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SYNTHESIS AND SOME CONVERSIONS OF 4-ARYL-6-METHYL-2-METHOXY(PHENYL)-5-NITRO-1,4-DIHYDROPYRIMIDINES

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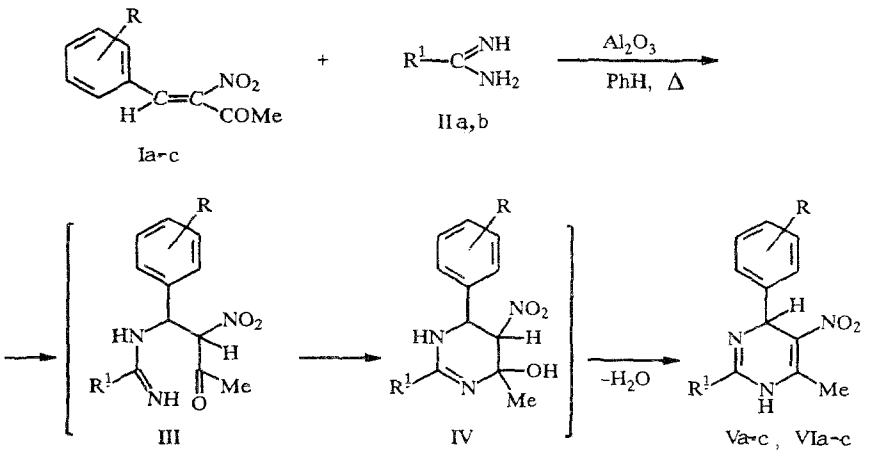
The reaction of 1-arylidene-1-nitropropan-2-ones with O-methylisourea (or benzamidine) in the presence of aluminum oxide gave 4-aryl-6-methyl-2-methoxy(phenyl)-5-nitro-1,4-dihydropyrimidines. It was shown that the reactions of the compounds synthesized with electrophilic agents proceed at the exocyclic methyl group, as well as at the $N_{(1)}$, $N_{(3)}$, and $C_{(5)}$ atoms of the 1,4-dihydropyrimidine fragment of the molecule.

Interest in the chemistry of hydrogenated pyrimidines is determined by the fact that biologically active compounds and pharmacological preparations with a broad spectrum of action are found in their series [1, 2]. Much attention in the literature has been given to the synthesis of 5-alkoxycarbonyl-4-aryl-1,4(3,4)-di- and 1,2,3,4-tetrahydropyrimidines, which show the properties of calcium antagonists [3-5] and are not inferior in their pharmacological action to known cardiovascular preparations of the nifedipine group [6-10]. To a smaller extent, the 4-aryl-1,2,3,4-tetrahydropyrimidines containing acetyl [11], carbamoyl [12], cyano [12], and nitro [13-16] groups at the position 5 of the pyrimidine ring were studied.

We recently showed [17] that N-acetyl-N′-[(2-nitro-1-phenyl)ethyl]-O-methylisourea is formed together with 6-methyl-2-methoxy-5-nitro-4-phenyl-1,4-dihydropyrimidine (Va) in the reaction of 1-benzylidene-1-nitropropan-2-one (Ia) with O-methylisourea (IIa). The first stage of the reaction leads to the evident formation of the product of the Michael addition (III), which undergoes cyclization to the unstable 6-hydroxy-6-methyl-2-methoxy-5-nitro-4-phenyl-3,4,5,6-tetrahydropyrimidine (IV). As the result of the competition between two processes — the opening of the pyrimidine ring at the $C_{(5)}-C_{(6)}$ bond or the cleavage of a molecule of water — (IV) is converted to a derivative of O-methylisourea or to the dihydropyrimidine (Va) correspondingly. In the present work, we



I, V, VI a R = H, b R = 4-Cl, c R = 3,4-di-OCH_3; IIa, Va-c R^1 = OCH_3; IIb, VIa-c R^1 = Ph

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continued to study the conditions to carry out this cyclization, and also investigated the reaction of 2-substituted 4-aryl-6-methyl-5-nitro-1,4-dihydropyrimidines with some electrophilic agents.

In the reaction of the 1-arylidene-1-nitropropan-2-ones (Ia-c) with O-methylisourea (IIa) or benzamidine (IIb) in boiling benzene in the presence of the tenfold excess of activated aluminum oxide as a dehydrating agent, the sole products isolated from the reaction mixture were the 4-aryl-6-methyl-2-methoxy-5-nitro- (Va-c) and -2-phenyl-5-nitro-1,4-dihydropyrimidines (VIa-c). Therefore, the formation of an acyclic product can be avoided if this reaction is performed in the presence of aluminum oxide, but these conditions do not lead to an increase in the yield of the 1,4-dihydropyrimidine derivatives.

The double set of signals in the PMR spectra of the compounds (Va-c) (Table 1) may be explained by the fact that they exist as the mixture of two tautomeric forms. The signal of the proton at the position 4 of the pyrimidine ring appears in the form of a singlet lying in the range 5.86-5.90 ppm and corresponds with the 1,4-dihydropyrimidine form, whereas the doublet lying in the range 5.78-5.83 ppm with the SSCC 2.2-3.2 Hz corresponds with the 3,4-dihydropyrimidine form. The ratio of the 1,4- and 3,4-tautomers is independent of the nature and position of the substituents in the phenyl fragment of the molecule, and equals ~1:3 for each compound. According to the PMR spectra, the compounds (VIa-c) only exist in the 1,4-dihydropyrimidine form; this is evidently explained by the steric influence of the phenyl substituents. Comparison of the results obtained for the compounds (V) and (VI) with the literature data for 2-substituted 5-alkoxycarbonyl-4-aryl-6-methyldihydropyrimidines [9, 18], in which the influence of the nature of the substituents at the position 2 of the pyrimidine ring on the tautomeric ratio was investigated in detail, shows that the substitution of the ester group by the nitro group at the position 5 of the pyrimidine ring has practically no influence on the tautomeric equilibrium.

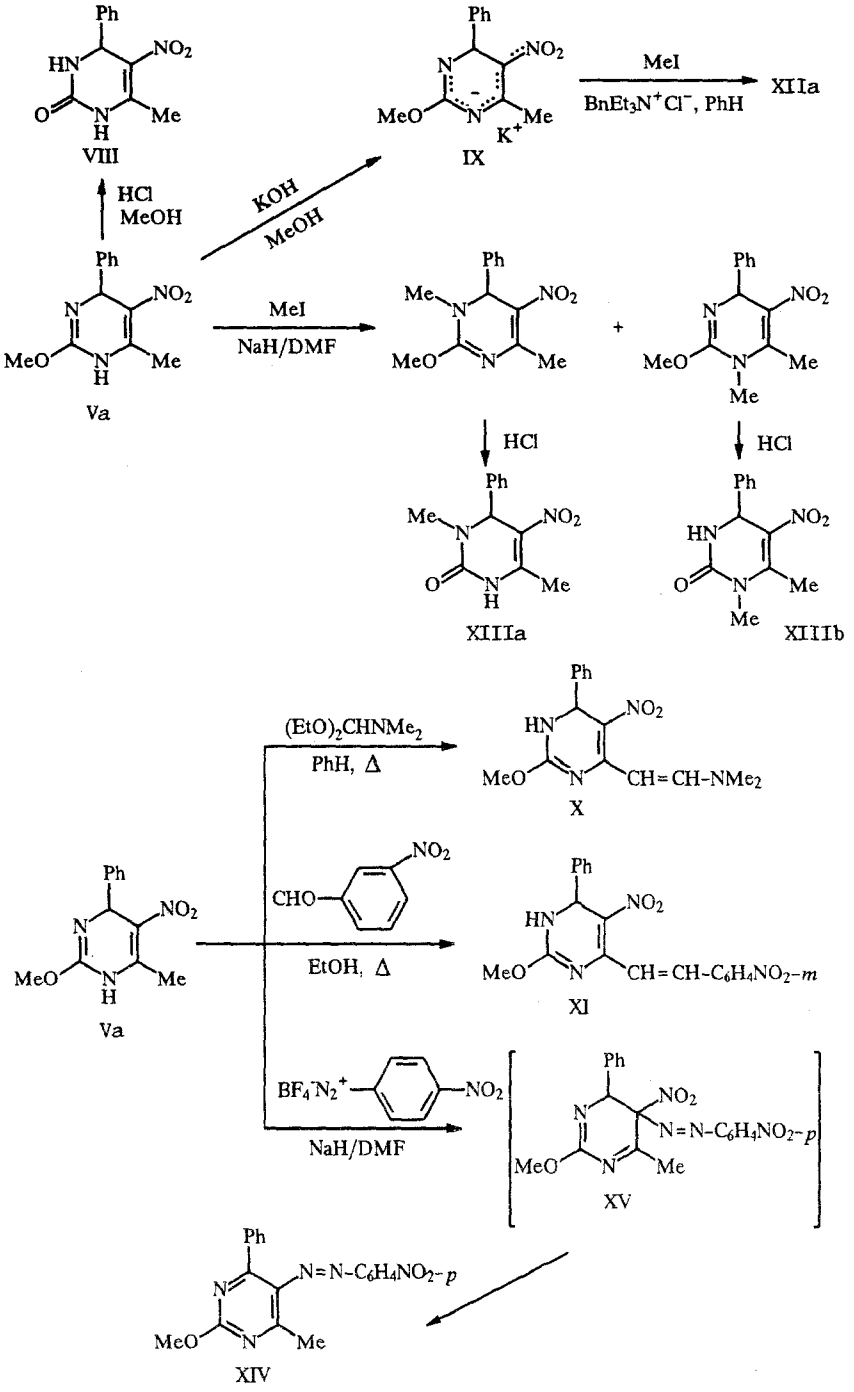
The position of the long-wave absorption band in the electronic spectra of the compounds (V) and (VI) (377-401 nm) corresponds with that described earlier for 5-nitrodihydropyrimidines [19]; this also confirms the structure of the compounds synthesized. Moreover, the 1,4-dihydropyrimidine (VIa) [by analogy with (Va) [17]] is readily dehydrogenated by 2,3-dichloro-5,6-dicyanobenzoquinone to the pyrimidine (VII).

The 2-substituted 4-aryl-6-methyl-5-nitro-1,4-dihydropyrimidines are characterized by the presence of several reaction centers. Therefore, some of their conversions were studied in the given work taking the example of (Va).

As a result of the acid hydrolysis of the methoxyl group, (Va) is converted to 6-methyl-5-nitro-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine (VIII), described in [16]. When (Va) reacted with the equimolecular amount of potassium hydroxide in methanol, the anionic σ-complex (IX) of the Meisenheimer type of complex was obtained and isolated in the individual state. The PMR spectrum of this compound shows the singlet signal at 5.58 ppm associated with the proton at the position 4 of the pyrimidine ring, together with the signals of the methyl and methoxyl groups. Moreover, the bathochromic shift of the absorption band of the σ-complex (IX) by comparison with (Va) describes the delocalization of the electron density at the pyrimidine fragment of the molecule; this corresponds with the electronic spectra of the anionic σ-complexes in the series of 5-nitropyrimidine [20].

The presence of the nitro group in the pyrimidine ring of the compounds synthesized significantly increases the availability of the hydrogen atoms of the vicinal methyl group. The enamine (X) was obtained by the reaction of (Va) with the diethylacetal of DMF. By analogy, the styryl (XI) is formed by the action of 3-nitrobenzaldehyde on (Va). The compounds (X) and (XI) exist in the 3,4-dihydropyrimidine tautomeric form which is indicated by the doublet signals in the PMR spectra (see scheme at top of following page).

In the alkylation of the dihydropyrimidine (Va) by methyl iodide in DMF in the presence of sodium hydride, the electrophilic attack is accomplished at the $N_{(3)}$ and $N_{(1)}$ atoms with the formation of two isomeric N-methyl derivatives (XIIa) and (XIIb), which are isolated from the reaction mixture chromatographically in the individual state. At the same time, the alkylation of the anionic σ-complex (IX) by methyl iodide in benzene in the presence of the equimolar amount of benzyltriethylammonium chloride proceeds regioselectively at the $N_{(3)}$ with the sole formation of the isomer (XIIa). In the ^{13}C NMR spectrum of this compound, which was registered without the suppression of the spin–spin interaction with the protons, the signal of the $N-CH_3$ group appears in the form of a doublet of quartets (in the region of 33.96 ppm) in consequence of the interaction of the carbon atom of the methyl group with the methine proton (SSCC 2.41 Hz). Therefore, the position and character of this signal show the presence of the methyl group unambiguously at the $N_{(3)}$. Moreover, the acid hydrolysis of (XIIa) leads to 3,6-dimethyl-5-nitro-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine (XIIIa), in the PMR spectrum of which the hydrogen atom appears in the form of a singlet signal at 5.58 ppm; this also confirms the position of the N-methyl group. By analogy, the acid hydrolysis of (XIIb) leads to 1,6-dimethyl-5-nitro-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine (XIIIb), which is identical to the sample described in [16].



The reaction of (Va) with an N-electrophilic reagent, which was chosen to be a 4-nitrophenyldiazonium salt, proceeds differently. When this reaction is performed in DMF in the presence of sodium hydride, 5-(4′-nitrophenyl)aza-6-methyl-2-methoxy-4-phenylpyrimidine (XIV) is obtained. In the given case, the electrophilic attack by the diazonium ion is evidently accomplished at the position 5 of the pyrimidine ring with the formation of the unstable intermediate product, the 5-(4′-nitrophenyl)aza-5-nitro-4,5-dihydropyrimidine (XV), which undergoes aromatization in the alkaline medium as the result of the elimination of nitrous acid and is converted to the pyrimidine (XIV).

Therefore, the investigation of the reaction of 6-methyl-2-methoxy-5-nitro-4-phenyl-1,4-dihydropyrimidine (Va) with some electrophilic agents showed that, depending on the nature of the electrophile, the attack is accomplished at the exocyclic methyl group, as well as at the $N_{(1)}$, $N_{(3)}$, and $C_{(5)}$ atoms of the 1,4-dihydropyrimidine ring.

TABLE 1. Characteristics of the Synthesized Compounds (V)-(VII) and (IX)-(XIV)

Compound	Empirical formula	R*	mp, °C	UV spectrum, λ_{max}, nm (log ε) in methanol)	PMR spectrum, δ, ppm (SSCC, J, Hz)						Yield, %
					$N_{(1)}H$, s	$N_{(3)}H$	CH	OCH_3, s	CH_3, s	other signals	
Va	$C_{12}H_{13}N_3O_3$	0,21	151...153	239 (3,74), 382 (3,91), 459 (2,97)	— 6.36	5,78 broad s —	5,83d (3,2) 5,90 s	3,93 3,72	2,59 2,50	— —	11
Vb	$C_{12}H_{12}ClN_3O_3$	0,20	183...185	244 (3,76), 377 (3,87)	— 6,28	5,73 broad s —	5,82 d (2,4) 5,88 s	3,94 3,74	2,60 2,52	— —	20
Vc	$C_{14}H_{17}N_3O_5$	0,16	156...159	278 (3,60), 382 (3,92)	— 6,30	5,77 broad s —	5,79 d (2,2) 5,86 s	3,93 3,88	2,59 2,51	3,85, 3,75 (OCH_3)	10
VIa	$C_{17}H_{15}N_3O_2$	0,17	166...168	260 (4,05), 389 (3,88)	7,77	—	6,03 s	—	2,68	—	16
VIb	$C_{17}H_{14}ClN_3O_2$	0,22	93...95	260 (4,06), 382 (3,82)	7,68	—	5,89 s	—	2,59	—	19
VIc	$C_{19}H_{19}N_3O_4$	0,16	84...86	264 (4,05), 401 (3,67)	7,43	—	6,99 s	—	2,67	3,81, 3,83 (OCH_3)	20
VII	$C_{17}H_{13}N_3O_2$	0,83	119...121	269 (4,55)	—	—	—	—	2,70	—	89
IX	$C_{12}H_{12}KN_3O_3$	—	—	238 (3,51), 393 (3,95)	—	—	5,58 s	3,83	2,35	—	94
X	$C_{15}H_{18}N_4O_3$	0,10	210...212	273 (4,15), 388 (4,11), 455 (4,60)	—	8,82 d (3,2)	5,60 d (3,2)	3,85	—	8,38 d (12,2), 6,98 d (12,2) (CH=CH), 3,22 bs 2,96 bs [$N(CH3)_2$]	53
XI	$C_{19}H_{16}N_4O_5$	0,38	201...202	271 (4,18), 340 (4,11), 431 (3,79)	—	8,48 d (2,0)	5,94 d (2,0)	4,06	—	8,42 d (10,4), 817 d (10,4) (CH=CH)	78
XII a	$C_{13}H_{15}N_3O_3$	0,55	Oil	249 (3,79), 401 (4,12)	—	—	5,60 s	3,98	2,58	2,86 s (NCH3)	39
XII b	$C_{13}H_{15}N_3O_3$	0,43	Oil	241 (3,68), 373 (3,89)	—	—	5,93 s	3,78	2,62	3,22 s (NCH3)	6
XIII c	$C_{12}H_{13}N_3O_3$	0,15	233...234	235 (3,77), 342 (4,05)	—	9,11 s	5,58 s	—	2,56	2,90 s (NCH3)	66
XIV	$C_{18}H_{15}N_5O_3$	0,56	165...167	286 (4,33), 344 (4,30)	—	—	—	4,16	2,72	8,10 dd (C_6H_4)	38

*In the 99:1 system of chloroform–methanol.

**From ethanol.

***The aromatic protons of (V)-(VII) and (IX)-(XIV) resonate in the region of 6.80-8.30 ppm.

EXPERIMENTAL

The NMR spectra were recorded on the Bruker WP-200 spectrometer in DMSO-D_6 and $CDCl_3$ with TMS as the internal standard. The IR spectra were registered on the Specord M-80 instrument. The UV spectra were registered on the Specord M-40 instrument. The monitoring of the course of the reactions and the individuality of the compounds synthesized was accomplished by the method of TLC on plates of Silufol UV-254 in the 99:1 solvent system of chloroform–methanol; the development was performed in UV light. The compounds (Va-c), (VIa-c), (VII), (X), (XIIa, b), and (XIV) were purified by chromatography on a column with silica gel 40/100 (the mass 30 g); the eluent was chloroform.

The data of the elemental analyses of the synthesized compounds for C, H, and N correspond with the calculated data. The 1-arylidene-1-nitropropan-2-ones (Ia-c) were obtained according to the method of [21].

6-Methyl-2-methoxy-5-nitro-4-phenyl-1,4-dihydropyrimidine (Va) ($C_{12}H_{13}N_3O_3$). To the suspension of 0.28 g (3.8 mmoles) of O-methylisourea and 8.0 g of activated Al_2O_3 in 20 ml of dry benzene is added, rapidly, 0.35 g (3.9 mmoles) of 1-benzylidene-1-nitropropan-2-one (Ia). The reaction mixture is boiled for 2 h with stirring prior to its filtration. The solvent is evaporated in vacuo, and the residue is chromatographed.

By analogy, O-methylisourea and (Ib) yield the 1,4-dihydropyrimidines (Vb, c).

By analogy, benzamidine and (Ia-c) yield the 1,4-dihydropyrimidines (VIa-c).

6-Methyl-5-nitro-2,4-diphenylpyrimidine (VII) ($C_{17}H_{13}N_3O_2$). To the solution of 0.1 g (0.34 mmole) of the 1,4-dihydropyrimidine (VIa) in 5 ml of dry benzene is added, with stirring, 0.08 g (0.35 mmole) of 2,3-dichloro-5,6-dicyanobenzoquinone. After 18 h, the precipitated residue of the hydroquinone is filtered off. The solvent is evaporated in vacuo, and the residue is chromatographed.

Potassium Salt of the Anion of 6-Methyl-2-methoxy-5-nitro-4-H-4-phenylpyrimidine (IX) ($C_{12}H_{12}KN_3O_3$). To the solution of 0.16 g (0.65 mmole) of the 1,4-dihydropyrimidine (Va) in 5 ml of dry methanol is added, with stirring, 0.04 g (0.71 mmole) of ground KOH. After 90 min, the reaction mixture is concentrated by 4/5 of the initial volume, and the anionic σ-complex (IX) is precipitated with 200 ml of ether.

2-Methoxy-5-nitro-4-phenyl-6-(2′-dimethylaminoethenyl)-3,4-dihydropyrimidine (X) ($C_{15}H_{18}N_4O_3$). The mixture of 0.14 g (0.56 mmole) of (Va) and 0.12 ml (0.9 mmole) of DMF-diethylacetal in 10 ml of dry benzene is boiled for 45 min. The solvent is evaporated in vacuo, and the residue is chromatographed.

2-Methoxy-5-nitro-4-phenyl-6-(3′-nitrostyryl)-3,4-dihydropyrimidine (XI) ($C_{19}H_{16}N_4O_5$). The mixture of 0.27 g (1.09 mmoles) of (Va), 0.16 g (1.05 mmoles) of 3-nitrobenzaldehyde, and 0.1 ml of piperidine in 10 ml of ethanol is boiled with stirring for 2 h. It is then evaporated in vacuo. The residue is crystallized.

Reaction of the 1,4-Dihydropyrimidine (Va) with Methyl Iodide. To the solution of 0.30 g (1.2 mmoles) of (Va) in 3 ml of DMF is added 0.04 g (1.3 mmoles) of the 80% suspension of sodium hydride. Then, 1 h after the complete release of hydrogen, 0.1 ml (1.6 mmoles) of methyl iodide is added. After 14 h, the reaction mass is poured into water (100 ml) prior to the extraction with chloroform (3 × 60 ml) and the drying over $MgSO_4$. The solvent is evaporated in vacuo, and the residue is chromatographed. The 3,6-dimethyl-2-methoxy-5-nitro-4-phenyl-3,4-dihydropyrimidine (XIIa) is eluted from the lower zone. The ^{13}C NMR spectrum (DMSO-D_6) is as follows: 25.11 ppm (CH_3), 33.96 ppm (NCH_3), 55.77 ppm (OCH_3), 63.01 ppm (CH), 125.53-128.70 ppm (C_6H_5), 139.14 ppm (C–NO_2), 157.40 ppm, and 159.46 ppm (C=N). On further elution, 1,6-dimethyl-2-methoxy-5-nitro-4-phenyl-1,4-dihydropyrimidine (XIIb) is washed out.

3,6-Dimethyl-2-methoxy-5-nitro-4-phenyl-3,4-dihydropyrimidine (XIIa) ($C_{13}H_{15}N_3O_3$). To the suspension of 0.20 g (0.7 mmole) of the σ-complex (IX) and 0.18 g (0.8 mmole) of benzyltriethylammonium chloride in 10 ml of dry benzene is added, with stirring, 0.1 ml (1.6 mmoles) of methyl iodide. After 18 h, the residue is filtered off. The solvent is evaporated in vacuo, and the residue is chromatographed. The yield is 0.12 g (66%).

3,6-Dimethyl-5-nitro-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine (XIIIa) ($C_{12}H_{13}N_3O_3$). To the solution of 0.12 g (0.46 mmole) of the 3,4-dihydropyrimidine (XIIa) in 4 ml of methanol is added 0.05 ml of concentrated HCl. After 4 h, the reaction mixture is concentrated to dryness. The residue is dissolved in 30 ml of chloroform, washed with water to neutrality, and dried over $MgSO_4$. The solvent is evaporated in vacuo. The residue is crystallized. The IR spectrum (KBr) is as follows: 3150 cm^{-1} (NH) and 1687 cm^{-1} (C=O).

By analogy, (XIIb) yields 1,6-dimethyl-5-nitro-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine (XIIIb). The yield is 52%. It is identified with the sample described in [16].

By analogy, (Va) yields 6-methyl-5-nitro-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine (VIII). The yield is 73%. It is identified with the sample described in [16].

5-(4′-Nitrophenyl)aza-6-methyl-2-methoxy-4-phenylpyrimidine (XIV) ($C_{18}H_{15}N_5O_3$). To the solution of 0.15 g (0.6 mmole) of (Va) in 3 ml of DMF is added, with stirring, 0.02 g (0.66 mmole) of the 80% suspension of sodium hydride. At 1 h after the complete release of hydrogen, 0.15 g (0.63 mmole) of 4-nitrophenyldiazonium tetrafluoroborate is added. The reaction mixture is stirred for 20 h. It is poured into 100 ml of water, extracted with 200 ml of chloroform, and dried over $MgSO_4$. The solvent is evaporated in vacuo, and the residue is chromatographed.

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