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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME SEC-BUTYLMALONYLDIHYDRAZONES

BAZI SEK-BUTİLMALONİLDİHİDRAZONLARIN SENTEZ VE ANTİMİKROBİAL AKTİVİTELERİ

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Several N,N'-Bis (arylidene/aralkylidene) mono (1-methylpropyl)malonic acid dihydrazides (3-15) were synthesized by the condensation of mono(1-methylpropyl) malonic acid dihydrazide (2) with aromatic aldehydes. Analytical and spectral data (IR, ^{1}H-NMR, EIMS) confirmed the proposed structures. The above compounds (3-15) were evaluated for in vitro antimicrobial activity against Staphylococcus aureus ATCC 6538, Staphylococcus epidermidis ATCC 12228, Klebsiella pneumoniae ATCC 4352, Pseudomonas aeruginosa ATCC 1539, Escherichia coli ATCC 8739 and Candida albicans ATCC 10231 using the macrodilution method. The results demonstrated that compounds 9 and 15 were active against Staphylococcus aureus and Staphylococcus epidermidis.

Mono (1-metilpropil)malonik asid dihidrazidinin (2) aromatik aldehidlerle kondensasyonu ile çeşitli N,N'-bis (ariliden/aralkiliden) mono (1-metilpropil) malonik asid dihidrazidleri (3-15) sentezlenmiştir. Analitik ve spektral veriler (IR, ^{1}H-NMR, EIMS) amaçlanan yapıları doğrulamaktadır. Kazanılan maddelerde (3-15), Staphylococcus aureus ATCC 6538, Staphylococcus epidermidis ATCC 12228, Klebsiella pneumoniae ATCC 4352, Pseudomonas aeruginosa ATCC 1539, Escherichia coli ATCC 8739 ve Candida albicans ATCC 10231'e karşı makrodilüsyon yöntemi kullanılarak in vitro antimikrobial aktivite araştırması yapılmıştır. Sonuçları, 9 ve 15 maddelerinin Staphylococcus aureus ve Staphylococcus epidermidis'e karşı aktif olduğu göstermiştir.

Keywords : *Sec-butylmalonyldihydrazones; Synthesis; Antimicrobial activity*

Anahtar kelimeler : *Sek-butilmalonildihidrazonlar; Sentez; Antimikrobial aktivite*

Introduction

The observation that several hydrazide hydrazones showed various pharmacological activities such as antibacterial (1,2) anthelmintic (3), antifungal (4), CNS active and antiinflammatory (5) and that hydrazones of malonanilic acid hydrazide possessed antituberculous activity (6) led us to synthesize thirteen new hydrazide hydrazones. In continuation of our studies on the synthesis and biological activity of mono(1-methylpropyl) malonic acid (sec-butylmalonic acid) derivatives (7,8) we report here synthesis, characterization and antimicrobial evaluation of new N,N'-Bis (arylidene/aralkylidene) mono (1-methylpropyl) malonic acid dihydrazides.

Materials and Methods

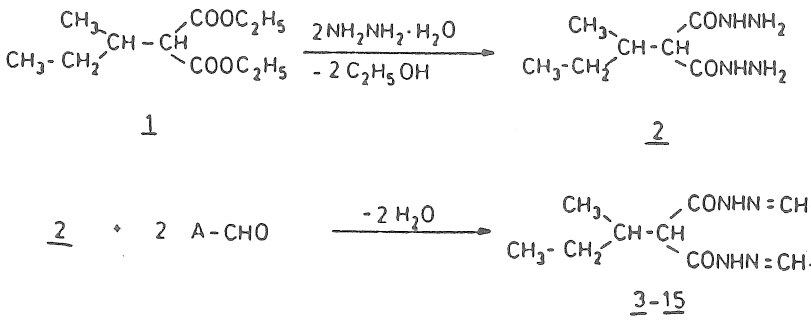
Melting points were determined on a Büchi 530 apparatus (open capillaries) and were uncorrected. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer. IR spectra (KBr) were recorded on a Perkin-Elmer 577 Grating spectrophotometer. ^{1}H-NMR spectra were obtained with a Bruker AC 200 (200 MHz) spectrophotometer using TMS as the internal standard. EIMS were recorded on a VG Zab Spec (70 eV) instrument.

General procedure for the synthesis of N, N'-Bis (arylidene/aralkylidene) mono (1-methylpropyl) malonic acid dihydrazides (3-15);

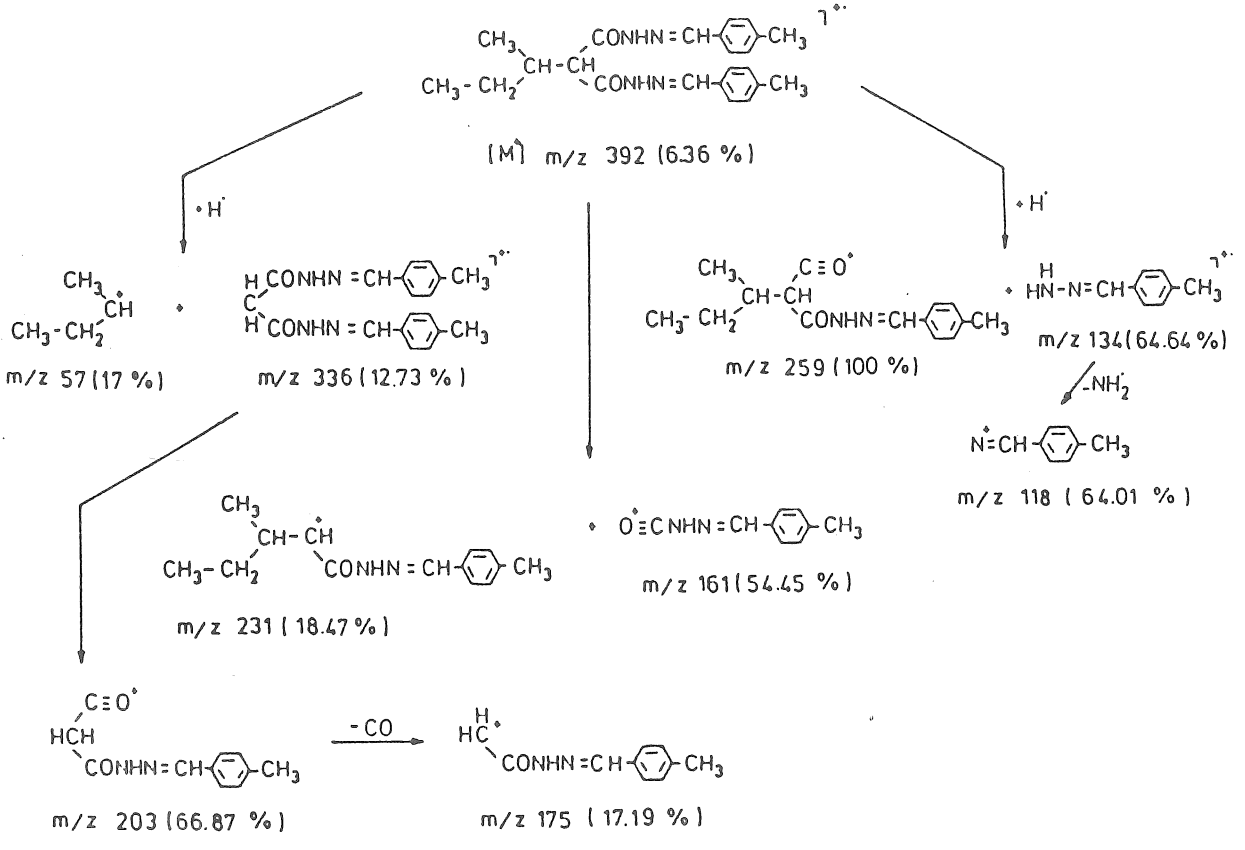
0.005 mol of 2 was refluxed with 0.01 mol of the appropriate aromatic aldehyde in 40 ml of EtOH (96%) for 3h. The precipitate obtained from the hot ethanolic solution was purified either by washing with hot EtOH (6,7,9,10,12,13,15) or recrystallization from EtOH (3-5,8,11,14).

3: IR (KBr) $\bar{\nu}$ (cm^{-1}): 3180 (N-H), 1670 (C=O). ^{1}H-NMR (DMSO-d_6) δ ppm: 11.35, 11.21 (2s, 2H, 2NH), 8.23, 7.91 (2s, 2H, 2N=CH), 7.61-7.48, 7.25-6.96 (2m, 8H, Ar-H), 4.95, 3.92-3.85 (d, J=8.14 Hz, m, 1H, CO-CH-CO), 2.39-2.24 (m, 7H, 2Ar-CH_3, CH), 1.63-1.47, 1.35-1.09 (m, 1H, m, 1H, CH_2), 1.00-0.86 (m, 6H, $2CH_3$).

15: IR (KBr) $\bar{\nu}$ (cm^{-1}): 3160 (N-H), 1685(C=O). ^{1}H-NMR (DMSO-d_6) δ ppm: 11.51, 11.41 (2s, 2H, 2 NH), 8.10, 7.79 (2s, 2H, 2N=CH), 7.75-7.66 (m, 2H, 2 furan 4-H), 7.29-6.81 (m, 6H, 2 CH=CH, 2 furan 3-H), 4.73, 3.92-3.87 (d, J= 8.20 Hz, m, 1H, CO-CH-CO), 2.32-2.16 (m, 1H, CH), 1.52-1.41, 1.23-1.15 (m, 1H, m, 1H, CH_2), 0.95-0.84 (m, 6H, 2 CH_3).



Scheme 1



Scheme 2

Determination of antimicrobial activity

All of the compounds (3-15) were tested for antimicrobial action against some bacteria (Staphylococcus aureus ATCC 6538, Staphylococcus epidermidis ATCC 12228, Klebsiella pneumoniae ATCC 4352, Pseudomonas aeruginosa ATCC 1539, Escherichia coli ATCC 8739 and one fungus (Candida albicans ATCC 10231) using the macrodilution method (9). Mueller Hinton Broth (Difco) and Mueller Hinton Agar (Difco) media were used in the tests.

Table 1. Some characteristics of compounds 3-15

Comp.	A	Formula (mol.wt.)	M.p. [°C]	Yield (%)	Analysis calcd./found C	H	N
3	$C_6H_4CH_3$(4-)	$C_{23}H_{28}N_4O_2$ (392.5)	249-50	89.68	70.38 70.83	7.18 7.21	14.27 14.50
4	$C_6H_4OCH_3$(2-)	$C_{23}H_{28}N_4O_4 \cdot 1/2H_2O$ (433.50)	241-42	90.69	63.72 64.00	6.74 6.50	12.92 13.05
5	$C_6H_4OCH_3$(3-)	$C_{23}H_{28}N_4O_4$ (424.5)	218-19	88.20	65.07 65.26	6.64 6.67	13.19 13.42
6	C_6H_4COOH(4-)	$C_{23}H_{24}N_4O_6$ (452.47)	>300	81.11	61.05 61.70	5.34 5.00	12.38 11.64
7	$C_6H_4NO_2$(2-)	$C_{21}H_{22}N_6O_6$ (454.45)	256-57	90.65	55.50 55.43	4.88 4.90	18.49 18.56
8	$C_6H_4NO_2$(4-)	$C_{21}H_{22}N_6O_6 \cdot H_2O$ (472.47)	260-61	87.13	53.38 53.17	5.11 4.64	17.78 17.58
9	$C_6H_3(NO_2)_2$(2,4-)	$C_{21}H_{20}N_8O_{10}$ (544.45)	237-38	90.55	46.32 46.43	3.70 3.56	20.58 20.40
10	$C_6H_3(Cl)_2$(2,6-)	$C_{21}H_{20}Cl_4N_4O_2$ (502.22)	244-45	96.17	50.22 50.51	4.01 3.88	11.15 11.11
11	$C_6H_3(OH)(Br)$(2,5-)	$C_{21}H_{22}Br_2N_4O_4$ (554.26)	263-64	92.73	45.50 45.40	4.00 3.88	10.10 9.64
12	$C_6H_3(OC_2H_5)(OH)$(3,4-)	$C_{25}H_{32}N_4O_6 \cdot H_2O$ (502.59)	241-42	97.61	59.74 59.44	6.81 6.52	11.14 10.58
13	$C_6H_3(OCH_2O)$(3,4-)	$C_{23}H_{24}N_4O_6$ (452.47)	229-30	88.62	61.05 60.21	5.34 5.43	12.38 12.97
14	2-thienyl	$C_{17}H_{20}N_4O_2S_2$ (376.5)	233-34	84.84	54.23 54.60	5.35 5.40	14.88 14.99
15	5-Nitro-2-furylethenyl	$C_{21}H_{22}N_6O_8$ (486.45)	228-29	93.53	51.85 51.85	4.55 4.42	17.27 17.23

Results and Discussion

Mono (1 - methylpropyl) malonic acid dihydrazide (2), was obtained by refluxing the corresponding ethyl ester (1) with hydrazine hydrate (7,10). Condensation of 2 with appropriate aromatic aldehydes (11) yielded the corresponding hydrazones (3-15) (Table 1 and Scheme 1). The synthesized compounds were confirmed by the elemental analyses and their structures were elucidated by using IR, ^{1}H-NMR and EIMS spectrometric data.

In the IR spectra of the compounds N-H and C=O stretching absorption bands were

observed between 3200-3140 and 1700-1670 cm^{-1}, respectively. The absorption bands associated with other functional groups appeared in the expected regions. The ^1H-NMR spectral data were also consistent with the assigned structures. The ^1H-NMR spectrum of 3 and 15 revealed the presence of two geometric isomers as the NH, N=CH and C-H protons resonated as two singlets at δ 11.35, 11.21; 8.23, 7.91 and 11.51, 11.41; 8.10, 7.79 ppm (12) and a doublet and multiplet at δ 4.95, 3.92-3.85; 4.73, 3.92-3.87 ppm, respectively. The signals of these protons appeared as a pair of signals owing to different steric arrangement of hydrazide-hydrazone functionality in the stereoisomers. This steric arrangement might be attributed to the hindered rotation of azomethine linkage (13). The absorbtion bands associated with other functional groups appeared in the expected regions(8).

EIMS of a representative example from the series, 3, supported the expected structures (14). The molecular weight was confirmed by the molecular ion at m/z 392 (6.36%). EI mass fragmentation pattern of 3 is depicted in Scheme 2.

Compounds 3-15 were evaluated for antimicrobial activity against some bacteria and one fungus. 9 and 15 showed activity against Staphylococcus aureus ATCC 6538 and Staphylococcus epidermidis ATCC 12228 with MIC values of 15.62, 0.97 µg/ml and 0.24, 0.97 µg/ml, respectively.

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