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Note

Studies in anthraquinone: Synthesis of 3-amino/3-alkyl-2,4-dioxo-1,2,3,4-tetrahydropyrimido[4,5-*a*]anthraquinone derivatives

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Starting with ethyl 1-aminoanthraquinone-2-carboxylate, the synthesis of 3-amino/3-alkyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidol[4,5-*a*]anthraquinones and some related compounds is described.

During the last years, special attention has been focused on the synthesis and biological properties of pyrimidin-4-ones and particularly on their 3-amino derivatives, fused with different carbocyclic or heterocyclic systems, such as benzene (quinazolinones), benzothiophene, pyrozoles, imidazole and 1,2,3-triazole due to their potential pharmacological interest[1-10]. These compounds are generally obtained by the cyclisation of *o*-aminoaryl hydrazine with orthoesters[1-10]. However, this reaction may yield different products, namely 3-aminopyrimidin-4-ones, the respective triazepinones or also oxadiazoles, depending on the reagents, their molar proportion, the solvents and other conditions. The most suitable conditions to obtain each product, and the mechanisms, have been studied in detail with the anthranilichydrazides[1-4]. In continuation of our earlier work on the synthesis and biological properties of fused systems of anthraquinone[11-18], we describe herein the synthesis of 3-amino/3-alkyl-2,4-dioxo-1, 2, 3,4-tetrahydropyrimido[4,5-*a*]anthraquinones. The compounds were obtained as illustrated in Scheme I. Boiling a solution of **1** with ethyl/methyl chloroformate in xylene gave **2a, b** which were cyclised to **3** with hydrazine hydrate. The ^{1}H NMR spectra of **3** showed a signal at δ 5.7 (s, 2H), which was assigned to the 3-amino group. According to the literature[1,3,8-10] 3-aminopyridazin-4-ones show in the ^{1}H NMR spectra a signal at δ 5.0-6.0 (s, bs, 2H, 3-NH_2), which disappears on addition of deuterium oxide. In the isomeric triazepinones the signals for the protons of the system –CO–NH–NH–CX-(X=N, O) appear at values of >8.0[2] as two different signals (s, bs). On refluxing compounds **2a-b** with excess aliphatic amines, gave **4a-d**. Treatment of **1** with hydrazine hydrate gave compound **5**. Further, reaction of **5** with ethyl orthoformate yielded compound **6** (80%). ^{1}H NMR spectra of **6** showed a signal at δ 5.5 for the 3-amino group. In view of the wide range of pharmacological properties reported for various quinone[19-24] structures and several other related compounds, the various anthraquinone derivatives prepared now would be screened for their biological activity and the results would be published elsewhere.

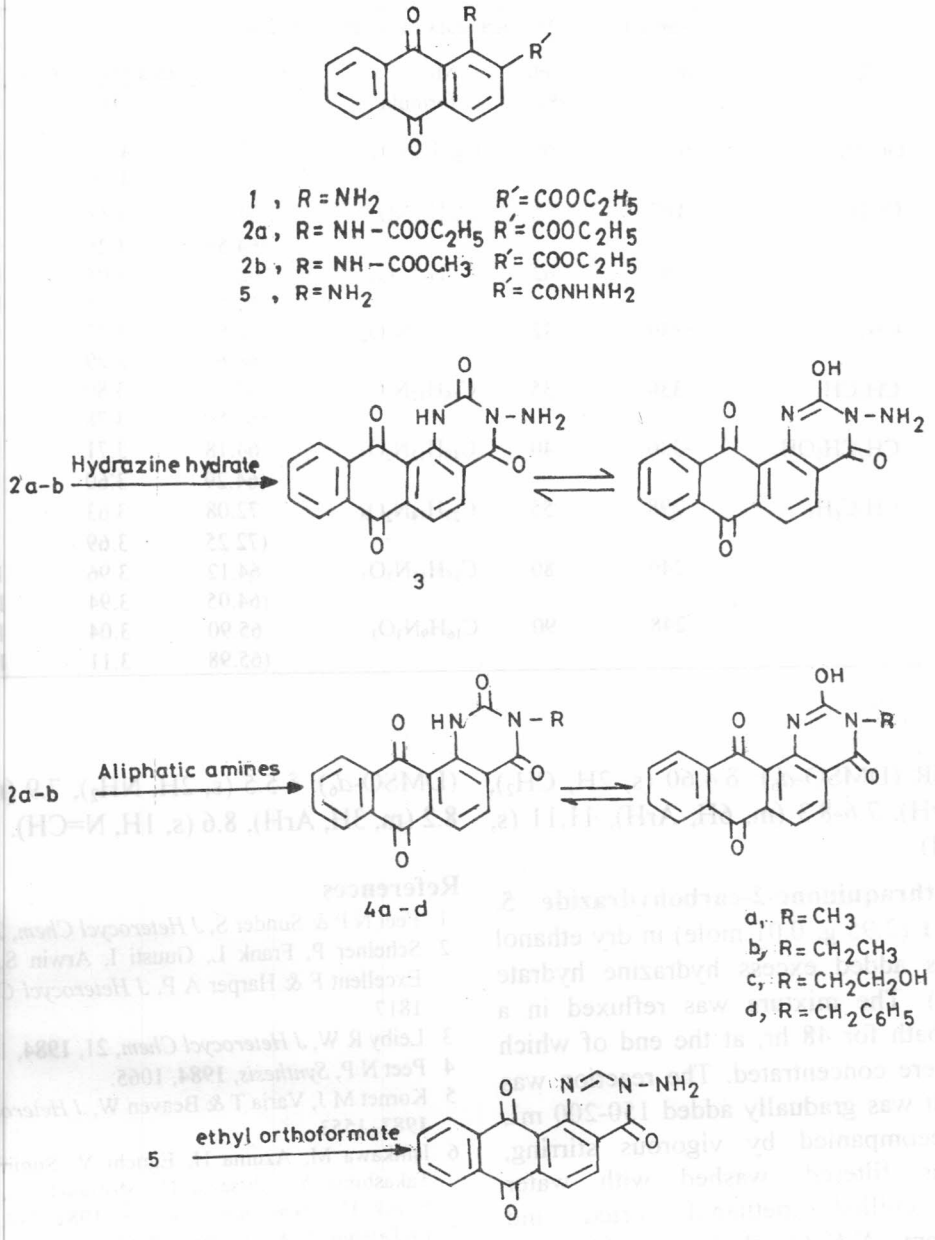
Experimental Section

All melting points are uncorrected. The IR spectra were recorded on a Perkin-Elmer 157 spectrophotometer using potassium bromide, ^{1}H NMR spectra in DMSO-d_6 on a Varian Gemini 300 MHz spectrophotometer (chemical shifts in δ, ppm downfield from TMS as internal standard), and mass spectra on Kartos MS 80 RFA mass spectrometer at 70ev. Satisfactory, C, H, N analysis were obtained.

Ethyl 1-[(ethoxycarbonyl)amino]anthraquinone-2-carboxylate 2a. To a suspension of **1** (0.591 g, 0.002 mole) in xylene (10 mL) excess ethyl chloroformate (3 mL) was added. The reaction mixture was then refluxed for 7 hr. The precipitate obtained on cooling was filtered, washed with cold ethanol and crystallised from ethanol. IR (KBr): 3200 (NH), 1735, 1672 (C=O), 1640 (C=N), 1592, 1509 (C=C).

Ethyl 1-[(methoxycarbonyl)amino]anthraquinone-2-carboxylate 2b. The above procedure was repeated with a modification wherein, methyl chloroformate was used instead of ethyl chloroformate. IR (KBr): 3284 (NH), 1741, 1691, 1669 (C=O); ^{1}H NMR ($CDCl_3$): δ 1.3 (t, 3H, $-CH_3$), 3.8 (s, 3H, $-OCH_3$), 4.3 (q, 2H, $-CH_2$), 7.4 (d, 1H, ArH, *J*=8.4 Hz), 7.8 (m, 2H, ArH), 8.2 (m, 3H, ArH), 9.1 (bs, 1H, NH).

3-Amino/3-alkyl-2, 4-dioxo-1,2,3,4-tetrahydro-



Scheme I

pyrimido[4,5-*a*]anthraquinone 3,4a-d. A mixture of **2a** or **2b** (0.001 mole) and excess hydrazine hydrate or the aliphatic amine (four folds), was heated under reflux in an oil-bath for 10 hr. The solvent was removed, cooled and poured into crush-ice. Hydrochloric acid was added dropwise until the precipitation was complete, filtered, washed with cold water and crystallised from *N,N*-dimethylformamide:ethanol (90:10). The physical data are recorded in Table I.

3: IR (KBr): 3428, 3324, 3238 (OH, NH), 1695, 1678 (C=O), 1645 (C=N), 1584, 1497 (C=C); ^{1}H NMR (DMSO-d_6): δ 5.7 (s, 2H, NH_2), 7.9-8.0 (m, 3H, ArH), 8.3-8.5 (m, 3H, ArH), 11.88 (s, 1H, OH or NH).

4a: ^{1}H NMR (DMSO-d_6): δ 3.7 (s, 3H, CH_3), 7.8-7.9 (m, 3H, ArH), 8.1-8.3 (m, 3H, ArH), 11.22 (s, 1H, OH or NH).

4b: ^{1}H NMR (DMSO-d_6): δ 1.35 (t, 3H, CH_3), 4.28 (q, 2H, CH_2), 7.8-8.3 (m, 6H, ArH), 11.15 (s, 1H, OH or NH).

4c: ^{1}H NMR (DMSO-d_6): δ 3.60 (t, 2H, CH_2O), 3.90 (t, 2H, NCH_2), 4.90 (br, 1H, OH), 7.8-8.3 (m, 6H, ArH), 11.21 (s, 1H, OH or NH).

Table I—The physical data of compounds **2-6**

Compd	R	mp °C	Yield (%)	Mol. formula	Found (%) (Calc.) C	H	N
2a	OC_2H_5	161	86	$C_{20}H_{17}NO_6$	65.45 (65.39	4.72 4.66	3.70 3.81)
2b	OCH_3	167	75	$C_{19}H_{15}NO_6$	64.72 (64.59	4.31 4.28	3.89 3.96)
3	–	281	62	$C_{16}H_9N_3O_4$	62.50 (62.54	3.05 2.95	13.28 13.68)
4a	CH_3	>330	32	$C_{17}H_{10}N_2O_4$	66.52 (66.67	3.32 3.29	9.27 9.15)
4b	CH_2CH_3	>330	35	$C_{18}H_{12}N_2O_4$	67.33 (67.50	3.80 3.78	8.90 8.75)
4c	CH_2CH_2OH	>330	40	$C_{18}H_{12}N_2O_5$	64.18 (64.29	3.71 3.60	8.33 8.33)
4d	$CH_2C_6H_5$	298	55	$C_{23}H_{14}N_2O_4$	72.08 (72.25	3.63 3.69	7.40 7.31)
5	–	240	80	$C_{15}H_{11}N_3O_3$	64.12 (64.05	3.96 3.94	14.98 14.99)
6	–	248	90	$C_{16}H_9N_3O_3$	65.90 (65.98	3.04 3.11	14.31 14.43)

4d: ^{1}H NMR (DMSO-d_6): δ 4.60 (s, 2H, CH_2), 7.1 (s, 5H, ArH), 7.6-8.3 (m, 6H, ArH), 11.11 (s, 1H, OH or NH).

1-Aminoanthraquinone-2-carbohydrazide 5. To compound **1** (2.95 g, 0.01 mole) in dry ethanol (100 mL) was added excess hydrazine hydrate (98%, 10 mL). The mixture was refluxed in a boiling water-bath for 48 hr, at the end of which the contents were concentrated. The reaction was cooled and to it was gradually added 150-200 mL cold water accompanied by vigorous stirring, precipitate was filtered, washed with water followed by chilled methanol, dried and crystallised from *N,N*-dimethylacetoamide. mp 240°, yield 2.25 g; IR: 3433, 3393, 3324 (NH), 1660 (C=O), ^{1}H NMR (DMSO-d_6): δ 4.6 (bs, 2H, NH_2), 7.4-8.3 (m, 6H, ArH), 8.8 (bs, 2H, NH_2), 9.9 (bs, 1H, NH); MS: M^+ at m/z 281, and 250, 223, 193, 164.

3-Amino-4(3*H*)-oxopyrimido[4,5-*a*]anthraquinone 6. A mixture of **5** (0.562 g, 0.002 mole) and ethyl orthoformate (2 mL) was heated under reflux for 10 hr. The solvent was then removed in vacuum, and the residue was dispersed in ethanol. The solid material obtained was filtered and crystallised from *N,N*-dimethylformamide:ethanol (80:20). IR (KBr): 3405, 3288 (NH), 1690, 1667 (C=O), 1625 (C=N), 1592, 1567 (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).

References

1 Peet N P & Sunder S, *J Heterocycl Chem*, 21, **1984**, 1807.
2 Scheiner P, Frank L, Guusti I, Arwin S, Pearson S A, Excellent F & Harper A P, *J Heterocycl Chem*, 21, **1984**, 1817.
3 Leiby R W, *J Heterocycl Chem*, 21, **1984**, 1825.
4 Peet N P, *Synthesis*, **1984**, 1065.
5 Kornet M J, Varia T & Beaven W, *J Heterocycl Chem*, 20, **1983**, 1553.
6 Ishikawa M, Azuma H, Eguchi Y, Sugimoto A, Ito S, Takashima Y, Ebisawa H, Moriguchi S, Kotoku I & Suzuki H, *Chem Pharm Bull*, 30, **1982**, 744.
7 El-Telbany F & Hutchins R O, *J Heterocycl Chem*, 22, **1985**, 401.
8 Wamhoff H, Ertas M & Alta S M S, *Ann Chem*, **1985**, 1910.
9 Schneider P, Arwin S, Eliacin M & Tu J, *J Heterocycl Chem*, 22, **1985**, 1435.
10 Bridson P K, Davis R A & Renner L S, *J Heterocycl Chem*, 22, **1985**, 753.
11 Kangani C O & Master H E, *Indian J Heterocycl Chem*, 5, **1996**, 253.
12 Kangani C O & Master H E, *Indian J Heterocycl Chem*, 5, **1996**, 257.
13 Kangani C O & Master H E, *Indian J Heterocycl Chem*, 5, **1996**, 261.
14 Kangani C O & Master H E, *Indian J Heterocycl Chem*, 6, **1996**, 85.
15 Kangani C O & Master H E, *J Heterocycl Chem*, 34, **1997**, 1699.
16 Kangani C O & Master H E, *Indian J Chem*, in press.

17 Kangani C O & Master H E, *Indian J Chem*, communicated.
18 Kangani C O & Master H E, *J Med Chem*, communicated.
19 Chang P & Chia-Fu Chen, *J Heterocycl Chem*, 33, **1996**, 367.
20 Kalyanaraman B, Perez-Reyes E & Mason R P, *Biochem Biophys Acta*, 630, **1980**, 119.
21 Lown J W, Sim S & Chen H, *Can J Biochem*, 56, **1978**, 1042.
22 Lown J W, Sim S, Majumdar K & Chang R,*Biochem Biophys Res Commun*, 76, **1977**, 705.
23 Driscoll J S, Hazard (Jr) G F, Wood (Jr) B & Goldin A, *Cancer chemother Rep*, Part 2, 4(2), **1974**, 1.
24 Jiang J B, Johnson M G, Defauw J M, Beine T M, Ballas L M, Janzen W P, Loomis C R, Seldin J, Cofield D, Adams L, Cianciolo G, Degen D & Von Hoff D D, *J Med Chem*, 35, **1992**, 23, 4259.