Fused s-Triazino Heterocycles. V. 1,3,4,6,9b-Pentaazaphenalenes. Reactions of a Carboxylic Acid Side Chain

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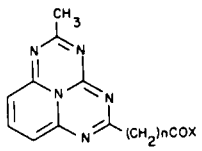
Procedures were developed to convert 4-(2-methyl-1,3,4,6,9b-pentaazaphenalene-5-yl)butanoic acid (Ia) and 3-(2-methyl-1,3,4,6,9b-pentaazaphenalene-5-yl)propanoic acid (IIa) to a series of esters and amides.

J. Heterocyclic Chem., 14, 341 (1977).

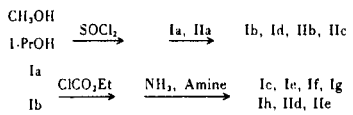
A previous paper (2) reported the preparation of 4-(2-methyl-1,3,4,6,9b-pentaazaphenalene-5-yl)butanoic acid (Ia) and 3-(2-methyl-1,3,4,6,9b-pentaazaphenalene-5-yl)-propanoic acid (IIa). The present paper describes the results of attempts to convert the carboxyl group of Ia and IIa to several typical derivatives.

Esterification of Ia using the Fischer procedure with methanol and sulfuric acid gave only a 14% yield of methyl-4(2-methyl-1,3,4,6,9b-pentaazaphenalene-5-yl)-butanoate (Ib). A significant improvement in yield of Ib (55%) was obtained by adopting a procedure developed by Brenner and Huber (3) for the esterification of amino acids. In this method, which was used to prepare the esters listed in Table I, a cold solution of excess alcohol is successively treated with approximately equimolar amounts of thionyl chloride and a carboxylic acid.

Figure 1



I, II



Ia, n = 3, X = OH
Ib, n = 3, X = OCH_3
Ic, n = 3, X = p-$NHC_6H_4OCH_3$
Id, n = 3, X = $OCH_2CH_2CH_3$
Ie, n = 3, X = NH_2
If, n = 3, X = $N(CH_2CH_3)_2$
Ig, n = 3, X = $N(CH_2)_5$
Ih, n = 3, X = p-NHC_6H_4Cl
IIa, n = 2, X = OH
IIb, n = 2, X = OCH_3
IIc, n = 2, X = $OCH_2CH_2CH_3$
IId, n = 2, X = NH_2
IIe, n = 2, X = p-$NHC_6H_4OCH_3$

In an effort to prepare amide derivatives, we attempted to convert Ia or IIa to the acid chloride which would then be reacted with ammonia and other amines. Having used thionyl chloride in the esterification procedure, it came somewhat of a surprise to find that direct reaction of Ia or IIa with thionyl chloride in the cold (with or without inert solvent, and in the presence or absence of pyridine or catalytic quantities of dimethylformamide) resulted in gross decomposition of the acids. With the acid chloride intermediate precluded, the use of dicyclohexylcarbodiimide was investigated as means of preparing amide derivatives of Ia or IIa. Unfortunately, acylurea formation turned out to be the major or sole reaction product in most cases. Reaction of Ib or IIb with ammonia or amines was extremely sluggish. A moderate success at amide formation was achieved (Table I) using as acylating agent the mixed anhydride derived from ethyl chloroformate/-triethylamine and Ia or IIa.

Attempted reduction of Ia with diborane or Ib with sodium bis-(2-methoxyethoxy)aluminum hydride, led in each case to intractible tars.

EXPERIMENTAL

Melting points were determined in open capillaries on a Thomas-Hoover melting-point bath and are uncorrected. Infrared spectra were recorded using a Perkin-Elmer Infracord, Model 137. Pmr spectra were determined on a Varian EM-360 spectrometer using TMS as an internal reference. Analyses were performed by Micro-Analysis Inc., Marshallton, Delaware.

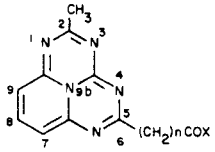
4-(2-Methyl-1,3,4,6,9b-pentaazaphenalene-5-yl)butanoic Acid (Ia) and 3-(2-methyl-1,3,4,6,9b-pentaazaphenalene-5-yl)propanoic Acid (IIa).

Both of these compound were prepared by methods given in the literature (2).

Methyl 4(2-Methyl-1,3,4,6,9b-pentaazaphenalene-5-yl)butanoate (Ib).

Table I

Esters and Amides from Ia and IIa



I, II

Compound Number	n	X	Recrystallization Solvent	M.p., °C (a)	Yield (%) (b)	Molecular Formula	Calcd. Analysis Found C	H	N
Id	3	$OCH_2CH_2CH_3$	Petroleum ether (120-140°)	106-108	34	$C_{16}H_{19}N_5O_2$	61.32 61.07	6.11 6.19	22.36 22.18
Ie	3	NH_2(c)	1-Butanol	239-241	37	$C_{13}H_{14}N_6O$	57.76 57.84	5.22 5.45	31.10 31.10
If	3	$N(CH_2CH_3)_2$	Benzene-hexane	118-120	79	$C_{17}H_{22}N_6O$	62.55 62.62	6.80 6.77	22.75 22.59
Ig	3	$N(CH_2)_5$	Benzene	148-150	46	$C_{18}H_{22}N_6O$	63.88 64.10	6.55 6.62	24.84 24.60
Ih	3	*p*-NHC_6H_4Cl	1-Propanol	208-210	77	$C_{19}H_{17}ClN_6O$	59.92 60.10	4.50 4.50	22.07 22.04
IIb	2	OCH_3	Carbon tetrachloride	175-176	60	$C_{13}H_{13}N_5O_2$	57.56 57.84	4.83 5.04	25.81 25.60
IIc	2	$OCH_2CH_2CH_3$	Petroleum ether (120-140°)	125-127	22	$C_{15}H_{17}N_5O_2$	60.18 60.07	5.73 5.87	23.40 23.12
IId	2	NH_2 (c)	1-Propanol	264-266	14	$C_{12}H_{12}N_6O$	56.24 56.12	4.72 4.66	32.80 32.79
IIe	2	*p*-$NHC_6H_4OCH_3$	1-Propanol	257-259	8	$C_{19}H_{18}N_6O_2$	62.97 62.98	5.01 4.97	23.19 23.32

(a) The melting points were taken on recrystallized products. (b) Crude yield, (c) Excess ammonia was slowly bubbled into the reaction mixture in place of the *p*-anisidine used in the general procedure.

The reaction conditions for preparing Ib are illustrative of the method used to prepare the esters listed in Table I.

A stirred solution of 45 ml. of anhydrous methanol (under dry nitrogen) was maintained at -5° while 3.92 g. (0.033 mole) of thionyl chloride was added dropwise over a period of 5 minutes. Then, after adding in portions, 8.31 g. (0.03 mole) of Ia at 0°, the mixture was allowed to warm to room temperature and was stirred for an additional 22 hours. The tacky residue obtained after removing the volatile material on the rotary evaporator under reduced pressure, was treated with 30 ml. of methanol, neutralized with 1*N* methanolic sodium methoxide and then taken up in 150 ml. of chloroform. The chloroform solution was washed (three-30 ml. portions of 5% sodium bicarbonate, followed by one 30 ml. portion of water), dried (anhydrous sodium sulfate) and then evaporated (rotary evaporator/reduced pressure) to yield 4.68 g. (55%) of crude Ib, m.p. 135-140°. Recrystallization from toluene gave an analytical sample, pink crystals, m.p. 154-156°; ir λ (Nujol): 5.73 μ (-C(=O)-O-); nmr (deuteriochloroform): δ 2.00 (s, 3H, CH_3), δ 2.20 (m, 6H, $(CH_2)_3$), δ 3.65 (s, 3H, CH_3O), δ 6.05 (d, J = 8 Hz, 2H, H_7 and H_9), δ 7.22 (t, J = 8 Hz, 1H, H_8).

Anal. Calcd. for $C_{14}H_{15}N_5O_2$: C, 58.93; H, 5.30; N, 24.55. Found: C, 58.89; H, 5.20; N, 24.54.

N-*p*-Methoxyphenyl-4-(2-methyl-1,3,4,6,9b-pentaazaphenalene-5-yl)butanamide (Ic).

The reaction conditions used to prepare Ic were also used to prepare the other amide derivatives listed in Table I. However, the isolation of the products in certain cases (IId, Ie, If, Ig) was sufficiently different to warrant a separate brief description in the paragraphs below.

A stirred solution of 2.71 g. (0.01 mole) of Ia and 1.01 g. (0.01 mole) of freshly distilled triethylamine in 50 ml. of dry chloroform (under dry nitrogen) was maintained at -5° while adding dropwise a solution of 1.3 g. (0.012 mole) of freshly distilled ethyl chloroformate in 10 ml. of dry chloroform. The mixture was stirred for 10 minutes at -5° and then a solution of 2.46 g. (0.02 mole) of *p*-anisidine in 10 ml. of dry chloroform was added dropwise over 10 minutes. After an additional reaction period of 2 hours at 0°, the mixture was allowed to stir at room temperature overnight. The reaction mixture (referred to below in the alternative isolation procedures as reaction mixture "A") was distilled to dryness and the solid residue was successively stirred with 50 ml. of ether and 50 ml. of 5% sodium bicarbonate. Collection of the solids by filtration followed by air drying gave 1.39 g. (37%) of crude Ic m.p. 208-213°. Recrystallization from 1-propanol gave pink crystals, m.p. 207-209°; ir λ (Nujol): 3.00