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Neighboring Group Interaction in Ortho-Substituted Aminopyridines. Pyridopyrimidines and Related Systems[1]

M. Debeljak-Šuštar, B. Stanovnik, M. Tišler,* and Z. Zrimšek

Department of Chemistry, University of Ljubljana, 61000 Ljubljana, Yugoslavia

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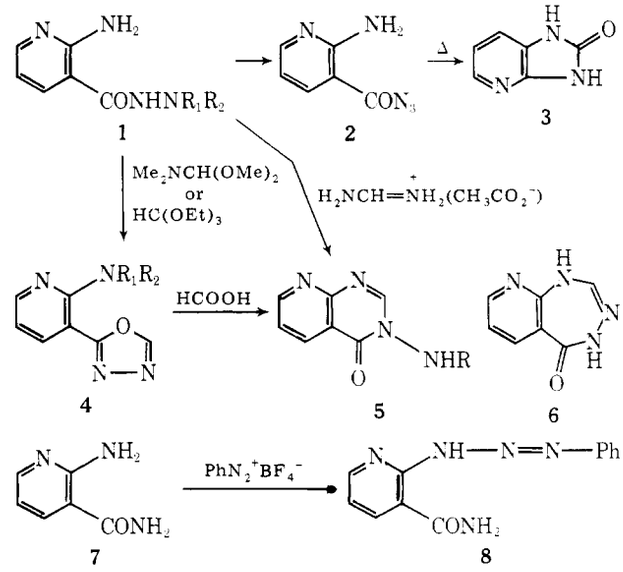
Hydrazides of isomeric *o*-aminopyridinecarboxylic acids have been used for syntheses of various bicyclic heterocycles. Derivatives of pyrido[2,3-*d*]-, pyrido[3,2-*d*]- or pyrido[3,4-*d*]pyrimidine, pyrido[3,2-*d*]- or pyrido[3,4-*d*]-*v*-triazine, and pyrazolo[1,5-*a*]pyrido[2,3-*d*]pyrimidine have been prepared. Some other transformations are also described.

Our recent interest in pyridopyrimidines[2,3] and related systems prompted us to investigate these systems and, in particular, some aspects of their preparation. Many synthetic approaches have been reported,[4] but in view of our recent findings it seemed worthwile to explore the possibilities of application of either *N,N*-dimethylaminomethylene derivatives[5-9] or participation of diazo or azido groups[10-19] in the construction of these bicyclic heterocycles. *N,N*-Dimethylformamide dimethyl acetal has been frequently used as a methine group source for various ring closures.

As starting material we have used hydrazides of 2-aminonicotinic acid, 3-aminopicolinic acid, and 3-aminoisonicotinic acid. 2-Aminopyridine-3-carboxylic acid hydrazide (**1**, $R_1 = R_2 = H$) was transformed with either isoamyl nitrite or benzenediazonium tetrafluoroborate under the conditions for azo-transfer reaction[13] into the acyl azide **2,** which was thermally converted into imidazo[4,5-*b*]pyridin-2-one (**3**). This transformation is an example of a Curtius rearrangement with subsequent intramolecular cyclization involving the isocyanato and *o*-amino groups. By monitoring this rearrangement in a NMR probe, the reaction is shown to be completed in 40 min at 80 °C. The hydrazide, when heated with either *N,N*-dimethylformamide dimethyl acetal or triethyl orthoformate, was transformed into an oxadiazolylpyridine (**4**, $R_1 = R_2 = H$). In the IR spectrum there was no evidence for a carbonyl group, and the NMR spectrum also revealed, in addition to three vicinal pyridine protons, a signal at δ 9.35, arising apparently from a CH group. In the literature, chemical shifts of few



1,3,4-oxadiazoles[20,21] and pyridopyrimidones[4] are recorded, and a differentiation between a H_2 of the oxadiazole system or a H_2 of the pyridopyrimidinone system is not reliable. On the basis of theoretical considerations and the determined molecular weight (162 g), besides the oxadiazole derivative (**4**), two other structures, i.e., the pyrido[2,3-*d*]pyrimidine (**5,**

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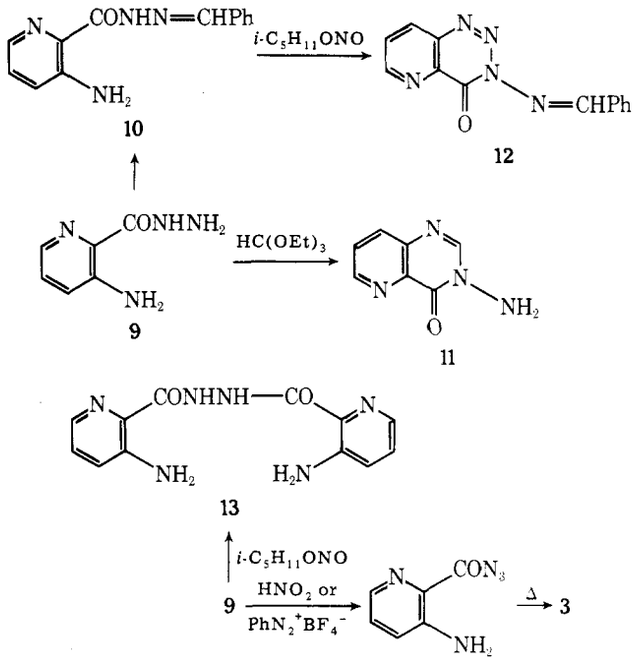
R = H) and pyridotriazepine (**6**), are also possible. Structure **5** is excluded since we have prepared this compound earlier,[3] and structure **6** can also be eliminated because of IR spectroscopic evidence and transformations which are described further. Also, it should be mentioned that benzo-1,3,4-triazepin-5-ones are readily rearranged into derivatives of 3-aminoquinazolin-4-one.[22]

The oxadiazolypyridine (**4**, $R_1 = R_2 = H$) afforded with excess *N,N*-dimethylformamide dimethyl acetal the corresponding *N,N*-dimethylaminomethylene derivative (**4**, $R_1R_2 = CHNMe_2$), whereas with hot formic acid it was transformed into the pyridopyrimidinone (**5**, R = H). This compound could be prepared also from **1** ($R_1 = R_2 = H$) and formamidine acetate directly. The transformation of **4** into **5** takes place most probably via the ring-opened product, i.e., **1**, since it is known that oxadiazoles are cleaved by acids,[21] and cyclization of *o*-aminobenzoic acid hydrazide with formic acid to 3-aminoquinazolin-4-one is well-known.[23] Although pyrido[2,3-*d*]-pyrimidine and some of its derivatives are readily hydrolyzed in acid solution to substituted pyridines,[21] compound **5** (R = H) could be formylated at the 3-amino group in a normal way to give the 3-formylamino compound (**5**, R = HCO). In this connection, it is noteworthy to mention that *o*-aminobenzoic acid hydrazide when heated with either *N,N*-dimethylformamide dimethyl acetal or triethyl orthoformate is converted to 3-aminoquinazolin-4-one. It has been reported previously[23] that this hydrazide is transformed with triethyl orthoformate into 3-ethoxymethyleneaminoquinazolin-4-one.

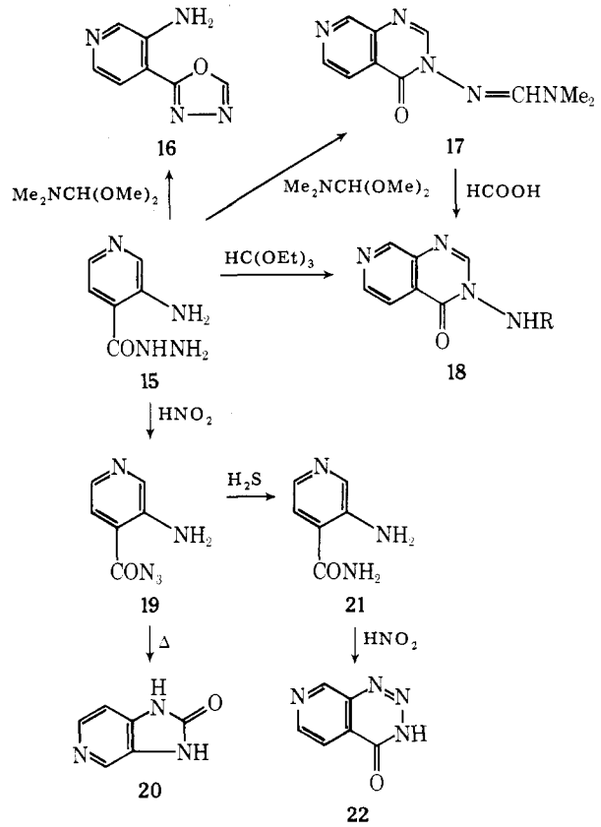
In view of our previous interest in barriers to rotation in some *N'*-heteroaryl *N,N*-dimethylformamidines,[8] we have examined compound **4** ($R_1R_2 = CHNMe_2$). The chemical shift of H_2 at the oxadiazole ring in **4** is dependent on the size of the ortho group in the pyridine part of the molecule. When this group is small, as in the case of an amino group (**4**, $R_1 = R_2 = H$), the oxadiazole ring appears to be coplanar with the pyridine ring (the signal for H_2 of the oxadiazole appears at δ 9.35). If the ortho group is bigger, such as formylamino (**4**, $R_1 = H$, $R_2 = HCO$) or *N,N*-dimethylaminomethyleneamino (**4**, $R_1R_2 = CHNMe_2$), the oxadiazole ring is no longer coplanar with the pyridine ring, and the signal for H_2 of the oxadiazole ring appears at δ 8.15 and 8.62, respectively. This steric hindrance is also reflected in the magnitude of barriers to rotation which is 12.5 kcal/mol for **4** ($R_1R_2 = CHNMe_2$) when compared to 16 kcal/mol for 2-(*N,N*-dimethylaminomethyleneamino)-pyridine and its 3-methyl derivative.[8]

We have reported previously on the synthesis of pyrido[3,2-*d*]-*v*-triazin-4-one,[24] and therefore syntheses of the isomeric systems were tempting. from 2-aminonicotinamide, if diazotized in the usual manner, an easily hydrolyzable diazonium group is generated, and therefore the desired and unknown pyrido[2,3-*d*]-*v*-triazin-4-one is not produced. Therefore, we have attempted to prepare this system from **7** using the aza-transfer reaction with benzenediazonium tetrafluoroborate. However, only the corresponding stable triazene (**8**) could be isolated.

The isomeric 3-aminopyridine-2-carboxylic acid hydrazide (**9**) reacted with *N,N*-dimethylformamide dimethyl acetal to yield the *N,N*-dimethylaminomethylene derivative of **9**, whereas with triethyl orthoformate, 3-aminopyrido[3,2-*d*]-pyrimidin-4-one (**11**) was formed. In nitrosation of **9** with isoamyl nitrite, the desired azide (**14**) was not obtained but the corresponding bishydrazide (**13**) was obtained, apparently by the nitrite ion functioning as an oxidant. Similar conversions with other mild oxidants are known.[25-28] Azide **14** could be obtained with sodium nitrite in acetic acid or by aza transfer from a benzenediazonium ion, and it could be rearranged to **3**. If the benzylidene derivative (**10**) was first prepared from **9** and then diazotized, the *v*-triazine (**12**) could be obtained in good yield.



Synthetic approaches for the preparation of another system, pyrido[3,4-*d*]pyrimidine, were also investigated since there are not many reports regarding this bicyclic system. The hydrazide (**15**) gave with *N,N*-dimethylformamide dimethyl acetal either the oxadiazolylpyridine (**16**) or compound **17**.



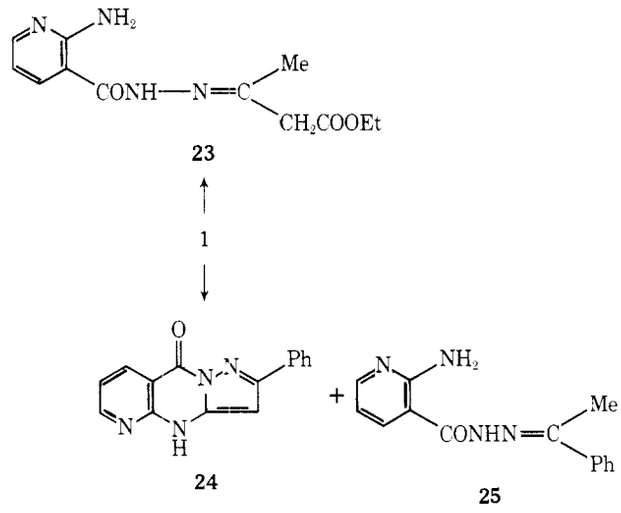
The reaction with triethyl orthoformate proceeded differently, and 3-aminopyrido[3,4-*d*]pyrimidin-4-one (**18**, R = H) could be prepared in moderate yield. This compound was prepared also from ethyl 3-aminopyridine-4-carboxylate and *N,N*-dimethylformamide dimethyl acetal. The intermediate *N,N*-dimethylaminomethylene derivative was not isolated in pure form and was immediately transformed with hydrazine into the bicyclic compound (**18**, R = H). This is an example of dimethylamine as a leaving group, and this contrasts

the known methods of cyclization where an acyl group is eliminated. Compound **17** is transformed with formic acid into the formylamino derivative (**18**, R = HCO), obtainable also by direct formylation of the amine (**18**, R = H).

3-Aminopyridine-4-carboxylic acid azide (**19**) was prepared from **15** and nitrous acid, and on heating it was transformed by Curtius rearrangement into imidazo[4,5-*c*]pyridin-2-one (**20**). The azide was easily transformed with hydrogen sulfide into the amide (**21**), obtainable also under severe reaction conditions from the corresponding ester and ammonia. The easy conversion of the azide into amide is another example of this useful transformation tested already on other compounds.[29] On diazotization the amide (**21**) afforded pyrido[3,4-*d*]-*v*-triazin-4-one (**22**).

In this connection it should be mentioned that the formation of azides **2** and **19** from the corresponding hydrazides contrasts the reactivity of *o*-aminobenzoic acid hydrazide. This, depending upon the acidity of the reaction mixture, is transformed with nitrous acid into either the azide or a mixture of the azide and 3-aminobenzotriazin-4-one.[30,31]

In view of the ready availability of pyrazolo[5,1-*b*]quinazolines from *o*-aminobenzoic acid hydrazides and esters of 1,3-keto carboxylic acids or related compounds with a reactive methylene group,[32] it seemed worthwile to investigate this reaction with the corresponding pyridine analogues. Although the reaction proceeds smoothly in the benzene series, we could only obtain condensation products in the pyridine series in a few cases. The hydrazide (**1**, R = R_1 = H) afforded with ethyl acetoacetate in boiling ethyl acetate only the condensation product (**23**). A similar reaction with ethyl benzoylacetate in



boiling diethylene glycol dimethyl ether gave a mixture of a tricyclic compound (**24**) and a derivative of the so far unknown pyrazolo[1,5-*a*]pyrido[2,3-*d*]pyrimidine system, together with an acyclic compound (**25**) as the major product. The latter compound resulted evidently from condensation, followed by hydrolysis of the ester function and subsequent decarboxylation. The structures of these compounds were ascertained by elemental analyses and spectroscopic evidence.

Experimental Section

Melting points were determined on a Kofler hot-plate melting point apparatus. The NMR spectral measurements were performed on a Jeol JNM C-60 HL spectrometer with Me_4Si as an internal standard. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6L spectrometer.

2-Aminopyridine-3-carboxylic Acid Azide (2). Method A. 2-Aminopyridine-3-carboxylic acid hydrazide[33] (**1**, R_1 = R_2 = H, 0.152 g) was dissolved in glacial acetic acid (5 mL), and isoamyl nitrite (0.12 g) was added slowly while stirring. The reaction mixture was left at room temperature for 12 h and evaporated in vacuo to dryness, and the residue extracted several times with hot *n*-heptane. The product which separated from *n*-heptane on cooling was filtered off: mp 128–130 °C (lit.[34] mp 124 °C), and from the melt new crystals separated, mp 270–273 °C (formation of imidazo[4,5-*b*]pyridin-2-one, **3**); IR 2150 cm^{-1} (N_3); ^1H NMR ($CDCl_3$) δ 8.05 (dd, H_4, $J_{4,5}$ 8.2, $J_{4,6}$ = 2.0 Hz), 6.55 (dd, H_5, $J_{5,6}$ = 5.0 Hz), 8.25 (dd, H_6), 6.9 (broad, NH_2); MS *m/e* 163 (M).

Anal. Calcd for $C_6H_5N_5O$: C, 44.17; H, 3.09; N, 42.93. Found: C, 44.46; H, 3.34; N, 42.75.

The above-mentioned transformation of the azido compound into imidazo[4,5-*b*]pyridin-2-one (**3**) could be followed in a NMR probe. For synthetic purposes, a solution of the azido compound (0.2 g) in diethylene glycol dimethyl ether (5 mL) was heated at 130 °C for 1.5 h. The solvent was evaporated in vacuo and the residue had mp 270–273 °C (lit.[33] mp 270–272 °C); MS *m/e* 135 (M).

Anal. Calcd for $C_6H_5N_3O$: C, 53.33; H, 3.73; N, 31.10. Found: C, 53.06; H, 3.92; N, 31.42.

Method B. A solution of the hydrazide (**1**, R_1 = R_2 = H, 0.875 g) in dimethyl sulfoxide (10 mL) was treated while stirring with benzendiazonium tetrafluoroborate (1.105 g). After some time, the resulting reddish solution was poured into ice, and the separated solid was filtered off. The crude product was crystallized from water, mp 126 °C (with the formation of bicyclic compound **3**). The compound was found to be identical with that obtained from method A.

2-Amino-3-(1′,3′,4′-oxadiazolyl-5′)pyridine (4, R_1 = R_2 = H). Method A. A mixture of 2-aminopyridine-3-carboxylic acid hydrazide (**1**, R_1 = R_2 = H, 0.75 g), *N,N*-dimethylformamide dimethyl acetal (0.7 g), and diethylene glycol dimethyl ether (20 mL) was heated under reflux for 2 h. On evaporation to dryness in vacuo, the residue was sublimed at 120 °C (0.1 mm) or crystallized from water: yield 0.35 g; mp 162–163 °C; IR (no CO absorption band); ^1H NMR (Me_2SO-d_6) δ 8.10 (dd, H_4, $J_{4,5}$ = 8.1, $J_{4,6}$ = 1.8 Hz), 6.75 (dd, H_5, $J_{5,6}$ = 4.8 Hz), 8.25 (dd, H_6), 9.35 (s, H_2), 7.35 (broad, NH_2); MS *m/e* 162 (M).

Anal. Calcd for $C_7H_6N_4O$: C, 51.85; H, 3.73; N, 34.56. Found: C, 51.80; H, 4.21; N, 34.31.

Method B. A mixture of the hydrazide (**1**, R_1 = R_2 = H, 0.75 g), triethyl orthoformate (0.75 g), and diethylene glycol dimethyl ether (10 mL) was heated under reflux for 1.5 h. On standing overnight at room temperature and after filtration, the solution was evaporated to dryness in vacuo. The oily residue was treated with water and filtered. On crystallization from water, the product had mp 163 °C (yield 0.33 g) and was found to be identical in all respects with the product obtained as described in method A.

If the crude product from the reaction in method A was crystallized from ethyl acetate, a small amount of a product with mp 246–248 °C separated from the solvent and was identified by the use of analytical data and comparison with an authentic specimen as 3-aminopyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**5**, R = H) (lit.[3] mp 249–250 °C). The same compound was also obtained if the 2-amino-3-(1′,3′,4′-oxadiazolyl-5′)pyridine (**4**, R_1 = R_2 = H) from method B was heated with excess formic acid under reflux for 1.5 h. On evaporation in vacuo, the residual oil crystallized after some time and was sublimed at 180 °C (0.1 mm) to give pyridopyrimidone **5** (R = H), mp 248 °C.

Finally, 3-aminopyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**5**, R = H) was also obtained if 2-aminopyridine-3-carboxylic acid hydrazide and formamidine acetate were heated in 2-ethoxyethanol for 2 h and the crude product sublimed at 200 °C (0.1 mm).

2-(*N,N*-Dimethylaminomethyleneamino)-3-(1′,3′,4′-oxadiazolyl-5′)pyridine (4, R_1R_2 = CHNMe$_2$). A mixture of the oxadiazolypyridine (**4**, R_1 = R_2 = H, 0.5 g) and *N,N*-dimethylformamide dimethyl acetal (8 mL) was heated under reflux for 2.5 h. On evaporation in vacuo, the semisolid residue was crystallized from carbon tetrachloride and hexane: yield 0.35 g; mp 90–91 °C; ^1H NMR ($CDCl_3$) δ 8.20 (dd, H_4, $J_{4,5}$ = 7.8, $J_{4,6}$ = 2.0 Hz), 7.01 (dd, H_5, $J_{5,6}$ = 4.8 Hz), 8.48 (dd, H_6), 8.62 (s, H_2 and CH=), 3.10 (s, NMe_2); MS *m/e* 217 (M).

Anal. Calcd for $C_{10}H_{11}N_5O$: C, 55.29; H, 5.10; N, 32.24. Found: C, 55.06; H, 5.10; N, 32.42.

3-Formylaminopyrido[2,3-*d*]pyrimidin-4(3*H*)-one (5, R = HCO). A mixture of the 3-amino compound (**5**, R = H, 0.4 g), pyridine (1 mL), and formic acid (3 mL of 100%) was heated under reflux for 1 h. The solution was evaporated to dryness in vacuo, and the residue was treated with boiling ethanol. The filtered product had mp 255–263 °C dec; ^1H NMR (Me_2SO-d_6) δ 8.58 (s, H_2), 8.63 (dd, H_5, $J_{5,6}$ = 8.0, $J_{5,7}$ = 2.0 Hz), 7.63 (dd, H_6, $J_{6,7}$ = 4.5 Hz), 9.08 (dd, H_7); MS *m/e* 190 (M).

Anal. Calcd for $C_8H_6N_4O_2$: C, 50.53; H, 3.18. Found: C, 50.34; H, 3.40.

Reaction between Anthranilamide and *N,N*-Dimethylformamide Dimethyl Acetal or Triethyl Orthoformate. A mixture of

equivalent amounts of anthranilamide and *N,N*-dimethylformamide dimethyl acetal (or triethyl orthoformate) in diethylene glycol dimethyl ether was heated under reflux for 2 h. The reaction mixture was evaporated to dryness, some 1-propanol was added, and the separated product was filtered off, mp 208–211 °C (lit.[23] mp 202–207 °C from triethyl orthoformate). The compound was found to be identical in all respects with an authentic specimen of 3-aminoquinazolin-4-one.

2-Phenyltriazenylpyridine-3-carboxamide (8). A solution of 2-aminonicotinamide[35] (**7**, 1.37 g) in dimethyl sulfoxide (10 mL) was treated with benzenediazonium tetrafluoroborate (1.92 g). The resulting solution was left at room temperature for 10 min and extracted with diethyl ether (six times with 30 mL). On drying the extracts, the solvent was evaporated, and to the residual oil some water was added. The yellow crystals that formed were filtered off: mp 159–161 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.22 (dd, H_4, $J_{4,5}$ = 8.0, $J_{4,6}$ = 1.8 Hz), 7.25 (dd, H_5, $J_{5,6}$ = 5.0 Hz), 8.53 (dd, H_6), 7.9 and 7.5 (m, Ph); MS *m/e* 241 (M).

Anal. Calcd for $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60. Found: c, 60.01; H, 4.82.

The Dimethylaminomethylene Derivative of 3-Aminopyridine-2-carboxylic Acid Hydrazide. A mixture of 3-aminopyridine-2-carboxylic acid hydrazide[33] (**9**, 0.75 g), *N,N*-dimethylformamide dimethyl acetal (0.7 g), and diethylene glycol dimethyl ether (10 mL) was heated under reflux for 2 h. After standing at room temperature overnight, the mixture was evaporated to dryness in vacuo, the residue was dissolved in hot water, and on cooling the product crystallized; yield 0.57 g; mp 82–86 °C (from water); ^{1}H NMR (Me_2SO-d_6) δ 7.10 (m, H_4 and H_5, $J_{4,5}$ = 3.5, $J_{4,6}$ = 2.1, $J_{5,6}$ = 8.4 Hz), 7.74 (dd, H_6), 7.98 (s, N=CH), 2.75 (s, Me); MS *m/e* 207 (M).

Anal. Calcd for $C_9H_{13}N_5O$: C, 52.16; H, 6.32; N, 33.80. Found: C, 51.98; H, 6.62; N, 33.48.

If, however, instead of the above acetal, triethyl orthoformate was used in the reaction under the same reaction conditions, 3-aminopyrido[3,2-*d*]pyrimidin-4(3*H*)-one (**11**) was obtained. The semisolid crude reaction product was treated with a small quantity of hot ethanol and filtered and the residue crystallized from ethanol, mp ~280–285 °C (lit.[3] mp 285–287 °C).

Treatment of 3-Aminopyridine-2-carbohydrazide with Isoamyl Nitrite in Glacial Acetic Acid. Formation of the Bishydrazide (13). A solution of 3-aminopyridine-2-carbohydrazide (**9**, 0.6 g) in glacial acetic acid (10 mL) was treated with isoamyl nitrite (0.47 g), and the yellow solution was left to stand overnight at room temperature. The reaction mixture was diluted with water (70 mL), and the yellow product was filtered and crystallized from ethanol: yield 0.19; mp 227–230 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.90 (dd, H_6), 7.30 (m, H_4 and H_5, $J_{4,5}$ = 8.0, $J_{4,6}$ = 1.8, $J_{5,6}$ = 4.0 Hz), 2.80 (broad, NH_2), 10.25 (broad, NH); MS *m/e* 272 (M).

Anal. Calcd for $C_{12}H_{12}N_6O_2$: C, 52.93; H, 4.44; N, 30.87. Found: C, 52.91; H, 4.36; N, 31.13.

If the hydrazide was treated with sodium nitrite in dilute aqueous acetic acid the corresponding azido compound (**14**) could be obtained: mp 135–140 °C (lit.[34] mp 116 °C); ^{1}H NMR (Me_2SO-d_6) δ 8.75 (dd, H_4, $J_{4,5}$ = 9.5, $J_{4,6}$ = 1.8 Hz), 8.25 (dd, H_5, $J_{5,6}$ = 4.5 Hz), 9.28 (dd, H_6); IR 4.68 (N_3), 5.96 μm (CO); MS *m/e* 163 (M), 135 (M − N_2). At the melting point temperature, the compound is transformed into imidazo[4,5-*b*]pyrimidin-2-one (**3**), obtainable also by heating the azido compound in diethylene glycol dimethyl ether for 30 min, mp 275–273 °C (lit.[34] mp 270–272 °C).

The azide is also obtained if a solution of the hydrazide in dimethyl sulfoxide is treated with benzenediazonium tetrafluoroborate and after 30 min the reaction mixture is diluted with water.

The Benzylidene Derivative of 3-Aminopyridine-2-carbohydrazide (10). The hydrazide (0.76 g), benzaldehyde (0.53 g), and 1,2-dimethoxyethane (10 mL) were heated 4 h under reflux. The reaction mixture was evaporated to dryness, and the residue was crystallized from ethanol: yield 0.86 g; mp 170–172 °C; MS *m/e* 240 (M).

Anal. Calcd for $C_{13}H_{12}N_4O$: C, 64.98; H, 5.03; N, 23.32. Found: C, 64.66; H, 5.42; N, 23.10.

The benzylidene derivative of 2-aminopyridine-3-carboxylic acid hydrazide (1, R_1R_2 = CHPh) was prepared in an analogous way from 2-aminopyridine-3-carboxylic acid hydrazide: yield 0.77 g; mp 181 °C (from ethyl acetate and *n*-hexane); MS *m/e* 240 (M).

Anal. Calcd for $C_{13}H_{12}N_4O$: C, 64.98; H, 5.03; N, 23.32. Found: C, 64.68; H, 5.51; N, 23.57.

The Benzylidene Derivative of 3-Aminopyrido[3,2-*d*]-*v*-triazin-4-one (12). A solution of compound **11** (0.24 g) in glacial acetic acid (5 mL) was treated with isoamyl nitrite (0.117 g), and the product which separated was filtered off; yield 0.23 g; mp 207–209 °C (from diethylene glycol dimethyl ether); ^{1}H NMR (Me_2SO-d_6) δ 9.13 (dd, H_6, $J_{6,7}$ = 4.5, $J_{6,8}$ = 1.6 Hz), 8.05 (dd, H_7, $J_{7,8}$ = 8.2 Hz), 8.63 (dd, H_8), 9.22 (s, CH), 8.05 and 7.6 (m, Ph); MS *m/e* 251 (M).

Anal. Calcd for $C_{13}H_9N_5O$: C, 62.14; H, 3.61; N, 27.88. Found: C, 62.42; H, 3.64; N, 27.36.

Reaction between 3-Aminopyridine-4-carboxylic Acid Hydrazide and *N,N*-Dimethylformamide Dimethyl Acetal. Method A. A mixture of the acid hydrazide[33] (**15**, 0.75 g), *N,N*-dimethylformamide dimethyl acetal (0.75 g), and diethylene glycol dimethyl ether (10 mL) was heated under reflux for 2 h. After standing overnight at room temperature, the separated product was filtered off, and the filtrate was evaporated to dryness to give 3-(*N,N*-dimethylaminomethyleneimino)pyrido[3,4-*d*]pyrimidin-4-one (**17**). The combined products were crystallized from water: yield 0.32 g; mp 225 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.44 (s, H_2), 8.0 (dd, H_5, $J_{5,6}$ = 5.0, $J_{5,8}$ = 1.0 Hz), 8.75 (d, H_6), 9.16 (d, H_8), 8.16 (s, N=CH), 3.0 (s, Me); MS *m/e* 217 (M).

Anal. Calcd for $C_{10}H_{11}N_5O$: C, 55.29; H, 5.10; N, 32.24. Found: C, 55.73; H, 5.22; N, 32.45.

Method B. If in the above reaction *N,N*-dimethylformamide dimethyl acetal was used in a quantity less than equivalent (0.5 g) to the amount of hydrazide, the obtained product had mp 160 °C (from water) and was identified as 3-amino-4-(1′,3′,4′-oxadiazolyl-5′)pyridine (**16**); ^{1}H NMR (Me_2SO-d_6) δ 8.40 (s, H_2), 7.52 (d, H_5, $J_{5,6}$ = 4.0 Hz), 7.90 (d, H_6), 9.40 (s, H_2); MS *m/e* 162 (M).

Anal. Calcd for $C_7H_6N_4O$: C, 51.85; H, 3.73; N, 34.56. Found; c, 51.56; H, 4.20; N, 34.62.

3-Aminopyrido[3,4-*d*]pyrimidin-4(3*H*)-one (18). Method A. A mixture of 3-aminopyridine-4-carboxylic acid hydrazide (**15**, 0.75 g), triethyl orthoformate (0.75 g), and diethylene glycol dimethyl ether (10 mL) was heated under reflux for 1.5 h. On evaporation to dryness in vacuo, the semisolid residue was crystallized form ethanol: yield 0.25 g; mp 201 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.60 (s, H_2), 8.10 (dd, H_5, $J_{5,6}$ = 5.4, $J_{5,8}$ = 0.9 Hz), 8.85 (d, H_6), 9.25 (d, H_8); MS *m/e* 162 (M).

Anal. Calcd for $C_7H_6N_4O$: C, 51.85; H, 3.75; N, 34.56. Found: C, 51.95; H, 3.90; N, 34.73.

Method B. A mixture of ethyl 3-aminopyridine-4-carboxylate (1.66 g) and *N,N*-dimethylformamide dimethyl acetal (4 mL) was heated under reflux for 2 h. On evaporation to dryness, the dark oily residue was treated with hydrazine hydrate (2 mL of 100%), and the mixture was heated to boiling for a few minutes. The separated product was filtered off and washed with water, mp 202–205 °C (from ethanol). The compound was found to be identical in all respects with the product obtained as described in method A.

3-Formylaminopyrido[3,4-*d*]pyrimidin-4(3*H*)-one (18, R = HCO). Method A. A mixture of compound **17** (0.25 g) and formic acid (5 mL of 85%) was heated under reflux for 1 h and evaporated to dryness. The residue was treated with ethyl acetate (7 mL) and heated to boiling for a few minutes. On filtration the residue had mp 226–231 °C (0.11 g); ^{1}H NMR (Me_2SO-d_6) δ 8.57 (s, H_2), 8.10 (dd, H_5, $J_{5,6}$ = 5.2, $J_{5,8}$ = 0.9 Hz), 8.83 (d, H_6), 9.20 (d, H_8), 8.48 (s, CH); MS *m/e* 190 (M).

Anal. Calcd for $C_8H_6N_4O_2$: C, 50.53; H, 3.18; N, 29.47. Found: C, 50.65; H, 3.25; N, 29.30.

Method B. A mixture of 3-aminopyrido[3,4-*d*]pyrimidin-4(3*H*)-one (**18**, R = H, 0.4 g), pyridine (1 mL), and formic acid (3 mL of 100%) was heated under reflux for 2 h. On evaporation to dryness in vacuo, the residue was crystallized from methanol, mp 228–230 °C. The compound was found to be identical in all respects with the product obtained as described in method A.

3-Aminopyridine-4-carboxylic Acid Azide (19). A cold solution of 3-aminopyridine-4-carboxylic acid hydrazide (**15**, 1.0 g) in aqueous acetic acid (12 mL of 25%) was treated with sodium nitrite (0.46 g). The product which separated was filtered off and dried: mp 120–130 °C, with formation of a new compound (**20**) with mp 315 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 8.30 (s, H_2), 7.33 (d, H_5, $J_{5,6}$ = 5.0 Hz), 7.70 (d, H_6); MS *m/e* 163 (M), 135 (M − N_2).

Anal. Calcd for $C_6H_5N_5O$: C, 44.17; H, 3.09. Found: C, 44.32; H, 3.01.

Imidazo[4,5-*c*]pyridin-2-one (**20**) was prepared from the above compound (**19**) by heating it in diethylene glycol dimethyl ether: mp 315 °C dec (lit.[36] mp 304–305 °C); ^{1}H NMR (M_2SO-d_6) δ 8.18 (d, H_4, $J_{4,7}$ = 0.7 Hz), 8.07 (d, H_6, $J_{6,7}$ = 5.3 Hz), 6.95 (dd, H_7); MS *m/e* 135 (M).

Anal. Calcd for $C_6H_5N_3O$: C, 53.33; H, 3.73. Found: C, 53.11; H, 4.12.

3-Aminopyridine-4-carboxylic Acid Amide (21). Method A. Ethyl 3-aminopyridine-4-carboxylate (2 g) and liquid ammonia (20 mL) were heated in an autoclave at 130 °C for 7 h. The crude product

was sublimed in vacuo to give the pure amide: mp 149 °C (lit.[37] mp 151–152 °C); MS *m/e* 137 (M).

Anal. Calcd for $C_6H_7N_3O$: C, 52.54; H, 5.15. Found: C, 52.66; H, 5.12.

Method B. Into a solution of 3-aminopyridine-4-carboxylic acid azide (**19**, 0.15 g) in ethanol (5 mL) hydrogen sulfide was introduced for 30 min. The precipitated sulfur was filtered off, and the solution was evaporated to dryness to give the amide, mp 148 °C. The compound was found to be identical in all respects with the product obtained as described in method A.

Pyrido[3,4-*d*]-*v*-triazin-4(3*H*)-one (22). A solution of the above amide (**21**, 0.137 g) in glacial acetic acid (5 mL) was treated with sodium nitrite (69 mg) in a little water while stirring. The product which separated was filtered off and had mp 251 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 8.14 (dd, H_5, $J_{5,6}$ = 5.1, $J_{5,8}$ = 0.9 Hz), 9.11 (d, H_6), 9.64 (d, H_8); MS *m/e* 148 (M).

Anal. Calcd for $C_6H_4N_4O$: C, 48.65; H, 2.72. Found: C, 49.03; H, 2.99.

Reaction between 2-Aminopyridine-3-carboxylic Acid Hydrazide and Ethyl Acetoacetate to Give 23. 2-Aminonicotinic acid hydrazide (**1**, 0.5 g), ethyl acetoacetate (0.43 g), ethyl acetate (60 mL), and a drop of triethylamine were heated under reflux for 3 h. The reaction mixture was evaporated to dryness in vacuo, the residue was treated with benzene, and the separated product was filtered off and crystallized from benzene: yield 0.45 g; mp 99–101 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.75 (dd, H_4, $J_{4,5}$ = 8.0, $J_{4,6}$ = 1.8 Hz.), 6.60 (dd, H_5, $J_{5,6}$ = 5.0 Hz), 8.17 (dd, H_6), 2.0 (s, Me), 3.40 (s, CH_2CO_2Et).

Anal. Calcd for $C_{12}H_{16}N_4O_3$: C, 54.55; H, 6.10; N, 21.10. Found: C, 55.01; H, 6.47; N, 21.01.

Reaction between 2-Aminopyridine-3-carboxylic Acid Hydrazide and Ethyl Benzoylacetate. A mixture of the hydrazide (**1**, 0.5 g), ethyl benzoylacetate (0.65 g), and diethylene glycol dimethyl ether (10 mL) was heated at 160 °C for 2 h. After about 1 h of heating, crystals started to separate. The product was filtered off and had mp over 290 °C (yield 0.11 g). The tricyclic product (**24**) showed the following spectrum: ^{1}H NMR (Me_2SO-d_6, 147 °C) δ 6.45 (s, H_3), 8.85 (dd, H_6, $J_{6,7}$ = 4.0, $J_{6,8}$ = 1.8 Hz), 8.40 (dd, H_7, $J_{7,8}$ = 8.0 Hz), 8.70 (dd, H_8), 8.10 and 7.5 (m, Ph).

Anal. Calcd for $C_{15}H_{10}N_4O$: C, 68.69; H, 3.84; N, 21.37. Found: C, 68.51; H, 4.30; N, 21.19.

The filtrate was evaporated in vacuo to dryness, and the residue was suspended in *n*-hexane, filtered, and washed with ethanol. The product (**25**) was crystallized from ethanol: yield 0.45; mp 209–212 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.85 (dd, H_4, $J_{4,5}$ = 7.5, $J_{4,6}$ = 1.8 Hz), 6.75 (dd, H_5, $J_{5,6}$ = 4.5 Hz), 8.10 (dd, H_6), 2.30 (s, Me), 7.85 and 7.4 (m, Ph).

Anal. Calcd for $C_{14}H_{14}N_4O$: C, 66.12; H, 5.55; N, 22.04. Found: C, 65.99; H, 5.08; N, 21.65.

Registry No.—1 (R_1 = R_2 = H), 5327-31-1; 1 (R_1R_2 = CHPh), 64189-07-7; **2**, 64189-06-6; **3**, 16328-62-4; **4**, (R_1 = R_2 = H), 64189-05-5; **4** (R_1R_2 = $CHNMe_2$), 64189-04-4; **5** (R = H), 37554-48-6; **5** (R = HCO), 64189-03-3; **7**, 13438-65-8; **8**, 64189-01-1; **9**, 3303-28-4; **10**, 64201-58-7; **11**, 37554-49-7; **12**, 64189-02-2; **13**, 64189-10-2; **14**, 64189-09-9; **15**, 64189-08-8; **16**, 64188-99-4; **17**, 64189-00-0; **18** (R = H), 64201-55-4; **18** (R = HCO), 64201-57-6; **19**, 64188-98-3; **20**, 7397-68-4; **21**, 64188-97-2; **22**, 64188-96-1; **23**, 64188-95-0; **24**, 64188-94-9; **25**, 64188-93-8; *N,N*-dimethylformamide dimethyl acetal, 4637-24-5; formic acid, 64-18-6; anthranilamide, 88-68-6; triethyl orthoformate, 122-51-0; 9-dimethylaminomethylene derivative, 64188-92-7; benzenediazonium tetrafluoroborate, 369-57-3; benzaldehyde, 100-52-7; ethyl 3-aminopyridine-4-carboxylate, 14208-83-4; ethyl acetoacetate, 141-97-9; ethyl benzoylacetate, 94-02-0.

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Stable Arene Imines

Ytzhak Ittah, Israel Shahak, and Jochanan Blum*

Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem, Israel

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The syntheses of stable *N*-alkyl arene imines are described. The general route to 1-butyl-, 1-cyclohexyl-, and 1-benzyl-1a,9b-dihydrophenthr[9,10-*b*]azirine includes the reaction of phenanthrene 9,10-oxide with the appropriate amine followed by cyclodehydration of the amino alcohol with PPh_3–CCl_4 reagent. The preparation of 1-acetyl-1a,11b-dihydrochrysen[5,6-*b*]azirine from *trans*-6-acethoxy-5-acetylamino-5,6-dihydrochrysene and NaH is described as an example of an unstable arene imine that rearranges at room temperature to the corresponding *N*-acetyl aryl amine.

It is widely accepted that polycyclic aromatic hydrocarbons exert their carcinogenic properties through metabolically induced binding to tissue constituents.[1] Arene oxides are generally described as the primary intermediates that alkylate amino acid and nucleic acid residues to form hydrocarbon-bound cell substances with new C–O, C–S, or C–N linkages.[2]

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