A NEW METHOD FOR THE CONSTRUCTION OF PYRYLIUM AND PYRIDINE RINGS FUSED TO DERIVATIVES OF FURAN AND INDOLE

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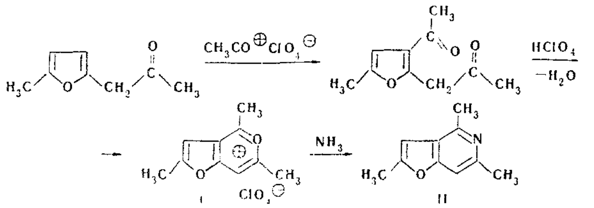
A simple method is described for the construction of the pyrylium ring fused to furans and indoles, by the acylation of 2-methyl-5-acetonylfuran, 3-acetonylindole and its 1-alkyl derivatives with acid anhydrides in presence of 70% perchloric acid. The previously unknown furano[3, 2-c]-and indolo[2, 3-c]pyrylium salts are prepared. A method for the preparation of 4-methyl-harman and its alkyl homolog has been developed.

Pyrlium salts fused to heterocyclic compounds have been almost unknown until recently. It might be expected that such heteropyrylium salts would possess aromatic character, and the ability to undergo a variety of reactions by virtue of the high reactivity of the pyrylium ring [1].

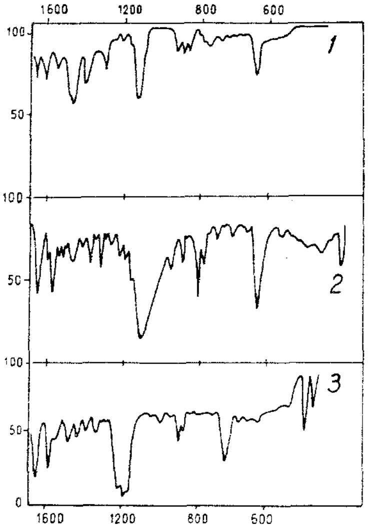
We have recently put forward a new method for the synthesis of 2-benzopyrylium salts, by the acylation of benzyl alkyl ketones and of desoxybenzoin, containing electron-donating substituents in the m-position of the aromatic ring [2–6]. This method is also very convenient for the construction of pyrylium rings fused to the thiophene nucleus [3, 4].

The aim of the present work is to examine the possibility of applying this method of constructing the pyrylium and pyridine rings fused to compounds of the furan and indole series. We succeeded in synthesizing 2, 4, 6-trimethylfurano[3, 2-c]pyrylium perchlorate (I) in low yield (17%), by acetylating 2-methyl-5-acetonylfuran, obtained by reduction of the product from the alkaline condensation of furfural with nitroethane [7], by the following route:



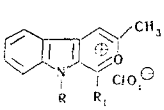
The acetylation proceeded readily under mild conditions (0° C), on adding a solution of acetyl perchlorate in acetic anhydride to 2-methyl-5-acetonylfuran. The structure of the pyrylium salt I was confirmed by its IR spectrum, which has bands at 1646 and 1540 cm^{-1} characteristic for the symmetric and antisymmetric valency stretching in the pyrylium cation [8, 9] (see figure), and also by the ease of replacement of the heterocylic oxygen by nitrogen. Treatment of the pyrylium salt I with aqueous ammonia gave 2, 4, 6-trimethylfurano[3, 2-c]pyridine (II) in almost quantitative yield (identified as the picrate). Attempts to synthesize furano[3, 2-c]pyrylium salts by the acylation of 2-furylacetonitrile were unsuccessful, apparently as a result of electrophilic attack by the acyl cation on the more reactive free α-position of the furan ring.

The method here described for the synthesis of pyridines fused to a furan ring is interesting in view of the fact that furano[3, 2-c]pyridines are difficultly-accessible compounds, and have been prepared only recently by Herz and Tocker [10] by a complex, multistage route.



IR Spectra of Pyrylium salts: 1) 2, 4, 6-trimethylfurano[3, 2-c]pyrylium perchlorate: 2) 1-ethyl-2, 4-dimethylindolo[2, 3-c]pyrylium perchlorate; 3) 2, 4-dimethylindolo[2, 3-c]pyrylium perchlorate.

We were much attracted by the possibility of applying this same method for the construction of pyrylium and pyridine rings fused to indole and its derivatives. Indolopyrylium salts could be of interest as convenient starting materials for the preparation of carbolines, the synthesis of indole alkaloids (harman, harmine, melinonine etc. [11]) and their homologs, which possess high hypotensive activity [12]. With the object of developing a method of preparation of the hitherto unknown indolo[2, 3-c]pyrylium salts, and of the β-carbolines and homologs of the alkaloid harman derived therefrom, we investigated the acylation of 3-indolyacetone and its 1-alkyl derivatives. Acetylation of 3-indolylacetone with acetic anhydride in presence of 70% perchloric acid under mild conditions gave a low yield (10%) of 2, 4-dimethylindolo[2, 3-c]pyrylium perchlorate (III, R = H), which on treatment with ammonia gave 4-methylharman (IV, R = H).



R	R₁	Mp, ° C (from water)	Molecular formula	Found %			Calculated %			Yield
				C	H	Cl	C	H	Cl	
CH_3*	C_2H_5	182—184	$C_{15}H_{16}ClNO_5$	55.53	5.16	11.02	55.30	4.95	10.88	72.8
C_2H_5	CH_3	200—202	$C_{15}H_{16}ClNO_5$	55.92	5.16	10.61	55.30	4.95	10.88	36
C_2H_5**	C_2H_5	193—195	$C_{16}H_{18}ClNO_5$	56.62	5.31	10.25	56.55	5.30	10.44	25
$C_6H_5CH_2$	CH_3	212—214	$C_{20}H_{18}ClNO_5$	62.03	4.91	9.18	61.94	4.68	9.14	23

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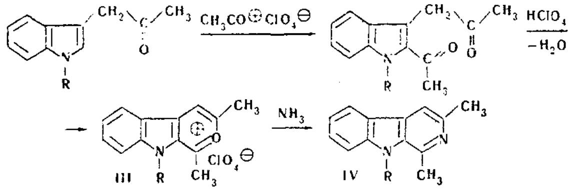
* Carboline picrate: yellow-green needles, mp 234–235° C (from ethanol). Found,%: N 15.56, 15.6. Calculated for $C_{15}H_{16}N_2 \cdot C_6H_3N_3O_7$,%: N 15.67.

** Carboline picrate: yellow crystals, mp 186–188° C (from ethanol). Found,%: N 14.51. $C_{16}H_{18}N_2 \cdot C_6H_3N_3O_7$. Calculated for,%: N 14.99.



R = H, CH_3, C_2H_5, $CH_2C_6H_5$

The low yield of the pyrylium salt (III, R = H) may be explained by the occurrence of N-acylation of the indole and of a number of products arising from the lability of the indole ring under strongly acid conditions. In order to suppress the occurrence of these side reactions, we examined the acylation of 1-alkyl-substituted 3-indolylacetones. It has been shown that in this case the yield of the pyrylium salt is increased substantially. For example, acetylation of 1-methyl-3-indolylacetone affords the pyrylium salt (III, R = CH_3) in 68% yield, while propionylation gives 72%. The structure of the compounds prepared is confirmed by their IR spectra, and by the conversion of the salts into the corresponding β-carbolines on treatment with ammonia. The carboline thus obtained (IV, R = H) proved to be identical with 4-methylharman obtained by dehydrogenation of the corresponding tetrahydro-derivative [13].

As was to be expected, the IR spectra of the 1-alkyl-substituted indolo[2,3-c]pyrylium perchlorates (figure) show a great resemblance to those of 2-benzopyrylium salts [5, 14]. The main absorption bands of these compounds are shifted by only a small amount in comparison with the positions of these bands in the isochromnylium salts [5]. In the spectrum of indolo[2,3-c]pyrylium salt with a free NH group, there is a strong absorption band due to the pyrylium ring (1638 cm^{-1}), much displaced towards the high-frequency region (figure). The wide band in the 3490–3550 cm^{-1} region confirms the presence in this compound of a free NH group.

All the indolo[2,3-c]pyrylium salts which we have prepared are very readily converted into the corresponding β-carbolines, which are usually obtained by dehydrogenation of the dihydro-and tetra-hydrocarbolines synthesized by the Pictet-Spengler [15, 16] and Bishler-Napieralski [17] reactions. In view of the high yields of indopyrylium salts, it is suggested that our method may be of value for the preparation of β-carbolines.

It is known that the hypotensive and ganglion-blocking activity of heterocylic amines, and in particular of carbolines, increases rapidly with the extent of methylation of the nitrogen atom and of the adjacent carbon atoms [12, 18, 19]. Our N-alkylated 4-methylharmans may well, therefore, be of possible interest as physiologically active substances.

EXPERIMENTAL

2,4,6-Trimethylfurano[3,2-c]pyrylium perchlorate (I). The 2-methyl-5-acetonylfuran starting material was prepared by the alkaline condensation of 5-methylfurfural with nitroethane [20], followed by reduction of the furylnitroethylene by the method given in [21]. 2-Methyl-5-acetonylfuran was synthesized in 40% yield as a colorless liquid, bp 72–74° C (7 mm). Semicarbazone, mp 126–128° C. Found,%: N 21.65; $C_9N_{13}N_3O_2$ requires N 21.53%.

An acylating mixture consisting of 15 ml of acetic anhydride and 0.96 ml of 70% $HClO_4$ was added dropwise with stirring and with cooling during 15 min to 4.14 g of 2-methyl-5-acetonylfuran in 5 ml of acetic anhydride. The resulting warm solution was kept at 0° C for 30 min, poured into cooled ether, and the resulting dark-colored, tarry material filtered off and stirred with 30 ml of n-propanol. The crystalline product was filtered off, washed with ether and dried in vacuo. There was obtained 1.35 g (17%) of the pyrylium salt as light brown crystals, mp 180–181° C (from chloroform). IR spectrum cm^{-1}: 1646 (med.), 1620 (weak), 1596 (strong), 1540 (med.), 1455 (strong), 1390 (strong), 1105 (very strong). Found,%: C 45.47; 45.35; H 4.44; 4.12; Cl 13.69; 13.31. Calculated for $C_{10}H_{11}ClO_6$,%: C 45.73; H 4.22; Cl 13.50.

2,4,6-Trimethylfurano[3,2-c]pyridine (II). Treatment of the pyrylium salt I with aqueous ammonia gives this as liquid. Picrate, lemon-colored needles, mp 160–162° C (from ethanol). Found,%: N 14.07. Calculated for $C_{16}H_{14}N_4O_8$,%: N 14.36.

Indolo[2,3-c]pyrylium salts and β-carbolines. The synthesis of the starting 3-indolyacetones was accomplished as follows: Vilsmayer formylation of indole [22] gave indole-3-aldehyde, which was alkylated by the alkyl halide in presence of potassium t-butoxide [23]. The aldehydes obtained were condensed with nitroethane to give the 3-indolynitroethylenes [24], which were reduced by the usual method [21] to the corresponding 3-indolylacetones.

2,4-Dimethylindolo[2,3-c]pyrylium perchlorate. A 1.73 g quantity of 3-indolylacetone was mixed with 5 ml of glacial acetic acid, and to the cooled mixture was added an acylating reagent consisting of 5 ml of acetic anhydride and 0.8 ml of 70% $HClO_4$. After addition of all the acylating mixture, stirring was continued for 2 hr; then the mixture was poured into ether (50 ml). The precipitate was filtered off to give 2.8 g of a black, amorphous material. Crystallization from water with the addition of 3 drops of $HClO_4$ and activated charcoal gave 0.3 g (10%) of the pyrylium salt as pale brown crystals, mp above 260° C (decomp.). Found, %: C 53.04; H 4.00; Cl 12.40; N 5.15%. Calculated for $C_{13}H_{12}ClNO_5$,%: C 52.45; H 4.06; Cl 11.91; N 4.78.

4-Methylharman. Obtained in good yield by treatment of the pyrylium salt **III** (R=H) with ammonia, mp 179° C ($CHCl_3$–petroleum ether); lit. mp 180° C [13]; 174° C [18]. Found,%: N 14.03; 14.11. Calculated for $C_{13}H_{12}N_2$, %: N 14.28.

1, 2, 4-Trimethylindolo[2, 3-c]pyrylium perchlorate. The 1-methyl-3-acetonylindole used as starting material was prepared in the usual way from 1-methyl-3-formylindole and nitroethane. The yield of ketone in the last stage was 33%. The product was a viscous, orange-colored liquid, bp 156–162° C (1 mm), n_D^{20} 1.5903. Found,%: N 7.21; 7.2. $C_{12}H_{13}NO$. Calculated: N 7.48.

A mixture of 15 ml of acetic anhydride and 2.4 ml of 70% $HClO_4$, cooled to 0° C, was added quickly with vigorous stirring to 5.6 g of 1-methyl-3-acetonylindole. The reaction mixture became very hot and turned brown, crystals separating at the same time. After cooling, 20 ml of ether was added, the solid filtered off, washed with ether, and dried. Crystallization from water with charcoal gave 6.3 g(67.7%) of the pyrylium salt as light brown crystals with a green iridescence, mp 250–251° C (decomp., from ethanol). Found,%: C 53.59; 54.11; H 4.79; 4.59; Cl 11.05; 10.90. $C_{14}H_{14}ClO_5N$. Calculated: C 53.94; H 4.53; Cl 11.37. The alcoholic solution of the salt shows a bright reddish-green fluorescence. The other indolo[2, 3-c]pyrylium salts were prepared similarly (see table).

1, 4-Dimethylharman. This was prepared by treatment of 1, 2, 4-trimethylindolo[2, 3-c]pyrylium perchlorate with aqueous ammonia in 75–80% yield. Colorless crystals, mp 77–79° C (benzene-light petroleum). Found,%: N 13.64; 13.73. Calculated for $C_{14}H_{14}N_2$, %: N 13.9%. Picrate: yellow needles, mp 244–245° C (from 4 : 1 ethanol-nitromethane). Found, %: N 16.22; 16.27. Calculated for $C_{14}H_{14}N_2 \cdot C_6H_3N_3O_7$, %: N 15.94. Hydrochloride: colorless needles, mp 324–326° C (from acetone-water). Found,%: C 59.97; H 7.03; Cl 11.79. Calculated for $C_{14}H_{14}N_2$,%: C 59.57; H 6.74; Cl 12.22.

The IR spectra of the pyrylium salts were taken in vaseline oil on a UR-10 spectrophotometer.

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