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26.* ALKYLATION OF 4-BENZYLIDEN-1-PHENYL-3,5-DIOXOPYRAZOLIDINES

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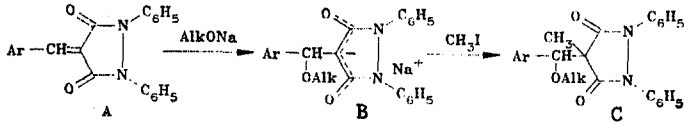
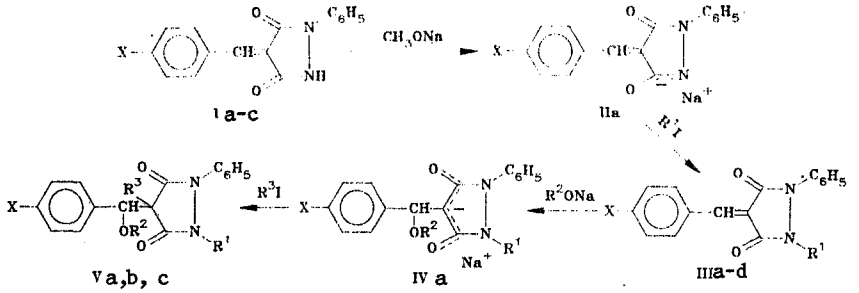
The reaction of 4-benzyliden-1-phenyl-3,5-dioxopyrazolidines with alkyl halides in the presence of sodium alkoxide gave 1-phenyl-2-alkyl-4-benzyliden- and 1-phenyl-2,4-dialkyl-4-(α-alkoxybenzyl)-3,4-dioxopyrazolines. The structures of these compounds were confirmed by UV, IR, and PMR spectroscopy, and by mass-spectrometry.

Previously, it was shown [2] that 4-benzyliden-1,2-diphenyl-3,5-dioxopyrazolidines react with sodium alkoxides to give sodium salts of the 4-(α-alkoxybenzyl) compounds B, which do not show the characteristic long-wave UV absorption bands present in the spectrum of A. The enolates B react with methyl iodide to give 4-methyl derivatives C.



It was of interest to perform this reaction with the 4-benzyliden-1-phenyl-3,5-dioxopyrazolidines (Ia-c), since there are two possible reaction products — the product of the reaction with alkoxide, and the alkylation product.



Ia-Va X = H, Ib, IIIb, Vb, e X = NO_2; Ic, IIIc, d X = OCH_3; IIIa-c, IVa, Va, b, e R^1 = CH_3; IIIa, R^1 = C_2H_5; IVa, Va, b R^2 = CH_3; Ve R^2 = C_2H_5; Va, b, e R^3 = CH_3

In the UV spectra of compounds Ia-c in alkaline ethanol, the position and intensity of the long-wave band do not change significantly (experimental section). From this it can be concluded that these compounds, unlike the 1,2-disubstituted analogs (A), react with sodium alkoxide not as Lewis acids, but as NH-acids, which form the enolates II. For compounds B, as a result of bonding with the alkoxy-anion, the benzyl proton signal is shifted upfield to 5.2-5.4 ppm [2], however, in the PMR spectrum of compound Ia in CD_3ONa, there is no signal in this region, confirming that the exocyclic double bond has been retained (Table 1). In the IR spectrum of compound IIa, obtained by the reaction of Ia with sodium methoxide and isolated by a precipitation with absolute ether, both the C=O absorption band at 1670 cm^{-1} and

*For communication 25 see [1].

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TABLE 1. PMR Spectra of the Starting Compounds and Their Alkylation Products

Compound	N—C_6H_5	—C_6H_4—X	R^1	C_α—H (1H)	R^2	R^3
Ia	7,11—7,78 (m, 8H);	8,32—8,65 (q, 2H)		7,80 (s); 7,93 (s)		
Ib	7,11—7,58 (m, 3H); 7,71 (d, 2H, J=4 Hz)	8,21 (d, 2H, J=8 Hz); 8,45—8,76 (q, 2H)		7,81 (s); 7,93 (s)		
Ic	7,20—7,68 (m, 5H)	6,94—7,17 (m, 2H); 8,42—8,72 (q, 2H); 3,81 (s, 3H)		7,79 (s); 7,92 (s)		
IIIa	7,01—7,48 (m, 8H);	7,98—8,45 (m, 2H)	3,07 (s, 3H)	7,82 (s)		
IIIb	7,15—7,62 (m, 5H)	8,15—8,52 (m, 2H); 8,52—8,81 (m, 2H)	3,18 (s, 3H)	7,90 (s); 7,94 (s)		
IIIc	7,22—7,65 (m, 5H)	6,83—7,15 (m, 2H); 8,63 (d, 2H, J=9 Hz); 3,87 (s, 3H)	3,18 (s, 3H)	7,91 (s); 7,95 (s)		
IVa	6,9—7,3 (m, 8H);	7,3—7,58 (m, 2H)	2,81 (s, 3H)	5,13 (s)	3,23 (s, 3H)	
Va	6,65—7,38 (m, 10H)		2,83 (s, 3H)	4,33 (s)	3,16 (s 3H)	1,27 (s, 3H)
Vb	7,08—7,42 (m, 5H)	7,42—7,68 (m, 2H); 8,02—8,32 (m, 2H)	2,85 (s, 3H)	4,55 (s)	3,18 (s 3H)	1,25 (s, 3H)
Vd	7,25—7,65 (m, 5H)	7,65—7,82 (m, 2H); 8,15—8,42 (m, 2H)	3,05 (s, 3H)	4,65 (s)	3,28 (m, 2H); 1,01 (m, 3H)	1,21 (s, 3H)

*Spectrum of I was taken in DMSO, III-V in $CDCl_3$.

the C=C band at 1625 cm^{-1} are retained, in agreement with the proposed structure; in this it differs from compound B. The dual character of the products of the reaction of Ia-c with sodium alkoxide, and the previously reported [2] course of the alkylation of compound A indicates that alkylation of compounds Ia-c with alkyl halides in the presence of excess sodium alkoxide can occur at either the N or O atom.

The reaction with excess sodium alkoxide and alkyl halides was carried out with compound Ia, (without a substituent at position 4), and also compounds with electron-acceptor (Ib) and electron-donor (Ic) substituents. Under the conditions employed, the N-alkylation products IIIa-d, and also the products of further alkylation of the latter, V, were obtained (Table 2). No O-alkylation products could be detected.

The alkylation of compounds Ia-c occurs in a step-wise manner, as shown in the reaction scheme; this was confirmed by the formation of compound IVa from the N-methyl derivative IIIa and sodium methoxide, and by the formation of complete alkylation products Va and b from 4-benzyliden- (IIIa) and 4-p-nitrobenzyliden- (IIIb) derivatives from methyl iodide in the presence of sodium methoxide, and of the 4-methyl-4-(α-ethoxy-p-nitrobenzyl)- (Ve) derivative from methyl iodide and sodium ethoxide.

Evidence for the structure proposed for III comes from infrared spectra, and also from ultraviolet spectra, where the long-wave maxima of IIIa-d disappear on going from an acidic to an alkaline medium. In the PMR spectra, signals from the benzylidene proton, and also signals from protons of the N-alkyl groups are observed (Table 1).

Because of the asymmetry of the molecule, compounds I and III are obtained as mixtures of Z- and E-isomers. This is confirmed by the presence of two spots with very similar R_f values on thin-layer chromatograms of compounds Ia and b and IIIa and b, and also by the splitting of the signal from the single benzylidene proton (Table 1).

In the PMR spectrum of the intermediate IVa, the signal from the benzylidene proton, which is bonded to the methoxy anion, is shifted from 7.82 to 5.13 ppm. At the same time, in the IR spectrum, bands at 1785 and 1718 cm^{-1} (C=O) or 1618 cm^{-1} (C=C), which are present in III, disappear, and are replaced by a strong enolate band at 1565 cm^{-1} [2]. From these data we can definitely conclude that no O-alkylation products are present.

The IR spectra of the products of complete alkylation of V are similar to the spectra of 1,2,4,4-tetrasubstituted dioxopyrazolidines, which are in the fixed dioxo form [3], and contain two strong bands at 1750-1740 cm^{-1} and 1710-1700 cm^{-1}, and no band at 1630-1618 cm^{-1}. In the UV spectra of compounds V, an absorption maximum occurs at 232-240 nm and is independent of the pH of the medium; this also is characteristic for 1,2,4,4-tetrasubstituted derivatives

TABLE 2. Alkylation Products

Compound	mp, °C (from ethanol)	$R_f^* \cdot 100$	IR spectrum, cm^{-1}	UV spectrum, λ_{max}, nm (log ε), ethanol	Found, %	Empirical formula	Calculated, %	Yield, %
IIIa	152--153	65,7	1718 (s, 1685 (s), 1618 (s), 1592, 1568	235 (4,01), 244 (3,95), 330 (4,24)	9,7	$C_{17}H_{14}N_2O_2$	10,1	40,2
IIIb	164--165	55,6	1730, 1693 (s), 1630, 1595, 1515	260 (4,38), 324 (4,15)	13,0	$C_{17}H_{13}N_3O_4$	13,0	36,0
IIIc	148--149	21	1718, 1682 (s), 1620, 1588, 1510	235 (4,35) sh 247 (4,40), 374 (4,66), 379 (4,60)	9,4	$C_{18}H_{18}N_2O_3$	9,1	16,2
IIId	142--143	25	1718, 1682, 1620, 1585	252 (4,46), 374 (4,46)	9,0	$C_{19}H_{20}N_2O_3$	8,7	15,0
IVa			1650, 1595, 1565 (s)		8,5	$C_{18}H_{17}N_2O_3Na$	8,4	100,0
Va	113—114	43	1750, 1710 (s), 1590	235 (4,04)	8,6	$C_{19}H_{20}N_2O_3$	8,7	50,0
Vb	182—183	27	1748, 1710 (s), 1595	240 (3,88)	11,3	$C_{19}H_{19}N_3O_5$	11,4	47,0
Ve	176—178	29	1740, 1700, 1595	237 (4,15)	11,2	$C_{20}H_{21}N_3O_5$	11,0	19,4

*For compounds IIIa and b, ethyl acetate—heptane, 1:1 (after drying the chromatogram and repeatedly chromatographing in the same solvent system, each spot gave two spots with the same R_f); for IIIc and d, ethyl acetate—heptane, 3:4; for Va, b, and e, ethyl acetate—hexane, 1:7; Vb and c were chromatographically uniform also in the systems: ethyl acetate—hexane, 1:2; chloroform—petroleum ether, 5:1, benzene—chloroform, 1:3.
†Va. Found: C 70.2; H 6.3%. Calculated: C 70.4; H 6.2%. Vb. Found: C 61.9; H 5.4%. Calculated: C 61.8; H 5.2%. Ve. Found: C 62.5; H 5.3%. Calculated: C 62.7; H 5.5%.

[3]. The PMR spectra of compounds V contains signals from the alkyl group protons and signals from the single proton at the α-carbon of the benzylidene residue.

Additional confirmation of the structures of compounds I, III, and V was obtained from their mass spectra. For compounds Ia-c, the decay of the molecular ion under electron bombardment is independent of the nature of the substituent in the para-position, and involves the rearrangement of the molecular ion and the ejection of a C_3HO_2 (similar to the fragmentation of the benzylidene derivative of 1,2-diphenyl-3,5-dioxopyrazolidine [4]), and splitting of the C—N and C—C bonds in the heterocyclic ring to form the $X-C_6H_4-CH=CH-C\equiv O^+$ ion, which then decays further with loss of the para-substituent. In the mass spectra of the monomethyl derivatives (IIIa-c) (Table 3), the formation of the $M - CH_3$ fragment and the unchanged values of the ketene fragments (Ia, IIIa m/z 130, Ib, IIIb m/z 175, and Ic, IIIc, IIId m/z 160) indicate that the $CH_3(C_2H_5)$ group was joined to the nitrogen atom and did not affect the exocyclic double bond. Additional evidence is the absence of an acyl ion from the spectra of IIIa-d — since the molecule does not contain a labile hydrogen atom (NH), which in compounds Ia-c migrates to $C_{(4)}$ with the formation of the $X-C_6H_4-CH=CH-C\equiv O^+$ ion.

The low intensity of the molecular ion peak of the final alkylation product V and the formation of the $X-C_6H_4-CH=\overset{+}{O}R$ fragment is consistent with the absence of conjugation between the heterocyclic ring and the benzyl group as a result of the addition of the alkoxy group at C=C.

The presence of two asymmetric carbon atoms in the product of complete alkylation V leads to the formation of a mixture of isomers. Thus, Vb was isolated initially as a mixture of substances with a wide melting-point range (132-142°C). Thin-layer chromatography gave two very close spots; the PMR spectrum of this mixture had split signals from the $N-CH_3$, $O-CH_3$, and —CH groups. After purification until chromatographically homogeneous, the PMR spectrum of Vb (mp 182-183°) contained no split signals.

EXPERIMENTAL

IR spectra were obtained on UR-20 and Specord IR-75 spectrometers (mineral oil). UV spectra were taken on SF-16 and SF-26 spectrometers using the following solvents: ethanol, ethanol

TABLE 3. Mass Spectra of Compounds I, III, and V

Compound	m/z (relative intensity, %)*
Ia	51 (18), 63 (6), 76 (10), 77 (41), 91 (6), 102 (42), 103 (16), 105 (6), 107 (7), 129 (9), 130 (51), 131 (44), 132 (8), 134 (8), 158 (7), 173 (5), 187 (7), 195 (28), 196 (26), 263 (7), 264 (100, M^+)
Ib	75 (10), 77 (37), 78 (6), 89 (6), 91 (5), 101 (16), 102 (6), 105 (8), 106 (6), 107 (7), 117 (6), 121 (5), 129 (8), 130 (6), 134 (16), 175 (22), 176 (17), 187 (6), 240 (16), 241 (14), 279 (5), 309 (100, M^+)
Ic	51 (12), 57 (6), 63 (10), 77 (22), 89 (21), 117 (22), 118 (5), 121 (6), 132 (7), 133 (6), 134 (5), 145 (21), 147 (7), 160 (49), 161 (34), 225 (22), 226 (30), 227 (5), 294 (100, M^+)
IIIa	51(17), 63(5), 77 (78), 78 (7), 91 (5), 102 (32), 105 (24), 121 (16), 130 (48), 131 (7), 201 (9), 209 (18), 263 (5), 278 (100, M^+)
IIIb	51 (15), 77 (79), 78 (6), 89 (5), 91 (5), 101 (13), 105 (20), 119 (6), 129 (6), 175 (24), 201 (7), 254 (13), 323 (100, M^+)
IIIc	51 (6), 77 (35), 89 (11), 105 (12), 117 (11), 145 (13), 160 (55), 161 (8), 239 (7), 308 (100, M^+)
IIId	51 (8), 77 (59), 78 (6), 89 (15), 105 (18), 117 (15), 135 (5), 145 (15), 160 (51), 161 (15), 162 (6), 204 (6), 225 (12), 279 (7), 293 (18), 294 (19), 307 (48), 308 (15), 332 (100, M^+)
Va	77 (14), 83 (6), 91 (6), 121 (100), 122 (10), 324 (4, M^+)
Vb	77 (10), 83 (14), 120 (15), 166 (100), 167 (9), 369 (5, M^+)
Vc	77 (19), 78 (6), 83 (20), 94 (5), 105 (6), 106 (9), 152 (75), 153 (6), 180 (100), 181 (11), 383 (4, M^+)

*Peaks with intensities greater than 4% are given.

containing 0.35% HCl, and 0.1% KOH in ethanol (concentration $(1-4)\cdot10^{-5}$ mole/liter). PMR spectra were recorded on Varian T-60 and Tesla BS-487 C instruments, internal standard HMDS. Mass spectra were recorded on a LKB-2091 mass spectrometer with direct introduction of the sample into the ion source, temperature of source 250°, temperature of vaporization of sample 20-250°, ionization energy 70 eV.

Chromatography was carried out on Silufol UV-254 plates. Preparative chromatography for the isolation of V was conducted using alumina activity II in a thin layer (4 mm) on plates measuring 20 × 20 cm, solvent chloroform.

4-Benzyliden-1-phenyl-3,5-dioxopyrazolidines (Ia-c) were obtained in 50-56% yield by refluxing ethanolic solutions of equimolar amounts of 1-phenyl-3,5-dioxopyrazolidine and the corresponding aldehyde for 2-3 h with subsequent recrystallization of the precipitated material. Ia, mp 278-280° with decomposition (from butanol). IR spectrum: 1713, 1683, 1663 (s), 1615, 1592 cm^{-1}. UV spectrum, λ_{max} (log ε): acidic ethanol, 249 (4.15), 325 (4.39); alkaline ethanol, 232 (3.95), 270 (4.1), 312 (4.39). Found: N 10.6%. $C_{16}H_{12}N_2O_2$. Calculated: N 10.7%. Ib, mp 282-284° with decompositon (from dioxane). IR spectrum: 1710, 1675 (s), 1620 (s), 1592 cm^{-1}. UV spectrum, λ_{max} (log ε): acidic ethanol, 250 (4.14), 319 (4.10); alkaline ethanol, 270 (4.30), 320 (4.05). Found: N 13.2%. $C_{16}N_{11}N_3O_4$. Calculated: N 13.6%. Literature data [5], mp 280°. Ic, mp 249-250° (from aqueous DMFA). IR spectrum: 1705, 1675 (s), 1658 (s), 1590, 1572 cm^{-1}. UV spectrum, λ_{max} (log ε): acidic ethanol, 252 (4.33), 372 (4.54); alkaline ethanol, 246 (4.33), 348 (4.37). Found: N 9.5%. $C_{17}H_{14}N_2O_3$. Calculated: N 9.5%. Literature data [6], mp 246°.

Sodium Salt of 1-Phenyl-4-benzyliden-3,5-dioxopyrazolidine (IIa). Absolute ether (50 ml) was added to 0.264 g (1 mmole) of compound Ia dissolved in a freshly-prepared solution of 0.046 g (2 mmoles) of sodium in 10 ml of absolute methanol. The product (0.26 g) was isolated as a red material. IR spectrum: 1670, 1625, 1595, 1565 (s) cm^{-1}.

1-Phenyl-2-alkyl-4-benzyliden-3,5-dioxopyrazolidine (III). Methyl (ethyl) iodide (300 mmoles) was added to a solution of 50 mmoles of compound Ia-c dissolved in a freshly prepared solution of 10 mmoles of sodium in 50-100 ml of methanol. The mixture was left at 20°, the solution evaporated to half-volume, diluted twice with water, brought to pH 9 with 5% sodium hydroxide solution, and exhaustively extracted with ether. Acidifying the aqueous solution gave IIIa-d (Table 2).

Compound IIIb, before evaporation gave 11.6% of Vb as a coloress crystalline substance.

Sodium Salt of 1-Phenyl-2-methyl-4-(α-methoxybenzyl)-3,5-dioxopyrazolidine (IVa). Compound IIIa (0.28 g, 1 mmole) was dissolved in a freshly prepared solution of 0.046 g (2 mmoles of sodium in 10 ml of absolute methanol. Addition of ether gave white, finely divided cyrstals of IVa in quantitative yield.

1-Phenyl-2,4-dimethyl-4-(α-alkoxybenzyl)-3,5-dioxopyrazolidine (V). A. The combined ether extracts, obtained during the synthesis of compounds IIIa and b were dried with sodium sulfate, filtered, and evaporated to dryness, to afford a pale-yellow oil (IIIa) or precipitate (IIIb), from which after thin-layer chromatographic purification of alumin was obtained a colorless oil (IIIa) or crystals (IIIb), containing (TLC) two spots with very similar R_f values. Further recrystallization from ethanol gave chromatographically homogeneous Va and b. Pure Vb was also isolated during the synthesis of IIIb (see above).

B. Methyl iodide (0.24 mole) was added to a solution of 40 mmoles of compound IIIa or b in a freshly prepared solution of 80 mmoles of sodium in 80 ml of absolute methanol (for Ve, 170 ml of absolute ethanol). The mixture was left at 20° for 96-120 h and worked up as in the preparation of IIIa-d; compound V was isolated from the ether extract as described in A. During the preparation of Vb, after extraction, an additional 22% of chromatographically homogeneous Vb was isolated.

On acidifying the aqueous solutions, the starting materials IIIa and b were recovered.

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REACTION OF 4-AMINOIMADAZO[4.5-c]PYRIDIN-2-ONES WITH α-BROMOMETHYLKETONES

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The reactions of 4-amino derivatives of imidazo[4.5-c]pyridin-2-ones with α-bromomethylketones have been studied. Depending on the nature of the reagents and the reaction conditions, either 5-acylmethyl salts of the starting amine or 2-substituted imidazo[4.5-c]imidazo[1.2-a]pyridin-8-ones can be obtained. The latter compounds are also easily obtained by treatment of the 5-acylmethyl salts with alkali.

The facile nitration of imidazo[4.5-c]pyridin-2-one in the 4-position has opened up many new possibilities for the preparation of a wide variety of substituted derivatives of this compound [1-3]. Two of these new compounds which are of widespread interest are 4-amino-1-methylimidazo[4.5-c]pyridin-2-one (Ib) and its 3-methyl congener (Ia). Previous work has established that the base Ia can be readily alkylated at the nitrogen atom of the pyridine ring upon treatment with alkyl halides [4]. In the present paper we report our results of the study of the reactions of Ia and b with α-bromomethylketones (IIb-h) and α-bromoacetaldehyde (IIa).

The addition of the aliphatic α-bromomethylketones IIa-d to amine Ia occurs upon reflux in alcoholic solution over 1-2 h and gives salts IIIa-d in high yield (Table 1). Clemmenson reduction of the acetonyl bromide IIIb gives, after acidification of the reaction mixture with hydrogen iodide, the iodide salt of 4-amino-5-n-propyl-1,3-dimethylimidazo[4.5-c]pyridinium-2-one (V), which has been previously prepared form amine Ia with n-propyl iodide [4]. This observation, coupled with the similarities in the UV spectra of the quaternary salts IIIa-d (Table 1), leads us to believe that reaction of amine Ia with the α-bromomethylketones IIa-d generates the 5-acylmethyl salts IIIa-d.

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