Institut de Chimie des Substances Naturelles du C.N.R.S.

Nitrogen Heterocyclic Analogs of Polyaryls

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Nitrogen heterocyclic analogs of polyaryls, derived from pyridine, quinoline, benzo[h]-quinoline, indole, indolizine, and imidazo[1,2-a]pyridine, have been prepared from 1,4-diacetyl- and 1,3,5-triacetylbenzene and 2,6-diacetylpyridine, for study of their physical, chemical and biological properties.

Polyaryls are of interest as scintillators in liquid scintillation counters used in nuclear physics, and some of their heterocyclic analogs, especially 2,2'-*p*-phenylenebis(5-phenyloxazole) (POPOP) and its homologs, have also been employed with success for that purpose (1). In biology, one polyaryl, *viz.* 1,3,5-tri-*p*-xenylbenzene (I), has been found to be carcinogenic, producing, on skin-painting in mice, not only epitheliomas *in situ* but also tumors of the liver (2); earlier, another polyaryl, 1,3,5-triphenylbenzene, had also been reported as carcinogenic (3) but this claim could not be confirmed later (4). Further, in our laboratory we are interested in investigating the behavior of polyaryls and their nitrogen heterocyclic analogs in Rayleigh light diffusion studies, as a means of determining electron delocalization in these molecules (5). These various interests led us to synthesize a number of nitrogen-containing analogs of polyaryls which include in their molecule the following heterocycles: pyridine, quinoline, benzo[h]quinoline, indole, indolizine, and imidazo[1,2-a]pyridine.

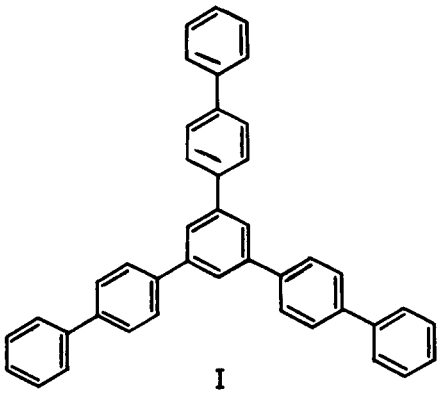
The intermediates used were three polyketones: 1,4-diacetylbenzene, 1,3,5-triacetylbenzene, and 2,6-diacetylpyridine. In the indole group, 1,4-diacetylbenzene, heated with phenylhydrazine, gave a bisphenylhydrazone which could be cyclized with either zinc chloride or polyphosphoric acid to the pentacyclic 1,4-di-(2-indolyl)benzene (II); replacement of phenylhydrazine by *p*-xenylhydrazine afforded the heptacyclic 1,4-di-(5-phenyl-2-indolyl)-benzene (III). The bisphenylhydrazone and bis-*p*-tolylhydrazone of 2,6-diacetylpyridine were cyclized by polyphosphoric acid to 2,6-di-(2-indolyl)pyridine (IV) and 2,6-di-(5-methyl-2-indolyl)pyridine (V) respectively. Interestingly, these two compounds gave monopicrates with picric acid, which suggests that the heterocycle involved in this complex formation was the pyridine one rather than the indole one. 1,3,5-Triacetylbenzene readily gave trisarylhydrazones on heating at 180° with phenyl- and *p*-tolylhydrazine, but not when the usual procedure for the preparation of hydrazones (use of arylhydrazine salts in ethanol) was employed; indolization, effected with polyphosphoric acid, furnished 1,3,5-tri-(2-indolyl)-benzene (VI) and 1,3,5-tri-(5-methyl-2-indolyl)-benzene (VII) respectively. It is interesting to note that compound VI gave with tetrachlorophthalic anhydride a stable charge-transfer complex (6) made up of three molecules of the electron acceptor for one molecule of the electron donor; this indicates that the three indole nuclei behave here as separate units in the charge-transfer phenomenon with the halogenated anhydride.

In the quinoline series, a Pfitzinger reaction performed on one mole of 1,3,5-triacetylbenzene and 3 moles of isatin readily afforded "tri-atophan" (VIII), which Lublin (7) had tested for uric acid eliminating properties and found inactive; the compound was stated to have been supplied by von Braun but we could find no mention of its preparation and properties in the chemical literature. This triacid underwent thermal decarboxylation, with extensive charring, to give 1,3,5-tri-(2-quinolyl)benzene (IX); the homologous 1,3,5-tri-(6-methyl-2-quinolyl)benzene (XI) was similarly prepared from the "tri-methyl-atophan" (X). Surprisingly, both compounds (IX) and (XI) yielded a monopicrate, despite the presence in their molecule of three quinoline rings, whereas 1,4-di-(2-quinolyl)benzene (XII) readily gave a dipicrate; this seems to indicate that complex formation with picric acid is highly dependent on the geometry of the molecule. 2,6-Diacetylpyridine underwent double Pfitzinger reactions with isatin and 5-methylisatin to give the dicinchoninic acids (XIII) and (XV), which could be easily decarboxylated to 2,6-di-(2-quinolyl)-pyridine (XIV) and 2,6-di-(6-methyl-2-quinolyl)pyridine (XVI) respectively; 2,6-di-(9-benzo[h]quinolyl)-pyridine (XVIII) was similarly synthesized from α-naphthisatin *via* the diacid (XVII). Here again, it was surprising to find that the heptacyclic compound (XVIII), in spite of its three basic heterocycles, afforded a monopicrate.

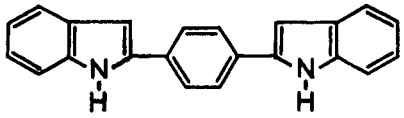
In the indolizine series, the condensation of 1,4-di-(bromoacetyl)benzene with 2-methyl- and 2,4-dimethylpyridine furnished pyridinium salts which underwent Tschitschibabin cyclizations to 1,4-di-(2-indolizinyl)benzene (XIX) and 1,4-di-(7-methyl-2-indolizinyl)benzene (XX). These high-melting compounds, treated with sodium nitrite and hydrochloric acid, yielded the dinitroso compounds (XXI) and (XXII).

In the imidazo[1,2-a]pyridine series, 1,4-di-(2-imidazo[1,2-a]pyridyl)benzene (XXIII) and 1,4-di-(7-methyl-2-imidazo[1,2-a]pyridyl)benzene (XXIV) were obtained by direct condensation of 1,4-di-(bromoacetyl)benzene with 2-aminopyridine and 4-methyl-2-aminopyridine; both compounds gave a stable monopicrate.

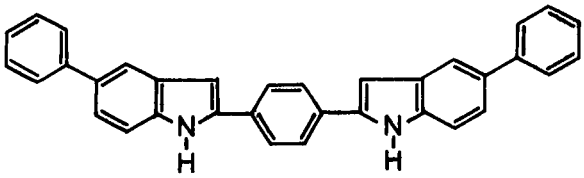
Results of the electron delocalization studies will be reported at a later date.



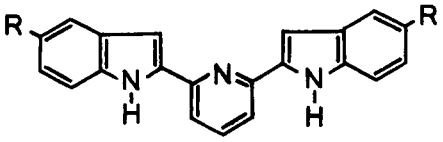
I



II

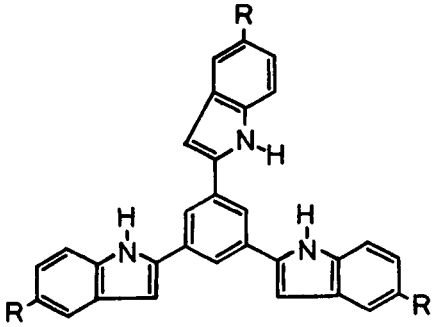


III



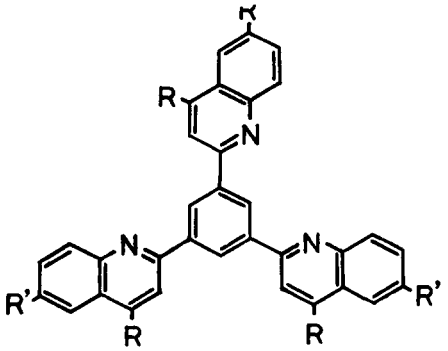
IV; R = H

V; R = CH_3



VI; R = H

VII; R = CH_3

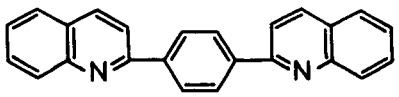


VIII; R = CO_2H, R' = H

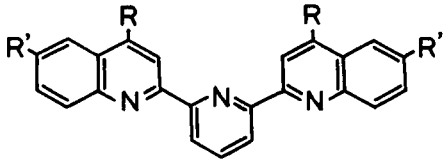
IX; R = R' = H

X; R = CO_2H, R' = CH_3

XI; R = H, R' = CH_3



XII

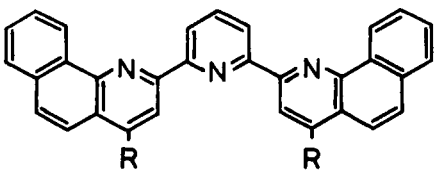


XIII; R = CO_2H, R' = H

XIV; R = R' = H

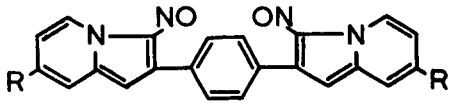
XV; R = CO_2H, R' = CH_3

XVI; R = H, R' = CH_3



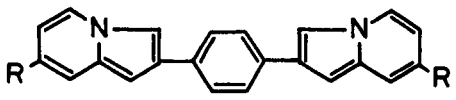
XVII ; R = CO_2H

XVIII , R = H



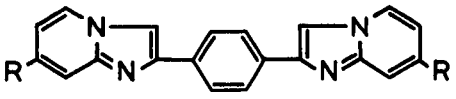
XXI ; R = H

XXII , R = CH_3



XIX ; R = H

XX ; R = CH_3



XXIII ; R = H

XXIV , R = CH_3

EXPERIMENTAL

Melting points were taken on a Maquenne block and are uncorrected.

1,4-Di-(2-indolyl)benzene (II).

Bisphenylhydrazone of 1,4-diacetylbenzene.

This compound was prepared by heating for 10 min. at 150-170° a mixture of 3.24 g. of the diketone and 2.2 g. of phenylhydrazine; the yellow solid obtained on cooling was recrystallized from toluene, giving pale yellow leaflets (4 g.), m.p. 243°.

Anal. Calcd. for $C_{22}H_{22}N_4$: C, 77.2; H, 6.5. Found: C, 77.4; H, 6.4.

Cyclization (a) with zinc chloride. The foregoing hydrazone (1 part) was heated at 280° for 15 min. with 5 parts of anhydrous zinc chloride, and the melt obtained was treated with hydrochloric acid after cooling; the precipitate which formed was collected, washed first with dilute aqueous sodium hydroxide, then with water, dried, and sublimed *in vacuo* at 340°/10 mm. The sublimate of compound II was recrystallized from acetone, giving pale yellow leaflets, m.p. *circa* 436°. Yield, 30%.

Cyclization (b) with polyphosphoric acid. A mixture of the hydrazone (1 part) and 10 parts of polyphosphoric acid (prepared from 40 parts phosphoric acid and 60 parts phosphorus pentoxide) was heated for 15 min. at 150°; after cooling, the mixture was treated with water and the precipitate collected, washed thoroughly with hot water, dried, and purified as above. Yield, 50%. This compound did not give stable complexes with picric acid or tetrachlorophthalic anhydride.

Anal. Calcd. for $C_{22}H_{18}N_2$: C, 85.7; H, 5.2; N, 9.1. Found: C, 85.7; H, 5.4; N, 9.3.

1,4-Di-(5-phenyl-2-indolyl)benzene (III).

1,4-Diacetylbenzene bis-*p*-xenylhydrazone.

This compound was prepared by heating, at 200°, 3.7 g. of *p*-xenylhydrazine with 1.62 g. of the diketone; the mixture solidified rapidly, and 20 ml. of xylene was then added and the reaction completed by 15 min. refluxing. After cooling, the solid which formed was collected and recrystallized from toluene, giving lemon yellow leaflets (4 g.), m.p. 293° (dec. above 260°).

Anal. Calcd. for $C_{34}H_{30}N_4$: C, 82.6; H, 6.1; N, 11.3. Found: C, 82.5; H, 6.1; N, 11.4.

Cyclization was effected by heating for 10 min. at 170-180° with polyphosphoric acid, as above. The reaction-product was purified by sublimation *in vacuo* followed by recrystallization from tetralin, to give fine yellow prisms, m.p. 348°. Yield, 50%.

Anal. Calcd. for $C_{34}H_{24}N_2$: C, 88.6; H, 5.3; N, 6.1. Found: C, 88.2; H, 5.5; N, 6.0.

2,6-Di-(2-indolyl)pyridine (IV).

2,6-Diacetylpyridine bisphenylhydrazone.

This compound was obtained in 90% yield by heating for 10 min. at 170° a mixture of 1.65 g. of the diketone and 2.5 g. of phenylhydrazine; it crystallized from benzene in pale yellow needles, m.p. 216°.

Anal. Calcd. for $C_{21}H_{21}N_5$: N, 20.4. Found: N, 20.5.

Indolization, effected with polyphosphoric acid at 150° for 15 min., gave a 50% yield of compound IV, which crystallized from a mixture of benzene and cyclohexane in fine colorless needles, m.p. 258°.

Anal. Calcd. for $C_{21}H_{15}N_3$: C, 81.5; H, 4.9; N, 13.6. Found: C, 81.6; H, 4.9; N, 13.6.

It gave a monopicrate, which crystallized from toluene in brick red microscopic needles, m.p. 212°.

Anal. Calcd. for $C_{27}H_{18}N_6O_7$: N, 15.7. Found: N, 15.7.

2,6-Di-(5-methyl-2-indolyl)pyridine (V).

Similarly prepared from *p*-tolyhydrazine and 2,6-diacetylpyridine, this indole was purified by sublimation *in vacuo* at 300° and crystallization from benzene, to give colorless needles, m.p. 268°.

Anal. Calcd. for $C_{23}H_{19}N_3$: C, 81.9; H, 5.6; N, 12.5. Found: C, 81.9; H, 5.9; N, 12.4.

The corresponding picrate crystallized from benzene in brick red microscopic needles, m.p. 218° (dec. above 180°).

Anal. Calcd. for $C_{29}H_{22}N_6O_7$: N, 14.8. Found: N, 15.0.

1,3,5-Tri-(2-indolyl)benzene (VI).

A mixture of 2 g. of 1,3,5-triacetylbenzene and 3.2 g. of phenylhydrazine was heated at 180° for 15 min., and the solid mass thus obtained was treated with charcoal in boiling toluene. The precipitate which formed on cooling the filtrate was recrystallized from toluene, giving fine colorless needles, darkening in the light, m.p. 250° (dec. above 200°).

Anal. Calcd. for $C_{30}H_{30}N_6$: N, 17.7. Found: N, 17.5.

Cyclization, effected with polyphosphoric acid at 170°, gave a 30% yield of compound VI, which was purified by conversion into its 1:3 complex with tetrachlorophthalic anhydride; this crystallized from acetic acid in shiny orange-red needles, dissociating above 180° on gradual heating, and melting instantaneously at 312°.

Anal. Calcd. for $C_{30}H_{21}N_3 + C_{24}Cl_{12}O_3$: C, 50.6; H, 1.7; N, 3.3. Found: C, 51.3; H, 1.9; N, 3.3.

This complex was treated with boiling aqueous sodium hydroxide until the color had disappeared, and the solid obtained was washed thoroughly with hot water, dried, and recrystallized from benzene, giving compound VI as cream-colored needles, m.p. 327°.

Anal. Calcd. for $C_{30}H_{21}N_3$: C, 85.1; H, 5.0; N, 9.9. Found: C, 84.8; H, 5.2; N, 10.0.

1,3,5-Tri-(5-methyl-2-indolyl)benzene (VII).

Prepared as above, from *p*-tolylhydrazine, and in 30% yield, this indole crystallized from toluene in cream-colored leaflets, m.p. 314°.

Anal. Calcd. for $C_{33}H_{27}N_3$: C, 85.2; H, 5.9; N, 9.0. Found: C, 85.1; H, 5.9; N, 8.9.

Its complex with picric acid crystallized from nitrobenzene in fine reddish needles, m.p. 253° (dec. above 180°).

Anal. Calcd. for a monopicrate: N, 12.1. For a dipicrate: N, 13.6. For a tripicrate: N, 14.6. Found: N, 14.0, 14.1.

1,3,5-Tri-(2-quinolyl)benzene (IX).

"Tri-atophan" (VIII) was prepared by refluxing for 24 hr. a solution

of 4.1 g. of 1,3,5-triacetylbenzene, 8.8 g. of isatin, and 5 g. of potassium hydroxide in 20 ml. of ethanol and 2 ml. of water; the reaction-product was taken up in 200 ml. of water, and acidified with acetic acid, giving a precipitate which was purified by dissolution in dilute aqueous sodium hydroxide and reprecipitation with acetic acid. The pale yellow powder (9 g.) finally obtained was washed with ether, then with ethanol, and dried. It was insoluble in the usual organic solvents, and charred on gradual heating above 250°, without showing a melting point.

This triacid gave on pyrolysis, a 20% yield of 1,3,5-tri-(2-quinolyl)-benzene, crystallizing from toluene in fine colorless needles, m.p. 202°.

Anal. Calcd. for $C_{33}H_{21}N_3$: C, 86.3; H, 4.6; N, 9.1. Found: C, 85.9; H, 5.0; N, 9.1.

The monopicrate crystallized from nitrobenzene in bright yellow needles, m.p. 277° (dec. above 230°).

Anal. Calcd. for $C_{39}H_{24}N_6O_7$: N, 12.2. Found: N, 12.4.

1,3,5-Tri-(6-methyl-2-quinolyl)benzene (XI).

"Tri-methylatophan" (X), prepared as above from 1,3,5-triacetyl-benzene, 5-methylisatin, and potassium hydroxide, was a pale yellow, microcrystalline powder, showing no definite melting point.

Anal. Calcd. for $C_{39}H_{27}N_3O_6$: N, 6.6. Found: N, 6.5.

Thermal decarboxylation afforded compound XI, crystallizing from toluene in shiny colorless needles, m.p. 253°.

Anal. Calcd. for $C_{36}H_{27}N_3$: C, 86.2; H, 5.4; N, 8.4. Found: C, 85.9; H, 5.8; N, 8.4.

The corresponding monopicrate crystallized from nitrobenzene in bright yellow needles, m.p. 275° (dec. above 240°).

Anal. Calcd. for $C_{42}H_{30}N_6O_7$: N, 13.4. Found: N, 13.3.

1,4-Di-(2-quinolyl)benzene (XII).

This compound, prepared in 30% yield by thermal decarboxylation of the corresponding biscinchoninic acid, crystallized from toluene in shiny, pale yellow leaflets, m.p. 251°.

Anal. Calcd. for $C_{24}H_{16}N_2$: C, 86.7; H, 4.8; N, 8.4. Found: C, 86.8; H, 4.8; N, 8.6.

It gave a dipicrate, which crystallized from nitrobenzene in ochre yellow needles, m.p. 262°.

Anal. Calcd. for $C_{36}H_{22}N_8O_{14}$: N, 14.2. Found: N, 14.3.

2,6-Di-(2-quinolyl)pyridine (XIV).

2,6-Di-(4-carboxy-2-quinolyl)pyridine (XIII).

This compound was prepared by refluxing for 4 hr. a solution of 4.9 g. of 2,6-diacetylpyridine, 8.9 g. of isatin, and 4.5 g. of potassium hydroxide in 25 ml. of ethanol and 5 ml. of water (after the first hour of heating, the sodium salt of the diacid had already begun to precipitate); after dilution with water and acidification with acetic acid (to *p*H 5), the precipitate obtained was purified as for "tri-atophan", and formed a pale yellow, microcrystalline powder (11.5 g.).

Anal. Calcd. for $C_{25}H_{15}N_3O_4$: N, 10.0. Found: N, 9.7.

Decarboxylation was easier than for the above acids, and gave a 60% yield of compound XIV, which crystallized from benzene in colorless leaflets, m.p. 224°.

Anal. Calcd. for $C_{23}H_{15}N_3$: C, 82.9; H, 4.5; N, 12.6. Found: C, 83.2; H, 4.4; N, 12.7.

The complex with picric acid crystallized from a mixture of benzene and ethanol in bright yellow needles, m.p. 214° (dec. above 180°).

Anal. Calcd. for a monopicrate ($C_{29}H_{18}N_6O_7$): N, 14.9. For a dipicrate: N, 15.9. Found: N, 14.3.

2,6-Di-(6-methyl-2-quinolyl)pyridine (XVI).

2,6-Di-(4-carboxy-6-methyl-2-quinolyl)pyridine (XV).

This compound prepared in 90% yield from 5-methylisatin and 2,6-diacetylpyridine, was a pale yellow, microcrystalline powder.

Anal. Calcd. for $C_{27}H_{19}N_3O_4$: N, 9.4. Found: N, 9.1.

Decarboxylation afforded compound XVI, in 60% yield, crystallizing from toluene in fine colorless needles, m.p. 286°.

Anal. Calcd. for $C_{25}H_{19}N_3$: C, 83.1; H, 5.3; N, 11.6. Found: C, 83.0; H, 5.4; N, 11.5.

2,6-Di-(9-benzo[h]quinolyl)pyridine (XVIII).

2,6-Di-(7-carboxy-9-benzo[h]quinolyl)pyridine (XVII).

This compound prepared in 80% yield from α-naphthisatin, 2,6-diacetylpyridine, and potassium hydroxide in ethanol (10 hr. refluxing), was a pale yellow, microcrystalline powder.

Anal. Calcd. for $C_{33}H_{19}N_3O_4$: N, 8.1. Found: N, 7.9.

Decarboxylation gave, in only 20% yield, compound XVIII, which crystallized from toluene in colorless prisms, m.p. 311°.

Anal. Calcd. for $C_{31}H_{19}N_3$: C, 85.9; H, 4.4; N, 9.7. Found: C, 85.6; H, 4.3; N, 9.6.

The monopicrate crystallized from a mixture of ethanol and benzene in orange-yellow microscopic needles, m.p. 232° (dec. above 200°).

Anal. Calcd. for $C_{37}H_{22}N_6O_7$: N, 12.7. Found: N, 12.7.

1,4-Di-(2-indolizinyl)benzene (XIX).

1,4-Di-(bromoacetyl)benzene.

This compound was prepared in 85% yield by adding dropwise a solution of 6.4 g. of bromine in 10 ml. of acetic acid to a hot, stirred solution of 3.2 g. of 1,4-diacetylbenzene in 20 ml. of acetic acid; the precipitate obtained on cooling was recrystallized from acetic acid, giving colorless prisms, m.p. 166-170°. The Tschitschibabin indolizine cyclization (8) was effected as follows: A solution of 1.6 g. of this dibromoketone and 1 g. of 2-methylpyridine in 20 ml. of ethanol was refluxed for 1 hr.; the pyridinium salt which formed on cooling was collected, washed with a mixture of ether and ethanol, and cyclized by boiling for a few minutes its solution in 10% aqueous hydrogen sodium carbonate. Compound XIX which precipitated was collected, washed with water, dried, and purified first by sublimation *in vacuo*, then by recrystallization from chlorobenzene. Yield, 50% of fine, pale yellow needles, subliming instantaneously without melting, at 410°. This compound was soluble in dilute hydrochloric acid, its solutions showing an intense blue fluorescence.

Anal. Calcd. for $C_{22}H_{16}N_2$: C, 85.1; H, 5.2; N, 9.1. Found: C, 84.7; H, 5.2; N, 9.1.

1,4-Di-(3-nitroso-2-indolizinyl)benzene (XXI).

This compound was obtained by adding the appropriate amount of sodium nitrite (in aqueous solution) to a solution of compound XIX in dilute hydrochloric acid; the reaction-mixture became bright red, and deposited rapidly the dihydrochloride of compound XXI, as fine, bright red needles. Basification with aqueous sodium carbonate gave the free dinitroso compound (XXI), crystallizing from nitrobenzene in shiny green needles, decomposing above 260° on gradual heating, and instantaneously at *circa* 340°.

Anal. Calcd. for $C_{22}H_{14}N_4O_2$: N, 15.3. Found: N, 15.4.

1,4-Di-(7-methyl-2-indolizinyl)benzene (XX).

Prepared from 2,4-dimethylpyridine, as for XIX, this was purified by repeated sublimation *in vacuo* at 300-320°, and formed pale yellow leaflets, which had not yet melted at 400°.

Anal. Calcd. for $C_{24}H_{20}N_2$: C, 85.7; H, 6.0; N, 8.3. Found: C, 85.6; H, 6.1; N, 8.3.

1,4-Di-(7-methyl-3-nitroso-2-indolizinyl)benzene (XXII).

This compound was a green, highly oxidizable compound, which could not be crystallized, and gave with hydrochloric acid the corresponding dihydrochloride, as red leaflets, which decomposed above 200° without showing a definite melting point.

1,4-Di-(2-imidazo[1,2-a]pyridyl)benzene (XXIII).

The Tschitschibabin "pyrimidazole" cyclization (9) was effected as follows: A solution of 1.6 g. of 1,4-di-(bromoacetyl)benzene and 1 g. of 2-aminopyridine in 30 ml. of propanol was refluxed for 1 hr.; the precipitate obtained on cooling was washed first with ethanol, then with aqueous ammonia, dried, and recrystallized from chlorobenzene (with charcoal), giving a 75% yield of compound XXIII as fine colorless needles, m.p. 345°.

Anal. Calcd. for $C_{20}H_{14}N_4$: C, 77.4; H, 4.5; N, 18.1. Found: C, 77.5; H, 4.6; N, 18.1.

The corresponding picrate crystallized from nitrobenzene in brignt yellow prisms, decomposing above 280° on gradual heating, and instantaneously at *circa* 340°.

Anal. Calcd. for $C_{26}H_{17}N_7O_7$: N, 18.2. Found: N, 18.2.

1,4-Di-(7-methyl-2-imidazo[1,2-a]pyridyl)benzene (XXIV).

Prepared as for the lower isomer, from 4-methyl-2-aminopyridine, this compound was purified by sublimation *in vacuo*, and formed fine colorless needles, m.p. 365° (dec. above 280°).

Anal. Calcd. for $C_{22}H_{18}N_4$: C, 78.1; H, 5.3; N, 16.6. Found: C, 78.4; H, 5.2; N, 16.6.

The picrate crystallized from nitrobenzene in bright yellow prisms, decomposing slowly above 260° and instantaneously at 330°.

Anal. Calcd. for $C_{28}H_{21}N_7O_7$: N, 17.3. Found: N, 17.5.

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