Chemistry of Heterocyclic Compounds, Vol. 32, No. 1, 1996

SIGMA COMPLEXES IN THE PYRIMIDINE SERIES. 12.* ACYLATION AND ETHOXYCARBONYLATION OF ACETONYL ANIONIC SIGMA COMPLEXES OF 5-NITROPYRIMIDINE

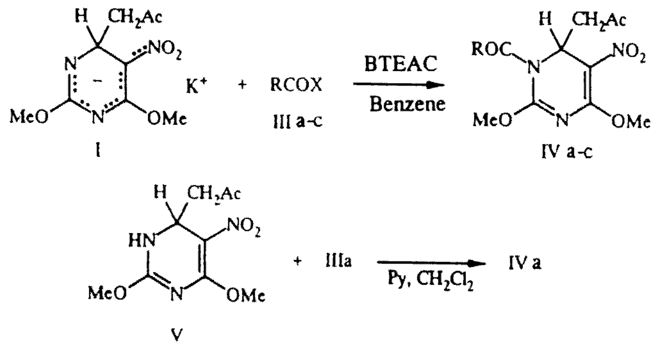
S. G. Vishnevskii, V. V. Pirozhenko, and G. Ya. Remennikov

As a result of acylation and ethoxycarbonylation of acetonyl anionic sigma complexes of 5-nitropyrimidine containing a geminal unit in the 6 and 2 positions, we have obtained $N_{(1)}$-substituted 5-nitro-1,6-dihydropyrimidines and $C_{(5)}$-substituted pyrimidines respectively.

Earlier, in studying the reaction of acetonyl anionic sigma complexes of the 5-nitropyrimidine series with alkyl halides [2] and aryldiazonium salts [1], we established that the orientation of electrophilic attack depends considerably on the structure of the sigma complex and the nature of the electrophile. Continuing the investigation of the chemical properties of anionic sigma complexes, in this paper we have studied the reaction of substituted 6-acetonyl-6H- and 2-acetonyl-2H-pyrimidinates of potassium (I and II respectively) with ethylchlorocarbonate, acetic anhydride, and benzoyl chloride. In the literature, the formation of the nitrosoacetyl derivative is described upon acetylation of an anionic *spiro* sigma complex of the Meisenheimer complex type, containing a nitroso group in the position *para* to the geminal unit [3]. We have also studied alkoxycarbonylation of sigma adducts of phenyllithium with diazines [4], as a result of which N-substituted derivatives are obtained.

By reaction of the sigma complex I (in which the geminal unit is located in the 6 position of the pyrimidine ring) with ethylchlorocarbonate (IIIa) in benzene in the presence of an equimolecular amount of benzyltriethylammonium chloride (BTEAC) (method A), we obtain 6-acetonyl-2,4-dimethoxy-5-nitro-1-ethoxycarbonyl-1,6-dihydropyrimidine (IVa). By acylation of the indicated complex with acetic anhydride (IIIb) and benzoyl chloride (IIIc) under the same conditions, the ketones (IVb) and (IVc) respectively are synthesized. The ether IVa is also obtained by ethoxycarbonylation of 1,6-dihydropyrimidine (V) [5] in methylene chloride in the presence of pyridine (method B).

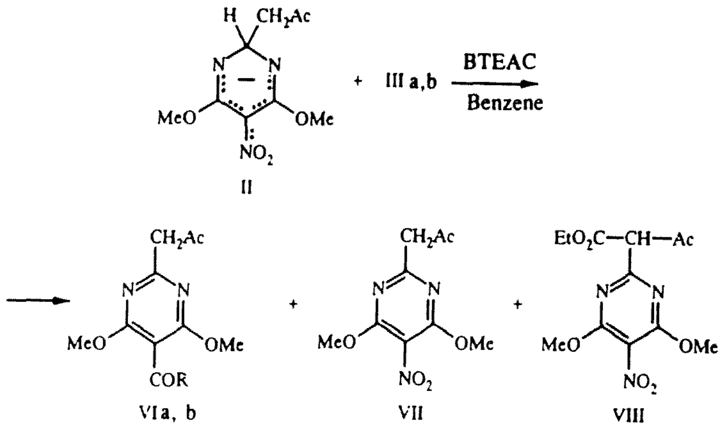
Scheme 1



---

*For Communication 11, see [1].

Institute of Bioorganic Chemistry and Petroleum Chemistry, National Academy of Sciences of Ukraine, Kiev 253660.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 77-80, January, 1996. Original article submitted May 12, 1995; revision submitted October 9, 1995.

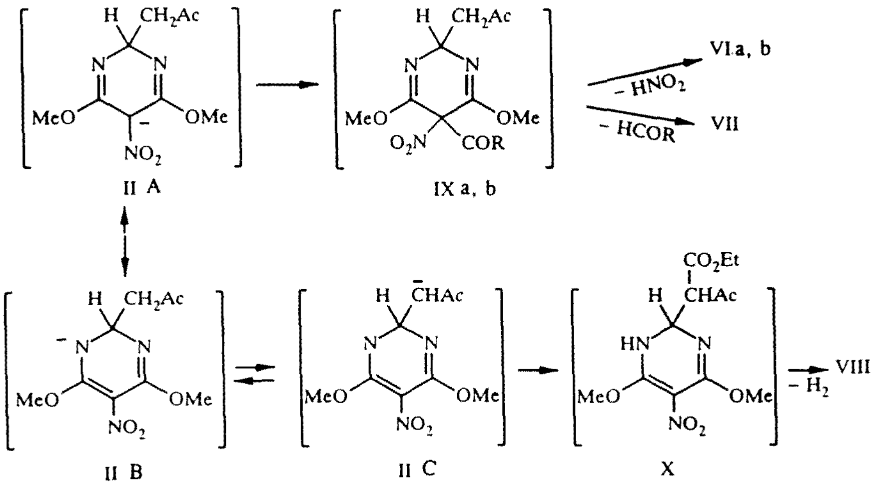


IIIa, c X = Cl, b X = OAc; III, IV, VI, IX a R = OEt, b R = Me, c R = Ph

In the PMR spectra of compounds IVa-c (see Table 1), there are signals from the methine proton in the form of a doublet of doublets in the 5.89-6.06 ppm region and from protons of the methylene group of the acetonyl moiety in the form of a multiplet in the 2.79-3.03 ppm region. The characteristic shape of these signals (an ABX spin system) suggests that the geminal unit is preserved upon conversion of the sigma complex I to dihydropyridines IVa-c. In the ^{13}C NMR spectrum of the ether IVa, recorded without proton spin decoupling, the signal from the $C_{(6)}$ atom appears in the 51.90 ppm region. Furthermore, the spin—spin coupling constant of the carbon atom of the carbonyl group with the proton of the geminal unit ($^3J_{CH}$ = 3.2 Hz) clearly suggests the presence of an ethoxycarbonyl group at the $N_{(1)}$ atom. Similar characteristics are also typical for the ^{13}C NMR spectrum of the ketone IVc (see the experimental part). In the electronic spectra of compounds IVa-c, we observe absorption bands in the 370 nm region, characteristic for the 1,6-dihydropyrimidines we described earlier in [2]. Thus the presented spectral characteristics clearly suggest that the electrophilic attack on the sigma complex I is accomplished regioselectively at the $N_{(1)}$ atom.

The following compounds are isolated upon ethoxycarbonylation of the sigma complex II, in which the geminal unit is found in the 2 position of the pyrimidine ring: 5-ethoxycarbonyl- (VIa) and 5-nitro-substituted (VII) 2-acetonyl-4,6-dimethoxypyrimidine and also 2[acetyl(ethoxycarbonyl)methyl]-4,6-dimethoxy-5-nitropyrimidine (VIII). By acylation of the same complex with acetic anhydride, we obtained the corresponding 5-acetyl-substituted derivative (VIb) and the product VII.

Scheme 2



The structure of the sigma complex II can be described by the resonant structures A and B. The acetonylpyrimidines VIa,b and VII are obviously obtained as a result of electrophilic attack at the 5 position of the pyrimidine ring (structure A)

TABLE 1. Data from UV Spectra and PMR Spectra of Synthesized Compounds

Compound	UV spectrum, λ_{max}, nm (lg ε)	PMR spectrum, δ, ppm: 6-H, d.d	PMR spectrum: CH_2COCH_3 ($CHCOCH_3$)*: CH_2 (CH)	PMR spectrum: CH_2COCH_3 ($CHCOCH_3$)*: CH_3	PMR spectrum: $2OCH_3$, s	PMR spectrum: Other protons (R, COOEt*)
IVa	241 (3,9), 368 (4,1)	5,89	2,83 m	2,22 s	4,13, 4,07	4,31 (2H, q, CH_2), 1,34 (3H, t, CH_3)
IVb	244 (3,9), 370 (4,0)	6,06	2,79 m	2,21 s	4,19, 4,07	2,42 (3H, s, CH_3)
IVc	236 (4,1), 368 (4,0)	5,90	3,03 m	2,28 s	4,12, 3,72	7,46 (5H,m, Ph)
VIa	229 (3,6), 245 (3,6), 294 (3,4)	—	3,82 s	2,24 s	3,94	4,28 (2H, q, CH_2), 1,35 (3H, t, CH_3)
VIb	233 (4,0), 245 (4,0), 294 (3,4)	—	3,85 s	2,28 s	3,95	2,32 (3H, s, CH_3)
VIII	244 (4,0), 274 (4,1)	—	6,31 q	2,56 d	4,03	4,26 (2H, q, CH_2), 1,34 (3H, t, CH_3)

---

*In the case of compound VIII.

TABLE 2. Characteristics of Synthesized Compounds

Compound	Found, % / Calculated, %: C	H	N	Empirical formula	T_{mp}, °C (ethanol)	R_f*	Yield, %
IVa	45,5 45,7	5,2 5,4	13,1 13,3	$C_{12}H_{17}N_3O_7$	95...97	0,42	35†
IVb	46,0 46,3	5,3 5,3	14,8 14,7	$C_{11}H_{15}N_3O_6$	133...135	0,38	23
IVc	55,2 55,3	4,7 4,9	12,2 12,1	$C_{16}H_{17}N_3O_6$	150...152	0,40	25
VIa	53,9 53,7	6,1 6,0	10,2 10,4	$C_{12}H_{16}N_2O_5$	70...72	0,65	27
VIb	55,2 55,4	5,7 5,9	12,0 11,8	$C_{11}H_{14}N_2O_4$	111...113	0,64	32
VIII	46,2 46,0	5,0 4,8	13,2 13,4	$C_{12}H_{15}N_3O_7$	112...114	0,82	13

---

*In the system chloroform—methanol, 99:1.

† According to method A; according to method B, the yield is 42%.

and then disproportionation in alkaline medium of the unstable 2,5-dihydropyrimidines (IXa,b), containing two electron-acceptor substituents in the 5 position. The structure of the pyrimidine VIII is confirmed by the PMR spectrum, in which the signals from the methine proton and the methyl group of the acetyl moiety appear as doublets (see Table 1). Formation of this compound is possible as a result of electrophilic attack at the methylene group, on which the negative charge is localized (in analogy with the data in [6]) as a consequence of the prototropic shift IIB → IIC. Further dehydrogenation of the intermediate 1,2-dihydropyrimidine (X) leads to the aromatic pyrimidine VIII. When the sigma complex II was reacted with benzoyl chloride, we could isolate only the nitropyrimidine VII from the reaction mixture.

The characteristics of the synthesized compounds are presented in Table 2.

EXPERIMENTAL

The ^1H and ^{13}C spectra were recorded on a Varian Gemini-200 in $CDCl_3$, internal standard TMS. The UV spectra were taken on a Specord M-40 (solutions in methanol). The course of the reaction and the purity of the synthesized compounds were monitored by TLC on Silufol UV-254 plates in the solvent system chloroform—methanol, 99:1 (visualization in UV light).

The elemental analysis data for the synthesized compounds relative to C, H, and N correspond to the calculated values (see Table 2).

The sigma complexes I and II were obtained according to the techniques in [7] and [8] respectively.

6-Acetonyl-2,4-dimethoxy-5-nitro-1-ethoxycarbonyl-1,6-dihydropyrimidines (IVa). A. 0.50 ml (5.2 mmole) ethylchlorocarbonate was added with stirring to a suspension of 1.40 g (5.0 mmole) of sigma complex I and 1.15 g (5.0 mmole) BTEAC in 20 ml absolute benzene. After 18 h, the reaction mixture was filtered and the filtrate was evaporated under vacuum using an aspirator. The product IV was isolated from the residue by chromatography on a column with silica gel (20 g, chloroform as the eluent). ^{13}C NMR spectrum ($CDCl_3$): 205.07 (CH_3CO), 159.25 ($C_{(2)}$), 156.84 ($C_{(4)}$), 150.80 ($—CO_2C_2H_5$, d, $^3J_{C—H}$ = 3.2 Hz), 110.22 ($C_{(5)}$), 64.31 (CH_2CH_3), 57.07, 55.53 (OCH_3), 51.90 ($C_{(6)}$), 45.52 (CH_2COCH_3), 30.07 ppm ($COCH_3$).

Compound IVb was synthesized similarly from complex I and acetic anhydride. ^{13}C NMR spectrum ($CDCl_3$): 205.95 (CH_3COCH_2), 169.05 (CH_3CO), 159.07 ($C_{(2)}$), 156.63 ($C_{(4)}$), 110.81 ($C_{(5)}$), 57.15, 55.78 (OCH_3), 50.29 ($C_{(6)}$), 45.46 (CH_2), 30.26 (CH_3COCH_2), 25.68 ppm (CH_3CO).

Compound IVc was synthesized similarly from complex I and benzoyl chloride. ^{13}C NMR spectrum ($CDCl_3$): 205.69 (CH_3CO), 168.97 (C_6H_5CO), 159.62 ($C_{(2)}$), 157.28 ($C_{(4)}$), 134.61-127.58 (C_6H_5), 110.81 ($C_{(5)}$), 56.32, 55.78 (OCH_3), 52.07 ($C_{(6)}$), 45.92 (CH_2), 30.19 ppm (CH_3).

B. 0.12 ml (1.5 millimoles) ethylchlorocarbonate was added to a mixture of 0.24 g (1.0 millimole) 1,6-dihydropyrimidine V and 0.10 ml pyridine in 5.0 ml anhydrous and ethanol-free methylene chloride at a temperature of 0°C. After 2 h, the reaction mixture was evaporated to dryness, and compound IVa was isolated from the residue by chromatography (see method A); this product was identical to a sample obtained by method A (mp, R_f).

Reaction of Sigma Complex II with Ethylchlorocarbonate. A mixture of products VIa, VII, and IX were obtained according to the technique A described above from complex II and ethylchlorocarbonate. These three products were separated on a column with silica gel (20 g), successively eluting with chloroform the compounds VIII, VII (yield 10%, mp 84-86°C [8]), and VIa.

Compounds VIb and VII were obtained similarly by reaction of the sigma complex II with acetic anhydride.

REFERENCES

1. G. Ya. Remennikov, S. G. Vishnevskii, V. V. Pirozhenko, S. I. Vdovenko, V. M. Cherkasov, D. S. Yufit, and Yu. T. Struchkov, Khim. Geterotsikl. Soedin., No. 2, 215 (1993).
2. G. Ya. Remennikov, S. G. Vishnevskii, V. V. Pirozhenko, and V. M. Cherkasov, Khim. Geterotsikl. Soedin., No. 9, 1238 (1990).
3. V. N. Drozd, N. V. Tokmakova (Grandberg), I. V. Stankevich, and Yu. M. Udachin, Zh. Org. Khim., **18**, 124 (1982).
4. R. E. van der Stoel, H. C. van der Plas, H. Jongejan, and L. Hoeve, Rec. Trav. Chim., **99**, 234 (1980).
5. V. M. Cherkasov, G. Ya. Remennikov, and E. A. Romanenko, Khim. Geterotsikl. Soedin., No. 6, 823 (1981).
6. P. Barczynski and H. C. van der Plas, Rec. Trav. Chim., **97**, 256 (1978).
7. V. M. Cherkasov, G. Ya. Remennikov, and E. A. Romanenko, Khim. Geterotsikl. Soedin., No. 10, 1389 (1978).
8. V. M. Cherkasov, G. Ya. Remennikov, A. A. Kisilenko, and E. A. Romanenko, Khim. Geterotsikl. Soedin., No. 2, 239 (1980).