THE PYRYLATION OF AROMATIC AND HETEROCYCLIC COMPOUNDS

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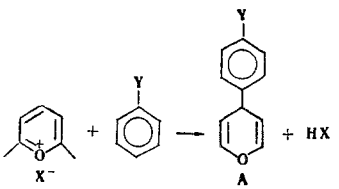
Pyrylium salts having no substituents in position 4 react with aromatic and heteroaromatic compounds forming 4-aryl- and 4-heterylpyrylium derivatives. The reaction takes place through the stage of the formation of a pyran which, with an excess of the initial pyrylium salt, splits out a hydride ion, aromatizing into a trisubstituted pyrylium cation.

The electron density in 2,4,6-trisubstituted pyrylium salts (with equivalent substituents) is such that nucleophilic attack takes place predominantly in the α position of the pyrylium cation. Almost all the transformations of pyrylium salts (into pyridines, substituted benzenes, azulenes, etc.) are based on this [1, 2]. If, however, the γ position is not substituted, nucleophilic attack in position 4 is possible. Thus, benzylmagnesium bromide and nitromethane (in the presence of potassium tert-butoxide) add to position 4 of 2,6-diphenylpyrylium salts [3]. Wizinger et al. [4, 5] have condensed γ-unsubstituted pyrylium and thiapyrylium salts with compounds containing active methylene groups in the presence of sodium acetate.

On the basis of the general ideas of the theory of electrophilic substitution reactions with the formation of carbon–carbon bonds, it may be assumed that pyrylium salts having no substituents in at least one of the α and γ positions will react with reactive aromatic and heterocyclic compounds in the manner of an electrophilic substitution:



Attempts to perform such a reaction in benzene or toluene (for convenience in separating the product A from the unchanged pyrylium salt) did not give the expected result. However, in polar solvents (dimethylformamide, acetic acid), α,γ-unsubstituted salts react with many aromatic and heterocyclic compounds with the formation of trisubstituted pyrylium salts. Thus, 2,6-diphenylpyrylium perchlorate readily acts with 1-methylindole even without a catalyst; however, contrary to expectations, this forms the crystalline 4-(1-methylindol-3-yl)-2,6-diphenylpyrylium perchlorate. 1-Methylpyrrole, 1-ethylindole, etc., react similarly. In a study of the reaction mechanism, it was found that the pyran formed as an intermediate splits out a hydride ion in the presence of an excess of 2,6-diphenylpyrylium perchlorate, being converted into a pyrylium cation in the following way:

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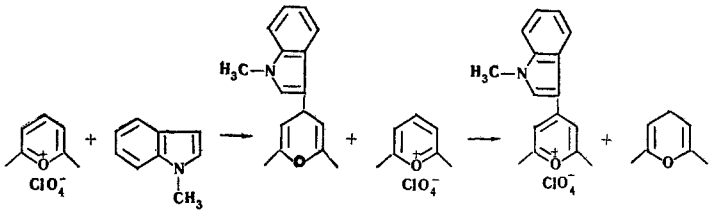
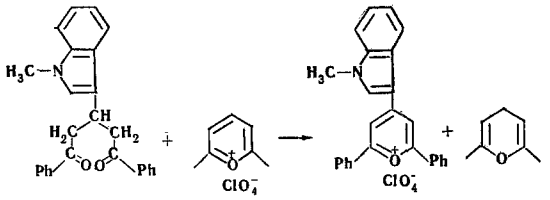


The last stage is confirmed by the fact that the 1,5-diketone obtained from 3-formyl-1-methylindole and acetophenone by a known method splits out hydride ion when it is boiled with 2,6-diphenylpyrylium perchlorate in dimethylformamide and undergoes aromatization into an indolyl-substituted pyrylium salt identical with that obtained by the dehydrogenation of this diketone with triphenylmethyl perchlorate and with the salt obtained by the pyrylation of 1-methylindole with the diphenylpyrylium cation:



Under similar conditions, the 1,5-diketone obtained from p-dimethylaminobenzaldehyde and acetophenone gives a 20% yield of 4-(p-dimethylaminophenyl)-2,6-diphenylpyrylium perchlorate. The proposed pyrylation mechanism is also confirmed by the isolation from the reaction mixture of 2,6-diphenyl-4H-pyran, identified by its conversion into 2,6-diphenylpyrylium perchlorate.

The splitting off of a hydride ion by a pyrylium cation is possible only if there is a sufficiently high electron density in the γ position of the pyran A (one greater than in a γ-unsubstituted pyran). In agreement with this, phenol ethers, dialkylanilines, 1-alkylindoles, and 1-tetrahydroquinolines, and also nitrogen heterocycles, readily undergo the pyrylation reaction with the formation of the corresponding pyrylium salts.

The high yields of the end-products (see Table 1), excluding the presence of any appreciable amounts of the intermediate pyran, show that the limiting stage in this synthesis is the pyranylation reaction and not the hydride transfer. In accordance with the mechanism of an electrophilic reaction, electron-donating substituents orient the electrophilic attack of the pyrylium cation to the para position of the aromatic nucleus. This was shown by the independent synthesis by known methods of a number of compounds: 4-(1-methylindol-3-yl)-2,6-diphenylpyrylium perchlorate, 4-(para-dimethylaminophenyl)-2,6-diphenylpyrylium perchlorate, etc.

Pyrylation takes place readily on boiling (30 min-2 h) a mixture of the reactants in a polar solvent, and the end-products are generally isolated by the addition of ether to the cooled reaction mixture.

Dimethylformamide and acetic acid have proved to be the most suitable solvents for this reaction, but in dimethylformamide the pyrylation of some compounds takes place more rapidly and with higher yields. Some compounds (for example, the dimethyl ether of resorcinol) do not undergo pyrylation in acetic acid.

Some time ago, Wizinger et al. [4, 5], condensing γ-unsubstituted benzopyrylium and thiapyrylium salts with compounds containing active methylene groups in boiling acetic acid in the presence of anhydrous sodium acetate in order to obtain cyanine dyes, mechanically transferred this method to the condensation of the salts mentioned with dimethylaniline. Proposing the reaction mechanism

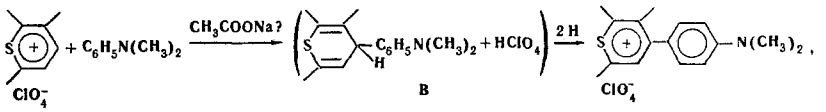
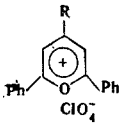


TABLE 1



Compound	R	Mp, °C	Empirical formula	Found, %				Calculated, %				Yield, %
				C	H	Cl	N	C	H	Cl	N	
I	4-Dimethylaminophenyl	380 (dec.)	$C_{25}H_{22}ClNO_5$	67,02	4,97	8,63	2,84	66,52	4,92	7,87	3,10	91,0
II	4-Diethylaminophenyl	280—1	$C_{27}H_{26}ClNO_5$	67,23	5,82	7,44	—	67,57	5,42	7,44	—	73,0
III	4-Piperidinophenyl	265—6	$C_{28}H_{26}ClNO_5$	69,06	5,34	7,37	—	68,43	5,29	7,23	—	12,2
IV	1,4-Diphenylpiperazine-4',4"-diyl	300 (dec.)	$C_{50}H_{40}Cl_2N_2O$	67,54	4,81	7,76	—	66,76	4,45	7,89	—	11,1
V	2,4-Dimethoxyphenyl	258—9	$C_{25}H_{21}ClO_7$	64,76	4,82	7,50	—	64,10	4,49	7,58	—	64,0
VI	2,4,6-Trimethoxyphenyl	150—3	$C_{26}H_{23}ClO_8$	61,71	4,77	7,20	—	62,38	4,61	7,12	—	15,1
VII	2,4-Dihydroxyphenyl	249—50	$C_{23}H_{17}ClO_7$	62,04	4,08	8,55	—	62,66	3,86	8,07	—	63,6
VIII	2,4,6-Trihydroxyphenyl	145—6	$C_{23}H_{17}ClO_8$	59,96	4,09	7,28	—	60,40	3,72	7,77	—	53,5
IX	1-Methyltetrahydroquinolin-5-yl	279—80	$C_{27}H_{24}ClNO_5$	68,47	5,17	7,33	—	67,92	5,03	7,44	—	77,7
X	1-Ethyltetrahydroquinolin-5-yl	262—3	$C_{28}H_{26}ClNO_5$	70,26	5,44	7,29	—	70,46	5,29	7,23		37,5
XI	1-Methyl-2,3-dihydroindol-5-yl	285—6	$C_{26}H_{22}ClNO_5$	67,88	4,92	7,97	2,95	67,38	4,75	7,66	3,02	86,6
XII	1-Ethyl-2,3-dihydroindol-5-yl	295—6	$C_{27}H_{24}ClNO_5$	67,97	5,32	7,40	—	67,92	5,03	7,44	—	92,0
XIII	1-Methylindol-3-yl	292	$C_{26}H_{20}ClNO_5$	67,64	4,55	8,06	3,19	67,68	4,34	7,70	3,05	91,2
XIV	1-Ethylindol-3-yl	254—5	$C_{27}H_{22}ClNO_5$	68,57	5,04	7,40	3,21	68,21	4,63	7,47	2,94	88,6
XV	1-Methylpyrrol-2-yl	250—1	$C_{22}H_{18}ClNO_5$	64,36	4,45	9,27	3,60	64,23	4,38	8,65	3,40	85,3

the authors explained the conversion of the intermediate pyran B into a pyrylium salt as being the result of oxidation with atmospheric oxygen. This hypothesis has proved to be erroneous, since, we have found, the condensation of γ-unsubstituted pyrylium salts with dialkylanilines takes place identically (with the same rates and yields) in the presence of atmospheric oxygen and in an atmosphere of oxygen-free nitrogen. The addition of sodium acetate to this condensation is obligatory, since it scarcely affects the course of the reaction. Thus, the condensation described by Wizinger et al. [4, 5] is identical with the pyrylation reaction discussed. This is confirmed by the isolation of 2,6-diphenyl-4H-pyran from the reaction mixture (condensation of 2,6-diphenylpyrylium perchlorate with dimethylaniline according to Wizinger).

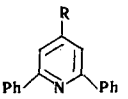
The trisubstituted pyrylium salts that we have obtained have similar properties to those already known (see, for example, [6, 7]); when ammonia is passed into an ethanolic suspension of such salts they are converted smoothly into the corresponding pyridines (the properties of some of the pyridine are given in Table 2).

Apparently the pyrylation reaction is a general one; however, if the nucleophile is incapable of creating the required electron density on the γ-carbon atom of the pyran A, the reaction may stop at this stage (pyranylation).

The IR spectra of the compounds obtained show a series of characteristic bands which can be used for their identification (Table 3).

The most characteristic changes in the spectra of the compounds considered are to be found in the 1650-1400 cm^{-1} region, were there is a group of bands of the symmetrical and antisymmetrical stretching vibrations of the pyrylium cation and of the aromatic substituents. A strong band in the 1620-1650 cm^{-1} region (not overlapped by other bands) corresponds to symmetrical stretching vibrations of the pyrylium ring (8a in Wilson's classification [8]). The band of the 8b antisymmetrical stretching vibrations in the 1520-1540 cm^{-1} region (see Table 3) is also extremely characteristic for the identification of the pyrylium ring. The separation of the 8a and 8b bands ($\Delta\nu_{8ab} = \nu_{8a} - \nu_{8b}$) amounts to 90-115 cm^{-1}, i.e., it is close to the values of 8a-8b in the spectra of other substituted pyrylium salts [9, 10]. The results given in Table 3 do not permit any kind of correlation between the shift of the 8a and 8b bands and the stability of the pyrylium ring.

TABLE 2



Compound	R	mp, °C (from ethanol)	Empirical formula	Found, %			Calculated, %		
				C	H	N	C	H	N
XVI	4-Dimethylaminophenyl	138	$C_{25}H_{22}N_2$	86,19	6,36	8,52	85,71	6,28	8,00
XVII	1-Methyltetrahydroquinolin-5-yl	124—5	$C_{27}H_{24}N_2$	86,08	6,84	6,86	86,16	6,38	7,44
XVIII	1-Methyl-2,3-dihydroindol-5-yl	151	$C_{26}H_{22}N_2$	86,62	5,91	—	86,19	6,07	—
XIX	1-Methylindol-3-yl	144,5	$C_{26}H_{20}N_2$	86,53	5,50	7,93	86,94	5,55	7,48
XX	1-Methylpyrrol-2-yl	138	$C_{22}H_{18}N_2$	85,78	5,83	—	85,16	5,80	—

TABLE 3. IR Spectra of the Pyrylium Salts Synthesized

Compound	Vibrations of the pyrylium ring				Vibrations of the benzene ring			
	8a	8b	19a	19b	8a	8b	19a	19b
I	1645s	1530s	—	1425s	1595infl	1557m	1495s	1450m
II	1620m	1532m	1475s	1425s	1590m	1555s	—	1445infl
III	1645s	1520m	1490s	1420infl	1600s	1550m	—	1440infl
IV	1630m	1535infl	1490s	1425s	1590infl	1570s	1520m	—
V	1630m	1540m	1488s	1420m	1600s	1560m	1517m	1445m
VI	1625s	1520infl	1490s	1420m	1600infl	1575infl	1490s	—
VII	1630infl	1540infl	1488s	1420m	1610s	1570s	1518m	1445m
VIII	1660m	1530infl	1486s	—	1600s	1575s	1517m	1445m
IX	1645m	1530m	1485s	1415m	1600s	1550m	1488s	1445infl
X	1645m	1530s	1485s	1425m	1600s	1550m	1490s	1440m
XI	1643m	1530m	1489s	1417s	1602s	1542m	1500s	1440infl
XII	1650m	1540m	1487s	1425infl	1610s	—	1503s	1445m
XIII	1640s	1545s	—	1425s	1590m	—	1500s	1450infl
XIV	1635s	1535s	1486s	1435m	1609infl	—	—	1445m
XV	1618s	1530s	1478s	1410m	—	1565m	1503infl	1440w

*The numbers correspond with those in Table 1.

Fairly strong bands in the 1480-1490 and 1410-1425 cm^{-1} region can be ascribed to the symmetrical and antisymmetrical stretching vibrations of a heterocycle of types 19a and 19b, respectively, in Wilson's classification [8]. They may also be used to confirm the presence of a pyrylium cation.

The groups of bands in the 1600 and 1550-1570 cm^{-1} regions (8a and 8b) and the 1490-1500 and 1440-1450 cm^{-1} regions (19a and 19b respectively) are connected with the absorption of the phenyl substituents. Band 8b has no independent value for identification. Band 8a, the strong band of C=C symmetrical stretching vibrations of the benzene ring (19a), and the middle band of the antisymmetrical vibrations (19b) (appearing here in the form of inflections) can be used for the identification of phenyl substituents.

EXPERIMENTAL

The IR spectra of the compounds synthesized were taken in paraffin oil on a UR-10 spectrophotometer.

4-(2,4-Dimethoxyphenyl)-2,6-diphenylpyrylium Perchlorate (V). A solution of 3.3 g (0.01 mole) of 2,6-diphenylpyrylium perchlorate and 1.4 g (0.01 mole) of the dimethyl ether of resorcinol in 20 ml of dry dimethylformamide was heated at the boil for 2 h. The cooled reaction mixture was treated with 50-70 ml of ether and left to crystallize in the refrigerator. The resulting brown crystalline material was filtered off and was washed with cold acetic acid and with ether. Yield 1.5 g (64%), mp 258-259°C (from nitromethane).

4-(1-Methyl-2,3-dihydroindol-5-yl)-2,6-diphenylpyrylium Perchlorate (XI). A mixture of 3.3 g (0.01 mole) of 2,6-diphenylpyrylium perchlorate and 0.7 g (5.3 mmole) of 1-methylindoline in 20 ml of dry dimethylformamide was boiled for 45 min. After cooling, the product formed crystallized, and it was filtered off, washed with ether, and dried. Yield 2.0 g (86.6%), mp 285-286°C (from nitromethane).

The pyrylation of N-substituted anilines, indoles, pyrroles, indolines, and tetrahydroquinolines and of phenol ethers and other compounds (Table 1) was carried out similarly. Some of the compounds obtained were converted into the corresponding pyridines (Table 2) by the usual methods.

4-(1-Methylindol-3-yl)-2,6-diphenylpyrylium Perchlorate (XIII). A mixture of 3.3 g (0.01 mole) of 2,6-diphenylpyrylium perchlorate and 1.3 g (0.01 mole) of 1-methylindole in 50 ml of glacial acetic acid was boiled for 3 h. The initial pyrylium salt first dissolved, and then the pyrylium perchlorate product precipitated. After cooling, it was filtered off, washed with a small amount of cold acetone and with ether, and dried. Yield 1.0 g (43.4%), mp 292°C (from nitromethane). It gave no depression of the melting point with an authentic sample [6] of 4-(1-methylindol-3-yl)-2,6-diphenylpyrylium perchlorate.

Similarly, dimethylaniline was pyrylated in acetic acid with a yield of 48.7%.

2,6-Diphenyl-4H-pyran was isolated from the reaction mixture (in the pyrylation of dimethylaniline and of 1-methylindole) by chromatography on a column of alumina with petroleum ether, bp 40-60°C, as the eluent; mp of the product 89-90°C (from petroleum ether). Found, %: C 86.47; H 6.31. $C_{17}H_{14}O$. Calculated, %: C 87.18; H 5.99.

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