THE REACTION OF 1,2-DIAMINES WITH A 2,3-DIOXOPYRROLIDINE AS AN APPROACH TO PYRROLO[2,3-b]PYRAZINES

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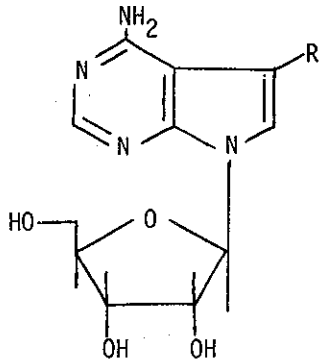
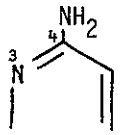
The reaction of 1-benzyl-2,3-dioxopyrrolidine with aromatic diamines as a means of preparing polycyclic molecules containing the pyrrolo[2,3-b]pyrazine moiety has been studied as a model route to molecules isomeric with the biologically active pyrrolo-[2,3-d]pyrimidines. The spiro derivatives 17-18, however, have been the realized products rather than the desired linear systems (e.g., 9).

Tubercidin (1), toyocamycin (2), and sangivamycin (3) are potentially valuable ring systems in the chemotherapeutic treatment of cancer.[1] To date, however, no attention has been devoted to considering the biosignificance of the atomic arrangement at the N-3/C-4 center (*i.e.*, 4) of 1-3. One approach to confront this question would be to consider the isomeric pyrrolo[2,3-b]pyrazine analogs as illustrated by 5 since such derivatives possess the focal functionality of 4 but in an altered arrangement. Therefore, our initial concern was to avail a simple and versatile synthesis of an appropriate pyrrolo[2,3-b]pyrazine ring system.



1, R=H
2, R=CN
3, R=$CONH_2$



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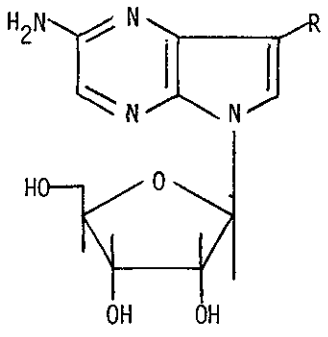

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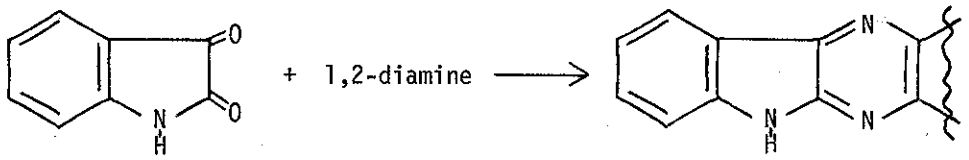
To this end the studies of Popp[2] in which isatin (6) was condensed with various diamines to form linear pyrazines (7) seemed to offer exciting possibilities if applied to an exploitable 2,3-dioxopyrrolidine. Thus, 1-benzyl-2,3-dioxopyrrolidine (8)[3] was chosen as the suitable candidate since the benzyl group could be easily removed[4] in subsequent steps (*i.e.*, beyond 13 below) to allow for the necessary judicious ribosylation. The overall plan is summarized in Scheme I wherein the intermediate 6,7-dihydro derivative (9) was anticipated to spontaneously dehydrogenate, or could be chemically induced to do same, to yield 10. The approach to a desired precursor of 5 (13) could then be completed by oxidizing 10 to 11 and subjecting 11 to reductive chlorination to achieve 12. Ammonolysis of 12 would then avail 13.



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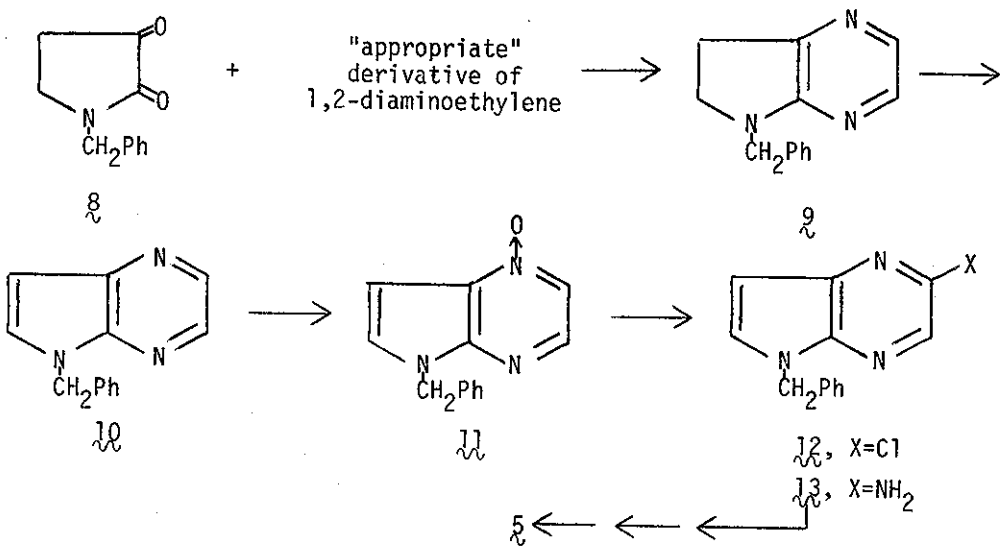
Scheme I

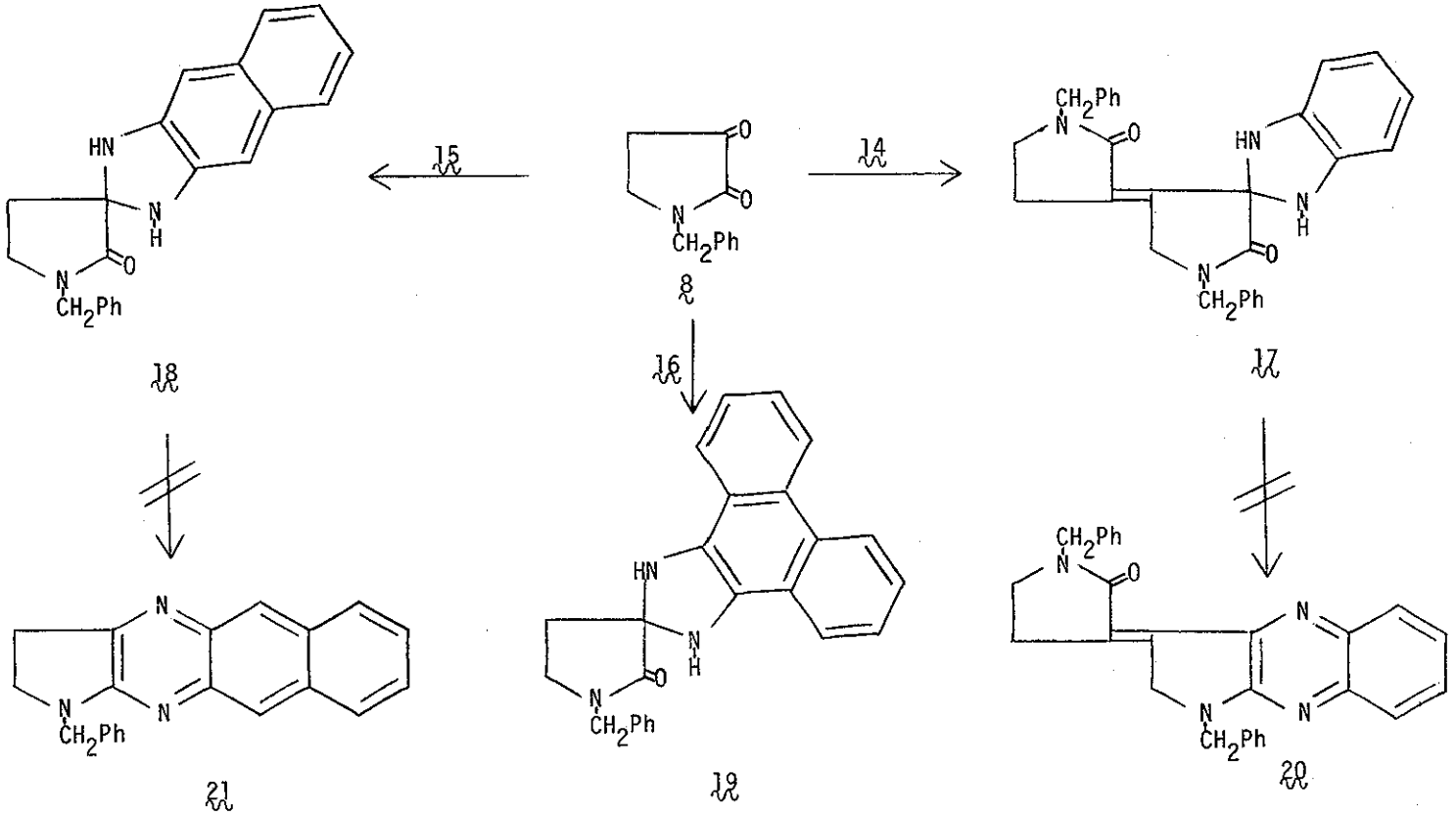
Proposed Synthetic Plan to the Pyrrolo[2,3-b]pyrazine Analogs (5)



As a model study to pyrrolo[2,3-b]pyrazines by this route, 8[3] was reacted under the same conditions and with the same 1,2-diamines (*i.e.*, *o*-phenylenediamine (14), 2,3-diaminonaphthalene (15), and 9,10-diaminophenanthrene (16)) with which Popp[2] achieved linear fusion when investigating isatin (6). However, only the spiro compounds 17-19[5] were realized (Scheme II). In the reaction of 8 with 14 to yield 17 (mp 190-191°; 42% yield; white needles recrystallized from 95% ethanol) the dioxopyrrolidine was found to undergo a self-condensation, most certainly prior to spiro formation. This was not surprising since it has been reported[6] that 1-substituted-2,3-dioxopyrrolidines undergo self-condensation with extreme ease. As noted in Scheme II, self-condensation occurred only with one of the three diamines examined and we believe this is due to a difference in the base strengths of the three diamines .

Scheme II

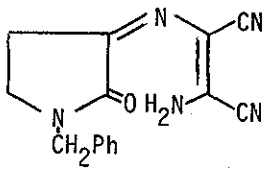
The Reactions of 8 with 14-16



The structural proof for 17 was based on its ir, pmr, mass spectra, and reproducible elemental microanalyses while the structural proof for 18 (mp 237-238°; 74% yield; white crystals recrystallized from dioxane) was based on ir and elemental microanalyses. Unfortunately, lack of success in finding an appropriate solvent for purification (dioxane seemed the most reliable) of 19 (mp 160-162°; 75% yield; white crystals) precluded the realization of its satisfactory elemental microanalytical data. However, its infrared spectral data was sufficiently consistent with that for 18 to allow for the structural assignment of 19 for the product from 8 and 16.

Popp[2] reported the successful acidic mediated conversions of analogous isatin-spiro derivatives to the linear polycyclic pyrrolo-[2,3-b]pyrazine systems. However, attempts to induce similar rearrangement of 17 and 18 to 20 and 21 failed by producing intractable tars.

Finally, to accomplish the goals of Scheme I, an aliphatic diamine must be ultimately considered. Thus, reacting 8 with diaminomaleonitrile was studied and found to produce 22 (mp 144-145°; 52% yield; light yellow crystals recrystallized from 95% ethanol) whose structural proof (in contrast to 23) was based on its elemental microanalytical data and its analogous physical and infrared spectral properties to those of the isatin product (24) previously reported by Popp.[7]



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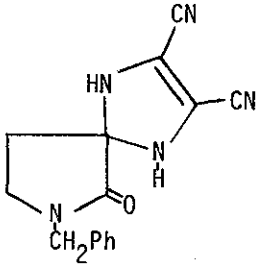

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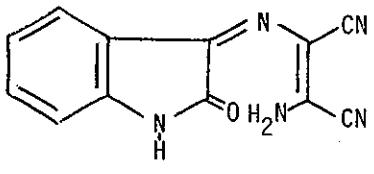

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5. All new compounds (except **19**) reported herein gave satisfactory microanalytical values. The microanalytical data was obtained by Het-Chem-Co., Harrisonville, Missouri USA. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected.
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