SIGMA-COMPLEXES IN THE PYRIMIDINE SERIES.

9.* ALKYLATION OF ACETONYL ANIONIC SIGMA-COMPLEXES OF 5-NITROPYRIMIDINE

G. Ya. Remennikov, S. G. Vishnevskii, V. V. Pirozhenko, and V. M. Cherkasov

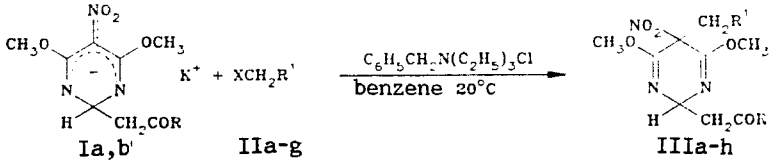
UDC 547.853'85:541.67: 543.422.25

The alkylation of acetonyl, anionic sigma-complexes of the 5-nitropyrimidine series with geminal substitution in the 2 or 6 position is studied. Depending on the position of the geminal substitution, the $C_{(5)}$ or the $N_{(1)}$ atom is alkylated to form 2,5- or 1,6-dihydropyrimidine, respectively.

Anionic σ-complexes are very reactive compounds with strong nucleophilic properties. Examples of the reaction of anionic σ-complexes of the benzene series with electrophilic reagents have been described. Thus, phenyldiazonium salts replace the nitro group in a position para to the geminal node of Yanovskii's σ-complex while simultaneously aromatizing it [2]. Alkylation of anionic spiro σ-complexes of the di- and trinitrobenzene series leads to esters of the nitronic acids [3, 4]. The reaction of electrophilic reagents with the anionic σ-complex of tetrazole [5] and with adducts of phenyllithium with diazinamine [6], as a result of which N-substituted azoles and azines are obtained, has been studied. Data have been presented concerning the ambidentate properties of lithium derivatives of 2-alkyl(aryl)-1,2-dihydropyridines, which are attacked by electrophilic agents at a nitrogen or ring carbon atom [7-9].

Previously, we described the alkylation of the anion of 2H-5-nitro-2-acetonyl-4,6-dimethoxypyrimidine [10]. The present work deals with a study of the alkylation of acetonyl σ-complexes of 5-nitropyrimidines geminally substituted in the 2 or 6 position.

In the alkylation of σ-complexes Ia, b with alkyl halides IIa-g, electrophilic attack occurs at the $C_{(5)}$ atom with the formation of 2,5-dihydropyrimidines IIIa-h. The optimum conditions for the alkylation were found for the case of the reaction of σ-complex Ia with methyl iodide. When this reaction was carried out in DMF, 2,5-dihydropyrimidine IIIa was formed in 15% yield. By using dibenzo-18-crown-6 as a catalyst, we succeeded in raising the yield of IIIa to 30%. When this reaction was carried out in benzene in the presence of an equimolar amount of benzyltriethylammonium chloride, the yield of IIIa rose to 40%. The alkylation of σ-complexes Ia, b with alkyl halides IIa-g was carried out under analogous conditions.



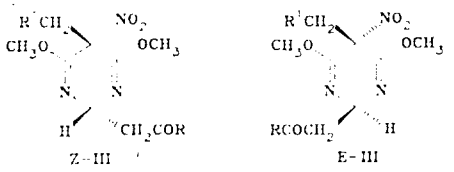
Ia, IIIa–g R=CH_3; Ib, IIIh R=C_6H_5; II, III a,h R^1=H; b R^1=CH_3; c R^1=C_2H_5; d R^1=C_3H_7; e R^1=C_6H_5; f R^1=*p*-$NO_2C_6H_4$; g R^1=*p*-$CH_3OC_6H_4$; X=Cl, Br, I

The structure of resultant 2,5-dihydropyrimidines IIIa-h were proved by the UV, PMR, and ^{13}C NMR spectra. The presence in the PMR spectra of triplets in the 4.59-5.84 ppm region and of doublets in the 1.27-3.27 ppm region (Table 1) is evidence that the geminal node is preserved at the 2 position of the pyrimidine ring on going from σ-complexes Ia, b to dihydropyrimidines IIIa-h. The presence of a double set of signals with compounds IIIa-h is evidence of the formation of a mixture of Z- and E-diastereomers, but the closeness of the chemical shift values does not allow them to be assigned to a specific isomer. The chemical shifts of the methyl (in compounds IIIa, h) and methylene (IIIb-g) groups show unambiguously a bond between these groups and carbon atoms of the pyrimidine ring.

*See [1] for Communication 8.

Institute of Bioorganic Chemistry, Academy of Sciences of the Ukrainian SSR, Kiev 252660. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1238-1243, September, 1990. Original article submitted November 28, 1988.

0009-3122/90/2609-1033$12.50

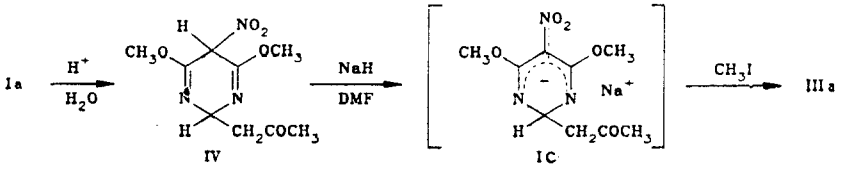


Z-III E-III

The strong-field shift of the signals from protons of the methylene groups of the acetonyl fragment of one form of compounds IIIe-g (~1.30 ppm) is obviously explained by the steric and electronic influence of the benzyl groupings. This is confirmed by the fact that it was possible to separate the mixture of diastereomers of IIIe chromatographically. As a result, two substances were obtained with different physical constants (see Experimental). This obviously allows the substance with the higher melting point to be assigned as the E-configuration.

In the ^{13}C NMR spectra of Meisenheimer's classical σ-complexes [11], the signal from the carbon atom bonded to the nitro group and located para to the geminal node, is reported to have the greatest strong-field chemical shift (~120 ppm), which is explained by the maximum localization of negative charge on this carbon atom. Analogous rules are also characteristic of the σ-complexes of the 5-nitropyrimidine series (Table 2). It follows from these comparisons of the NMR spectra of initial anionic σ-complexes Ia, b and compounds IIIa-h that one finds on the formation of the latter a significant strong-field shift of the signal from the $C_{(5)}$ atom (78-82 ppm) that marks a change in its hybridization from sp^2 to sp^3. Thus, the presence of two sp^3-hybridized carbon atoms in compounds IIIa-h proves their 2,5-dihydropyrimidine structure.

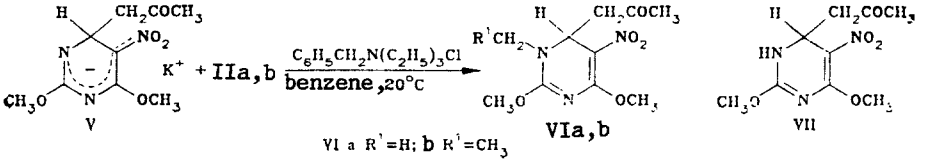
Our data [12] concerning the fact that σ-complex Ia is protonated at the N atom of the ring to form 1,2-dihydropyrimidine proved to be general. On acidification of an aqueous solution of σ-complex Ia, a precipitate forms, the PMR spectrum of which (Table 1) is characterized by a double set of signals (analogous to compounds IIIa-h). Moreover, the chemical shift of the $C_{(5)}$ atom in the ^{13}C NMR spectrum (Table 2) (73.79 ppm) and its coupling constant with the proton (155 Hz) confirm its sp^3-hybridization. Thus, the protonation of compound Ia takes place, as in the alkylation, at the $C_{(5)}$ atom, with the formation of 5-nitro-5-H-2-acetonyl-4,6-dimethoxy-2,5-dihydropyrimidine (IV). Due to the mobility of the hydrogen atom on the $C_{(5)}$ atom, dihydropyrimidine IV is methylated in basic solution, forming compound IIIa, probably through intermediate, σ-complex Ic:



The UV spectra of the synthesized dihydropyrimidines IIIa-h are characterized by absorption bands in the 191-201 nm region showing the presence of an imine fragment in the molecule and correspond to the electronic spectra of 2,5-dihydropyrimidines described in [13].

The 2,5-dihydropyrimidines are a poorly studied class of compounds, which is explained by their limited availability [14-17]. The formation of 2,5-dihydropyrimidines on the alkylation of the anionic, σ-complexes can serve as a preparative method.

In acetonyl σ-complex V, the geminal node is located ortho to the nitro group. In this case, the electrophilic attack by alkyl halides IIa, b occurs at the heteroatom with the formation of 1-methyl(ethyl)-5-nitro-6H-6-acetonyl-2,4-dimethoxy-1,6-dihydropyrimidines VIa, b, respectively.



The PMR spectra of dihydropyrimidines VIa, b (Table 1) show that the geminal node is preserved in the 6 position of the pyrimidine ring on going from σ-complex V to dihydropyrimidines VIa, b. The protons of the methylene group appear as the AB part of an ABX system because of nonequivalence. The chemical shifts of the alkyl groups characterize these groups as bonded to a nitrogen atom of the pyrimidine ring.

TABLE 1. Characteristics of Synthesized Compounds IIIa-h, IV, and VIa, b

Compound*[1]	Empirical formula	R_f*[2]	UV spectrum, λ_{max}, nm (log ε)	PMP spectrum, δ, ppm					Yield, %
				CH, t	OCH_3, s	acetonyl group		other signals	
						CH_2, d	CH_3, s		
IIIa	$C_{10}H_{15}N_3O_5$	0,25	198 (4,04)	5,58; 5,64	3,66	2,77; 2,79	2,19; 2,14	1,86 s (CH_3); 1,79 s (CH_3)	40
IIIb	$C_{11}H_{17}N_3O_5$	0,31	191 (4,07)	5,46; 5,63	3,34	2,41; 2,65	2,08; 2,09	2,26 d (CH_2); 0,15 b (CH_3)	25
IIIc	$C_{12}H_{19}N_3O_5$	0,30	199 (4,12)	5,44; 5,62	3,53	2,47; 2,64	2,07; 2,09	3,63 m (CH_2); 2,31 m (CH_2); 0,79 m (CH_3)	7
IIId	$C_{13}H_{21}N_3O_5$	0,28	198 (4,17)	5,50; 5,68	3,59	2,53; 2,70	2,12; 2,16	0,14...1,25 m ($CH_2CH_2CH_3$); 2,26 m (CH_2)	5
IIIe*[3]	$C_{16}H_{19}N_3O_5$	0,29	199 (4,19)	4,60	3,69	2,58	2,08	3,63 s (CH_2) | 6,91...7,28 m	17
IIIe*[4]	$C_{16}H_{19}N_3O_5$	0,25	199 (4,23)	5,49	3,72	1,27	1,87	3,66 s (CH_2) | (C_6H_5)	11
IIIf	$C_{16}H_{18}N_4O_7$	0,15	199 (4,63), 263 (4,31)	4,73; 5,46	3,66; 3,67	2,55; 1,36	2,03; 1,82	3,80 s (CH_2); 7,02...8,20 m (C_6H_4); 3,74 s (CH_2)	60
IIIh	$C_{17}H_{21}N_3O_6$	0,16	198 (4,46), 226 (4,01)	4,59; 5,43	3,62; 3,64	2,53; 1,27	2,02; 1,81	3,65 s (OCH_3); 3,52 s (CH_2); 6,55...6,80 m (C_6H_4); 3,67 (OCH_3); 3,55 s (CH_2)	23
IIIh	$C_{15}H_{17}N_3O_5$	0,20	200 (4,43), 243 (4,10)	5,72; 5,84	3,48; 3,52	3,20; 3,27	—	1,72 s (CH_3); 7,32...7,82 m (C_6H_5); 1,82 s (CH_3)	30
IV	$C_9H_{13}N_3O_5$	0,11	201 (4,35)	5,68; 5,66	3,70; 3,71	2,74; 2,78	2,18; 2,09	5,23 d (CH); 5,25 s (CH)	47
VIa	$C_{10}H_{15}N_3O_5$	0,45	253 (3,53), 385 (3,92)	5,16 d.d	3,84; 3,87	2,79 m	2,08	2,98 s (NCH_3)	27
VIb	$C_{11}H_{17}N_3O_5$	0,40	267 (3,47), 387 (3,89)	5,15 d.d	3,84; 3,87	2,72 m	2,01	3,52, 3,17 d.q (NCH_2); 1,06 d.t (CH_3)	5

*Compound VIa T_{mp} 161-162°C (from ethanol), VIb T_{mp} 90-91°C (from ethanol).

**Compounds IIIa-h and IV taken in chloroform and VIa, b in a 25:1 chloroform/methanol system.

***T_{mp} 84-86°C.

****Oil.

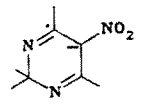
TABLE 2. ^{13}C NMR Spectra of Compounds Ia, b and V (in acetone-D_6) and Compounds IIIa-h, IV, VIa, b, and VII (in $CDCl_3$)

Compound	Chemical shift, δ, ppm							
	pyrimidine ring			acetonyl (phenacyl) group			OCH_3	other signals
	$C_{(2)}$	$C_{(4,6)}$*	$C_{(5)}$	CH_2	CO	CH_3		
Ia	71,19	159,83	105,52	57,95	208,10	31,49	53,97	—
IIIa	70,90 71,23	154,76 154,91	78,01	50,20 51,29	205,20 205,61	30,35 30,71	53,78	18,49 (CH_3) 18,88 (CH_3)
IIIb	71,32	153,46 153,61	82,59 82,68	51,44 52,66	205,20 205,73	30,20 30,83	53,84	16,79 (CH_2); 7,55 (CH_3) 17,67 (CH_2); 8,40 (CH_3)
IIIc	71,41 71,50	153,97 154,14	81,88 82,03	51,49 52,86	205,41 205,85	30,26 31,09	54,07	17,01 (CH_2); 32,54 (CH_2); 13,67 (CH_3) 17,79 (CH_2); 33,31 (CH_2); 13,79 (CH_3)
IIId	71,41 71,52	153,94 154,11	81,97 82,12	51,59 51,83	205,41 206,03	31,00 31,13	54,05	22,19 (CH_2); 26,24 (CH_2); 26,50 (CH_2); 13,58 (CH_3) 30,12 (CH_2); 30,74 (CH_2); 31,00 (CH_2); 13,64 (CH_3)
IIIe	71,03 71,47	152,82 153,14	82,31 82,38	48,42 49,24	205,25 205,73	28,79	51,71	35,27 (CH_2); 125,91 ... 130,52 (C_6H_5)
IIIf	71,12 71,29	152,30 152,52	81,42 81,52	49,10	204,26 205,28	28,38 29,83	52,04	36,74 (CH_2); 123,81 ... 147,66 (C_6H_4)
IIIg	71,15 71,56	153,03 153,30	82,47	48,70 49,37	205,28 205,90	28,70 29,00	51,77	36,52 (CH_2); 123,49 ... 159,47 (C_6H_4); 55,28 (OCH_3); 55,29 (OCH_3)
IV	71,80 73,40	149,49 150,17	68,67 70,39	48,96 51,27	205,45	28,68 28,80	53,98 53,84	—
Ib	71,68	159,43	105,10	56,05	199,59	—	53,46	125,73 ... 139,17 (C_6H_5)
IIIc	71,70	154,50 155,06	78,27	43,02 44,35	196,89 197,45	—	51,93	16,70 (CH_3); 128,02 ... 137,37 (C_6H_5) 16,93 (CH_3);
V	159,42	57,61 167,64	107,65	49,38	210,06	31,10	53,29 53,94	—
VIa	157,53	54,59 161,55	103,57	43,88	203,97	28,87	52,99 54,29	39,24 (NCH_3)
VIb	157,37	54,28 161,63	104,04	40,43	203,87	28,65	51,88 52,99	45,11 (NCH_2); 11,16 (CH_3)
VII	160,39	48,85 164,16	105,66	47,54	208,55	30,18	55,04 55,74	—

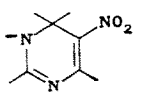
*For compounds V, VIa, b, and VII, the values given for $C_{(4)}$ and $C_{(6)}$, respectively.

In the ^{13}C NMR spectra, the chemical shift of the $C_{(5)}$ signal remains virtually unchanged on going from compounds V to VIa, b, showing that its hybridization is preserved. (For comparison, the NMR spectrum of 1,6-dihydropyrimidine VII, described in [12], is given.) The approximate equality of the absorption maxima of σ-complex V, and dihydropyrimidines VIa, b and VII marks the presence in these compounds of similar chains of conjugation. Thus, the NMR and UV spectra confirm the 1,6-dihydropyrimidine structure of compounds VIa, b.

We have shown earlier [18, 19] on the basis of the UV spectra that the distribution of electronic density in anionic σ-complexes Ia, b is described by a major contribution of structures A and B, respectively. This explains the direction of alkylation with different positions of the geminal node.



A (Ia,b)



B (VI)

Moreover, the stability of the resultant dihydropyrimidines agrees with the demands for stability of such systems [16].

EXPERIMENTAL

The NMR spectra were taken on a Bruker WP-200 (200 MHz) spectrometer in $CDCl_3$ and acetone-d_6 with a HMDS external standard. The electronic spectra were measured on a Specord UV-vis instrument (in methanol) in a nitrogen stream. The concentration of the solutions was 10^{-4} M. The purity of the substances synthesized was established by means of TLC on Silufol UV-254 plates, chloroform eluent.

The σ-complexes Ia, b and V were synthesized by the procedures in [20, 21]. The C, H, and N elemental analyses of compounds IIIa-h, IV, and VIa, b agreed with the calculated values.

5-Nitro-5-methyl-2-acetonyl-4,6-dimethoxy-2,5-dihydropyrimidine (IIIa, $C_{10}H_{15}N_3O_5$). **A.** Methyl iodide, 0.44 ml (7.0 mmoles), is added to a solution of 0.98 g (3.5 mmoles) of σ-complex Ia in 5 ml of DMF at 20°C with stirring. After 24 h, the solvent is evaporated to dryness under reduced pressure. The residue is dissolved with ethyl ether (50 ml), the ethereal solution is dried over $MgSO_4$, the solvent distilled off, and the residue chromatographed on silica gel (20 g), eluting with chloroform. The solvent is evaporated to dryness. The residue is an oil. Yield 0.13 g (15.2%).

B. Methyl iodide, 0.44 ml (7.0 mmoles) and dibenzo-18-crown-6, 0.14 g (0.4 mmole) are added to 0.98 g (3.5 mmoles) of σ-complex Ia in 5 ml of DMF at 20°C with stirring. After 24 h the product is separated by method **A**. Yield 0.26 g (30.2%).

C. A solution of 0.3 g (1.23 mmoles) of 2,5-dihydropyrimidine IV in 5 ml of DMF is added with stirring to a suspension of 0.03 g (1.25 mmoles) of NaH in 5 ml of DMF in a stream of argon. Thirty minutes after hydrogen evolution ceases, 0.21 g (0.6 mmole) of dibenzo-18-crown-6 and 0.16 ml (2.53 mmoles) of methyl iodide are added to the reaction mixture. After 24 h, the product is separated by method **A**. Yield 0.21 g (65%).

Dihydropyrimidine IIIa-g and VIa, b. The alkyl halide II, 7.0 mmoles, is added with stirring to a suspension of 3.5 mmoles of σ-complex Ia (Ib, V) and 3.5 mmoles of benzyltriethylammonium chloride in 10 ml of benzene at 20°C. After 24 h, the deposit is filtered off and the mother liquor evaporated to dryness. The residue is chromatographed on a column with 20 g of silica gel, eluting with chloroform. The solvent is evaporated to dryness.

In the case of IIIe, the residue is repeatedly separated on a column with silica gel (30 g) and two isomers are obtained. Isomer E-IIIe, yield 17%, T_{mp} 84-86°C (from hexane). Isomer Z-IIIe, yield 11%, oil.

5-Nitro-5H-2-acetonyl-4,6-dimethoxy-2,5-dihydropyrimidine (IV, $C_9H_{13}N_3O_5$). Ten milliliters of 0.6 N sulfuric acid solution is added with stirring to a solution of 1.5 g (5.4 mmoles) of σ-complex Ia in 20 ml of water. The mixture is stirred for 30 min. The white, crystalline precipitate is filtered off. Yield 0.60 g (47%).

LITERATURE CITED

1. G. Ya. Remennikov, L. K. Kurilenko, I. V. Boldyrev, and V. M. Cherkasov, *Khim. Geterotsikl. Soedin.*, No. 12, 1659 (1987).
2. A. Ya. Kaminskii, S. S. Gitis, I. L. Bagal, Yu. D. Grudtsyn, T. P. Ikher, L. V. Illarionova, and N. D. Stepanov, *Zh. Org. Khim.*, **13**, 803 (1977).
3. V. N. Drozd, V. N. Knyazev, and G. S. Bogomolova, *Zh. Org. Khim.*, **12**, 1833 (1976).
4. V. N. Drozd and N. V. Grandberg, *Zh. Org. Khim.*, **15**, 550 (1979).
5. F. Einberg, *J. Org. Chem.*, **35**, 3978 (1970).
6. R. E. van der Stoel and H. C. van der Plas, *Rec. Trav. Chim.*, **97**, 116 (1978).
7. C. S. Giam and J. L. Stout, *Chem. Commun.*, No. 8, 478 (1970).
8. R. F. Francis, C. D. Crews, and B. S. Scott, *J. Org. Chem.*, **43**, 3237 (1978).
9. A. I. Pavlyuchenko, N. I. Smirnova, N. I. Korotkova, and E. I. Kovshov, *Khim. Geterotsikl. Soedin.*, No. 10, 1389 (1985).
10. G. Ya. Remennikov, V. M. Cherkasov, and V. V. Pirozhenko, *Khim. Geterotsikl. Soedin.*, No. 4, 562 (1988).
11. G. A. Olah and H. Mayr, *J. Org. Chem.*, **41**, 3448 (1976).
12. V. M. Cherkasov, G. Ya. Remennikov, and E. A. Romanenko, *Khim. Geterotsikl. Soedin.*, No. 6, 823 (1981).
13. A. L. Weis, F. Frolow, and R. Viskautsan, *J. Org. Chem.*, **51**, 4623 (1986).
14. P. Petkov, *Voen.-Med. Godishnik*, No. 1, 83 (1961); *Ref. Zh. Khim.*, 16Zh230 (1962).
15. M. D. Mehta, D. Miller, and E. F. Mooney, *J. Chem. Soc.*, No. 12, 6695 (1965).
16. A. L. Weis and H. C. van der Plas, *Heterocycles*, **24**, 1433 (1986).
17. A. L. Weis, in: *Advances in Heterocyclic Chemistry*, A. R. Katritzky (ed.), Vol. 24, Academic Press, New York (1985), p. 3.

18. A. Ya. Il'chenko, G. Ya. Remennikov, and V. M. Cherkasov, *Khim. Geterotsikl. Soedin.*, No. 9, 1260 (1981).
19. G. Ya. Remennikov, "Synthesis and investigation of anionic sigma-complexes of 5-nitropyrimidine and its methoxy substituted derivatives," Dissertation, Candidate in Chemical Sciences, Kiev (1982).
20. V. M. Cherkasov, G. Ya. Remennikov, and E. A. Romanenko, *Khim. Geterotsikl. Soedin.*, No. 10, 1389 (1978).
21. V. M. Cherkasov, G. Ya. Remennikov, A. A. Kisilenko, and E. A. Romanenko, *Khim. Geterotsikl. Soedin.*, No. 2, 239 (1980).

CYCLOADDITION OF ANHYDRO BASES OF HETEROCYCLIC CATIONS.

1.* SYNTHESIS OF SPIROHETARENES IN THE REACTION OF s-TETRAZINES WITH THE ANHYDRO BASES OF ACRIDINIUM, XANTHYLIUM, AND THIOXANTHYLIUM SALTS

E. G. Kovalev, G. L. Rusinov, V. A. Anufriev, and L. G. Egorova

UDC 547.815'818.6'835.-1'836.1'852.3'883

A new method of spiro-ring formation by the reaction of s-tetrazines with anhydro bases was described. The prototropic transitions were detected in the pyridazine fragments of the resulting spirocyclic compounds. The heterocycles of the anhydro bases are converted to cyclic ketones as a result of the breaking of the spiro junction in the acidic hydrolysis of the spirohetarenes. The regioselectivity of the cycloaddition was established.

The anhydro bases of the heterocyclic cations having the exocyclic double bond, which is not stabilized by acceptor substituents, are very reactive and extremely unstable organic compounds. They are sensitive to moisture and the oxygen of the air [1], are readily converted to dimers and polymers [2, 3], and are even carbonized [4]. The traditional chemistry of these compounds is associated with their participation in the synthesis of the cyanin dyes; moreover, the formation of the anhydro bases is often postulated in recyclization reactions [5]. We previously first found [6] the principle possibility of the participation of anhydro bases in the reactions of the cycloaddition to s-tetrazines, in which the s-tetrazines emerge in the role of reversed dienes, and the anhydro bases have the role of reversed dienophiles (the Carboni–Lindsey reaction [7]). The increased acceptor characteristics of the s-tetrazines [8] render them so powerful among the reversed dienes [9] that the requirement for the very laborious isolation of the monomeric anhydro bases becomes superfluous since the rates of their oxidation and dimerization are significantly less than the rates of cycloaddition; at the moment of formation, they are "intercepted" in a practically quantitative manner by the s-tetrazines. After the completion of investigations with the involvement of practically all classes of heterocyclic cations in the Carboni–Lindsey reaction [10], we are commencing the given series of the work in which exomethylene compounds of acridan, xanthene, and thioxanthene (A) are utilized as the anhydro bases. The choice of these compounds for the first communication is explained by the possibility of considering them as model fixed structures with the single "essentially double" [11] exocyclic bond determining the reactivity in the cycloaddition. Moreover, the presence of the very bulky phenylene fragments at such a double bond somewhat stabilizes their monomeric composition and, consequently, allows the experimentation with the isolated anhydro bases. Finally, the general features obtained by the study of the reaction with these model compounds will possibly be extended to the initial phase of the reactions of the anhydro bases of all the remaining heterocyclic cations.

S. M. Kirov Urals Polytechnical Institute, Sverdlovsk 620002. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1244-1249, September, 1990. Original article submitted March 13, 1989.

 0009-3122/90/2609-1038$12.50