Synthesis of Some Pyridylamino-1,4-disubstituted Phthalazines

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Two general procedures involving the condensation of phthalonitrile or 1,3-diiminoisoindoline with various aminopicolines, followed by ring expansion with hydrazine to the corresponding phthalazine are described. Syntheses are reported of 1,4-di(3'-methyl-2'-pyridyl)aminophthalazine, 1,4-di(5'-methyl-2'-pyridyl)aminophthalazine, and 1,4-di(4',6'-dimethyl-2'-pyridyl)aminophthalazine.

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The current interest in obtaining models for the active site of hemocyanin and Type III copper centres has led to out interest in preparing metal complexes of polyfunctional diazines. In this connection we have synthesized a number of disubstituted phthalazine type ligands. These are quadridentate amines which tend to coordinate two metal centres simultaneously and constrain them in close proximity. A number of ligands of this general type have been reported in the literature (1-5). We have previously published the synthesis of the ligand 1,4-di(2'-pyridyl)-aminophthalazine (6) (Figure 1, R = H) and its complexes (6-10). Also, the preparation and complexes of the methyl substituted ligands 1,4-di(4'-methyl-2'-pyridyl)amino-phthalazine and 1,4-(6'-methyl-2'-pyridyl)aminophthala-zine have been reported (Figure 1, R = 4 Me, R = 6 Me), (11).

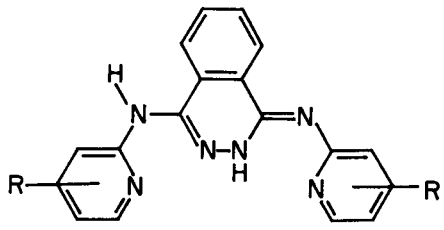

Figure 1. (I) R = 3-methyl, (II) R = 5-methyl, (III) R = 4,6-dimethyl, (IV) R = H, (V) R = 4-methyl, (VI) R = 6-methyl

In this paper, we report the preparation of three new phthalazine ligands in which further methyl substitution exists on the pyridine rings. The steric constraints imposed by the methyl groups in these new ligands are thought to influence the separation of metal centres in their complexes. This is a feature of some importance in determining magnetic exchange between the metal ions. Binuclear copper complexes of these ligands have been prepared and reported (12). 1,4-Disubstituted pyridylaminophthal-azines can all be prepared by two facile, general routes. The preferred method of synthesis is the fusion route, in which phthalonitrile and a methyl substituted 2-aminopyridine are fused together at high temperature with consequent evolution of ammonia, and the formation of a 1,3-disubstitutediminoisoindoline. Subsequent reaction of the isoindoline with hydrazine hydrate in methanol results in the ring expansion of the isoindoline to form the corresponding phthalazine.

An alternate route of preparation of the ligands involves the condensation of 1,3-diiminoisoindoline and the corresponding methyl substituted 2-aminopyridine in refluxing butanol, to produce the 1,3-dipyridyliminoisoindoline, followed by ring expansion.

Siegl (13) has described a route to the synthesis of 1,3-bis(arylamino)isoindolines using the alkaline earth salt catalysed nucleophilic addition of various primary aromatic amines to phthalonitrile in both alcoholic and hydrocarbon solvent media. We have opted for the fusion route as the general method of choice because of its superiority in terms of convenience, yield and reaction time required.

Discussion.

The synthetic routes to 1,4-diaminophthalazines are limited and include the reaction of 1,3-diiminoisoindoline with hydrazine hydrate to give 1,4-diaminophthalazine (17,18), the reaction of 1,4-dihydrazinophthalazine with various aldehydes (5,19) to give 1,4-phthalazinedihydra-zones (which are substituted aminophthalazines), and the reaction of 1,4-dichlorophthalazine with certain amines to give 1,4-disubstituted aminophthalazines (20). While this latter route works well for aniline it does not work successfully using aminopyridines of the type used in this study.

As an extension of the ring expansion of 1,3-diiminoiso-indoline to 1,4-diaminophthalazine (17,18) we have shown that 1,3-dipyridyliminoisoindolines can also be ring expanded to the corresponding phthalazines in a convenient general synthesis allowing a number of different derivatives to be made based on the choice of amino-pyridine.

The nmr spectra are in general fairly complex with some overlapping signals occurring in the aromatic region. One feature that stands out is the apparent asymmetric nature

in all cases of the resonance assigned to the α and β protons on the fused benzene ring of the phthalazine moiety. In the precursor isoindolines a typical AA'BB' splitting pattern is observed for these protons signifying a plane of symmetry at right angles to the benzene ring. Such symmetry is clearly absent in the phthalazines. Also, in agreement with this observation, a resonance assigned to one NH proton is observed for I, II and III at 8.7-8.8 ppm. A second resonance assignable to an NH proton occurs at 6.3-7.0 ppm in I and III (it is probably hidden beneath other resonances in II). It would seem reasonable to assume that the lower field resonance could be assigned to phthalazine NH while the higher field resonance would correspond to the exocyclic NH. This is substantiated by considering the chloroform nmr spectrum of 1,4-dihydrazinophthalazine which has no low field NH resonance and a symmetric AA'BB' pattern associated with the α,β fused benzene ring protons. The implication of these observations is that in chloroform solution I, II and III exist in the asymmetric tautomeric form illustrated in Fig. 1.

The 3-methyl derivative (I) exhibits two resonances at 2.3 and 2.5 ppm, attributable to methyl groups while only one signal was observed in the corresponding isoindoline (13). This observation can be rationalized by considering the proximity of the methyl group on the 3-position of the pyridine ring to the exocyclic nitrogen and the α-protons on the fused benzene ring. In the asymmetric tautomer one methyl group would see a completely different local environment from the other.

EXPERIMENTAL

Microanalyses were carried out by Canadian Microanalytical Service Ltd. (Vancouver). Mass spectra were measured on a Hitachi-Perkin Elmer RMU-6E with the direct insertion probe as well as a V. G. Micromass 7070 HS, also with a direct insertion probe. Proton nuclear magnetic resonance spectra were run at room temperature as solutions in deuterated chloroform using a Bruker WP80 spectrometer. The chemical shifts are quoted with respect to TMS as internal standard. Infrared data were obtained from nujol mulls using a Perkin-Elmer Model 283 spectrometer. Melting points were obtained on a Fisher-John's apparatus and are uncorrected. Reagents for the syntheses were prepared in our laboratories, or purchased from Aldrich Co.

Fusion Route.

1,4-Di(3'-methyl-2'-pyridyl)aminophthalazine (I).

Phthalonitrile (6.4 g, 50 mmoles) and 2-amino-3-picoline (10.4 g, 96 mmoles) were placed in a round bottomed flask equipped with a steam condenser and fused for several hours at 170°. Evolution of ammonia was noted as the reaction proceeded. The crude dark 1,3-di(3'-methyl-2'-pyridyl)iminoisoindoline intermediate was extracted and crystallized from ethanol as yellow needles, mp 135° (lit 135°-136°), yield = 10.5 g, 65%). Hydrazine hydrate (85%, 35 ml) was added to a solution of this product (10.5 g, 32 mmoles) in refluxing methanol (800 ml). The solution was boiled for several hours with the consequent evolution of ammonia, and allowed to cool overnight. The product was collected as yellow needles. It was recrystallized from methanol to give a pale yellow product, (yield = 9.5 g, 79%), mp 257°; ms: (m/e) 342 (M^+, 100%), 341 (18%), 327 (98%), 311 (26%), 234 (37%), 205 (13%), 171 (7%), 123 (4%), 107 (16%); ^{1}H nmr: 2.3 (s, 3H, methyl), 2.5 (s, 3H, methyl), 6.3 (b, 1H, NH), 6.8 (m, 2H, pyridine H_5), 7.4 (m, 2H, pyridine H_4), 7.7 (m, 4H, phthalazine CH), 8.0 (b, 2H, pyridine H_6), 8.7 (b, 1H, NH).

Anal. Calcd. for $C_{20}H_{18}N_6 \cdot 0.25(CH_3OH)$: C, 69.4; H, 5.43; N, 24.0. Found: C, 69.8, H, 5.48; N, 23.9.

1,4-Di(5'-methyl-2'-pyridyl)aminophthalazine (II).

The intermediate 1,3-di(5'-methyl-2'-pyridyl)iminoisoindoline was prepared by the same procedure which has also been described by Addison *et al.* (14). Hydrazine hydrate (85%, 35 ml) was added to a solution of this product (12.0 g, 36.6 mmoles) in methanol (1 l). The solution was boiled for 2 hours (with ammonia evolution) and then allowed to cool overnight. The product was collected as yellow crystals and recrystallized from methanol, (yield = 9.0 g, 72%) mp 114°; ms: (m/e) 342 (M^+, 100%), 341 (87%), 327 (2%), 235 (14%), 231 (9%), 171 (3%), 123 (3%), 108 (9%); ^{1}H nmr: 2.2 (s, 6H, methyl), 7.4 (m, 2H, pyridine H_4), 7.7 (m, 6H, pyridine H_3, phthalazine CH), 8.1 (s, 2H, pyridine H_6), 8.7 (b, 1H, NH).

Anal. Calcd. for $C_{20}H_{18}N_6$: C, 66.7; H, 5.56; N, 23.3. Found: C, 67.2; H, 5.55; N, 23.5.

1,4-Di(4',6'-dimethyl-2'-pyridyl)aminophthalazine (III).

This compound was prepared in the same manner as 1,4-di(3'-methyl-2'-pyridyl)aminophthalazine and obtained as a yellow solid (recrystallized from chloroform), (yield isoindoline = 59%, phthalazine = 66%), mp 288°; ms: (m/e) 370 (M^+, 100%), 356 (16%), 264 (11%), 249 (11%), 236 (10%), 185 (3%). 171 (4%), 122 (3%), 106 (13%); ^{1}H nmr : 2.3 (s, 6H, 4-methyl), 2.5 (s, 6H, 6-methyl), 6.6 (s, 2H, pyridine H_5), 7.0 (b, 1H, NH), 7.8 (bm, 6H, phthalazine CH, pyridine H_3), 8.8 (b, 1H, NH).

Anal. Calcd. for $C_{22}H_{22}N_6 \cdot 0.25\ (H_20)$: C, 70.5; H, 6.00; N, 22.4. Found: C, 70.4; H, 5.91; N, 22.5.

Other pyridylaminophthalazines, including 1,4-di(2'-pyridyl)aminophthalazine, 1,4-di(4'-methyl-2'-pyridyl)aminophthalazine and 1,4-di(6'-methyl-2'-pyridyl)aminophthalazine whose syntheses have already been published (6,11) can be prepared by a similar route.

1,3-Diiminoisoindoline Route.

1,4-Di(3'-methyl-2'-pyridyl)aminophthalazine (I).

1,3-Diiminoisoindoline (15,16) (14.5 g, 100 mmoles) and 2-amino-3-picoline (20.8 g, 200 mmoles) were refluxed in 1-butanol (400 ml) for approximately 2 days. Ammonia evolution was noted during the course of the reaction. The product of this reaction, 1,3-di(3'-methyl-2'-pyridyl)-iminoisoindoline was obtained as yellow crystals by allowing the solution to cool, filtering and recrystallizing from an ethanol/water mixture. This product was then ring expanded to obtain the pyridylaminophthalazine as described previously to give 1,4-di(3'-methyl-2'-pyridyl)aminophthalazine (yield 35%). All other isoindoline intermediates described in this paper can be prepared from 1,3-diiminoisoindoline.

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