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N-(Arylaminomethyl)-phtalimides

N-(Arilaminometil)-ftalimidler

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The action of phtalimide and formaldeyhde on amines to produce N-(arylaminomethyl)-phtalimides is a general reaction and it is useful for the identification of amines.

The same substances may be obtained by the action of N-(hydroxymethyl)-phtalimide on amines.

The N-(piperidinomethyl-,[1,2]), N-(morpholinomethyl)-([3]), N-(anilinomethyl)-, N-(phenylhydrazinomethyl)-([1]) and a series of N-(arylaminomethyl)-phtalimides ([4]) have been prepared by these methods.

The preparation of p-phtalimidomethylaminobenzoic acid, p-phtalimidomethylaminoethylbenzoate, m-phtalimidomethylamino-p-hydroxy-methylbenzoate, p-phtalimidomethylamino-2-diethylaminoethylbenzoate, p-phtalimidomethylaminophenylsulfonamide, 2-phtalimidomethylamino-4-phenylthiazole and N-phtalimidomethylsaccharin have been investigated.

The compounds mentioned above were prepared according to the method described by Winstead and Heine([4]). Thin-layer chromatography, C, H, N and S microdetermination and UV spectrophotometric methods were employed in order to identify and characterize the synthesized compounds.

EXPERIMENTAL

Preparation of N-(arylaminomethyl)-phtalimides: A mixture of 0.3 g (0.02 mol) of phtalimide, 3 ml of ethanol (80 %) and 2 ml of formaldeyhde (37 %) were refluxed until dissolution was complete. 5 to 10 ml of a solution of 0.023 mol amine in ethanol was added and

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refluxed again, for a different time period for each compound. The mixture was cooled, the crystals were collected by filtration.

p-Phtalimidomethylaminobenzoic acid was prepared with 3.15 g of PABA according to the general method, by heating 1.5 hr. Thin-layer chromatography was carried out with the following solvent systems: chloroform-methanol (8:3); ethanol-ammonia 25 % (8:2); n-butanol-acetic acid-water (4:1:5). The plates were sprayed with anilin (2 g) in n-butanol (100 ml), then were heated at 150° C for 5 minutes; the yellow colored spots were developed. The spots were also located under UV ligth. The Rf values of the spots were shown in table I.

Physical caracteristics: The buff colored, crystallin powder, m.p. 184°. $\lambda_{max.}^{EtOH}$ 216 mμ (ε 42 210), 297 mμ (ε 21 134).

Anal. Calc. for $C_{16}H_{12}N_2O_4$: C, 64.80; H, 4.05; N, 9.45. Found C, 65.01; H, 4.22; N, 9.49.

p-Phtalimidomethylaminoethylbenzoate was prepared with 3.8 g of benzocaine according to the general method, by heating 1.5 hr. Thin-layer chromatography was carried out with following solvent systems: ethanol-ammonia 25 % (8:2), n-butanol-acetic acid-water (4:1:5) and chloroform-methanol (10:8). The spots were visualized as above. The Rf values of the spots were shown in table I.

Physical caracteristics: A white, shiny, crystallin powder, m.p. 185° (lit. 4 m.p. 176°). $\lambda_{max.}^{EtOH}$ 221 mμ (ε 16 766), 299 mμ (ε 42 659).

Anal. Calc. for $C_{18}H_{16}N_2O_4$: C, 66.60; H, 4.93; N, 8.63. Found C, 66.53; H, 4.98; N, 8.79.

m-Phtalimidomethylamino-p-hydroxymethylbenzoate was prepared with 3.85 g of orthocaine according to the general method, by heating 6 hr. Thin-layer chromatography was carried out as above.

Physical characteristics: Red powder, m.p. 210°. $\lambda_{max.}^{EtOH}$ 230 and 309 mμ.

Anal. Calcul. for $C_{17}H_{14}N_2O_5$: C, 62.52; H, 4.29; N, 8.58. Found C, 62.30; H. 4.41; N, 8.29.

p-Phtalimidomethylamino-2-diethylaminoethylbenzoate was prepared with 5.4 g of procaine according to the general method, by heating 1.5 hr. It is a yellow colored oily substance, very hygroscopic.

p-Phtalimidomethylaminophenylsulfonamide was prepared with 3.96 g of sulfanilamide according to the general method, by heating for 1.5 hr. Thin-layer chromatography was carried out with chloroform-methanol (8:3). The spots were located under UV light.

Physical characteristics: Light yellow, crystallin powder, m.p. 220°. $\lambda_{max.}^{EtOH}$ 265 mμ (ε 20 154).

Anal. Calc. for $C_{15}H_{13}N_3O_4S$: C, 54.32; H, 3.92; N, 12.67; S, 9.65. Found C, 54.76; H, 4.02; N, 12.66; S, 9.65.

2-Phtalimidomethylamino-4-phenylthiazole was prepared with 4.05 g of 2-amino-4-phenylthiazole according to the general method, by heating for 1.5 hr. Thin-layer chromatography was carried out with chloroform-methanol (8:3). The spots were located under UV light (366 and 254 mμ).

Physical characteristics: Orange-yellow, crystallin powder, m.p. 135°. $\lambda_{max.}^{EtOH}$ 233 mμ (ε 21 130).

Anal. Calc. for $C_{18}H_{13}N_3O_2S$: C, 64.42; H, 3.87; N, 12.52; S, 9.54. Found C, 64.89; H, 4.00; N, 11.99; S, 9.64.

N-Phtalimidomethylsaccharin * was prepared with 4.21 g of saccharin by heating 1.5 hr. It is a cream colored powder, m.p. 193° (m.p. of the mixture with saccharin is 160°). $\lambda_{max.}^{EtOH}$ 354 mμ, 267 mμ (ε 11 751).

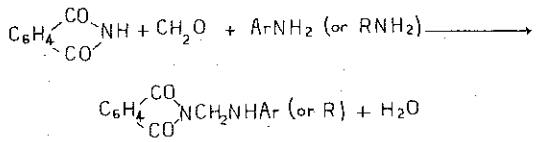
Anal. Calc. for $C_{16}H_{10}N_2O_5S$: C, 56.08; H, 2.92; N, 8.18; S, 9.35. Found C, 56.19; H, 2.89; N, 8.27; S, 9.42.

DISCUSSION

The formation of phtalimidomethyl derivatives of the above

* The compound was prepared by Hüsamettin Kutlu.

mentioned amines were carried out in ethanol solution. A possible mecanism of this reaction may be illustrated as follows:

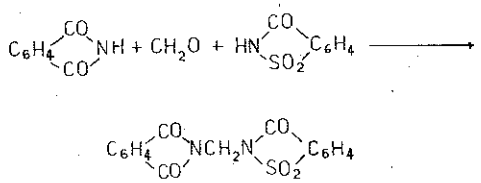


The compounds formed in this reaction were crystalline substances. The melting point of each derivative was distinctly different from that of the starting reagents. They were slightly soluble in methanol, ethanol, ether, chloroform, acetone and benzene, and especially one of them (m-phtalimidomethylamino-p-hydroxymethylbenzoate) was very slightly soluble in methanol and ethanol, therefore it was impossible to calculate the Σ max. for this compound.

Haworth et al.[5] showed that N-hydroxymethylamides condense with substances containing groupings such as hydroxyl, thiol, amino, carboxyl and amide. They also showed that in strong acid solution the N-hydroxymethylamides are converted into methylenebisamides of the type of:

R CO NH CH_2NH CO R

and these compounds are also obtained by condensing amides with formaldehyde in strongly acid media. Whereas in this laboratory the reaction of saccharin with phtalimide and formaldehyde was carried out in neutral solution, and a methylenebisamide type compound namely N-phtalimidomethylsaccharin,



was obtained according to the same reaction as amines.

TABLE I

Rf values of compounds

Compounds :	S_1	S_2	S_3	S_4
p-Phtalimidomethylaminobenzoic acid		0.66		0.47
p-Phtalimidomethylaminoethylbenzoate		0.80	0.78	0.47
m-Phtalimidomethylamino-p-hydroxy--methylbenzoate		0.70	0.61	0
p-Phtalimidomethylaminophenylsülfonamide	1			
2-Phtalimidomethylamino-4-phenylthiazole	0.92			
N-Phtalimidomethylaminosaccharin	1		0.88	

S_1 : chloroform-methanol (8 : 3)
S_2 : ethanol-ammonia % 25 (8 : 2)
S_3 : n-butanol-acetic acid-water (4 : 1 : 5)
S_4 : chloroform-methanol (10 : 8)

SUMMARY

A series of N-arylaminophtalimides were prepared from p-aminobenzoic acid, benzocaine, orthocaine, sulfanilamide, 2-amino-4-phenylthiazole and saccharin by heating a mixture of phtalimide, formaldehyde and of corresponding amine (or saccharin). Thin-layer chromatography was employed to separate the compounds from amines, hydroxymethylphtalimide and from each other. The ultraviolet absorption maxima were determined and C, H, N, and S microanalyses were done.

ÖZET

p-Aminobenzoik asid, benzokain, ortokain, prokain, p-aminofenilsulfonamid, 2-amino-4-feniltiazol ve sakkarin'in N-ftalimidometil

türevleri, amin, (sakkarin için imid) ftalimid ve formaldehitten elde edilmiştir. Herbir maddenin ince tabaka kromatografisi yapılmış ve ultraviole absorpsiyon maksimumları tâyin edilmiştir.

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