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Synthesis of Some N-[3(2H)-Benzofuranilidine] Aryloxyacetohydrazide Derivatives

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Summary: *Ten new N-[3(2H)-benzofuranylidene]- aryloxyacetohydrazide derivatives were synthesized by reacting aryloxyacetohydrazides and substituted 3 (2H) - benzofuranones in this study.*

The structures of the compounds were elucidated by spectral methods, i.e., IR, NMR and elemental analysis.

Keywords : *Benzofuranone, benzofuranylidene, hydrazide-hydrazone, aryloxyacetohydrazide.*

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Bazı N-[3(2H)-Benzofuraniliden] Ariloksiasetohidrazit Türevlerinin Sentezi

Özet: Bu çalışmada on yeni N-[3(2H)-benzofuraniliden]-ariloksiasetohidrazid türevi, ariloksiasetohidrazidlerin sübstitüe 3(2H)-benzofuranonlar ile reaksiyonu suretiyle sentezlendiler.

Bileşiklerin yapıları, IR ve NMR spektral metodları ve elementel analiz ile aydınlatıldı.

Anahtar kelimeler : *Benzofuranon, benzofuraniliden, hidrazid-hidrazon, ariloksiasetohidrazit.*

Introduction

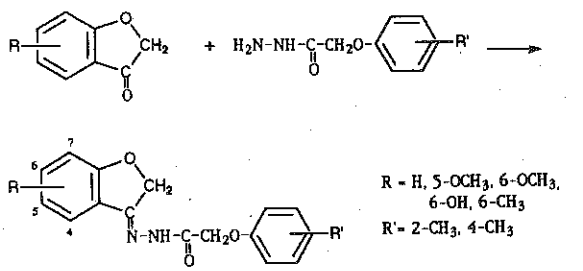
The compounds synthesized in this work are in hydrazide-hydrazone formed from 5-(or 6)- substituted 3(2H)-benzofuranones and 2-(or 4)-methylphenyloxyacetohydrazides.

Some benzofuran derivatives, such as griseofulvin, morphine and its analog compounds are available in nature and they have diverse biological activities. It was reported that dibenzofuran derivatives also possess antibacterial effects[1].

Various synthetic benzofuran derivatives have been known to be active, such as, some dihydrobenzofuran derivatives, are used as anticolinergic[2] and adrenergic reseptor blocker agents[3]. While 3(2H)-benzofuranone derivatives have antiinflammatory activities[4], some dihydrobenzofurans and 3(2H)-benzofuranone-2-carboxylate derivatives are antihyperlipidemic agents,[5,6] whereas dihydrobenzofuranamines have diuretic activities[7].

Some hydrazide-hydrazone derivatives have been reported to possess tuberculostatic[8-10], antibacterial and antifungal activities[11-12].

The present study was aimed to synthesize some new N-[3(2H)-benzofuranilidene] aryloxyacetohydrazide derivatives, which are predicted to have antibacterial activity, but their activity tests will be the subject of further studies.



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Material and Methods

M.p.s were determined by using a Gallenkamp melting point apparatus and are not corrected. Spectroscopic data were recorded on the following instruments: IR: Shimadzu IR 435 spectrophotomer; ^{1}H-NMR: Bruker 250 MHz NMR spectrometer.

C, H, N, analysis were performed in Centre National de la Recherches scientifique. Service Central d'Analyse, 6939-VERNAISON.

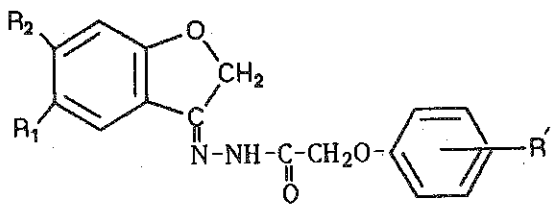
Synthesis

3(2H)-Benzofuranones and aryloxyacetohydrazide derivatives were prepared according to the methods reported in the literatures[13-18,19].

The Synthesis of N-[3(2H)-Benzofuranilidene] aryloxyacetohydrazide Derivatives:

A mixture of 3(2H)-Benzofuranone derivatives (10 mmole) and aryloxyacetohydrazide derivative (10 mmole) in n-butanol was refluxed for 3 hr. After cooling, the precipitate was collected and recrystallized from ethanol (Table 1 and 2).

Table 1. Some Characteristics of the Compounds



No	R_1	R_2	R'	Yield (%)	Melting Point (°C)	Formula (Molecular Mass)	Elemental Analysis Calc./Found % C	% H	% N
1	H	H	2-CH_3	57	155	$C_{17}H_{16}N_2O_3$ 296.32	68.90 68.95	5.44 5.60	9.45 9.24
2	H	H	4-CH_3	61	140	$C_{17}H_{16}N_2O_3$ 296.32	68.90 68.81	5.44 5.58	9.45 9.37
3	OCH_3	H	2-CH_3	43	160	$C_{18}H_{18}N_2O_4$ 326.34	66.24 66.05	5.55 5.70	8.58 8.46
4	OCH_3	H	4-CH_3	48	167	$C_{18}H_{18}N_2O_4$ 326.34	66.24 66.39	5.55 5.63	8.58 8.51
5	H	OCH_3	2-CH_3	52	117	$C_{18}H_{18}N_2O_4$ 326.34	66.24 66.47	5.55 5.27	8.58 8.40
6	H	OCH_3	4-CH_3	55	98	$C_{18}H_{18}N_2O_4$ 326.34	66.24 66.15	5.55 5.34	8.58 8.73
7	H	OH	2-CH_3	62	165	$C_{17}H_{16}N_2O_4$ 312.32	65.37 65.08	5.16 5.42	8.97 8.65
8	H	OH	4-CH_3	45	170	$C_{17}H_{16}N_2O_4$ 312.32	65.37 65.11	5.16 5.37	8.97 8.89
9	H	CH_3	2-CH_3	41	158	$C_{18}H_{18}N_2O_3$ 310.34	69.65 69.92	5.84 5.73	9.02 8.97
10	H	CH_3	4-CH_3	54	130	$C_{18}H_{18}N_2O_3$ 310.34	69.65 69.68	5.84 5.50	9.02 8.86

Table 2. ^{1}H-NMR and IR Spectral Data

	N. M. R.							I. R.		
No	R1	R2	R'	O-CH_2-C=N	N-C(=O)-CH_2	Aromatic protons	NH	N-H C-H	C=O O-H	C=N, C=C C-O-C
1	—	—	2.23 3H, s.	4.67 2H, s.	4.55-4.89 2H, t.s.	6.69-7.34 8H, m.	9.23 1H, s.	3280 2900-3100	1670	1640-1650 1000-1200
2	—	—	2.23 3H, s.	4.65 2H, s.	4.52-4.83 2H, t.s.	6.69-7.35 8H, m.	9.23 1H, s.	3280 2900-3100	1670	1640-1650 1000-1200
3	3.77 3H, s.	—	2.24 3H, s.	5.18 2H, s.	4.73-5.12 2H, t. s.	6.78-7.35 7H, m.,	10.54-10.88 1H, s.	3280 2900-3100	1660	1640-1650 1000-1200
4	3.77 3H, s.	—	2.23 3H, s.	5.12 2H, s.	4.65-5.17 2H, t. s.	6.78-7.35 7H, m.	10.58-10.85 1H, s.	3280 2900-3100	1670	1640-1660 1000-1200
5	—	3.87 3H, s.	2.23 3H, s.	4.44 2H, s.	4.33-4.77 2H, t. s.	6.68-7.56 7H, m.	9.32 1H, s.	3280 2900-3100	1670	1640-1660 1000-1200
6	—	3.87 3H, s.	2.23 3H, s.	4.50 2H, s.	4.33-4.77 2H, t. s.	6.68-7.57 7H, m.	9.23 1H, s.	3280 2900-3100	1670	1640-1660 1000-1200
7	—	10.40 1H, s.	2.22 3H, s.	4.71 2H, s.	4.50-4.91 2H, t.s.	6.50-7.50 7H, m.	9.30 1H, s.	3280 2900-3100	1680 3530-3400	1640-1660 1000-1200
8	—	10.40 1H, s.	2.23 3H, s.	4.70 2H, s.	4.43-5.13 2H, t.s.	6.40-7.50 7H, m.	9.30 1H, s.	3290 2900-3100	1685 3530-3420	1640-1680 1000-1200
9	—	2.22 (two CH_3) 6H, s.		4.50 2H, s.	4.34-4.90 2H, t.s.	6.80-7.20 7H, m.	9.23 1H, s.	3270 2900-3100	1670	1640-1680 1000-1200
10	—	2.23 (two CH_3) 6H, s.		4.51 2H, s.	4.40-5.13 2H, t.s.	6.80-7.14 7H, m.	9.23 1H, s.	3280 2900-3100	1670	1640-1650 1000-1200

s : Singlet t.s.: Two singlets m : Multiplet

Results and Discussion

10 new N-[3(2H)-Benzofuranilidene] aryloxyacetohydrazide derivatives were synthesized in this work.

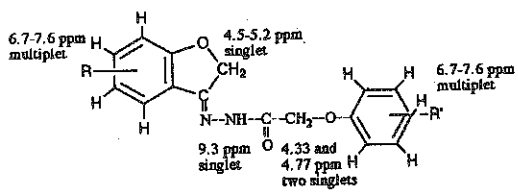
The products synthesized by condensation reaction between the derivatives of 3(2H)-benzofuranone and aryloxyacetohydrazide, were in E and Z isomer forms. These isomers were separated by crystallisation. A further study was not done for separating E and Z isomers.

In the IR spectra, some stretching bonds due to C-O-C, C=N, C=0 and N-H were observed at 1200-1000, 1650-1640, 1680-1660 and 3290-3260 cm^{-1}, respectively.

In the ^{1}H-NMR spectra, the signals of methyl and methoxy protons observed between 2.2-2.3 and 3.7-3.8 ppm as singlets, respectively. The signal due to O-H proton was observed at 10.4 ppm as a broad singlet. Phenyl protons were resonated at 6.7-7.6 ppm as multiplets. The cyclic methylene protons were observed between 4.5-5.2 ppm as singlet.

A pair of singlets, attributed to -$COCH_2$- group, was observed at 4.33-4.77 ppm, because of the geometrical isomerization. For each compound, the intensities of these two peaks differed from each other due to the variable amounts of E and Z, which are usually unequal.

The signals of cyclic methylene protons can be easily distinguished from the signals of methylene protons of $COCH_2$-O residue using integration values, since, the integration values of the first mentioned group of protons are equal to that of the two peaks from E and Z forms.



References

1. Dean, F. M., *Naturally Occuring Oxygen Ring Compounds*, London, Butterworths, pp. 640, 1963.
2. Mertes, M. P., Powers, L. J., Hava, M. M. "Synthesis and Pharmacological Activity of Dihydrobenzofurans", *J. Med. Chem.*, 14 (4), 361-365, 1971.
3. Fielden, R., Roe, A. M., Willey, G. L., "The Adrenergic-neuron Blocking Action of Some Coumaran Compounds"., *Brit. J. Pharmacol.*, 23 (3), 486-507, 1964.
4. Closse, A., Haefliger, W., Hauser, D., Gubler H. V., Dewald, B., Baggiolini, M., "2,3-Dihydrobenzofuran-2-ones: A New Class of Highly Potent Antiinflammatory Agents", *J. Med. Chem.*, 24 (12), 1465-1471, 1981.
5. Bondesson, G., Hogberg, T., Misiorny, A., Stjernstrom, N. E., "Potential Hypolipidemic Agents. XIV. Synthesis and Plasma Lipid-lowering Properties of Substituted Biphenyls, Diphenyl Ethers and Benzofurans Related to Ethyl 2-(4-dibenzofuranyloxy)-2-methylpropionate", *Acta Pharm. Soc.*, 13 (2), 97-106, 1976.
6. Witiak, D. T., Newman, H. A. I., Poochikian, G. K., Loh, W., Sankarappa, S. K., "Comparative Antilipidemic Effects of Various Ethyl 5-Substitutedbenzofuran-, 2,3-Dihydrobenzofuran-, and 3 (2H)-Benzofuranone-2-Carboxylate Analogs of Clofibrate in a Triton Hyperlipidemic Rat Model", *Lipids*, 11 (5), 384-391, 1976.
7. Hoffman, W. F., Woltersdorf, O. W. Jr., Novello, F. C., Cragoe, E. J. Jr., Springer, J. P., Watson, L. S., Fanelli G. M. Jr., "(Acrylaryloxy) Acetic Acid Diuretics, 3. 2,3-Dihydro-5-Acyl-2-Benzofuran Carboxylic Acids, a New Class of Uricosuric Diuretics", *J. Med. Chem.*, 24 (7), 865-873, 1981.
8. Yale, H. L., Losee, K., Martins, J., Holsing, M., Perry, M. F., Bernstein, J., "Chemotherapy of Tuberculosis (VIII) Synthesis of Acid Hydrazides, Their Derivatives., and Related Compounds", *J. Am. Chem. Soc.*, 75, 1933-1935, 1953.
9. Buu-Hoi, Ng. Ph., Xuong, Ng. H., Binnon, F., Royer, R., "Tuberculostatic Hydrazides and Their Derivatives", *J. Chem. Soc.*, 1953, 1938; ref: C.A. 48, 7580-7584, 1954.
10. Sah, P. P. T., Pepdles, S. A., "Isonicotinoylhydrazones as Antitubercular Agents and Derivatives for Identification of Aldehydes and Ketones", *J. Am. Pharm. Assoc.*, 43, 513-521, 1954.
11. Bhat, A. K., Bhamaria, R. P. Bellare, R. A., Deliwala, C. V., "Chemotherapy of Fungus Infections. III. Alkyl or Aryl Thiosemicarbazones, Acid Hydrazones and Styryl Aryl Ketones of 5-Bromo- and 5-Nitrosalicylaldehydes", *Indian J. Chem.*, 10, 694-697, 1972.
12. Gürsoy, A., Demirayak, Ş., Cesur, Z., Reisch, J., Ötük, G., "Synthesis of Some New Hydrazide-Hydrazones, Thiosemicarbazides, Thiadiazoles, Triazoles and Their Derivatives as Possible Antimicrobials", *Pharmazie*, 45 (4), 246-247, 1990.
13. Davieś, J. S. H., Crea, P. A., Norris, W. L., Ramage, G. R., "Furanochromones (IV). Synthesis of 2-Methylfurano (3', 2':6, 7)-Chromone and Derivatives Thereof", *J. Chem. Soc.*, 3, 3206-3213, 1950.
14. Fries, K., Finck, G., "Homologues of Coumaranone and Their Derivatives", *Chem. Inst., Univ., Marburg. Ber.*, 41, 4271-4284, 1908.
15. Higginbotham, L., Stephen, H., "Coumaranone Series (I). The Prearation of 4-, 5- and 6-methylcoumaran-2-ones, and Some Derivatives of o-, m- and p-Tolyloxyacetic acids", *J. Chem. Soc.*, 117, 1534-1542, 1920.
16. Kloetzel, M. C., Dayton, R. P., Abadir, B. Y., "Synthetic Analogs of Cortical Hormones (I). Homogentisic Acid and α,2,5-trihydroxyacetophenone Deri-

vatives from 2,5-diacteoxy-α-diazoacetophenone", *J. Org. Chem.*, 20, 38-49 1955.

17. Mameli, E., "1,3-Benzoxazine. Transition from Isonitrosocoumaranones to Derivatives of 1,3-Benzoxazine. (II)", *Gazz. Chim. Ital.*, 56, 759-772, 1926.
18. Slater, W. K., Stephen, H., "Some Derivatives of Fisetol", *J. Chem. Soc.*, 117, 309-318, 1920.
19. Mirec, J., "Urethans as Regulators of Plant Growth", *Ser. Nauk Mat. Przyrod. Mat. Fi. Chem.*, 4, 163-170, 1958.