO-d_6 as Solvent)

Compd	C_1	C_2	C_3	C_4	C_5	C_6	$C_{4'}$ and/or $C_{5'}$[b]	CH_3 in $C_{5'}$	Other absorptions
5a	202.6	61.9	46.25	65.8	77.35	52.3	138.3 and 139.7	7.7	CO_2Et in positions C_2 and $C_{4'}$, respectively, at 167.8 and 161.05
6a	192.4	57.95	51.3	60.6	158.3	126.4	136.7 and 140	8.05	CO_2Et in positions C_2 and $C_{4'}$, respectively, at 167.9 and 161.0
11							136.9 and 138.5	8.7	CO_2H at 162.9; CH_2 at 50.8
8a	200.65	67.85	46.1	56.9	72.5	53.7	139.9 and 138.7	7.9	CH_3 in position C_5 at 28; CO_2Et in positions C_4 and $C_{4'}$, respectively, at 170.3 and 161.4
9a	190.3	64.6	48.8	54.6	159.6	126.5	140.4 and 137	8.3	CH_3 in position C_5 at 21.3; CO_2Et in positions C_4 and $C_{4'}$, respectively, at 170.2 and 161.2

[a] In parts per million. [b] The signal attributions for the $C_{4'}$ and $C_{5'}$ carbon atoms are only tentative, since the absorptions of the phenyl carbon atoms attached to the cyclohexanone of compounds **5a**, **6a**, **8a**, and **9a** are situated in the same region.

atoms. This means that the equilibrium phenomenon cannot be explained by a conformational change of the cyclohexanone ring. A reasonable explanation is hindered rotation of the triazole ring resulting in a slow equilibrium between two forms. This is in line with the fact that dedoubling was most pronounced for the H_c and triazole methyl protons.

Noteworthy from the tabulated ^{13}C NMR data of **8a** is the upfield shift of the C_1 absorption (δ 200.65) compared with that in cyclohexanone (δ 208.8). This is attributed to the presence of a triazole ring in the α position to the ketone function. Indeed, this effect was also observed for compound **10a** (CH_YCOPh carbon absorption at δ 193.5 compared with the CH_2COPh carbon absorption at δ 198.1).

In contrast to the ^{1}H NMR spectrum of **8a**, that of **8b** did not clearly show the presence of conformational isomers, although the H_a, H_b, and H_c absorptions were broadened. Again, the hydroxyl proton at δ 5.64 exchanged for deuterium upon addition of D_2O. The acidic protons H_c and H_d exchanged at 90°, but H_a remained unaffected.

The ^{1}H NMR spectrum of **10a** (see Experimental Section) exhibited an ABX pattern with additional coupling between H_X and H_Y. For **10b**, the H_A and H_B protons happened to be magnetically equivalent in DMSO-d_6 solution, resulting in a simplification of the NMR pattern. During

the formation of **10a,b,** an ester group has been eliminated (decarbethoxylation under basic conditions). That this is not the triazole ester group is apparent from the ^{13}C NMR spectrum of **10a,** which showed a characteristic CO_2Et carbon absorption at δ 161.2 (compare this value with those reported in Table II).

Experimental Section

All melting points were obtained on a Leitz apparatus and are uncorrected. The ^1H NMR spectra were recorded with a Varian XL-100 spectrometer using Me_4Si as an internal reference. For ^{13}C NMR spectra, the XL-100 apparatus was equipped with a device for pulsed Fourier transform operation. Peak assignments were made by using the off-resonance spin-decoupling technique and by effecting selective proton decoupling experiments. Furthermore, the replacement of H for D in the deuteration experiments facilitated the interpretation of the ^{13}C NMR spectra.

The α-azidovinyl ketones used in this work were prepared as reported[10] by the reaction of α,β-dibromo ketones with 2 equiv of sodium azide in DMF at room temperature.

Reaction of Ethyl Acetoacetate (1a) with α-Azidochalcone (2a). Compound **1a** (0.02 mol) was allowed to react with **2a** (0.01 mol) in the presence of triethylamine (0.02 mol) with (2 ml) or without DMF as solvent. After 2 months the reaction was finished as observed by the disappearance of the azide band in the ir spectrum at ca. 2130 cm^{-1}. The precipitate (70%) was filtered and crystallized from ethanol (350 ml) to give white needles of **5a** (68%): mp 206–208°; ir (KBr) 3440 (br, OH), 1750, and 1720 with shoulder at 1700 cm^{-1}.

Anal. Calcd for $C_{27}H_{29}N_3O_6$ (491): C, 65.98; H, 5.90; N, 8.55. Found: C, 65.75; H, 5.90; N, 8.70.

Reaction of Ethyl Acetoacetate (1a) with α-Azido(*m*-nitrobenzylidene)acetophenone (2b). Compound **1a** (0.02 mol) was allowed to react with **2b** (0.01 mol) in the presence of triethylamine (0.02 mol) and DMF (2 ml) as solvent. The reaction, followed spectroscopically, was finished after 4 days. The precipitate was collected by filtration and washed with ethanol to give **5b** in 74% yield: mp 213–215° (EtOH); ir (KBr) 3460 (br, OH), 1740, 1720, 1700, 1530, and 1355 cm^{-1}.

Anal. Calcd for $C_{27}H_{28}N_4O_8$ (536); c, 60.45; H, 5.22; N, 10.45. Found: C, 60.55; H, 5.25; N, 10.40.

Reaction of Ethyl Acetoacetate (1a) with α-Azidobenzylideneacetone (7). When **1a** (0.02 mol) was allowed to react with **7** (0.01 mol) in the presence of triethylamine (0.02 mol) at room temperature, the reaction stopped after ca. 1 month, although the ir spectrum still showed the presence of 70% unreacted azide. The precipitate (26%) was collected, washed with ether, and crystallized from ethanol (150 ml) to give white needles of **8a** (23%) which decomposed at 178°, ir (KBr) 3500 (br, OH), 1730–1700 cm^{-1}.

Anal. Calcd for $C_{22}H_{27}N_3O_6$ (429): C, 61.55; H, 6.30; N, 9.80. Found: C, 61.50; H, 6.35; N, 9.85.

Reaction of Ethyl Benzoylacetate (1b) with α-Azidobenzylideneacetone (7). The reaction of **1b** (0.02 mol) with **7** (0.01 mol) in triethylamine (0.02 mol) at room temperature stopped after 6 days, leaving 60% of **7** unreacted. The precipitate was removed, dried, and crystallized from ethanol (40 ml) to give white needles of **8b** in 13% yield: mp 241–243°; ir (KBr) 3480 (br, OH) and 1705 cm^{-1}.

Anal. Calcd for $M^{\cdot+}$ (determined by high-resolution exact-mass measurements): 553.2212. Found: 553.2207.

From the mother liquor 1.12 g of unreacted azide was recovered.

Reaction of Ethyl Benzoylacetate (1b) with α-Azidochalcone (2a). Compound **1b** (0.02 mol) reacted with **2a** (0.01 mol) in the presence of triethylamine (0.02 mol) with evolution of gas. After completion of the reaction (14 days), the mixture was treated with ether (25 ml) to give **10a** in 60% yield. Crystallization from ethanol furnished white needles: mp 168–170°; ir (KBr) 1715 and 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (t, 3 H, J = 7 Hz), 3.6 (dd, H_A, J_{AB} = 17, J_{AX} = 4 Hz), 4.03 (dd, H_B, J_{AB} = 17, J_{BX} = 9 Hz), 4.24 (q, 2 H, J = 7 Hz), 4.72 (m, H_X), 6.17 (d, H_Y, J_{XY} = 6 Hz), 6.72–6.84 (m, 2 H), 7.10 (s, 5 H), 7.24–7.58 (m, 11 H), and 7.84–7.98 (m, 2 H).

Anal. Calcd for $C_{34}H_{29}N_3O_4$ (543): C, 75.13; H, 5.34; N, 7.73. Found: C, 75.10; H, 5.35; N, 7.75.

Reaction of Ethyl Benzoylacetate (1b) with α-Azido(*m*-nitrobenzylidene)acetophenone (2b). A DMF solution (2 ml) of **1b** (0.002 mol), **2b** (0.01 mol), and triethylamine (0.02 mol) was allowed to react at room temperature. After complete reaction (31 hr), the resulting oil was poured into water and this mixture was extracted three times with chloroform (50 ml). The combined chloroform extracts were washed with water and dried over $MgSO_4$. Removal of the solvent yielded a brown oil which was treated with ether (30 ml) to give **10b** in 50% yield: mp 198–201° (EtOH); ir (KBr) 1720, 1685, 1530, and 1350 cm^{-1}; NMR ($CDCl_3$) δ 1.13 (t, 3 H, J = 7 Hz), 3.64 (d, 2 H, J_{AX} = 7 Hz), 4.16 (q, 2 H, J = 7 Hz), 4.88 (m, H_X), 6.42 (d, H_Y, J_{XY} = 8.5 Hz), 6.90–7.05 (m, 2 H), 7.3–7.9 (m, 15 H), 7.9–8.1 (m, 2 H).

Anal. Calcd for $C_{34}H_{28}N_4O_6$ (588): C, 69.38; H, 4.76; N, 9.52. Found: C, 69.50; H, 4.70; N, 9.55.

Dehydration of Compounds 5a, 5b, 8a, and 8b. A solution of **5a,b** or **8a,b** (1 g) in ethanol (40 ml) containing 3 ml of sulfuric acid was refluxed for 3 hr. The solution was then cooled to room temperature and poured into water (100 ml). The white precipitate was filtered, washed several times with water until neutral reaction, dried in vacuo over P_2O_5 at 50°, and crystallized from ethanol.

Compound **6a** was obtained in 72% yield after crystallization: mp 181–184°; ir (KBr) 1740, 1720, 1680, and 1615 cm^{-1}; mass spectrum $M^{\cdot+}$ (6%) *m/e* 473.

Anal. Calcd for $C_{27}H_{27}N_3O_5$ (473): C, 68.49; H, 5.71; N, 8.88. Found: C, 68.25; H, 5.75; N, 8.90.

Compound **6b** was obtained in 88% yield after crystallization: mp 165–167.5°; ir (KBr) 1715, 1655, 1630, 1530, and 1350 cm^{-1}; mass spectrum $M^{\cdot+}$ (59%) *m/e* 518.

Anal. Calcd for $C_{27}H_{26}N_4O_7$ (518): C, 62.54; H, 5.02; N, 10.81. Found: 62.55; H, 5.05; N. 10.80.

Compound **9a** was obtained in 82% yield after crystallization: mp 176–178°; ir (KBr) 1725, 1680, and 1630 cm^{-1}.

Anal. Calcd for $M^{\cdot+}$ (determined by high-resolution exact-mass measurements): 411.179408. Found: 411.17998.

Compound **9b** was obtained as white needles in 86% yield after crystallization from ethanol (25 ml): mp 184–186°; ir (KBr) 1715, 1680, and 1610 cm^{-1}.

Anal. Calcd for $M^{\cdot+}$ (determined by high-resolution exact-mass measurements): 535.21070. Found: 535.21169.

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Registry No.—**1a,** 141-97-9; **1b,** 94-02-0; **2a,** 26309-08-0; **2b,** 51002-98-3; **5a,** 54698-61-2; **5b,** 54698-62-3; **6a,** 54698-63-4; **6b,** 54698-64-5; **7,** 26309-09-1; **8a,** 54698-65-6; **8b,** 54698-66-7; **9a,** 54698-67-8; **9b,** 54698-68-9; **10a,** 54698-58-7; **10b,** 54698-59-8; **11,** 54698-60-1.

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