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Studies in anthraquinones: Preparation of 1-aminoanthraquinone-2-carbohydrazide, 1,3,4-oxidiazoles, pyrazoles, pyrimidines and phthalazines

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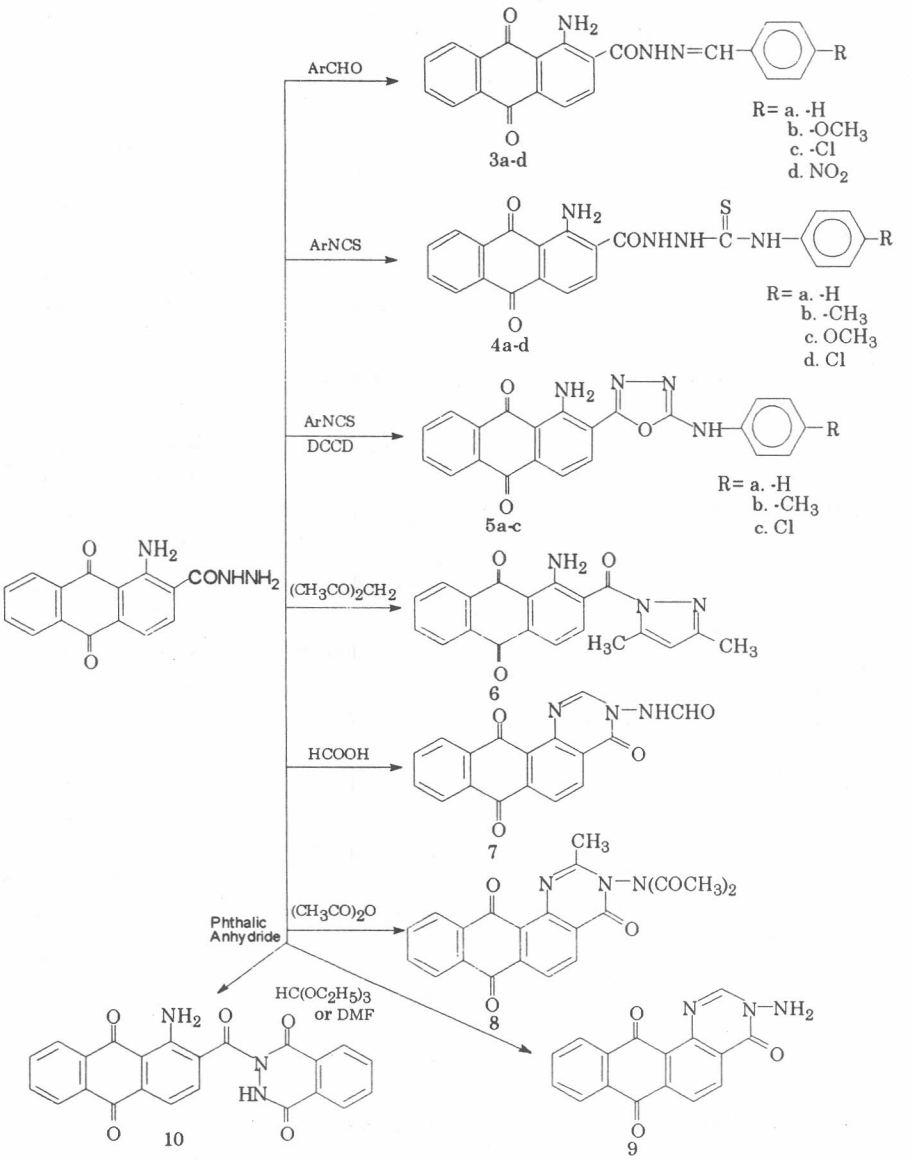
Arylidenehydrazones 3a-d, thiosemicarbazides 4a-d, 1,3,4-oxidiazole 5a-c, 3,5-dimethylpyrazole 6, pyrimidines 7,8,9, and phthlazine 10, have been prepared from 1-aminonanthraquinone-2-carbohydrazide 2.

Quinone structure occurs in numerous natural anticancer agents[1], such as mitomycins, streptonigrin and anthracyclines including doxorubicin and daunorubicin. Antitumor properties have also been observed for numerous synthetic quinones that have simpler structures[2]. The quinone unit is an important site of biochemical action and has often been directly implicated in the antitumor properties of these molecules[2-5]. Complex quinone-bearing molecules like anthracyclines are capable of mutiple mechanisms of action, at multiple biological sites[3,4,6-10]. Thus, structural changes that alter reactivity of the quinone function may significantly alter the overall pattern of biological effects [11], although specific effect cannot be targeted based on the current knowledge. Such changes offer an important approach to the development of analogs with improved properties. As part of a research program currently underway in our laboratory to develop new antineoplastic agents, we have been involved in the design and synthesis of novel anthraquinones as potential anticancer drugs[12-16]. Herein we report the synthesis of the title compounds. The ring-closure reactions of carbo-hydrazides are well known and has been thoroughly studied. In these reactions five- and six-membered heterocycles with two or three heteroatoms, such as 1,3,4-oxidiazoles,1,2,4-thiadiazoles, 1,2,4-triazoles, pyrimidophthalazines and substituted pyrimidines[17-28] are formed. The key intermediate, 1-aminoanthra-quinone-2-carbohydrazide **2**[12], was obtained in good yield by reacting ethyl 1-aminoanthraquinone-2-carboxylate **1** with hydrazine hydrate. Compound **2** reacted with several aromatic aldehydes to give hydrazones **3a-d**, in good yields (79-85%). The reaction of **2**, with aromatic isothiocyanates, afforded the expected thiosemicarbazides **4a-d** in nearly quantitative yields. Although the amino group at 1-position in compound **2**, was an equally possible reaction site, it didn't react under the reaction condition employed due to it's relatively low nucleophilicity.

For the ring-closure reaction of the hydrazide **2**, a number of different methods are reported in literature[18-26]. Reaction of **2**, with aromatic isothiocynates in the presence of N,N′-dicyclo-hexylcarbodiimide (DCCD) produced 1-amino-2-(2′-arylamino-1′,3′,4′-oxadiazolo-5′-yl)-anthraquinones **5a-c**. Refluxing **2**, with acetyl acetone in ethanol readily yielded 1-amino-2-(3′,5′-dimethyl-pyrazole-1′-carbonyl)anthraquinone **6**. Reaction of **2**, with formic acid, acetic anhydride and ethyl orthoformate or N,N-dimethylformamide afforded **7, 8** and **9**, respectively. Condensation of **2**, with phthalic anhydride gave 2-(1′-aminoanthra-quinone-2′-carbonyl) 1,2,3,4-tetrahydrophthalazine-1,4-dione **10**. Some of these compounds are currently being tested for their activity against cancerous cell lines. The results are awaited and will be presented elsewhere.

Experimental Section

General. Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 157 spectrophotometer using potassium bromide. ^{1}HNMR spectra in DMSO-d_6 on a Varian Gemini 300 MHz spectrophotometer (chemical shifts in δ, ppm down field form TMS as internal standard) and



mass spectra on a Kartos MS 80 RFA mass spectrometer at 70ev. Satisfactory C,H,N analyses were obtained.

N^2-Arylidenehydrazone of 1-aminoanthraquinone 2-carbohydrazide 3a-d: (a)Using ethanol as solvent. To compound **2** (0.562 g, 0.002 mole), dissolved in hot ethanol (150 mL) was added the respective aromatic aldehyde (0.002 mole). The reaction mixture was refluxed in a hot water-bath for 2 hr, concentrated to 10 mL, and cooled. The product that precipitated out, was filtered and washed with ethanol-water (1:1, 3 x 25).

(b) Using dioxane as solvent. The above experiment was repeated with modification wherein dioxane (15 mL) was used instead of ethanol (150 mL). The result obtained were similar. The physical data of **3a-d** are recorded in Table I.

3a: IR: 3480, 3420, 3380 (NH), 1690, 1650 (C=O), 1600 cm^{-1} (C=N). ^1H NMR(DMSO-d_6). δ 7.4-7.5 (s, 5H, ArH), 7.75-8.0 (s, 2H, NH_2), 7.9-8.3 (m, 6H, ArH), 8.45 (s, 1H, CH=N), 8.80-8.90 (bs, 1H, NH).

3b: IR: 3480, 3380, 3260 (NH), 1680, 1610 (C=O), 1560 (C=N).cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.88(s, 3H, OCH_3), 7.4-8.30 [m, 12H, ArH(10) + NH_2(2), D_2O exchangeable], 8.4 (s,1H, CH=N), 8.85-8.95 (bs, 1H, NH).

3c. IR: 3440, 3270 (NH), 1680, 1615 (C=O), 1570 (C=N). cm^{-1}; ^1H NMR (DMSO-d_6), δ 7.6-8.4

Table I — The physical data of compounds**3a-10**

Compd	R	m..p °C	Yield (%)	Mol. formula	Found (%) (Calcd.)		
					C	H	N
3a	H	255	82	$C_{22}H_{15}N_3O_3$	71.60	4.28	11.61
					(71.54	4.09	11.38)
3b	OCH_3	250	80	$C_{23}H_{17}N_3O_4$	69.36	4.51	10.41
					(69.17	4.29	10.52)
3c	Cl	275	69	$C_{22}H_{14}N_3O_3Cl$	65.20	3.60	10.54
					(65.43	3.49	10.41)
3d	NO_2	294	76	$C_{22}H_{14}N_4O_5$	63.79	3.38	13.41
					(63.77	3.41	13.52)
4a	H	262	96	$C_{22}H_{16}N_4O_3S$	64.43	3.75	13.48
					63.45	3.87	13.45)
4b	CH_3	288	91	$C_{23}H_{18}N_4O_3S$	63.94	4.13	13.15
					(64.17	4.21	13.01)
4c	OCH_3	275	93	$C_{23}H_{18}N_4O_4S$	61.74	4.02	12.43
					(61.87	4.06	12.55)
4d	Cl	260	85	$C_{22}H_{15}N_4O_3ClS$	58.54	3.41	12.63
					(58.60	3.35	12.43)
5a	H	260	40	$C_{22}H_{14}N_4O_3$	68.93	3.83	14.80
					(69.10	3.69	14.65)
5b	CH_3	275	65	$C_{23}H_{16}N_4O_3$	69.95	4.02	14.16
					(69.69	4.07	14.13)
5c	Cl	278	70	$C_{22}H_{13}N_4O_3Cl$	63.60	3.27	13.51
					(63.39	3.14	13.44)
6	–	227	70	$C_{20}H_{15}N_3O_3$	69.71	4.43	11.93
					(69.56	4.38	12.17)
7	–	197	53	$C_{17}H_9N_3O_4$	63.81	2.80	13.34
					(63.95	2.80	13.16)
8	–	234	60	$C_{21}H_{15}N_3O_5$	64.78	3.93	10.57
					(64.78	3.88	10.79)
9	–	248	90	$C_{16}H_9N_3O_3$	65.90	3.04	14.31
					(65.98	3.11	14.43)
10	–	285	78	$C_{23}H_{13}N_3O_5$	66.98	3.11	10.07
					(67.15	3.19	10.21)

[m, 12H, ArH(10) + NH_2(2), D_2O exchangeable],8.62(s, 1H, CH=N), 8.9-9.1 (bs,1H, CH=N).

3d. IR: 3420, 3360 (NH), 1689, 1630 (C=O), 1600 (C=N), 1501, 1320 (N=O).cm^{-1}; ^1H NMR (DMSO-d_6), δ 7.4-8.4 [m, 12H,ArH(10) + NH_2(2), D_2O exchangeable], 8.69 (s, 1H, CH=N), 8.9-9.1 (bs, 1H, NH).

4-Aryl-1-(o-aminoanthraquinone)-3-thiosemicarbazide 4a-c. To compound **2** (0.562 g, 0.002 mole) dissolved in benzene (50 mL) was added the appropriate aromatic isothiocyanate (0.002 mole). The reaction mixture was heated under reflux for 2 hr on a hot water-bath. On cooling, the thiosemicarbazide that crystallised out was filtered, washed with cold benzene, dried and crystallised from N,N-dimethylformamide.

4a. IR: 3420, 3309 (NH), 1669, 1645 (C=O). cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.1(s, 5H, ArH), 7.5(s, 2H, NH_2), 7.7(d, 1H, ArH), 8.0(m, 2H, ArH), 8.3(m, 3H, ArH), 8.8(bs, 1H, NH), 9.4(bs, 1H, NH), 10.3(bs, 1H, NH). The physical data of **4a-c** are recorded in Table I.

1-Amino-2-(2'-arylamino-1',3',4'-oxadiazol-5'-yl) anthraquinones 5a-c. To compound **2** (0.562 g, 0.002 mole) dissolved in toluene (25 mL) was added the appropriate aromatic isothiocyanate (0.002

mole). The reaction mixture was heated under reflux for 2 hr. To the hot solution was added N,N'-dicyclohexylcarbodiimide (1.2 g, 0.04 mole) and the mixture further refluxed for 24 hr. On cooling the product that precipitated out was filtered, washed with cold ethanol and crystallised from aqueous N,N-dimethyl formamide (10 : 90). The physical data of **5a-c** are recorded in Table I.

5b: ^{1}H NMR (DMSO-d_6): δ 2.1(s, 3H, CH_3), 6.9-7.3(two d, 4H, ArH), 7.5(d, 1H, ArH), 7.7(s, 2H, NH_2), 7.9(m, 2H, ArH), 8.1(d, 1H, ArH), 8.4(m, 2H, ArH), 8.8(bs, 1H, NH); MS: m/z 396(M^+,80%), 325(21%), 290(7%), 248(60%).

1-Amino-2-(3',5'-dimethylpyrazole-1'-carbonyl) anthraquinone 6. To compound **2** (0.562 g, 0.002 mole) dissolved in ethanol (150 mL), was added acetyl acetone (0.2 g, 0.002 mole). The reaction was heated under reflux for 8 hr, concentrated and cooled. The solid obtained was filtered, washed with methanol (10 mL) dried and crystallised from aqueous N,N-dimethylformamide (20 :80). ^{1}H NMR(DMSO-d_6): δ 1.9(s, 3H, CH_3), 2.1(s, 3H, CH_3), 5.8(s, 1H, pyrazole), 7.4(d, 1H, ArH), 7.6(bs, 2H, NH_2), 7.9(m, 2H, ArH), 8.1-8.3(m, 3H, ArH). MS: m/z 345 (M^+).

3-Formylamino-4(3*H*)-oxopyrimido[4, 5-*a*]anthraquinone 7. Compound **2** (0.562 g, 0.002 mole) was refluxed for 6 hr with formic acid (20 mL). The reaction mixture was diluted with water, and the precipitate product filtered, washed with sodium bicarbonate solution and then with water, dried and crystallised from N,N-dimethylform-amide: ethanol (70 : 30).

IR: 3229 (NH), 1695, 1670 (C=O).cm^{-1}; ^{1}H NMR(DMSO-d_6): 7.8(d, 1H, ArH), 8.0(m, 2H, ArH), 8.3(m, 3H, ArH), 8.7(s, 1H, N=CH), 8.8(s, 1H, CHO), 9.4(bs, 1H, NH).

2-Methyl-3-diacetylamino-4(3*H*)-oxopyrimido [4,5-*a*]anthraquinone 8. Compound **2** (0.562 g, 0.002 mole) was refluxed with acetic anhydride (20 mL) for 7 hr. The reaction mixture was cooled, diluted with water, and the precipitate product filtered and crystallised from N,N-dimethylform-amide; ^{1}H NMR(DMSO-d_6): δ 2.2(s, 3H,CH_3), 2.4[s, 6H, $(COCH_3)_2$], 7.8(d, 1H, ArH), 8.0(m, 3H, ArH), 8.2-8.4(two d, 2H, ArH).

3-Amino-4(3*H*)-oxopyrimidoanthraquinone 9. a) Using N,N-dimethylformamide. Compound **2** (0.562 g, 0.002 mole) was refluxed for 24 hr with N,N-dimethylformamide (10 mL). The solvent was distilled and the residual dispersed in ethanol. The solid was filtered and crystallised from N,N-dimethylformamide:ethanol (80 :20).

(b)Using triethyl orthoformate. A mixture of compound **2** (0.562 g, 0.002 mole), triethyl ortho-formate (7.5 mL) and 1 drop 10 *M* hydrochoric acid was refluxed for 26 hr, cooled and diluted with ether (10 mL). The solid obtained was stirred at room temperature with 50% aqueous acetic acid (4 mL) for 19 hr. The solid was filtered and crystallised from N,N-dimethylform-amide:ethanol (80:20); IR 3405, 3288 (NH), 1690, 1667 (C=O), 1625 (C=N), 1592 ,1567 cm^{-1} (C=C); ^{1}H NMR (DMSO-d_6): δ 5.5(s, 2H, NH_2), 7.9(m, 3H, ArH), 8.2(m, 3H, ArH), 8.6 (s, 1H, N=CH).

2-(1'-aminoanthraquinone-2'carbonyl)1,2, 3,4-tetrahydrophthalazine-1,4-dione10. To compound **2** (0.562 g, 0.002 mole) in N,N-dimethylacetamide (10mL) was added phthalic anhydride (0.296 g, 0.002 mole). The reaction mixture was refluxed for 12 hr . The solid that precipitated out on cooling was filtered and dissolved in a solution of sodium hydroxide (2*N*), filtered and reprecipitated by acidifing with gl. acetic acid. The precipitate was washed with cold ethanol, dried and crystallised from N,N-dimethylformamide. IR: 3549 (OH), 3409, 3313(NH), 1793, 1738(C=O phthalic anhydride), 1661 cm^{-1} (C=O); ^{1}H NMR (DMSO-d_6): 7.5(d, 1H, ArH), 7.8-7.9(m, 7H, ArH), 8.2-8.3(m, 2H, ArH), 8.7(bs, 2H, NH_2), 11.51(s, 1H, NH).

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