SYNTHESIS AND OXIDATION OF 2,6-DIMETHYL-3,5-DI(PHENOXYCARBONYL)-1,4-DIHYDROPYRIDINES

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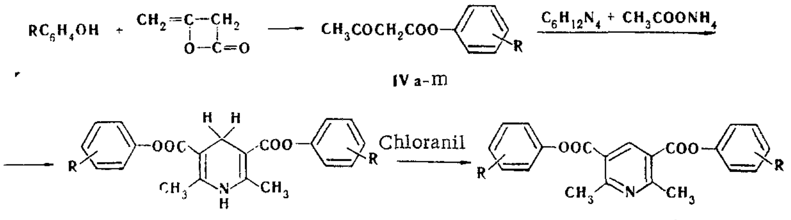
A number of new aryl esters of acetoacetic acid were obtained in the reaction of phenols with diketene in the presence of triethylamine. Reaction of the esters thus obtained with hexamethylenetetramine gave, for the first time, aryl esters of 1,4-dihydropyridine-3,5-dicarboxylic acid, the oxidation of which with chloranil gave the corresponding pyridines.

It was recently established that alkyl esters of 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid (I), which were described by Hantzsch in 1881 [1], are antioxidants [2]. Up until now, aryl esters of this acid have been unknown.

The anitoxidant capacity depends on the electron-donor properties of the compound, but in esters I possibilities for variation of the electron-donor capacity are extremely limited. The electron-donor and hydrogen-donor properties and the antioxidant capacity of 1,4-dihydropyridines can be regulated over wide limits in aryl esters of 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid (II) by introduction of various electron-donor and electron-acceptor substituents in the benzene ring.

In addition, esters II can be the starting compounds for the preparation of a number of other compounds, for example, aryl esters of 2,6-dimethylpyridine-3,5-dicarboxylic acid (III) and others.

The most convenient method for the preparation of esters I was found to be condensation of alkyl esters of acetoacetic acid with hexamethylenetetramine in the presence of ammonium acetate [2, 3]. We have shown that aryl esters of acetoacetic acid (IV) also react similarly to give II [4]. It was therefore initially necessary to synthesize esters IV with various substituents in the phenyl ring.



IV a-m

II a-j

III a-c, f, g

a R=H; b R=4-Cl; c R=4-CH_3; d R=4-OH; e R=3-OH; f R=4-$OCH_2C_6H_5$; g R=4-OCH_3; h R=2-$CH(CH_3)_2$, 5-CH_3; i R=3-OCH_3; j R=4-$NHCOCH_3$; k R=2,4-Cl_2; l R=4-NO_2; m R=4-$COOCH_3$

The only described method for the preparation of IV is the reaction of phenols with diketene in the presence of basic or acidic catalysts [5, 6]. Strongly acidic phenols undergo the reaction with diketene with more difficulty and do not react in the presence of pyridine or sulfuric acid [6]. Pratt and Bruice [7] were unable to obtain esters IV from strongly acidic phenols, nor was Lacey able to obtain them at 70-80°C in the presence of triethylamine, and the reaction with phenols of this type was therefore carried out at room temperature for a longer time (24 h) [7].

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TABLE 1. Aryl Esters of Acetoacetic Acid (IV)

Compound	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %*
			C	H	Cl	N	C	H	Cl	N	
IVf	100—101	$C_{17}H_{16}O_4$	71,8	5,5	—	—	71,8	5,7	—	—	63
IVg	57—59	$C_{11}H_{12}O_4$	63,4	5,7	—	—	63,5	5,8	—	—	88
IVh	25—28	$C_{14}H_{18}O_3$	72,0	8,1	—	—	71,8	7,7	—	—	8
IVi	30—33	$C_{11}H_{12}O_4$	63,5	5,9	—	—	63,5	5,8	—	—	43
IVj	126—128	$C_{12}H_{13}NO_4$	61,0	5,5	—	5,7	61,3	5,6	—	6,0	75
IVk	25—28	$C_{16}H_8Cl_2O_3$	48,6	3,4	28,5	—	48,6	3,3	28,7	—	12

* The yields of IV*l* and IVm were 43 and 24%, respectively.

TABLE 2. 2,6-Dimethyl-3,5-di(phenoxycarbonyl)-1,4-dihydropyridines (II)

Compound	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
			C	H	Cl	N	C	H	Cl	N	
IIa	219—221	$C_{21}H_{19}NO_4$	71,8	5,4	—	3,7	72,2	5.5	—	4,0	63
IIb	162—163	$C_{21}H_{17}Cl_2NO_4$	60,5	4,2	17,3	3,4	60,3	4,1	17,0	3,3	48
IIc	196—198	$C_{23}H_{23}NO_4$	73,4	5,9	—	3,5	73.2	6.1	—	3,7	66
IId	176—178	$C_{21}H_{19}NO_6$	66,2	5,2	—	3,9	66.1	5,0	—	3,7	68
IIe	203—206	$C_{21}H_{19}NO_6$	66,5	5,4	—	4,0	66,1	5,0	—	3,7	65
IIf	195—197	$C_{35}H_{31}NO_6$	74,4	5,5	—	2,8	74,8	5,6	—	2,5	48
IIg	181—183	$C_{23}H_{23}NO_6$	67,5	5,5	—	3,3	67,5	5,7	—	3,4	61
IIh	173—175	$C_{29}H_{35}NO_6$	75,5	7,6	—	2,8	75,5	7.6	—	3,0	49
IIi	180—182	$C_{23}H_{23}NO_6$	67,5	5,7	—	3,2	67,5	5.7	—	3,4	24
IIj	210—214*	$C_{25}H_{25}N_3O_6$	64,2	5,4	—	8,8	64.7	5.4	—	9,1	32

* This compound is converted to the form with mp 237-240° on storage.

We have shown that the method in [5] makes it possible to introduce even such strongly acidic phenols as p-nitro- and p-methoxycarbonylphenols in the reaction with diketene and to obtain new esters (IVf-k, Table 1), as well as the already known IVa-e [5] and IV*l*, m [7].

In the case of p-acetamidophenol, it was necessary to take into account the possibility of the reaction of diketene with the amide group to give the diacylamide rather than ester IVj. The correctness of the IVj structure is confirmed by the IR spectrum in dichloroethane, in which stretching vibrations of an N−H group appear at 3433 cm^{-1} and stretching vibrations of ester, ketone, and amide C=O groups appear at 1764, 1723, and 1695 cm^{-1}, respectively (the C=O band appears at 1763 and 1724 cm^{-1} in the spectrum of IVa); the formation of a diacylamide was not observed.

Esters IV, particularly those that contain electron-acceptor substituents, are unstable and decompose slowly at room temperature (IV*l* decomposes in a few days).

The reaction to obtain II from esters IV and hexamethylenetetramine in the presence of ammonium acetate proceeds in aqueous alcohol smoothly for all IV except for esters IVk-m, which contain electron-acceptor substituents. Diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate is formed from esters IV*l*, m instead of the expected II*l*, m. The reaction with esters IV*l*, m in methanol gives the dimethyl ester of this acid. Transesterification of IV*l*, m to the ethyl or methyl ester evidently occurs very rapidly during reaction in alcohol solutions, and the ethyl or methyl esters then undergo the Hantzsch reaction. Compounds II are yellow substances that fluoresce in UV light, are quite soluble in chloroform and dioxane, and are crystallized from ethanol and methanol (Table 2). Compound IIj exists in two crystalline forms: the first form, with mp 210-214°, is gradually converted to the form with mp 237-240° on storage; the latter is converted reversibly to the lower-melting form on recrystallization from methanol. The UV and IR spectra of the two forms are identical except for small differences in the intensities of some of the bands in the IR spectra of the solids; for example, the bands at 1698 and 1627 cm^{-1} in the spectrum of the lower-melting form are relatively less intense. As compared with the corresponding esters IV, substances II are more stable and do not change after several months at room temperature.

Five characteristic maxima, three of which at 233-238, 252-258, and 383-386 nm are characteristic for the 1,4-dihydropyridine structure [8], appear in the UV spectra of esters II. The maxima at 383-386 nm are shifted bathochromically by 11-14 nm as compared with the long-wave maximum of I [3] and are not strictly symmetrical; the highest point is, as a rule, found on the longer-wave side of the maximum. The maxima at 232-238 and 252-258 nm frequently appear only as a shoulder. The appearance of maxima

TABLE 3. Spectral Data for 3,6-Dimethyl-3,5-di(phenoxycarbonyl)-1,4-dihydropyridine (II)

Compound	UV spectrum, λ_{max}, nm (log ε)	IR spectrum (% absorption)	
		ν_{N-H}	1480-1730 cm^{-1}
IIa	204 (4,33); 238 (4,24); 256[a] (4,09); 384 (3,92)	3359 (85)	1693 (67)[c]; 1670 (74); 1598 (42); 1505 (69)[a]; 1498 (73)
IIc	205 (4,34); 218 (4,29); 233 (4,27); 254[a] (4,15); 386 (3,93)	3360 (80)	1715 (73); 1674 (73); 1635 (52)[a]; 1605 (31)[a]; 1510 (73)[a]; 1498 (77)
IId	205 (4,34); 225 (4,39); 237[a] (4,31); 255[a] (4,15); 278[a] (3,86); 385 (3,92)	3352 (75)	1689 (65)[d]; 1662 (71); 1606 (70); 1511—1508 (78)
IIe	204 (4,48); 218[a] (4,43); 233[a] (4,31); 252[a] (4,13); 278[a] (3,81); 385 (3,95)	3371 (71)	1696 (53)[e]; 1668 (53); 1620—1615 (54); 1507 (54)[a]; 1487 (72)
IIf	204 (4,68); 220[a] (4,55); 237[a] (4,38); 258 (4,28); 282[a] (3,94); 385 (3,98)	3379 (74)	1727 (63); 1661 (77); 1633 (56); 1596 (47); 1510 (65); 1490 (74)
IIg	203 (4,41); 225 (4,44); 236[a] (4,36); 258 (4,30); 276[a] (4,08); 283[a] (3,99); 384 (4,03)	3355 (79)	1723 (57); 1676 (68); 1656 (62); 1630 (49); 1613 (40)[a]; 1515 (76); 1505 (75)[a]
IIh	204 (4,43); 212 (4,44); 237 (4,28); 256[a] (4,18); 386 (3,96)	3360 (78)	1719 (54); 1664 (76); 1634 (46)[a]; 1507 (62)[a]; 1495 (75)
IIi	204 (4,42); 222 (4,43); 236[a] (4,28); 255[a] (4,13); 277[a] (3,76); 386 (3,98)	3362 (76)	1720 (64); 1670 (79); 1637 (56); 1608 (71); 1594 (65); 1498 (78)
IIj[b]	204 (4,72); 245 (4,67); 383 (4,00)	3318 (62); 3338 (61); 3388 (39)	1722 (39); 1698 (47)[f]; 1667 (65); 1627 (46); 1550 (56); 1506 (67)

[a] Shoulder. [b] This is the IR spectrum of the higher-melting form. [c] At 1715 cm^{-1} in dichloroethane. [d] At 1720 cm^{-1} in dioxane. [e] At 1710 cm^{-1} in dimethyl sulfoxide (DMSO). [f] Appears as a shoulder in DMSO.

TABLE 4. 2,6-Dimethyl-3,5-di(phenoxycarbonyl)pyridines (III)

Compound	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
			C	H	Cl	N	C	H	Cl	N	
IIIa	125—126	$C_{21}H_{17}NO_4$	72,5	4,6	—	3,6	72,4	5,2	—	4,0	50
IIIb	109—111	$C_{21}H_{15}Cl_2NO_4$	60,4	3,7	17,4	3,6	60,6	3,6	17,0	3,4	67
IIIc	98—100	$C_{23}H_{21}NO_4$	73,2	5,8	—	4,1	73,4	5,0	—	3,7	60
IIIf	120—121	$C_{35}H_{29}NO_6$	75,0	5,3	—	2,7	75,1	5,2	—	2,5	61
IIIg	137—138	$C_{23}H_{21}NO_6$	67,7	5,5	—	3,3	67,8	5,2	—	3,4	63

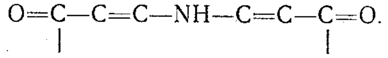
TABLE 5. Spectral Data for 2,6-Dimethyl-3,5-di(phenoxycarbonyl)-pyridines (III)

Compound	UV spectrum, λ_{max}, nm (log ε)	IR spectrum (% absorption) at 1480-1750 cm^{-1}
IIIa	209 (4,95); 238 (4,44); 273* (4,02); 283* (3,90)	1743 (60); 1592 (40); 1558 (34); 1490 (72)
IIIb	211 (4,62); 237* (4,18); 274* (3,81); 284* (3,64)	1745 (79); 1595 (15); 1557 (21); 1492 (74)
IIIc	211 (4,79); 238 (4,30); 270* (4,03); 282* (3,91)	1738 (71); 1600 (23); 1591 (29); 1553 (29); 1513 (56)
IIIf	210 (4,76); 223* (4,58); 235* (4,24); 276 (4,03); 283* (3,97)	1741 (77); 1594 (42); 1557 (40); 1507 (70)
IIIg	211 (4,68); 223* (4,53); 238* (4,20); 277 (4,09); 282* (4,03)	1746 (74); 1604 (28); 1558 (27); 1516 (75)

* Shoulder.

at 203-205 and 218-225 nm is due to the aromatic portion of the molecule. The second maximum in the spectrum of IIh is shifted hypsochromically and is found at 212 nm, and it is not observed at all in the spectrum of IIa. The second maximum is also absent in the spectrum of ester IIj, and, in addition, only one intense maximum at 245 nm is observed at 230-260 nm; it can be assumed that this is the result of superimposition of the two absorption bands characteristic for the 1,4-dihydropyridine structure.

An N−H band at 3350-3380 cm^{-1} appears in the IR spectra of II in hexachlorobutadiene. The spectrum of a Nujol suspension of ester II contains three bands due to the conjugated grouping below at 1480-1730 cm^{-1}:



$O{=}C{-}C{=}C{-}NH{-}C{=}C{-}C{=}O.$

The highest-frequency band in this region is due mainly to C =O stretching vibrations. This band is shifted by ~20 cm^{-1} to the higher-frequency side as compared with I [3]. This shift is in agreement with the shift generally observed on passing from alkyl to aryl esters [9]. In individual cases (IIa, d, e) this band in the spectra obtained from suspensions of the solids in Nujol is ~20 cm^{-1} lower than in the spectra of the remaining II. However, this band is found at 1710-1720 cm^{-1} in the spectra of solutions of the compounds. In the solid state the molecules of these compounds evidently exist in an associated state. Two bands (1722 and 1698 cm^{-1}) are found in this region in the spectrum of IIj; in the spectrum taken in dimethyl sulfoxide (DMSO) the lower-frequency band appears only as a shoulder, and this indicates that the IIj molecules are partially associated in the solid state.

The second characteristic band of II is more intense than the first characteristic band and is found at 1660-1675 cm^{-1}. The second band of the dihydropyridine group and the amide I band are observed together in the spectrum of IIj at 1667 cm^{-1}, and the amide II band appears distinctly at 1550 cm^{-1}.

It is quite difficult to accurately detect the third characteristic band (at ~1500 cm^{-1}) for II, inasmuch as it lies in the region of absorption of benzene rings. In the case of I [3], this region contains a sharp peak, but a band with a broad tail or a shoulder is observed here in the case of II. These bands are separated only in the case of II*f*, which contains four benzene rings, and two individual peaks appear. It might be assumed that the lower-frequency band of the superimposed bands is related to the benzene rings and that the higher-frequency band is related to the dihydropyridine system, inasmuch as this band is above 1500 cm^{-1} in the case of I [3] (Table 3).

The oxidation of IIa-c, *f*, g, was carried out with chloranil in benzene solution by the method in [10]. The reaction gave the corresponding pyridines (IIa-c, *f*, g), which have lower melting points than II but do not fluoresce in UV light (Table 4). The UV spectra of pyridines III are practically the same as the spectra of oxidized compounds I [3] except for somewhat more intense absorption; in contrast to II, absorption above 300 nm is absent in their spectra.

As compared with dihydro compounds II, the IR spectra of pyridines III do not contain the band of N−H stretching vibrations, and the C =O band is found at ~1740 cm^{-1}, i.e., it is shifted by 20 cm^{-1} to the high-frequency region, and the band at 1660-1675 cm^{-1} is absent, whereas bands characteristic for aromatic systems appear (Table 5).

We thank I. V. Dipan for recording the IR spectra.

EXPERIMENTAL

The individuality of the substances was established by thin-layer chromatography (TLC) on a loose layer of aluminum oxide in chloroform. The UV spectra of ethanol solutions of the compounds were recorded with a Specord UV-vis spectrophotometer. The IR spectra of Nujol and hexachlorobutadiene suspensions of the compounds were recorded with a UR-20 spectrometer. The melting points were determined with a Boetius microheating apparatus.

Aryl Esters of Acetoacetic Acid (IV). A 0.5-ml sample of triethylamine was added to 1 mole of the appropriate phenol, after which 1 mole (84 g) of diketene was added with stirring at 70-80° in the course of 1 h (the reaction was carried out in benzene in the preparation of IVf, j, *l*, m), and the mixture was held at 70-80° for 0.5-1.5 h. It was then allowed to stand overnight in a refrigerator, and the precipitate was removed by filtration. Compounds IVf, k, m were crystallized from ethyl acetate, IVg, *l* were reprecipitated from ethyl acetate solution by the addition of petroleum ether, and IVh, i, k were frozen out from ethyl acetate solution at −50 to −60° (Table 1). IR spectrum in dichloroethane: IVa 1763 and 1724; IVj 3433, 1764, 1723, and 1695 cm^{-1}.

2,6-Dimethyl-3,5-di(phenoxycarbonyl)-1,4-dihydropyridines (II). A 1.4-g (0.01 mole) sample of urotropin and 0.4 g (0.005 mole) of ammonium acetate were added to a solution of 0.1 mole of the appropriate ester IV in 60-65% ethanol, after which the mixture was refluxed on a water bath for 10 min. Cooling gave a yellow precipitate. Compounds IIa-e, g were recrystallized from ethanol, II*f* was recrystallized from ethyl acetate, and IIh-j were recrystallized from methanol (Table 2).

2,6-Dimethyl-3,5-di(phenoxycarbonyl)pyridines (III). A 2.46-g (0.01 mole) sample of chloranil was added to a solution of 0.01 mole of the appropriate dihydro compound II in benzene, after which the mixture was refluxed on a water bath for 10 min. It was then cooled, and the resulting precipitate was removed by filtration. The filtrate was treated with aqueous potassium hydroxide solution until the products of the reduction of chloranil were completely removed (verified chromatographically), after which it was washed with distilled water. The benzene layer was dried with anhydrous sodium sulfate and evaporated. The precipitate was recrystallized from petroleum ether (Table 4).

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