SYNTHESIS OF CERTAIN 2-ACYL-4-METHYLPHENOLS

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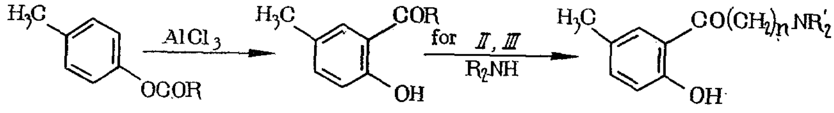
With the object of finding substances with pharmacological activity, a number of new members of the 2-acylphenols (I-III) were synthesized on the basis of the Fris rearrangement of complex esters of n-cresol. The latter were obtained by heating n-cresol with the chloranhydrides of dihydrocinnamic acid, w-chlorobutyric acid, or w-chlorovaleric acid. The cresyl esters were extracted by distillation under vacuum, and the raw products obtained by this means were treated with anhydrous aluminum chloride. The resulting 2-acyl-4-methylphenols (I-III) were purified by distillation under vacuum. The chloro- containing acylphenols (II and III) can be successfully used for obtaining aminoacylphenols, and this method has been demonstrated by us in the synthesis of compounds IV-VIII:



I–III IV–VIII

I: R = $(CH_2)_2C_6H_5$
II: R' = $(CH_2)_3Cl$
III: R = $(CH_2)_4Cl$

IV, VI: NR'_2 = piperidino
V, VII: NR'_2 = morpholino
VIII: NR'_2 = pyrrolidino

IV, V: n = 3
VI, VII, VIII: n = 4

According to the method of Baker [1], acylphenol (I) was converted into 3-benzyl-6-methylchromone carbonic-2 acid (IX), and from the latter through its chloranhydride, obtained by the method described, the γ-dimethylaminopropyl ester of this acid (X) and also the β-diethylaminoethyl ester of N-(3'-benzyl-6'-methylchromonoyl-2')-4-aminobenzoic acid (XI) were synthesized.

No pronounced coronary dilating, spasmolytic, or psychosedative activity was found among the aminoacylphenols obtained.

EXPERIMENTAL

2-ω-Phenylpropionyl-4-methylphenol (I). A 99.2 g quantity of dihydrocinnamic acid and 57 ml of $SOCl_2$ were heated in a boiling water bath for one hour. The resulting impure chloranhydride was gradually added to 72 g of molten n-cresol, the mixture was heated for four hours at 100°, and distilled under vacuum. A 136 g quantity of raw cresyl ester of dihydrocinnamic acid was obtained, bp 158-159° (1 mm).

A 136 g quantity of the obtained ester was rapidly added to 151 g $AlCl_3$ with mechanical stirring (vigorous evolution of hydrogen chloride), the reaction mixture was heated to 140° in an oil bath as rapidly as possible, and maintained at this temperature for one hour. After cooling, the mixture was separated with water containing ice and extracted with ether. The ether was removed by distillation and the residue was distilled under vacuum. A 45 g quantity (40%) of acylphenol (I) was obtained, bp 171-174° (2 mm), n_D^{20} 1.5920. Found %: C, 80.25, 80.04; H, 6.72, 6.67; $C_{16}H_{16}O_2$. Calculated, %: C, 79.99, H, 6.71.

2,4-Dinitrophenylhydrazone. Found,%: C, 63.07, 63.20; H, 4.81, 4.67; N 13.44. $C_{22}H_{20}N_4O_5$. Calculated,%: C, 62.82; H, 4.80; N, 13.33.

2-ω-Chlorobutyroyl-4-methylphenol (II) and 2-ω-chlorovaleroy-4-methylphenol (III). A 126 g quantity of $AlCl_3$ was added in portions to a solution of 134 g of the n-cresyl ester of ω-chlorobutyric acid (bp 120-121° (1 mm), n_D^{20} 1.5121, obtained by heating equimolar quantities of n-cresol with the acid chloride of

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TABLE 1. Chlorohydrates of 2-ω-Aminoacyl-4-methylphenols (IV-VIII)

Substance	Yield (%)	Melting point	Empirical formula	Found (%)		Calculated %	
				Cl	N	Cl	N
IV[*]	43,6	186,5—187,5 Absolute alcohol	$C_{16}H_{24}ClNO_2$[†]	11,83 11,93		11,92	
V[†]	48,3	237—8 Alcohol	$C_{15}H_{22}ClNO_3$	11,99 11,89	4,91 4,74	11,82	4,67
VI[‡]	74,8	197—8 Alcohol	$C_{17}H_{26}ClNO_2$	11,29 11,25		11,37	
VII	76	172—3 Absolute alcohol	$C_{16}H_{24}ClNO_3$[**]	11,24 11,24	4,85 4,72	11,30	4,46
VIII[††]	44,5	158—9 Absolute alcohol	$C_{16}H_{24}ClNO_2$	11,76 11,88		11,91	

[*] Toluene was used in place of xylene .

[†] Found,%: C, 64.62, 64.71; H, 8.16, 8.27. Calculated, %: C, 64.52; H, 8.12

[‡] At the end of the reaction a 10% solution of hydrochloric acid was added, and the resulting precipitate of chlorohydrate was separated.

[**] Found,%: C, 60.94, 61.09; H, 7.88, 7.88. Calculated, %: C, 61.24; H, 7.71

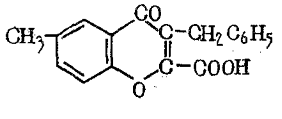
[††] The chlorohydrate was precipitated from ether.

ω-chlorobutyric acid for 2.5 h at 100°, in 630 ml of dry nitrobenzene. The mixture was heated for 6 h at 60-70°, left overnight, and then poured into iced water. Nitrobenzene was removed by steam distillation, the residue was extracted with carbon tetrachloride, the extract was dried with $MgSO_4$, and the acyl phenol (II) was extracted by distillation. Yield, 61%, bp 149-152°, (1 mm), mp 42° (from methanol). Found,%: C, 61.93, 61.80; H, 6.13, 6.05; Cl, 16.54, 16.49. $C_{11}H_{13}ClO_2$. Calculated, %: C, 62.11; H, 6.16; Cl, 16.67.

Phenylhydrazone. mp 99-100° (from methanol). Found,%: C, 67.54; H, 6.44; Cl, 11.76. $C_{17}H_{19}ClN_2O$. Calculated,%: C, 67.43; H, 6.32; Cl, 11.71.

Acylphenol (III) (yield, 47%, mp 150-154° (1 mm), $n_D^{17.5}$ 1.5565) was obtained in an analogous manner. The raw product was used in the subsequent reactions. Phenylhydrazone, mp 124-124.5° (from alcohol). Found,%: C, 68.59, 68.42; H, 6.83, 6.70; Cl, 11.34, 11.39. $C_{18}H_{21}ClN_2O$. Calculated,%: C, 68.25; H, 6.68; Cl, 11.19.

Aminoketones (IV-VIII). A mixture of 9.06 g of acyl phenol (III) and 10.32 g of morpholine in 30 ml of dry toluene was boiled for 10 h; the mixture was cooled, shaken with dilute hydrochloric acid, and the aqueous layer was removed and made alkaline with sodium carbonate. The separated oil was extracted with 100 ml xylene. The morpholine was removed from the extract by distillation, and the xylene was partially removed at the same time. Dry hydrogen chloride was bubbled into the remaining solution. The precipitate was removed by filtration, and 1.5 g (76%) of the chlorohydrate of aminoacylphenol (VII) was obtained. Chlorohydrates of other aminoacylphenols were synthesized by a similar method. Data concerning the chlorohydrates of aminoacylphenols (IV-VIII) are presented in the table.



3-Benzyl-6-methylchromone Carbonic-2 Acid (IX). A 3.68 g quantity of ethoxalyl chloride was added dropwise to a solution of 2.25 g of acylphenol (I) in 4 ml of dry pyridine, and the mixture was boiled for 3 h. On cooling 16 ml of acetic acid and 20 ml of water were added to the reaction mixture, and the latter was extracted with ether. The ethereal extract was washed with water, dried over $MgSO_4$, and evaporated. A 15 ml volume of acetic acid and 5 ml concentrated HCl were added to the resulting residue, and the mixture was boiled for 6 h and then evaporated under vacuum. The residue was treated with a solution of $NaHCO_3$ and ether. The bicarbonated solution was separated and acidified with concentrated HCl. The precipitate was removed by filtration, washed, and dried over P_2O_5 under vacuum. A 1.91 g quantity (72%) of the acid (IX) was obtained, mp 229-230° (from aqueous methanol and then from a mixture of methanol and alcohol). Found,%: C, 73.82, 73.90; H, 4.75, 4.84; $C_{18}H_{14}O_4$. Calculated,%: C, 73.50; H, 4.79.

The Ethyl Ester was obtained by esterification of the acid (IX) with alcohol in the presence of concentrated H_2SO_4. The yield was 89%, mp 92.5-93° (from alcohol). Found,%: C, 74.73, 74.48; H, 5.68, 5.60. $C_{20}H_{18}O_4$. Calculated,%: C, 74.52; H, 5.62.

The Chlorohydrate of the γ-Dimethylaminopropyl Ester of 3-Benzyl-6-methylchromone Carbonic-2 Acid (X). A solution of 2.7 g (0.009 mole) of impure chloranhydride of the acid (IX) in 50 ml dry dichlorethane was added dropwise to a solution of 0.9 g of γ-dimethylaminopropanol in 3 ml dry dichlorethane, and the resultant mixture was left overnight. The precipitate was removed by filtration and the chlorohydrate of the aminoester (X) was obtained. Yield, 2.55 g (68%), mp 158-159 (from alcohol). Found,%: Cl, 8.42, 8.43. $C_{23}H_{26}ClNO_4$. Calculated,%: Cl, 8.53.

The Chlorohydrate of the β-Diethylaminoethyl Ester of N-(3'-Benzyl-6-methylchromonoyl-2)-4-aminobenzoic Acid (XI). A 1.17 g quantity of sodium carbonate and 5 g of ice were added to a solution of 1.36 g novocaine in 5 ml water, and on cooling from outside with ice a solution of 1.5g of the chloranhydride of the acid (IX) in 30 ml of dry dichlorethane was added dropwise. After 4 h the precipitate was removed by filtration, and 2.15 g (86%) of the chlorohydrate of Compound XI was obtained, mp 244-246° (from methanol). Found,%: C, 67.60, 67.38; H, 6.01, 6.07; Cl, 6.45, 6.47. $C_{31}H_{34}ClN_2O_5$. Calculated,%: C, 67.79; H, 6.06; Cl, 6.46.

CONCLUSION

On the basis of the Fris rearrangement of complex esters of n-cresol, 2-acyl-4-methylphenols (I-III) were synthesized and used for certain subsequent conversions.

LITERATURE CITED

1. W. Baker, I. Chadderton, J. B. Harborne, et al., J. Chem. Soc., 1852 (1953).
2. V. A. Zagorevskii and Sh. M. Glozman, Zh. Obshchei Khimii, 34, 1506 (1964).