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THE SYNTHESIS OF SOME SUBSTITUTED α-(BENZAMIDOMETHYL)PHENYL HYDRAZINES AND α-(BENZAMIDOMETHYL)PHENYLHYDRAZONES

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Some substituted α-(Benzamidomethyl)phenylhydrazines have been synthesized starting from the corresponding N-chloromethylbenzamides and phenylhydrazine as nucleophylic agent. The obtained phenylhydrazines in reaction with carbonyl compounds (benzaldehyde, salicylaldehyde, furfuraldehyde and acetone) have given a series of substituted α-(benzamidomethyl)phenylhydrazones.

Key words: synthesis; benzamides, phenylhydrazine; condensation; dehydration.

INTRODUCTION

This work is part of a wider research of the reaction possibilities of N-chloromethylbenzamides with nucleophylic agents, specifically with amine components. Beside N-methylaniline and N-methylbenzylamine, phenylhydrazine was chosen, as an amine component with hypernucleophylic properties (α- effect) [1, 2].

We synthesized a series of substituted α-(benzamidomethyl)phenylhydrazines, as condensed derivatives of the corresponding N-chloromethylbenzamides with phenylhydrazine. Our aim was to obtain new compounds with a potential biological activity, because it is well known that a large number of hydrazine derivatives are used as antituberculostatics, antiinflammatics and antidepressants [3, 4]. In literature we met only one case of condensation between N-chloromethylbenzamide and phenylhydrazine. It was a paper of Polish authors [5], who had worked with N-chloromethyl-4-nitrobenzamide in rather severe conditions for a pretty long time (over 24 h).

Furthermore, in the treatment of the obtained phenylhydrazines with carbonyl compounds, we have got another series of new compounds of the type α-(benzamidomethyl)phenylhydrazones. It was expected that they would show fungistatic and psychopharmacological activities [6, 4]

EXPERIMENTAL

Spectral data have been obtained using these instruments: IR, Perkin-Elmer 297 and ^{1}H-NMR, Jeol FX 90 Q. The reactions and the purity of the obtained products have been followed by TLC chromatography on silica gel in the diluents: $CHCl_3$ / CH_3OH = 15/1 and C_6H_6/CH_3OH=19/1.

The compounds 2 – 3 have been prepared by the literature procedure [7, 8].

N-Chloromethylbenzamides 4a–d; General Procedure [9]:

To an intensively stirred suspension of N-hidroxymethylbenzamide 3a–d (20 mmol) in dry CCl_4 (7 ml), cooled in an ice bath, $SOCl_2$ (4.4 ml, 60 mmol) is added dropwise within 15 min. After 1,5 h stirring, a thick suspension is filtered off by suction, while the precipitate is washed with dry CCl_4 (4.5 ml) and dried in a vacuum excicator affording 4a–d as colourless crystals. The melting points of 4a and 4c are in agreement with reported values [9], while the melting points of 4b and 4d are determined now. (In the literature [10] it is stated that they have been synthesized, but there are no data for their mp.) The yield of the crude product is 95 – 99%.

α-(Benzamidomethyl)phenylhydrazines 6 and bis(benzamido)dimethylethers 7; General Procedure

Freshly synthesized N-chloromethylbenzamide 4 (20 mmol) is dissolved in dry dioxan (50 ml). After

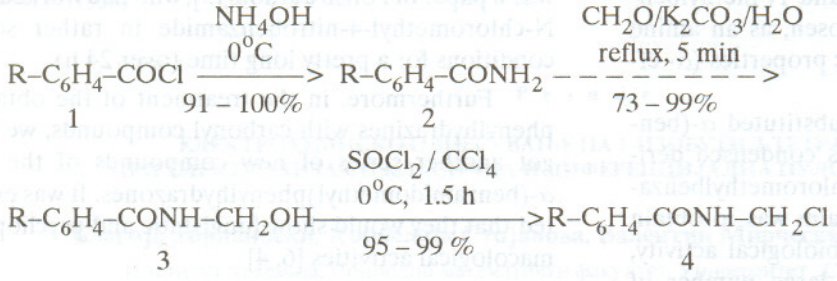
cooling, triethylamine (2.5 ml, 20 mmol) is added slowly, with intensive stirring. A thick suspension is formed, to which phenylhydrazine (2 ml, 20 mmol) in dry dioxan (3 ml) is dropped within 30 min. Stirring is continued for 20 – 30 min, after which the mixture is poured into cold water (alkalysed to pH 8) and left to stay for 24 h. The precipitate is separated by suction and dried. A pale yellow crude product is obtained in nearly quantitative yield. The crude product is treated with cold 96% EtOH, after which a smaller part of it is dissolved, while the larger, undissolved part is filtered off. A white glittering product of α-(benzamidomethyl)phenylhydrazine 6a–d is obtained in a yield of 60 – 65% from the crude product. It is purified from 96% EtOH. The filtrate is precipitated with water, giving a yellow product. Later, the further purification of this precipitate from dilute EtOH gives colourless crystals of bis(benzamido)dimethylether 7a–c in a yield of 17 – 25%.

α-(Benzamidomethyl)phenylhydrazones 8; General Procedure:

A solution of equimolar amounts of corresponding α-(benzamidomethyl)phenylhydrazine 6 and corresponding carbonyl compound in 96% EtOH is refluxed for a few minutes, after which it is left to crystallize with cooling. The precipitate is filtered off giving a very pure product of α-(benzamidomethyl) phenylhydrazone (8a-g in nearly quantitative yields. Later it can be recrystallized from EtOH.

RESULTS AND DISCUSSION

The synthesis of N-chloromethylbenzamides was carried out through a convenient procedure [7, 8, 9]. Thus, the corresponding benzoyl chlorides 1 were aminated with concentrated solution of ammonia, after which the obtained benzamides 2 by means of formaldehyde were transformed into N-hydroxymethylbenzamides 3; the latter, in the medium of anhydrous carbontetrachloride, with thyonyl chloride as chlorating agent, gave corresponding N-chloromethylbenzamides 4 in near quantitative yields (Table 1). (N-chloromethylbenzamides are extremely reactive in the contact with air moisture and should be freshly synthesized before each condensation.)



1 – 4	R
a	H
b	4–CH_3
c	4–Cl
d	4–Br

Table 1.

Compounds 2-4 Prepared

Product	Yield (%)[a]	mp (°C)[b]	Lit. mp (oC)[c]	
2a	99	126 – 127	130	[11]
2b	91	155	155	[11]
2c	100	175 – 176	179	[11]
2d	92	187 – 189	189 – 190	[11]
3a	73	100	104 – 106	[10]
3b	88	114	102 – 104	[10]
3c	84	135 – 136	127 – 136	[9]
3d	99	138 – 140	138 – 140	[10]
4a	99	86 – 87	87 – 88	[9]
4b	96	122	–	[10]
4c	98	132 – 133	131 – 137	[9]
4d	95	142 – 145	–	[10]

[a] Yield of isolated product.

[b] Uncorrected, of crude product.

[c] In the reference 10, 4b and 4d are mentioned as known compounds, but without any physical data.

As we have mentioned above, in literature [5] there is only one case of dehydrochloration between N-chloromethylbenzamide and phenylhydrazyne, and it has taken place in a rather unsatisfactory manner.

In our case the reaction of N-chloromethylbenzamides 4 with phenylhydrazine (5) was performed under mild conditions, in anhydrous dioxan, with triethylamine as an acceptor of hydrochloric acid, within 30 min. A crude crystalline product was obtained from the reaction mixture in nearly quantitative yield. When checking its purity on TLC-plates, it was noticed that this substance was constituted of several products, among which one was dominant. With a further treatment two kinds of products were separated: α-derivatives 6 in yield of 60–65%, and etheric compounds 7 in yield of 17–25% of the crude product.

In this way, we obtained two series of unknown compounds of the type α-(Benzamidomethyl)phenylhydrazines 6 a–d and bis(benzamido)dimethylethers 7 a–c (except 7a which has already been obtained, but in a different way [12, 13, 14]). The new compounds were characterized by their melting points, microanalyses, IR and ^{1}H–NMR data (Table 2).

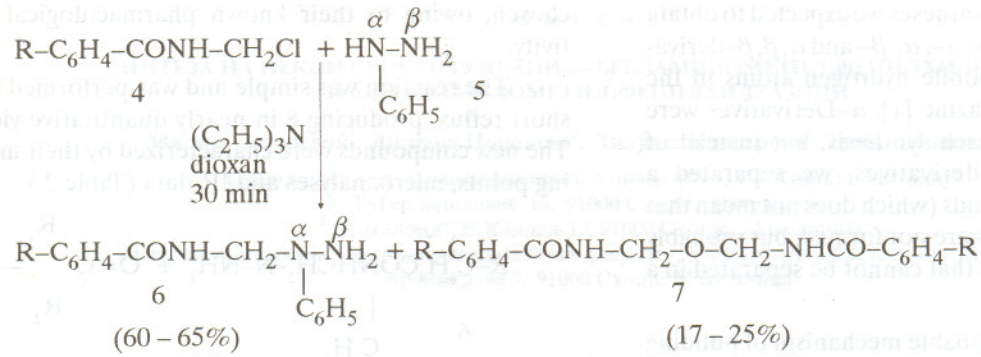


Table 2.

Characteristics of prepared α–(Benzamidomethyl)phenylhydrazines (6), Bis(benzamido)dimethylethers (7) and α-(benzamidomethyl)phenylhydrazones (8)

Product	mp (°C)	Molecular formula[a]	IR (KBr) ν (cm^{-1})	δ(^{1}H–NMR ($CDCl_3$ / TMS)
6a	94 – 5	$C_{14}H_{15}N_3O$ (241.2)	3360 – 3260, 1630, 1500 – 1470, 1310 – 1290	4.1 (s, 2H, NH_2), 4.6 – 4.65 (d, 2H, NCH_2N), 6.15 – 6.4 (H, NH), 7.15 – 7.45 (m, 9Ar)
6b	136 – 7	$C_{15}H_{17}N_3O$ (255.2)	3360 – 3260, 1625, 1500 – 1470, 1300	1.9 (s, 3H, CH_3–Ar), 4.15 (s, 2H, NH_2), 4.55 – 4.65 (d, 2H, NCH_2N), 6.15 – 6.35 (H, NH), 7.25 – 7.5 (m, 9Ar)
6c	161 – 2	$C_{14}H_{14}ClN_3O$ (2757)	3355 – 3290, 1630, 1490 – 1470, 1290	4.15 (s, 2H, NH_2), 4.57 – 4.65 (d, 2H, NCH_2N), 6.15 – 6.4 (H, NH), 7.15 – 7.4 (m, 9Ar)
6d	157 – 8	$C_{14}H_{14}BrN_3O$ (320.1)	3350 – 3280, 1630, 1490 – 1470, 1290	4.15 (s, 2H, NH_2), 4.6 – 4.65 (d, 2H, NCH_2N), 6.2 – 6.35 (H, NH), 7.2 – 7.5 (m, 9Ar)
7a	182 – 3	$C_{16}H_{16}N_2O_3$ (284.2)	3320, 1660, 1030	
7b	167 – 9	$C_{18}H_{20}N_2O_3$ (312.3)	3330, 1650, 1060	
7c	179 – 81	$C_{16}H_{14}Cl_2N_2O_3$ (353.2)	3330, 1645, 1060	
7d	it couldn't be isolated			
8a	148 – 9	$C_{21}H_{19}N_3O$ (329.4)	3300, 1640, 1540	
8b	134 – 5	$C_{21}H_{19}N_3O_2$ (345.4)	3240, 1630, 1485	
8c	174 – 5	$C_{22}H_{21}N_3O$ (343.4)	3260, 1620, 1495	
8d	163 – 4	$C_{22}H_{21}N_3O_2$ (359.4)	3240, 1625, 1500	
8e	133 – 4	$C_{20}H_{19}N_3O_2$ (333.4)	3340, 1625, 1500	
8f	167 – 70	$C_{18}H_{21}N_3O$ (295.4)	3280, 1620, 1495	
8g	169 – 71	$C_{21}H_{18}ClN_3O$ (363.8)	3300, 1635, 1485	
8h	186 – 8	$C_{21}H_{18}ClN_3O_2$ (379.8)	3240, 1630, 1490	
8i	171 – 2	$C_{19}H_{16}ClN_3O_2$ (353.8)	3335, 1620, 1495	
8j	174 – 6	$C_{17}H_{18}ClN_3O$ (315.8)	3285, 1625, 1485	
8k	175 – 6	$C_{21}H_{18}BrN_3O_2$ (424.3)	3240, 1630, 1480	

[a] Satisfactory microanalyses obtained: C±0.31, H±0.22, N±0.38.

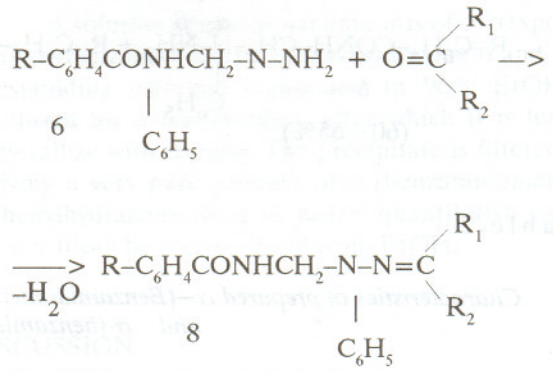
Performing these syntheses we expected to obtain several kinds of products: α–, α, β– and α,β,β–derivatives, owing to three mobile hydrogen atoms in the molecule of phenylhydrazine [1]. α–Derivatives were the main products of each synthesis, but instead of expected combined β–derivatives, we separated a series of etheric compounds (which does not mean that the previous compounds are not formed, but probably in such a small amounts that cannot be separated in a conventional way).

Thinking of the probable mechanism of building of the etheric compounds, we supposed that it went through two steps: 1) partial hydrolysis of N-chloromethylbenzamides 4 in the presence of even the minimum moisture, which led to forming of N-hydroxymethylbenzamides 3, and 2) a dehydration of two molecules of 3 in an acid medium, where the liberated hydrochloric acid served as a dehydrating agent.

This mechanism was partly proved by an independent reaction between the corresponding N-hydroxymethylbenzamides 3 and bromourea in the presence of hydrochloric acid, when corresponding N,N'–methylene-bis-benzamides and bis(benzamido)dimethylethers were obtained.

During the identification of α-(benzamidomethyl)phenylhydrazines 6, beside instrumental methods, a characteristic reaction was used. The α– derivatives have a free amino-group that can react with carbonyl compounds, giving corresponding phenylhydrazones 8. Thus few carbonyl compounds (benzaldehyde, salicylaldehyde, furfuraldehyde and acetone) were chosen, owing to their known pharmacological activity.

The reaction was simple and was performed at a short reflux, producing 8 in nearly quantitative yield. The new compounds were characterized by their melting points, microanalyses and IR-data (Table 2.).



8	R	R_1	R_2
a	H	H	C_6H_5
b	H	H	2–OH–C_6H_4
c	4–CH_3	H	C_6H_5
d	4–CH_3	H	2–OH–C_6H_4
e	4–CH_3	H	
f	4–CH_3	CH3	CH_3
g	4–Cl	H	C_6H_5
h	4–Cl	H	2–OH–C_6H_4
i	4–Cl	H	
j	4–Cl	CH_3	CH3
k	4–Br	H	2–OH–C_6H_4

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Р е з и м е

СИНТЕЗА НА НЕКОИ СУПСТИТУИРАНИ α-(БЕНЗАМИДОМЕТИЛ)ФЕНИЛХИДРАЗИНИ И α-(БЕНЗАМИДОМЕТИЛ)ФЕНИЛХИДРАЗОНИ

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Клучни зборови: синтеза; бензамиди; фенилхидразин; кондензација; дехидратација

Синтетизирани беа некои супституирани α-(бензамидометил)фенилхидразини, тргнувајќи од соодветните N-хлорметилбензамиди и од фенилхидразинот како нуклеофилен реагенс. Добиените фенилхидразини во реакција со карбонилни соединенија (бензалдехид, салицилалдехид, фурфуралдехид и ацетон) дадоа една серија супституирани α-(бензамидометил)фенилхидразони.