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ACETYLENIC FRAGMENTATION OF ACYL DERIVATIVES OF THE FISCHER BASE

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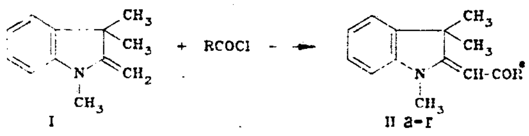
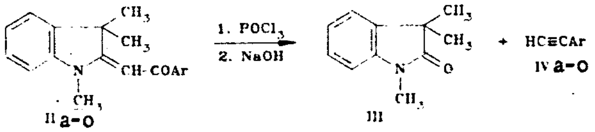
Indolenium salts, which readily undergo cleavage in aqueous alkali to give a monosubstituted acetylene and 1,3,3-trimethyl-2-oxindole, are formed when acyl derivatives of the Fischer base are heated with phosphorus oxychloride. Various aryl- and hetarylacetylenes can be conveniently obtained by this method.

Enamino ketones of the indoline series (II), which are readily obtained by acylation of 1,3,3-trimethyl-2-methylene-indoline (I) — called the Fischer base in the literature — are characterized by high reactivities. They are used as intermediates for the synthesis of cyanine dyes [1] and thermochromic compounds [2] and for other purposes [3].



R= alkyl, aryl, hetaryl

We recently established [4] that acyl derivatives (II) of the Fischer base are convenient starting compounds for the synthesis of aromatic derivatives of acetylene. The new method for obtaining arylacetylenes consists in heating 1,3,3-trimethyl-2-phenacylideneindolines II with phosphorus oxychloride in dioxane and subsequent treatment with aqueous alkali; this leads to the formation of 1,3,3-trimethyl-2-oxindole (III) and a monoarylacetylene (IV):



To determine the limits of applicability of the new method for introducing an ethynyl group into organic compounds we obtained various indoline enamino ketones IIa-r, which contain acyl groups of aliphatic, aliphatic-aromatic, aromatic, and heterocyclic acids (Table 1); IIa-r were then used for the synthesis of the corresponding monosubstituted acetylenes IVa-o (Table 2).

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TABLE 1. Enamino Ketones IIa-r

Compound	R	mp, °C[a,b]	PMR spectrum, δ, ppm			Found, %			Empirical formula	Calc., %			Yield, %
			3,3-(CH$_3$)$_2$	1-CH$_3$	=CH–	C	H	N (Hal)		C	H	N (Hal)	
IIa	p-Nitrophenyl	193—196	1,84	3,34	5,88	70,5	5,8	8,3	$C_{19}H_{18}N_2O_3$	70.8	5.6	8,7	75
IIb	o-Nitrophenyl	166—168	1,77	3,25	5,36	70,5	5,5	8,9	$C_{19}H_{18}N_2O_3$	70.8	5.6	8,7	51
IIc	m-Nitrophenyl	216—218	1,77	3,38	5,87	70,4	5,6	8,4	$C_{19}H_{18}N_2O_3$	70,8	5,6	8.7	71
IId	3,5-Dinitrophenyl	215—220	1,84	3,40	5,86	61,9	4,8	11,1	$C_{19}H_{17}N_3O_5$	62,1	4,7	11,4	84
IIe	2,4-Dinitrophenyl	225—228	1,83	3,22	5,32	61,9	4,7	11,5	$C_{19}H_{17}N_3O_5$	62,1	4,7	11,4	65
IIf	p-Bromophenyl	156—158	1,82	3,27	5,87	63,8	5,0	4,1 (21,9)	$C_{19}H_{18}BrNO$	64,1	5,1	3,9 (22,4)	67
IIg	2,4-Dichlorophenyl	129—130	1,82	3,20	5,51	65,9	5,1	4,2 (20,9)	$C_{19}H_{17}Cl_2NO$	65,6	5,0	4,0 (20.5)	62
IIh	p-Methoxyphenyl	148—150	1,83	3,25	5,96	80,6	6,7	4,8	$C_{20}H_{21}NO_2$	80,8	6,9	4.6	55
IIi	3,4-Dimethoxyphenyl	138—139	1,81	3,38	6,17	74,6	6,9	4,3	$C_{21}H_{23}NO_3$	74.5	6.8	4,2	31
IIj	3-Nitro-1-naphthyl	159—161	1,94	3,23	5,67	74,4	5,5	7,6	$C_{23}H_{20}N_2O_3$	74.2	5.4	7.5	66
IIk	4-[(1,3,3-Trimethylindolin-2-ylidene)-acetyl]phenyl	282—284	1,77	3,35	5,83	80,5	6,9	5,6	$C_{32}H_{32}N_2O_2$	80,6	6,8	5,9	68
IIl	3-Nitro-4-[(1,3,3-trimethylindolin-2-ylidene)-acetyl]phenyl	246—247	1,86	3,21 3,35	5,43 5,93	73,8	5,8	8,0	$C_{32}H_{31}N_3O_4$	73,7	6,0	8,1	75
IIm	4-Pyridyl	157—159	1,82	3,30	5,86	78,0	6,3	9,9	$C_{16}H_{18}N_2O$	77.7	6.5	10.1	41
IIn	1-Methyl-3-pyrazolyl	203—205	1,78	3,33 3,93	6,34	72,7	6,8	15,3	$C_{17}H_{19}N_3O$	72.6	6.8	15.0	71
IIo	2-Benzofuryl	170—172	1,84	3,33	6,14	79,4	6,1	4,4	$C_{21}H_{19}NO_2$	79,5	6,0	4.4	83
IIp	Methyl	96—98	—	—	—	—	—	—	—	—	—	—	80
IIq	Decyl	47—48	1,71	3,12	5.25	80,6	10,1	3,8	$C_{23}H_{35}NO$	80.9	10.3	4.1	65
IIr	Benzyl	102—105	1,69	3,06	5,23	82,6	7,0	4,5	$C_{20}H_{21}NO$	82.5	7,2	4,8	69

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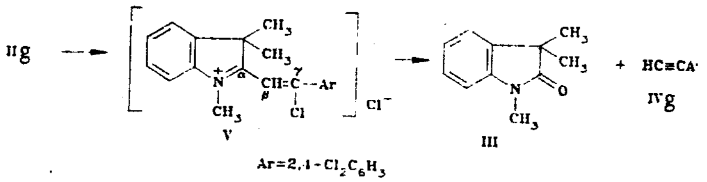
[a] The compounds were crystallized: IIa-k, m-o from isopropyl alcohol, IIl from acetic acid, and IIp, q from hexane. Compound IIr was chromatographed on aliuminum oxide with petroleum ether—ether (4:1).

[b] IIa, mp 194-196°C [5]; IIk, mp 289-291°C [6]; IIp, mp 97-98°C [7]; IIr, mp 103-105°C [5].

The aryl- and heterarylacetylenes and the simultaneously formed III were isolated from the reaction mixtures by column chromatography.



Alkylacetylenes could not be obtained from enamino ketones IIp-r (Table 1), although fragmentation also occurred in this case, as evidenced by the formation of III. The more labile alkylacetylenes evidently undergo resinification under the conditions used for fragmentation or isolation.

When the indoline enamino ketones are heated with phosphorus oxychloride, they are converted to styryl-substituted 1,3,3-trimethylindolinium chlorides that contain a chlorine atom in the γ position with respect to the immonium nitrogen atom. A salt of this type (V) was isolated in the action of phosphorus oxychloride on enamino ketone IIg, which was obtained in the acylation of the Fischer base with 2,4 dichlorobenzoyl chloride.

The PMR spectrum of salt V contains solitary signals of equivalent gem-methyl groups (1.73 ppm) and an N^+-methyl group (4.31 ppm). Similar chemical shifts are characteristic for the PMR spectrum of 1,2,3,3-tetramethylindoleninium iodide [17]. Compound V reacts with the nucleophile OH^- at the α-carbon atom with simultaneous displacement of a chloride ion from the γ position, thereby undergoing cleavage to give 1,3,3-trimethyl-2-oxindole (III) and 2,4-dichlorophenylacetylene (IVg, Table 2).

Thus we have shown that to obtain a monaryl- or monoheterarylacetylene from an acyl derivative of the Fischer base one must convert the starting enamino ketone, by means of phosphorus oxychloride, to an active γ-chloroindoleninium salt of the V type, which is capable of undergoing cleavage by the action of alkali to give 1,3,3-trimethyl-2-oxindole and a monosubstituted acetylene.

TABLE 2. Aryl- and Hetarylacetylenes IVa-o (R—C≡CH)

Compound	R	mp, °C[a]	IR spectrum, ν, cm⁻¹		PMR spectrum, δ, ppm, ≡CH	Yield of acetylene, %	Yield of oxindole, %
			—C≡C—	≡CH			
IVa	p-Nitrophenyl	148—150	2115	3260	3,33	87	87
IVb	o-Nitrophenyl	81—82	2115	3270	3,37	80	76
IVc	m-Nitrophenyl	25—26	2130	3300	3,80	87	86
IVd	3,5-Dinitrophenyl	110—112	2120	3280	3,43	78	72
IVe	2,4-Dinitrophenyl	93—94	2115	3270	3,83	39	48
IVf	p-Bromophenyl	64—65	2100	3310	3,08	79	76
IVg	2,4-Dichlorophenyl	58—59	2120	3290	3,37	78	69
IVh	p-Methoxyphenyl	25—26	—	—	—	48	57
IVi	3,4-Dimethoxyphenyl	72—73	—[b]	3270	3,00	50	24
IVj	3-Nitro-1-naphthyl	120—122	2120	3260	3,56	73	76
IVk	p-Ethynylphenyl	94—95	—	—	—	48	62
IV*l*	2-Nitro-4-ethynylphenyl	127—128	2105	3270	3,32 3,61	51	—[c]
IVm	4-Pyridyl	96—97	2110	3310	—	35	48
IVn	1-Methyl-3-pyrazolyl	Liquid[d]	2130	3310	3,06	57	77
IVo	2-Benzofuryl	Liquid[e]	2120	3310	3,45	67	62

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[a] IVa, mp 147-148°C [9]; IVb, mp 80-81°C [9], 81-82°C [8]; IVc, mp 24-25°C [9]; IVf, mp 64-65°C [10]; IVg, mp 52-55°C [11]; IVh, mp 26-28°C [12, 13]; IVk, mp 92-93°C [9]; IVm, mp 96-96.5°C [14].

[b] The IR spectrum did not contain an absorption band.

[c] The oxindole was not isolated.

[d] The liquid had bp 121°C (30 mm) and n_D^{20} 1.538 [bp 86.5°C (12 mm), n_D^{20} 1.5250 [15]].

[e] According to the data in [16], this compound darkened rapidly in air.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in $CDCl_3$ were recorded with a Bruker WH-200 SY spectrometer with tetramethylsilane as the internal standard. The IR spectra of suspensions in mineral oil were recorded with a UR-20 spectrometer. The R_f values were determined on Silufol UV-254 plates (elution with chloroform). Chromatography of the reaction mixtures was carried out on silica gel (100/160 μm) in columns with a height of 540 mm and a diameter of 30 mm; the mass of the silica gel was 150 g.

1,3,3-Trimethyl-2(p-nitrophenacylidene)indoline (IIa). A mixture of 16.7 g (0.1 mole) of p-nitrobenzoic acid and 17.84 g (0.15 mole) of thionyl chloride in 50 ml of dry benzene was refluxed for 1.5 h, after which the excess thionyl chloride was evaporated in vacuo. For complete removal of the thionyl chloride, 50 ml of petroleum ether was added to the residue and then removed by distillation. The acid chloride obtained was dissolved in 50 ml of dry benzene, the solution was added to a mixture of 17.3 g (0.1 mole) of the Fischer base and 12.1 g (0.12 mole) of triethylamine in 200 ml of dry benzene, and the mixture was maintained at 40°C for 2 h, after which it was allowed to stand overnight at 20°C. The resulting precipitate was separated and washed successively with water and isopropyl alcohol. The yield was 24 g (75%); the orange crystals had mp 193-196°C (from isopropyl alcohol) (Table 1).

The remaining emanimo ketones IIb-r were similarly obtained (Table 1).

p-Nitrophenylacetylene (IVa). A mixture of 3.32 g (0.01 mole) of IIa and 3.06 g (0.02 mole) of phosphorus oxychloride in 25 ml of dioxane was heated at 80°C for 4 h, after which it was poured into 44 ml of 10% NaOH solution. The alkaline mixture was extracted with chloroform, and the chloroform solution was dried with sodium sulfate. The solvent was removed by distillation, and the residue was passed through a column packed with silica gel by elution with benzene. The yield was 1.28 g (87%); the yellow crystals (R_f 0.71) had mp 148-150°C (Table 2). Subsequent elution of the residue with chloroform—ether (10:1) gave 1.52 g (87%) of 1,3,3-trimethyl-2-oxindole (III) (R_f 0.52) with mp 54-55°C (mp 55.5°C [18]).

The remaining aryl- and hetarylacetylenes IVb-o (Table 2) were similarly obtained.

1,3,3-Trimethyl-2-(α-chloro-2,4-dichlorostyryl)indolenium Chloride (V). A mixture of 6.9 g (0.02 mole) of enamino ketone IIg and 6.1 g (0.04 mole) of phosphorus oxychloride in

50 ml of tetrahydrofuran (THF) was refluxed for 1.5 h, after which the resulting precipitate was separated, washed with THF, and dried. The yield was 7.2 g of a crystalline substance (90% based on enamino ketone II) with mp 167-170°C. PMR spectrum: 1.73 [6H, s, $3,3\text{-}(CH_3)_2$], 4.31 (3H, s, CH_3N), 7.39 (1H, s, $C{=}CH$), and 7.40-7.78 ppm (7H, m). Found: C 56.5, H 4,4, Cl 35.1, N 3.66%. $C_{19}H_{17}Cl_4N$. Calculated: C 56.9, H 4.2, Cl 35.4, N 3.50%.

2,4-Dichlorophenylacetylene (IVg). A mixture of 6.02 g (0.015 mole) of salt V in 100 ml of dioxane was heated to the boiling point and added with stirring to 55 ml of 10% KOH solution. The mixture was extracted with chloroform, and the chloroform solution was dried with sodium sulfate. The solvent was removed by distillation, and the residue was chromatographed with a column packed with silica gel. Initial elution with petroleum ether gave 1.6 g (62%) of IVg (R_f 0.57) with mp 58-59°C. Subsequent elution with chloroform–ether (10:1) gave 1.73 g of III with mp 52-53°C (R_f 0.52).

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